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THE RISK OF DEVELOPING RHEUMATOID ARTHRITIS: EPIDEMIOLOGICAL STUDIES ON ASSOCIATIONS WITH SOCIOECONOMIC STATUS, PSYCHOSOCIAL WORK STRESS AND SMOKING

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Ju mer man tänker, ju mer inser man
att det inte finns något enkelt svar.
Nalle Puh

Ibland när jag säger det jag tänker så
märker jag att jag inte alltid tycker så.
Nalle Puh

Förmågan att idag tänka annorlunda än
igår skiljer den vise från den envise.
John Steinbeck

Till min pappa

Lars-Åke Bengtsson

ABSTRACT

Rheumatoid arthritis (RA) is a chronic, inflammatory disease. Knowledge about the contribution of genetics is rapidly increasing, but data on environmental factors that may cause RA is scarce. The aim of this thesis was to contribute to better knowledge about the aetiology of the disease by investigating the association between RA and socioeconomic status, psychosocial work stress and smoking. A further aim was to evaluate participation/non-participation and late response in a large population-based case-control study (1931 cases, 2214 controls) on incident cases of RA, called EIRA.

The thesis is based on data from EIRA, comprising the population, aged 18-70 years, in parts of Sweden. A case was defined as a person in the study base with newly diagnosed RA, in accordance with the American College of Rheumatology criteria. Controls were randomly selected from the study base, taking age, gender and residential area into consideration. Cases and controls answered a questionnaire regarding e.g. socioeconomic status, psychosocial work stress and smoking. The response proportion was 96% among cases and 82% among controls. A blood sample was taken in order to analyse rheumatoid factor (RF) and HLA-DRB1 shared epitope (SE) alleles. In order to evaluate possible selection bias in EIRA, socio-demographic data were collected from registers at Statistics Sweden, for all identified study subjects.

According to the results, low socioeconomic status (low formal education and low occupational class, respectively) was associated with increased risk of RA. This increased risk was more pronounced for RF positive RA as compared to RF negative RA. Low decision latitude, a marker of psychosocial work stress, was associated with an increased risk of developing RA. No major differences were observed according to RF status. Cigarette smokers had an increased risk of developing RF positive RA, but not RF negative RA. This increased risk occurred after a long duration, but of merely moderate intensity of smoking, and remained for several years after smoking cessation. A striking gene-environment interaction between smoking and HLA-DRB1 SE alleles was seen for RF positive RA but not for RF negative RA. In a methodological study, the decreasing participation in epidemiologic studies seen in recent years was not observed in EIRA. According to both the high participation and results from a non-participation analysis, selection bias due to non-participation is probably of minor magnitude in EIRA and the results in the thesis are likely to be only marginally biased by this source of systematic error. In a late response analysis, inclusion of smoking and occupational class data from late respondents did not alter the results compared with those of the early respondents only. Thus, several reminders to include reluctant or difficult-to-find study subjects in epidemiological studies might not be worthwhile if the costs and efforts to include these study subjects are high.

In conclusion, the results in this thesis add to the likelihood that socioeconomic status and psychosocial factors in the work environment influences the risk of developing RA. With regard to smoking the results indicate that the effect of smoking is complex, slow, or delayed. The striking gene-environment interaction between smoking and HLA-DRB1 genotypes for RF positive but not RF negative RA, emphasizes that we are only at the beginning of an era where it will be possible to disentangle the complex interactions between different environmental and genetic risk factors and to understand what different biological mechanisms may be triggered in the context of various combinations of genes and environmental factors.

LIST OF PUBLICATIONS

I. **Bengtsson C,** Nordmark B, Klareskog L, Lundberg I, Alfredsson L; EIRA Study Group. Socioeconomic status and the risk of developing rheumatoid arthritis: results from the Swedish EIRA study. Ann Rheum Dis. 2005;64:1588-94. Copyright © Publishing Group Ltd & European League Against Rheumatism.

II. **Bengtsson C,** Theorell T, Klareskog L, Alfredsson L, The EIRA study group. Psychosocial stress at work and the risk of developing rheumatoid arthritis. Psychotherapy and Psychosomatics, forthcoming 2008. Copyright © S. Karger AG, Basel.

III. 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;62:835-41. Copyright © Publishing Group Ltd & European League Against Rheumatism.

IV. Padyukov L,[*] **Silva C**[*], Stolt P, Alfredsson L, Klareskog L. 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. Copyright © American College of Rheumatology
*Shared first authorship

V. **Bengtsson C,** Berglund A, Serra M-L, Nise L, Nordmark B, Klareskog L, Alfredsson L, The EIRA study group. Evaluation of participation and nonparticipation in a population-based case-control study of rheumatoid arthritis. Submitted.

CONTENTS

LIST OF ABBREVIATIONS

ACR	American College of Rheumatology
ACPA	Antibodies to citrullinated protein antigens
AP	Attributable proportion due to interaction
CI	Confidence interval
EIRA	Epidemiological Investigation of Rheumatoid Arthritis
JEM	Job exposure matrix
NYK	Nordisk yrkesklassificering
OR	Odds ratio
RA	Rheumatoid arthritis
RF	Rheumatoid factor
RF+	Rheumatoid factor positive
RF-	Rheumatoid factor negative
RR	Relativ risk
SAS	Statistical Analysis System
SE	Shared epitope
SUN	Svensk utbildningsnomenklatur

1 INTRODUCTION

Rheumatoid arthritis (RA) is an autoimmune, inflammatory disease affecting the joints in a symmetrical pattern. Untreated disease causes severe functional disability and permanent joint destruction.[1] In addition to physical and social suffering, RA also implies reduced life expectancy and an increased mortality from cardiovascular diseases, infections and respiratory diseases[2].

RA occurs worldwide and is more common in women than in men. Approximately 23 million people (16.5 million women and 6.5 million men) were suffering from RA in 2002[3]. There seem to be geographical differences in RA occurrence, with prevalence estimates of 0.5-1.0% in North America and in northern Europe, but with lower occurrence noted in southern Europe and in some developing countries. Knowledge about RA incidence is limited, but several Scandinavian countries have reported annual incidence rates of 24-36 cases/100 000 person-years.[4]

Apart from the health burden of the disease, the economic burden is considerable, not only in terms of direct health care costs but also in terms of indirect costs such as loss of work capacity. In Sweden the total cost of RA was about 7 billion SEK in 2006 and the cost of direct health care was about 2.5 billion SEK[5] which roughly was more than 1% of the total health care expenditures*.

RA is a disease with a long history. In North America, skeletons dating back several thousands of years show evidence of RA[6]. In 1859 the term rheumatoid arthritis was introduced by Garrod[7] and a set of criteria for the disease was developed by the American College of Rheumatology (ACR) in 1958. These criteria, revised in 1987, describe a syndrome characterized by chronic inflammation mainly in many joints (polyarthritis) including joints of the hands and feet[8].

Until some decades ago there was a lack of effective treatment and many patients experienced devastating disability. In recent years, new treatments have shown an impressive ability to slow down disease progression, prevent joint destruction and improve the health status of patients. The treatments are effective in the early stage of the disease and therefore a rapid referral from primary care is crucial to prevent further joint damage and disability.[9,10]

1.1 RISK FACTORS

The aetiology of RA is almost unknown, but it is evident that both genes and environment are involved in disease development as seen from both concordance data in twins and from a number of epidemiological and genetic studies[11-13]. While knowledge about the contribution of genetics is rapidly increasing[14] there is still a lack of data on environmental factors that may cause RA.

*Own calculations based on total expenditure on health care data from 2005, source: The National Board of Health and Welfare

1.1.1 Genetic risk factors

Twin studies have estimated the genetic risk of RA to be about 50%[11], and one of the major known genetic risk factors is the HLA-DRB1 shared epitope (SE) alleles[15]. Associations between SE alleles and an increased risk of RA have been demonstrated in several populations across the world[12]. There have also been indications that those carrying double SE alleles have higher risk of developing RA than those carrying single SE allele[16] and that SE alleles are associated with an increased risk of one well established subset of RA, i.e. rheumatoid factor (RF) positive disease[16-18]. This subgroup of RA patients experience worse disease outcome with more joint destruction, functional disability, extra-articular disease and premature mortality than those without rheumatoid factor[2,19].

1.1.2 Environmental risk factors

Except from smoking, relatively little is known about environmental factors that may cause the disease, although some evidence for exogenous hormone use and reproductive factors among women has been presented[13,20-22] as well as for some occupational exposures (mineral oil and silica)[23-25]. Notably, however, almost all such studies have been conducted for RA without division into subsets, and most studies on the environment have not taken the genetics into account.

1.1.2.1 Socioeconomic status

Socioeconomic differences in health exist in all industrialized countries where such differences have been studied, and low socioeconomic strata are disadvantaged concerning the vast majority of diseases investigated. This general pattern of worse health among those of low socioeconomic status is found across different time periods and is independent of the measures used to define socioeconomic status, e.g. income, education and occupation.[26-27] Evidence of differences in RA incidence between social classes is of interest from a public health point of view, but it is also of value in generating hypotheses about possible association between environmental/lifestyle factors and the risk of developing RA. A low social class has been associated with a worse clinical outcome in RA[28], but socioeconomic status in relation to disease incidence has as yet been poorly investigated. Low formal education has been associated with an increased risk of RA[29-31], while social class according to occupation was not related to RA incidence in two studies[29,32]. Only one of the previous studies was based on incident cases, but on a relatively small number of cases,[32]; and in neither of the previous studies was there a division into RF positive RA and RF negative RA.

1.1.2.2 Psychosocial stress at work

The indications of social class differences in RA incidence may possibly be explained by lifestyle and living conditions, but other factors, including psychosocial factors, may also be important. It has long been suspected that psychological stress is associated with an increased risk of RA, but the literature is scarce and equivocal[33]. Psychosocial stress at work, in terms of job strain (the combination of high psychological demands and low decision latitude), is associated with an increased risk of several diseases (e.g. cardiovascular disease including myocardial infarction[34,35] and musculoskeletal pain[36,37]), but has to our knowledge not been studied in relation to RA. There is, however, some indirect evidence from research on the relationship between

psychosocial work stress and immunological parameters (e.g. increased IL-6 levels[38] and increased fibrinogen levels[39]), suggesting a possible association also with inflammatory conditions including RA.

1.1.2.3 Smoking

Smoking is the main environmental factor that has consistently been related to an increased risk of RA[20,21,29,30,40-47]; however, almost half of the previous studies were based on prevalent cases[29,42,43,45,46]. Furthermore, there have been indications that smoking is mainly associated with risk of RF positive RA[29,30,41,44,45]. Seven of the ten studies examining women separately[20,21,30,42,43,45,47], and all four examining men separately[29,30,41,43] demonstrated an association between smoking and increased risk of RA. Three of the five studies investigating the effect of cumulative dose of smoking observed a dose-response relationship[30,45,46]. Duration of cigarette smoking has been associated with increased risk of RA in four of the five studies on this issue[41,42,45,47] but the effect of intensity of smoking is still controversial[20,21,29,40-42,47]. The effect of smoking cessation on the risk of RA has only been investigated to a limited extent[41,47]. In summary, previous studies have provided evidence for a link between smoking and the risk of RA but the effect of duration, intensity and cumulative dose of smoking and smoking cessation, needs further clarification.

1.1.2.4 Gene-environment interaction between HLA-DRB1 shared epitope alleles and smoking

Rheumatoid arthritis (RA), similar to other multifactorial diseases, is believed to occur as a result of the interaction between genetic constitution and environmental triggers. However, as in most other complex diseases, few such interactions have been described, and it has been assumed that very large studies would be needed to describe significant gene-environment interactions in these diseases. Nevertheless, the few existing examples, with the best one being a study of coeliac disease[48] have demonstrated how the definition of such interactions may open the field for new aetiological and pathogenetic studies. As described above one main genetic risk factor for RA is the HLA-DRB1 shared epitope (SE) alleles and an environmental factor of significant importance is smoking. A study on RA cases only has merely suggested that interactions between smoking and SE may exist[49], but no epidemiological population-based studies had previously, before our own study, been performed to address this question.

1.2 METHODOLOGICAL ISSUES

1.2.1 Changing conditions for epidemiologic studies of RA

One reason for the limited knowledge concerning environmental contribution to risk of RA, can be found in the difficulties in identifying incident cases in the study base. Until some decades ago many RA patients were treated in primary care and referred to rheumatologists after a long period of disease. Since clinical evidence has demonstrated the benefits of early diagnosis and early treatment, a rapid referral from primary care to a rheumatologist became crucial to prevent further progress of the disease.[9,10] In Sweden early arthritis clinics were introduced in the beginning of the 1990s[50]. This organization of early arthritis clinics made it possible to identify newly diagnosed RA cases in a defined population. In order to exploit this opportunity we initiated a

population-based case-control study in 1996 on incident cases of rheumatoid arthritis (RA) called EIRA (Epidemiological Investigation of Rheumatoid Arthritis) in Sweden. EIRA is one of the first and largest epidemiological investigations of RA and was designed to study interaction between genes and environment, and also to study different sub-groups of RA. The data collection is still ongoing, and data from 2500 cases and 3400 controls has been collected to date.

1.2.2 Participation and non-participation in epidemiologic studies

In epidemiologic studies, non-participation may result in selection bias[51]. Epidemiologists are thus concerned about the decrease in participation seen in recent years[52,53], which has been observed especially among controls in population-based case-control studies[53]. However, evaluations of time trends and reasons for increasing non-participation have been obstructed by a lack of consistent reporting of participation across studies[53,54].

Information on who is likely to participate is essential for the planning and interpretation of epidemiologic studies. It has been observed that non-participants are more likely to be men[55-59], young or old[55,57-64,66], single[57,58,62,65-67], urban residents[55,59], of low socioeconomic status[55-58,61,62,65-69] and to be at higher risk of death[70] (for a review see also[52]).

Many epidemiologists make considerable efforts to recruit reluctant or difficult-to-reach respondents in order to achieve an unbiased sample of participants. It is, however, unclear whether these efforts are worthwhile[71]. Some studies have found that even if the characteristics of early and late respondents differed, inclusion of data from late respondents had minor effects on the results[59-61,66,72-75]. Characteristics of non-participants, as well as late respondents, have mainly been studied in cross-sectional or cohort studies. Knowledge about non-participation and late response among incident cases is therefore limited.

2 AIMS OF THE THESIS

The general aim of the thesis was to evaluate whether socioeconomic status, psychosocial work stress and smoking is associated with the risk of developing rheumatoid arthritis.

The specific aims of the thesis were:

- To investigate whether markers of socioeconomic status (formal education and occupational class, respectively) are associated with incidence of rheumatoid arthritis.

- To study the association between psychosocial stress at work (in terms of high psychological job demands, low decision latitude and job strain, i.e. the combination of high psychological job demands and low decision latitude) and the risk of developing rheumatoid arthritis.

- To study the association between smoking and the risk of developing rheumatoid arthritis, with special focus on the influence of duration, intensity and cumulative dose of smoking, and smoking cessation.

- To study the interaction between the HLA-DRB1 shared epitope alleles and smoking, with regard to the risk of developing rheumatoid arthritis.

- To evaluate participation/non-participation, selection bias due to non-participation and late response in the EIRA study.

3 MATERIAL AND METHODS

3.1 THE STUDY BASE (PAPERS I-V)

The analyses of the present thesis were based on data from a population-based case-control study on incident cases of rheumatoid arthritis (RA) called EIRA (Epidemiological Investigation of Rheumatoid Arthritis), which started in May 1996. The study population was the residents, aged 18-70 years, living in a geographically defined area in the middle and southern parts of Sweden. EIRA is an on-going investigation where the observation period ended in June 2001 (Paper I), in December 2003 (Paper II), in June 2000 (Paper III), in February 2001 (Paper IV) and in December 2005 (Paper V).

3.2 STUDY DESIGN

3.2.1 Case identification and selection of controls (Papers I-V)

Incident cases of RA, as diagnosed by a rheumatologist in accordance with the American College of Rheumatology (ACR) criteria of 1987[8], were continuously identified in the study base. All public, and most of the privately run, rheumatology units within the study area participated. For each case, one control was randomly selected from the study base, taking sex, age and residential area into consideration. Selection of controls was conducted using the national population register, which is continuously updated and covers the entire Swedish population. If a control refused to participate, was not traceable or reported having RA (very few), a new control was selected using the same principles. All study subjects were required to be Swedish-speaking. A blood sample was taken from the cases locally at the rheumatology unit and from the controls in local medical wards which were sent by post to the investigators at Karolinska Institutet. When EIRA first began, some units also reported cases that did not fulfil the ACR criteria, in order to enable investigations of undifferentiated arthritis. These subjects were eventually excluded from the study. Controls belonging to excluded cases that did not fulfil the ACR criteria remained in the study in order to increase the power.

3.2.2 Data collection (Papers I-V)

A questionnaire, covering a wide spectrum of issues e.g. smoking, occupation and psychosocial work stress, was given to the cases at the rheumatology unit shortly after they had been informed about the diagnosis and was sent by post to the controls. Both cases and controls were to answer the questionnaires at home, and nonrespondents were reminded at most four times. With the exception of giving the questionnaires to the cases, the data collection was managed at the EIRA secretariat by experienced, purpose-trained persons who were not connected to the rheumatology units.

3.2.3 Evaluation of participation/non-participation and late response (Paper V)

Participation proportion. The participation proportion was calculated among cases and controls, respectively. The participation proportion among cases was defined as the proportion of invited cases (i.e. cases reported to the EIRA secretariat by a participating

centre) that returned an answered questionnaire. The participation proportion among controls was defined as the proportion of selected controls that returned an answered questionnaire. Selected controls included those that responded to the questionnaire, as well as those that refused to participate, did not respond or were not traceable. Furthermore, participation proportions were calculated according to sex, age, month and residential area at inclusion as well as every year of the study period.

Late response. Participation proportions after number of reminders (no reminder, one, two, three or four reminders) were calculated, among cases and controls respectively. Those with no reminder were defined as early respondents, those with one reminder as intermediate respondents and those with two or more reminders as late respondents. The frequencies of sex, age, smoking status and occupational class at inclusion were analysed among early, intermediate and late respondents, respectively.

Unidentified cases. In order to determine whether all RA cases that occurred in the study base were reported to EIRA, EIRA data was linked with data from the Swedish Rheumatoid Arthritis register (RA register). All public rheumatology units and the majority of private units are required to report incident RA patients to this national quality register. Inclusion criteria for incident rheumatoid arthritis in the RA register are the same as for EIRA but duration of symptoms must be less than 12 months (no time restriction for cases reported to EIRA).

Selection bias. In order to evaluate possible selection bias demographic and socioeconomic information was collected from registers at Statistics Sweden, for all identified study subjects, i.e. all selected controls and all cases reported to EIRA as well as cases included in the RA register but not in EIRA. Statistics Sweden conducted the matching of the variables, and the returned data file contained no personal identification of the study individuals. The distribution of each variable among participants and non-participants was analysed. Due to the secrecy rules of Statistics Sweden the returned data file contained no information on whether a case was reported to EIRA or not, i.e. it was not possible to perform separate analyses on the cases reported to EIRA, and on those included in the RA register but not reported to EIRA. Only information on rheumatology unit and on sex, age and marital status at inclusion in the study for reported and non-reported cases, respectively, could be retrieved. Through the RA register information about rheumatoid factor for both reported and non-reported cases was also collected.

3.3 EXPOSURES AND POTENTIAL CONFOUNDERS

3.3.1 Socioeconomic status (Paper I)

Formal education and occupational class were considered as markers of socioeconomic status and information about education and occupation was obtained from the questionnaire.

Formal education was divided into five levels: compulsory school, vocational upper secondary school, theoretical upper secondary school, other education and university degree. The categorization was done with guidance from Svensk utbildningsnomenklatur, SUN, which is used by Statistics Sweden in classifying the education of the population.

Occupational class. Cases and controls gave an extensive description of their recent and previous occupations. Each occupation, lasting at least one year, was given an occupational class code according to the Nordisk yrkesklassificering, NYK[76], which is

a Swedish classification system of occupations adjusted to international standards. The occupational classes were divided into: skilled and unskilled manual workers, and assistant, intermediate and higher non-manual employees. At the rheumatology unit each case was given a year and a month of onset of RA. The year in which symptoms first occurred was defined as the index year and this was also used for the corresponding control. In general, employment during the index year was used to classify occupational class.

Non-response analysis. An analysis was performed in order to evaluate possible bias due to non-response (4 % and 17 % of identified cases and controls, respectively, did not respond to the questionnaire). For all identified study subjects (967 cases and 1357 controls), information on education and occupational class was collected from the census of 1990, which is managed by Statistics Sweden.

3.3.2 Psychosocial stress at work (Paper II)

3.3.2.1 Self-reported psychosocial stress at work

Psychological job demands and job decision latitude were measured in accordance with questions developed by Karasek and Theorell[77,78]. Questions were posed about current work situation; five questions addressed psychological job demands and six questions addressed decision latitude (see appendix). Each question had four response alternatives graded from 1 to 4, giving 5 as the minimum and 20 as the maximum score for demands, and 6 as the minimum and 24 as the maximum score for decision latitude. Both demands and decision latitude were categorized into four groups, using the quartiles among the controls (each gender separately) as cut-off points. High psychological job demands were defined as a score above the upper quartile, and low psychological job demands were defined as a score below the lower quartile. High decision latitude was defined as a score above the upper quartile, and low decision latitude was defined as a score below the lower quartile. The values of the quartiles are presented in the appendix. Job strain was defined as the combination of high demands and low decision latitude.

3.3.2.2 Job exposure matrix

In addition to classifying psychological job demands and decision latitude according to the self-reported information, a classification based on a job exposure matrix (JEM) was performed, where cases and controls were classified according to the average circumstances (as reported by disease-free individuals, i.e. the controls) within their occupational group. The rationale for using a matrix was to avoid potential bias due to differential recall between cases and controls. The participants in the study reported a detailed occupational history and the occupations were coded according to an occupational class code (occupational family)[76]. Mean scores of demands and decision latitude were calculated for each occupational family among the controls (each gender separately) where the number of controls was at least 3. Cases and controls were then given the mean scores according to their latest reported occupation. Cut-off points for psychological job demands and decision latitude were calculated in the same way as described above. The values of the quartiles are presented in the appendix.

3.3.3 Smoking (Paper III)

The year in which the cases' symptoms first occurred was defined as the index year, and the same index year was used for the corresponding control. Only data on smoking habits from cases and controls up to the index year, and only data on cigarette smoking,

were analysed. Individuals who reported that they regularly smoked cigarettes during the index year were defined as current smokers; those who reported that they had stopped regular smoking before the index year or before were defined as ex-smokers and people who reported that they had never had smoked before or during the index year were defined as never-smokers. Ever-smokers were defined as subjects who fitted the definition of current smokers or ex-smokers. The intensity of smoking was categorized into: 1-5, 6-9, 10-19 and ≥ 20 cigarettes smoked per day. The duration of smoking was categorized into: <10, 10-19 and ≥ 20 years of smoking. The cumulative dose of cigarette smoking was expressed as pack-years. One pack-year was regarded as equivalent of 20 cigarettes smoked per day for one year. The duration from the year of the cessation of smoking to the index year was divided into the intervals: 1-9, 10-19 and ≥ 20 years.

3.3.4 Smoking (Paper IV)

As described above, only data on smoking habits from cases and controls up to the index year, and only data on cigarette smoking, was analysed. Individuals who reported that they regularly smoked cigarettes during the index year were defined as current smokers. Ex-smokers were also excluded, thus restricting the analysis to a comparison of current smokers of cigarettes with never smokers.

3.3.5 Potential confounders

In all papers, the results were adjusted for age and residential area according to the principle of control selection. When women and men were analysed together adjustment was made for sex. Smoking was considered as a potential explanatory factor in the analyses of socioeconomic status (Paper I) and as a potential confounder in the analyses of psychosocial work stress (Paper II). Adjustment for social class, body mass index, marital status, parity and oral contraceptive use was made in Papers III and IV.

3.4 BIOLOGICAL MEASURES

3.4.1 Rheumatoid factor (Papers I-V)

Rheumatoid factor status was determined locally using agglutination methods, where the cut-offs were selected to yield positive results for the highest 5% in healthy controls. Results were reported as rheumatoid factor positive (RF+) or rheumatoid factor negative (RF-).

3.4.2 Genotyping for HLA-DRB1 (Paper IV)

DNA from EDTA blood was extracted by the "salting-out" method[79] and analysis of HLA-DRB1 genotypes was made using the SSP-PCR method (DR low resolution kit, Olerup SSP AB, Saltsjöbaden, Sweden) as previously described[80]. Among HLA-DRB1 variants DRB1*01, DRB1*04 and DRB1*10 genes were defined as "shared epitope (SE) alleles". Any genotype with a combination of two of these alleles was considered as a double SE genotype. At the beginning of the study, individuals from a part of the material (81 cases) were subtyped for more precise identification of HLA-DRB1*01 and 04 alleles. We determined 89% frequency of DRB1*0101 and 98% frequency of DRB1*0401+*0404+*0405+*0408 alleles and for practical reasons decided to restrict genotyping to only DR low resolution analysis.

3.5 STATISTICAL ANALYSES

The analyses were performed with regard to the incidence of rheumatoid factor positive (RF+), rheumatoid factor negative (RF-) RA (Papers I-IV) and to RA overall, by calculating odds ratios with 95 % confidence interval (95% CI). Men and women were analysed separately, as well as together Both unmatched analyses (Mantel-Haenszel method in Papers I, III; unconditional logistic regression in Papers II, IV, V) and matched analyses (conditional logistic regression) were performed, but only the results from the unmatched analyses are presented, since in general, these had higher precision and were in close agreement with the matched analyses. Odds ratios were interpreted as incidence rate ratios (denoted as relative risks) (Papers I-IV) as the study was population-based and the controls were a random sample from the study base[81]. All analyses were performed using the Statistical Analysis System (SAS) version 8.2 (Papers I, IV), version 9.1 (Papers II, V), and version 4.0 (Paper III) .

3.5.1 Paper I

Subjects with different levels of education were compared with those with a university degree, and subjects in different occupational classes were compared with higher non-manual employees.

3.5.2 Paper II

The distribution of psychological job demands and decision latitude was highly centred on the median as reflected in the low difference between the lower (first) quartile and the upper (third) quartile for demands and decision latitude, both in the self-reported data and the job-exposure-matrix (JEM)-derived data (see appendix). The analyses were therefore focused on comparisons of the values above the upper and the values below the lower quartile. Those with high job demands were compared with those with low job demands, and those with low decision latitude were compared with those with high decision latitude. Those with job strain were contrasted to those without, and to those with relaxed work conditions (i.e. high decision latitude and low psychological job demands).

3.5.3 Paper III

Current smokers, ex-smokers, and ever-smokers, respectively, were compared with never-smokers. Because the results for women and men were similar, both sexes were analysed together in the calculations of duration, intensity, cumulative dose, and the effect of smoking cessation.

3.5.4 Paper IV

In the analyses, subjects with different genotypes and smoking habits were compared. Interaction between genotype and smoking habits was evaluated, using departure from additivity of effects as criteria for interaction, as suggested by Rothman[82]. To quantify the amount of interaction, the attributable proportion (AP) due to interaction was calculated together with the 95% confidence interval[83]. The AP due to interaction, which is expressed as a value between 0 and 1, is the proportion of the incidence among persons exposed to two interacting factors, that is attributable to the interaction per se (i.e. reflecting their combined effect beyond the sum of their independent effects).

3.5.5 Paper V

The effect of late response on estimated odds ratios associated with smoking and occupational class was investigated by calculating the odds ratios (OR) with 95% confidence intervals (CI) of developing RA associated with smoking and occupational class separately for early respondents, for early and intermediate respondents together and for all respondents. Furthermore, the effect of non-participation was investigated by calculating the odds ratios with 95 % confidence intervals of developing RA associated with different socio-demographic factors separately for participants as well as for participants and non-participants together.

4 RESULTS

4.1 SOCIOECONOMIC STATUS AND THE RISK OF RA (PAPER I)

In total, 967 cases and 1357 controls (i.e. all controls that were selected, including those who refused or were untraceable) were identified, and of these, 930 cases (654 women and 276 men) and 1126 controls (791 women and 335 men) answered the questionnaire.

Formal education
Subjects without a university degree had an increased risk of RA compared with those with a university degree (RR for women and men together=1.4 (95% CI 1.2-1.8)) (Table 1). When the cases were subdivided according to RF status at inclusion the increased risk for individuals without a university degree was overall mostly associated with RF+ RA (RR=1.6 (95% CI 1.3-2.1)), and this impact appeared to be mainly confined to women. The sub-analyses on men are however uncertain, due to the relatively low numbers of individuals in the subgroups, especially in the comparison group. Adjustment for smoking only marginally altered the estimated relative risks associated with educational attainment.

Occupational class
Taking women and men together, employees other than higher non-manual employees had an approximately 20 % higher risk of developing RA compared with higher non-manual employees, but the confidence interval was wide (Table 1). After dividing cases into RF+ RA and RF- RA, the influence of occupational class was mainly associated with RF+ RA, at least for women. From the relatively few observations on men, no substantial difference was observed with regard to RF status. Adjustment for smoking seemed to explain only a minor part of the association between occupational class and RA.

Analysis of non-response
The relative risks of RA associated with different educational levels, according to the census of 1990, were compared among respondents separately, and among respondents and non-respondents together. The relative risks were about the same in these comparisons. The same procedure was carried out for different occupational classes and with the same result. Only minor differences were observed between the two groups.

4.2 PSYCHOSOCIAL WORK STRESS AND THE RISK OF RA (PAPER II)

In total, 1272 cases and 1773 controls aged 18-65 years were identified, and of these, 1221 cases (879 women and 342 men) and 1454 controls (1038 women and 416 men) participated in the study.

Results based on self-reported information
High psychological job demands were not significantly associated with risk of developing RA among women, but were associated with a decreased risk of RA among men (RR=0.5 (95% CI 0.3-0.9)) (Table 2). An increased risk of RA was observed for those reporting low decision latitude (RR for women and men together=1.6 (95% CI

Table 1. Relative risk (RR) with 95% confidence interval (95% CI) of developing RF+ RA, RF- RA and RA overall (Total RA), for subjects without a university degree compared with subjects with a university degree, and for subjects that are not higher non-manual employees compared with higher non-manual employees.

		ca/co *	RR §	95 % CI	RR §§	95 % CI
RF+ RA	No university degree	502/844	1.6	1.3-2.1	1.7	1.2-2.2
	University degree †	104/279	1.0	-	1.0	-
RF- RA	No university degree	250/844	1.2	0.8-1.6	1.1	0.8-1.6
	University degree †	73/279	1.0	-	1.0	-
Total RA	No university degree	752/844	1.4	1.2-1.8	1.5	1.1-1.9
	University degree †	177/279	1.0	-	1.0	-
RF+ RA	Not higher non-manual employees	418/736	1.4	1.0-2.0	1.5	1.0-2.1
	Higher non-manual employees †	69/172	1.0	-	1.0	-
RF- RA	Not higher non-manual employees	208/736	0.8	0.6-1.2	0.9	0.6-1.3
	Higher non-manual employees †	54/172	1.0	-	1.0	-
Total RA	Not higher non-manual employees	626/736	1.2	0.9-1.5	1.2	0.9-1.6
	Higher non-manual employees †	123/172	1.0	-	1.0	-

* ca/co = number of exposed cases/number of exposed controls
§ RR adjusted for age, residential area and gender
§§ RR adjusted for age, residential area, gender and smoking
† Reference group

1.2-2.2)). Those reporting job strain had a 30% higher risk of developing RA compared with those with relaxed work conditions (RR=1.3 (95% CI 0.9-1.8)), and this association seemed to be entirely confined to women.

Results based on job-exposure-matrix information

High psychological job demands were associated with a decreased risk of developing RA (RR for men and women together=0.8 (95% CI 0.6-1.0)) (Table 2). Low decision latitude was associated with an increased risk of RA (RR for men and women together=1.3 (95% CI 1.0-1.7)), which seemed to be mainly confined to women. Job strain appeared not to be associated with risk of RA. However, the analyses on men, and on job strain among both women and men, respectively, were uncertain due to the low numbers of subjects in many subgroups.

In both the self-reported material and the JEM-derived data, analyses according to RF status were performed, but no specific pattern of associations with either RF+ or RF- RA was found.

Table 2. Relative risks (RR) together with 95% confidence interval (CI) of developing RA associated with working conditions according to self-reports and to a Job Exposure Matrix, respectively, by gender.

	Women			Men			
	ca/co[a]	RR[b]	95 % CI	ca/co[a]	RR[b]	95 % CI	c
	Self-reported psychosocial working conditions						
High job demands[d]	111/117	1.2	0.8-1.7	48/86	0.5	0.3-0.9	15
Low decision latitude[e]	152/172	1.5	1.0-2.2	64/73	2.0	1.1-3.4	21
Job strain versus relaxed[f]	91/102	1.4	0.9-2.2	49/62	1.0	0.5-1.9	14
Job strain versus others[g]	91/102	1.2	0.8-1.6	49/62	1.1	0.7-1.8	14
	Psychosocial working conditions according to the Job Exposure Matrix						
High job demands[d]	108/166	0.8	0.6-1.1	34/55	0.7	0.4-1.3	14
Low decision latitude[e]	202/219	1.4	1.0-1.9	42/58	1.1	0.6-2.0	24
Job strain versus relaxed[f]	34/53	1.1	0.6-2.0	14/26	0.9	0.3-2.6	4
Job strain versus others[g]	34/53	0.9	0.5-1.4	14/26	0.8	0.4-1.7	4

4.3 SMOKING AND THE RISK OF RA (PAPER III)

In total, 707 cases and 1020 controls were identified, and of these, 679 cases (489 women and 190 men) and 847 controls (602 women and 245 men) participated in the study. Higher relative risks of developing RA for ever-smokers compared with never-smokers (Table 3) were observed, and these higher relative risks were mainly associated with RF+ RA (RR=1.7 (95%CI 1.2-2.3) among women and RR=1.9 (95%CI 1.0-3.5) among men) and were evident in the older (50-70 years) but not in the younger (18-49 years) age group. Results similar to those for ever smokers were recorded among current smokers and ex-smokers of both sexes. No increased risk of RF- RA among smokers of any category was observed when compared with never-smokers.

No increased risk of RF+ RA was observed among subjects who had smoked for less than 20 years. Among subjects who had smoked for 20 years or more, an increased risk of RF+ RA was observed among those who smoked more than 5 cigarettes/day. The risk of developing RF+ RA increased as the number of pack-years increased, in a dose-dependent manner. The increased risk of RF+ RA remained for about 10-19 years after smoking cessation. Adjustments for social class, BMI, marital status, parity and oral contraceptive use had minor influence on the results and were not retained in the final analysis.

Table 3. Relative risk (RR) with 95% confidence interval (95% CI) of developing RF+ RA, RF- RA and RA overall (Total RA), for ever-smokers of cigarettes compared with never-smokers, by sex and age

	ca*	RR┼	95% CI
Women 18-70 years			
RF+ RA	198	1.7	1.2-2.3
RF- RA	76	0.8	0.6-1.2
Total RA	274	1.3	1.0-1.7
Women 18-49 years			
RF+ RA	60	1.0	0.6-1.6
RF- RA	32	0.6	0.4-1.1
Total RA	92	0.8	0.5-1.3
Women 50-70 years			
RF+ RA	138	2.4	1.6-3.6
RF- RA	44	1.1	0.6-1.8
Total RA	182	1.8	1.3-2.6
Men 18-70 years			
RF+ RA	81	1.9	1.0-3.5
RF- RA	31	0.8	0.4-1.6
Total RA	112	1.4	0.8-2.3
Men 18-49 years			
RF+ RA	19	1.2	0.5-3.4
RF- RA	9	1.0	0.3-3.4
Total RA	28	1.3	0.6-2.9
Men 50-70 years			
RF+ RA	62	2.4	1.0-5.5
RF- RA	22	0.7	0.3-1.7
Total RA	84	1.4	0.8-2.7

* number of exposed cases; ┼ relative risk adjusted for age and residential area

4.4 INTERACTION BETWEEN HLA-DRB1 SHARED EPITOPE ALLELES AND SMOKING (PAPER IV)

Of the 900 identified patients with rheumatoid arthritis, 858 (95%) completed the questionnaire (612 females and 246 males), and of these, 64% of the women and 66% of the men were RF positive. The total number of identified controls was 1263, and the overall response rate concerning completion of the questionnaire for these individuals was overall 83%, producing 1048 controls (736 females and 312 males). Blood samples from 843 (98%) of all the cases who answered the questionnaires and from 627 (60%) of the controls (448 females and 179 males) were received.

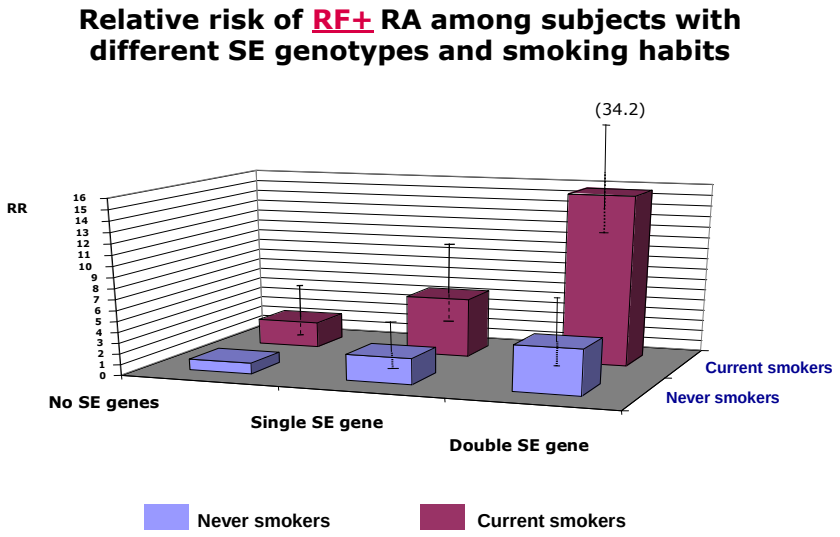
Cigarette smoking as a risk factor for RA
Among all cases and controls who responded to the questionnaire and provided information on smoking habits, the relative risk of developing RA was 1.5 (95% CI 1.2-2.0) for current smokers compared with never-smokers. After subdividing these RA cases according to RF status at inclusion, the relative risk of RF+ RA in current smokers was 2.2 (95% CI 1.7-3.0), but only 0.8 (95% CI 0.6-1.2) for RF- RA. The pattern was similar among women and men. Very similar relative risk values were obtained when the analysis was restricted to those individuals from whom blood samples were available for subsequent genetic analysis.

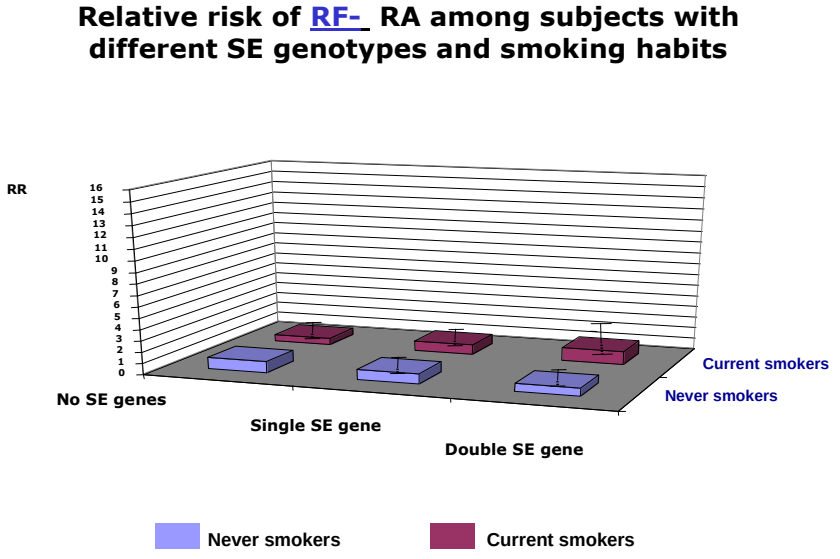
SE alleles as a risk factor for RA
Both single and double SE genotypes were associated with an increased risk of RA in men and in women, with double SE genotype conferring a higher risk than a single SE allele. When analysed further, both single and double SE genotypes were related to an increased risk of RF+ RA (single SE allele RR=2.5 (95% CI 1.9-3.3); double SE allele RR=6.0 (95% CI 4.2-8.5)), but not of RF- RA.

Interaction between smoking and SE alleles
The risk of RA associated with SE alleles among never smokers (women and men taken together) was only moderately increased (RR=1.5, 95% CI 1.0-2.2). For subjects who were smokers and carried any SE allele, the relative risk was 2.9 (95% CI 1.9-4.5). For this group the attributable proportion (AP) due to interaction was 0.4 (95% CI 0.2-0.7), indicating that the interaction between cigarette smoking and SE alleles is statistically significant. An even stronger interaction was observed between smoking and double SE allele (RR=5.6, 95% CI 2.9-11.1; AP=0.7, 95% CI 0.4-0.9). The relative risk for smokers carrying only a single SE allele was intermediate.

Interaction between smoking and SE alleles regarding RF+ RA and RF- RA
Compared with never-smokers without SE alleles, the relative risk of developing RF+ RA for never-smokers with SE alleles was 2.8 (CI 95% 1.6-4.8). The corresponding relative risk for current cigarette smokers without SE alleles was 2.4 (CI 95% 1.3-4.6). Thus, it is evident that smoking and SE alleles are independently related to the development of RF+ RA. Among current smokers with SE alleles the relative risk of developing RF+ RA was 7.5 (CI 95% 4.2-13.1). Therefore, an interaction between smoking and SE alleles was observed in association with RF+ RA, which was also reflected in the AP due to interaction: 0.4 (CI 95% 0.2-0.7). The interaction was even more pronounced for subjects who were smokers and carried double SE alleles, where the relative risk of RF+ RA was 15.7 (95% CI 7.2-34.2). The AP due to interaction for this group was 0.6 (95% CI 0.4-0.9). Neither smoking nor SE alleles, nor the combination of these factors, increased the risk of RF- RA. See figure 1.

Figure 1. Relative risk of RF+ RA and RF- RA, respectively, among subjects with different genotypes and smoking habits





4.5 EVALUATION OF PARTICIPATION AND NON-PARTICIPATION IN EIRA (PAPER V)

Participation proportion

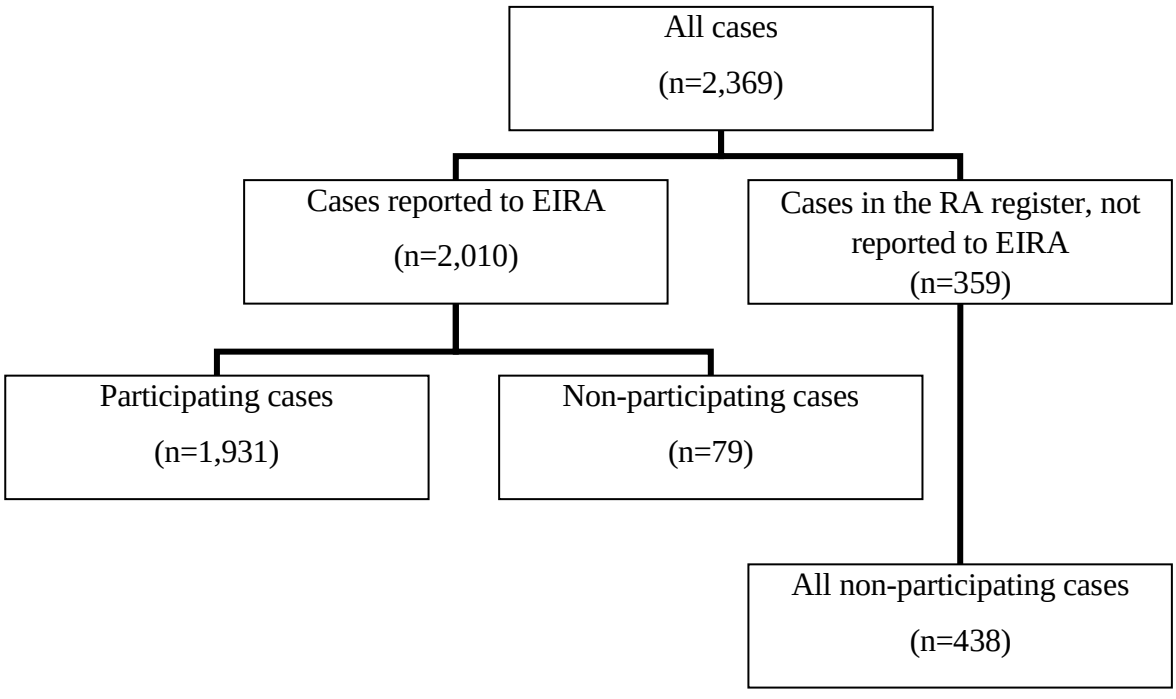
In total, 2010 cases were reported to EIRA during the study period and 2715 controls were selected: of these, 1931 cases (1371 women and 560 men) and 2214 controls (1565 women and 649 men) responded to the questionnaire, giving a participation proportion of 96% among the reported cases and 82% among the controls. The mean

duration of disease at inclusion in the study was ten months, and for 81% of the cases, disease duration was less than one year. The participation proportion among controls was higher among women than among men; it was seen to increase steadily with increasing age, and was slightly higher for those living outside the capital. The annual participation proportions fluctuated between 77 and 87% during the ten-year study period. The highest monthly participation proportions were achieved in January, June and August, and the lowest participation proportion was observed in May (no controls were included in July). Among cases, the participation proportion was the same for women and men; it differed slightly between different age groups and was somewhat higher for those living outside the capital. The annual participation proportions fluctuated between 94 and 97% during the ten-year study period and the highest monthly participation proportions were achieved during June-August.

Late response analysis

Among controls, the participation proportion was 55% without any reminder, 73% after one reminder and 78% after two reminders. A third and fourth reminder increased the participation proportion by a few more percentage points. Among cases the participation proportion was 74% without any reminder, 89% after one reminder and 93% after two reminders. These participation proportions, among cases as well as controls, were fairly stable every year of the study period. Among both cases and controls, late respondents were more likely to be men, young and never-smokers whereas early respondents were more likely to be former smokers. No major differences in time of response were observed according to current smoking. Among controls, higher non-manual employees responded later than not higher non-manual employees. The relative risk of developing RA for current and former smokers together compared with never-smokers was approximately the same for respondents with no reminder, for respondents with no and one reminder together and for all respondents. For higher non-manual employees compared with not higher non-manual employees, the relative risk of RA did not differ between respondents with no reminder, with no and one reminder together and for all respondents.

FIGURE 1. Identified cases in EIRA (Epidemiological Investigation of Rheumatoid Arthritis), Sweden, 1996-2005.



Non-participation analysis

Unidentified cases. In total, 359 cases with incident rheumatoid arthritis (fulfilling the ACR criteria with disease duration of at most 12 months) were included in the RA register but were not reported to EIRA. This means that a total of 2369 cases were identified in the study base (2010 cases reported to EIRA and 359 identified in the RA register), giving an actual participation proportion of 82% among all cases. Case identification is illustrated in Figure 1.

Non-participation analysis. Table 4 shows the distribution of demographic and socioeconomic information from the year 2001 for participants and non-participants. Among controls, non-participants were more likely to be men, slightly younger, unmarried, and urban residents. Non-participating cases were older than participating cases, but no major differences were seen according to sex, marital status and residential area. Having a low income, being less educated and not born in Sweden, were factors associated with non-participation in both cases and controls, with a stronger association among controls. Furthermore, the proportion of higher non-manual employees was higher among both participating cases and controls than among non-participants, but data was missing for many subjects. Being unmarried, divorced, or a widow/widower respectively, compared with being married yielded approximately the same relative risk regarding the risk of RA in participants alone and in participants and non-participants together. The relative risk of developing RA for higher non-manual employees compared with not higher employees, as well as for those with a university degree compared with those with no university degree, was also approximately the same for participants alone and for participants and non-participants together.

Comparison of reported cases to EIRA and cases identified in the RA register. Approximately the same proportion of the reported cases and cases identified in the RA register were women, married and RF+. Reported cases were, however, younger. A comparison of non-participating cases showed that non-participants who were reported to EIRA were younger, to a larger extent divorced and living in Stockholm, and to a somewhat lesser extent RF+, than those who were not reported. However, RF status was missing for 10% of the non-participating cases reported to EIRA.

Table 4. Demographic and socioeconomic characteristics 2001 for participants and non-participants, by case-control status in EIRA, 1996-2005.

	Cases				Controls			
	Participants (n = 1931)		Nonparticipants (n = 438)		Participants (n = 2214)		Nonparticipants (n = 501)	
	No.	%	No.	%	No.	%	No.	%
Sex								
Female	1371	71	313	71	1565	71	315	63
Male	560	29	125	29	649	29	186	37
Age								
15-34 year	249	13	48	11	301	14	88	17
35-54 year	720	37	141	32	840	38	194	39
55-75 year	962	50	249	57	1073	48	219	44
Marital status								
Married	1046	54	225	51	1204	54	192	38
Unmarried	442	23	86	20	538	24	177	35
Divorced	352	18	91	21	342	16	95	19
Widow/widower	80	4	29	7	101	5	24	5
Missing data	11	1	7	1	29	1	13	3
Individual income								
Low	389	20	127	29	470	21	178	36
Middle	1112	58	233	53	1155	52	227	45
High	424	22	73	17	567	26	89	18
Missing data[1]	6	0	5	1	22	1	7	1
Occupational class								
Higher manual* employees	349	18	54	12	454	21	60	12
Not higher non-manual employees	1194	62	275	63	1295	58	231	46
Missing data[1]	388	20	109	25	465	21	210	42
Educational level								
University degree┼	283	15	52	12	441	20	62	12
No university degree	1630	84	374	85	1732	78	412	82
Missing data	18	1	12	3	41	2	27	6
Birth country								
Sweden	1712	89	343	78	1916	87	377	75
Not Sweden	219	11	95	22	298	13	123	25
Missing data	0	0	1	0	1	0	1	0
Inhabitants in residential area								
<12.000	458	24	89	20	461	21	106	20
12.000-1.224.000	552	29	135	31	662	30	118	24
>1.224.000	682	35	143	33	787	35	218	44
Missing data	239	12	71	16	304	14	59	12

* Those in management and those with occupations requiring of theoretical specialist competence

┼ At least three years of education after upper secondary school and postgraduate studies

5 DISCUSSION

5.1 COMMENTS ON PRESENT RESULTS AND PREVIOUS STUDIES

5.1.1 Socioeconomic status and the risk of RA (Paper I)

According to the results of the present study, women as well as men, with a university degree or working as higher non-manual employees, had a lower risk of developing RA. These effects of socioeconomic status on risk of RA were more pronounced for RF positive RA as compared to RF negative RA, and were entirely confined to RF negative RA for women.

Low formal education has been associated with an increased risk of RA[29-31], while social class according to occupation was not related to RA incidence in two studies[29,32]. One of the previous studies was based on incident cases, but the number of cases was relatively small[32], and no studies were performed with division into RF positive RA and RF negative RA. However, the results of this thesis were confirmed in a later study from Denmark, where low formal education was associated with an increased risk of mainly RF positive RA[84]. Also in a later Swedish register study based on hospitalized RA cases a relation between year of education and risk of RA was observed[85].

In the present study, the interference of smoking, the major environmental risk factor identified to date, was studied. However, the observed differences could not be explained by differences in smoking habits. In a Norwegian study[29] the association between low formal education and higher risk of RA was explained by adjusting for age, sex, marital status, body mass index, employment category and current smoking in a multivariate model. In order to compare the results of this thesis with the Norwegian study, we adjusted the results for marital status and body mass index separately, but this had only a minor impact on the estimated relative risks. In a Swedish study[30] adjustment for smoking and employment in high risk occupations could not explain the association between low formal education and higher risk of RA. Also in the later Danish study[84], no life-style factor including e.g. smoking, BMI and marital status, could explain the observed difference in RA incidence between different educational levels.

5.1.2 Psychosocial work stress and the risk of RA (Paper II)

The main new finding of the current study was that low decision latitude was associated with an increased risk of developing RA. This finding was consistent when using both self-reported data and job-matrix-derived data. Furthermore, there were some indications in both kinds of data, that those with high psychological job demands had a decreased risk of disease. Self-reported job strain appeared to be associated with a higher risk of developing RA compared with relaxed work situations, but this was not confirmed by matrix-derived data.

Psychosocial stress at work, in terms of job strain (the combination of high psychological demands and low decision latitude), and the risk of RA have to our knowledge not previously been studied, but have been associated with an increased risk of other diseases (such as cardiovascular disease including myocardial infarction[34,35], and musculoskeletal pain[36,37]). The results from the current thesis on incident cases of RA add to the likelihood that psychosocial factors in the work environment also influence the risk of developing RA; at least this seems to be the case for decision

latitude. This is also the component in the demand-control model that has most consistently been related to risk of cardiovascular disease[34,35].

The results were adjusted for age, sex, residential area and smoking. Smoking is the main common environmental factor that has consistently been related to an increased risk of RA. In theory, there may, of course, be other risk factors that act as confounders and thus might explain the observed associations between psychosocial work stress and RA, but no such factors have so far been identified. It could be claimed that social class should be considered as a potential confounding factor. However, social class is probably not a risk factor per se (i.e. not causally related to risk of RA) and we therefore considered it appropriate not to stratify for social class in the initial analysis within the current study. Social class may, on the other hand, co-vary with other (unknown) risk factors; when we subsequently adjusted the observed relative risks for social class only marginal changes of the estimates were seen.

5.1.3 Smoking and the risk of RA (Paper III)

According to the results in this study, cigarette smokers of both sexes have an increased risk of developing RF positive RA, but not RF negative RA, compared with never-smokers. The increased risk of developing RA occurred after a long duration of smoking, but of merely moderate intensity of smoking, and remained several years after smoking cessation. The risk of developing RA increased also in a dose dependent manner, as the cumulative dose of smoking increased.

For smokers of both sexes there was an increased risk of developing RF positive RA, but not RF negative RA. These results are to some extent in agreement with the results of three previous studies[29,41,44] and in two later studies[31,86]. Our study is, however, the first to demonstrate that the association between smoking and RA among men, as well as among women, is mainly confined to RF positive RA.

The results in previous articles regarding the association between smoking and RA among women[20,21,29,30,40-43,45,47], have been somewhat inconsistent. However, the present study is the only population-based study using incident cases that has investigated the association between smoking and RA among women and men separately, and adds evidence to the notion that smokers of both sexes have an increased risk of developing RA, compared with never-smokers. This was also confirmed in a subsequent cohort study[86].

The risk of developing RA associated with smoking required a long duration, but merely a moderate intensity, of smoking. These results agree with previous studies[41,45] and there is increasing evidence for an association between duration of smoking and risk of RA, as it has now been observed in five of the six studies on this issue. However, as regards the effect of the intensity of smoking, the evidence is still conflicting[42,47]. The discrepancy in the results concerning the effect of the intensity of smoking on RA incidence may be due to a considerable degree of recall bias with regard to the number of cigarettes smoked per day, especially since the intensity has probably varied with time. The data on the effect of duration of smoking may be more accurate in this respect, as the number of years of smoking may be more easily recalled.

In this study the risk of developing RA was observed to increase as the cumulative dose of smoking increased, an observation that is in concordance with some previous results[30,45,46] and may be regarded as supporting the view that smoking is a causal factor

behind the development of RA. In a subsequent study the risk of RA was significantly elevated with 10 pack-years or more of smoking.[86] The increased risk of RF positive RA remained for up to anything between 10 and 19 years after smoking had stopped. This finding extends results by Heliovaara et al, who also observed increased risk of RA among ex-smokers also after more than 14 years of follow-up[41] and by a later study[86].

5.1.4 Interaction between HLA-DRB1 shared epitope alleles and smoking (Paper IV)

Two principal findings were presented in this study: First, a striking gene-environment interaction between smoking and HLA-DRB1 genotypes was seen for RF positive but not RF negative RA: this should have implications for formulations of pathogenetic hypotheses in these two conditions. Second, the data demonstrate that the risk associated with one of the classic genetically defined risk factors for an autoimmune disease is strongly influenced by the presence of an environmental factor: smoking.

The effects of smoking that were observed in our case-control study are in concordance with those previously reported by other groups. The results are consistent both with regard to the overall effect on the development of RA and with regard to the finding that smoking is primarily associated with RF positive RA[29,30,41,44,45,49,86]

In the study the analysis was restricted to comparing current and never smokers. Ex-smokers were excluded from the analysis. Previously we have extensively analysed the effects of various time courses and dosages of smoking on the risk of RA, as presented above in Paper III. Because we did not consider it possible to analyse the interactions between genes and smoking according to different timing and dosages of smoking into account (due to low numbers), we had to choose one way of categorizing smokers. We considered current smokers to be the best category in this context, since current smokers also had a high cumulative smoking history, whereas ex-smokers' cumulative smoking history varied considerably.

Concerning the genetic analyses, the observation of a relatively modest increased risk of RA in individuals with a single SE allele is consistent with the findings in several studies of early RA patients recruited directly from primary care[43]. Less information has been published on the risk conferred by double SE allele, although there are data indicating an increased risk of RA associated with double SE allele[16,87], which are in accordance with the findings in the present thesis.

The molecular mechanisms responsible for the observed interaction are not yet known, but several interesting possibilities exist which require further attention. Furthermore, a major finding of this study is that disease mechanisms dependent on an interaction between SE genotype and smoking are obviously only active in RF positive but not in RF negative RA, thus further emphasizing the need for subphenotyping of RA (here for RF status) in all pathogenetic and genetic studies of this disease.

5.1.5 Evaluation of participation/non-participation in EIRA (Paper V)

The participation proportion among cases as well as among controls in EIRA did not decrease during the ten-year study period. This is in contrast to previous observations of declining participation in epidemiologic studies over the past decades, with even

steeper declines in recent years[52,53], especially among controls in population-based case-control studies[53].

Former smoking was associated with early response and never smoking was associated with late response, among both cases and controls. No major differences in time of response were observed among current smokers. A few case-control studies have investigated smoking status among late responding controls. The findings in this thesis were in accordance with one of these studies[74], but in another study current smokers were more likely to be late respondents[88]. Interestingly the inclusion of smoking and occupational class data from late respondents in our study did not alter the results compared with those of the early respondents alone. The data indicates that a participation proportion of 70% among the controls yields the same estimated odds ratios, without loss of precision, as with a participation proportion of 82%, at least according to smoking and occupational class. Thus several reminders to include reluctant or difficult-to-find study subjects might not have been worthwhile, which has been suggested previously[71].

Demographic characteristics (male sex, young age, single marital status, and being an urban resident) were associated with non-participation among controls, but not among cases (except for old age). However, markers of low socioeconomic status, i.e. low income, less education, low occupational class and not being born in Sweden, were associated with non-participation in both cases and controls**.** The demographic characteristics of non-participating controls and the socioeconomic characteristics of both non-participating controls and cases in the present thesis are in accordance with findings in cross-sectional and cohort studies of non-participation[56-58,60,61,65-67]. Knowledge about characteristics of non-participants in case-control studies is limited. According to demographic characteristics of non-participants in case-controls studies, the findings are somewhat inconsistent regarding cases as well as controls[55,59,62,64]. According to socioeconomic characteristics, low socioeconomic status has been associated with non-participation among both cases and controls in two case-control studies[55,69] but only among controls in another[62].

The participation proportion in EIRA was high; 96% among reported cases, 82% among reported and not reported cases together and 82 % among controls. We believe that measures taken in the study design and data collection, such as introduction letters to controls, names on letters written by hand and several reminders including a second copy of the questionnaire, all contributed to these relatively high percentages. Furthermore, the questionnaire was well-designed and relatively short (25 pages) and on average it took approximately one hour to answer. All of these strategies were found to be successful in a review of 372 trials evaluating a total of 98 different strategies to increase responses to postal questionnaires[89]. According to the number of reminders, this number has been relatively constant during the study period. This is in contrast to previous findings, where the total number of contacts has increased over time in order to achieve similar response proportions[71].

5.2 METHODOLOGICAL CONSIDERATIONS

5.2.1 Study design

This thesis is based on data from the first phase of the EIRA study, the so-called EIRAI, which ran between 1996 and 2005. The second phase of EIRA, called EIRAII,

started in 2005 and is still in progress. In EIRAII, the questionnaire was extended with new questions, and two controls (instead of one) per case are now selected in order to obtain more blood samples from the control population. In EIRAI, controls were individually matched to the cases according to sex, age and residential area. Matching in case-control studies may provide more efficient stratified analyses, but it also implies that it is not possible to study the associations between the matching variables and the outcome of interest. In individual matching, each case-control pair is considered as a stratum, and data from each matched case-control must be kept in the analyses: i.e. if data from a case or control are missing, the data from the corresponding control or case must also be excluded from the analyses. When EIRA first began, some units reported cases that did not fulfil the ACR criteria, in order to enable investigations of undifferentiated arthritis. These subjects were eventually excluded from the study. However, for two reasons, data from the controls belonging to these excluded cases were kept in the analyses in the studies on which this thesis is based. Firstly, the results from the unmatched analyses were in close agreement with those from the matched analyses but had, in general, higher precision. Secondly, we considered it unethical to ask for extensive information from control individuals and subsequently not use this data. In order to avoid these problems, controls are frequency matched in EIRAII.

5.2.2 Selection bias

As described in Paper V, selection bias might have been introduced in EIRA, since 359 incident cases were included in a national rheumatoid arthritis register but were not reported to EIRA. We have not been able to determine whether this discrepancy was due to temporal inability in a specific rheumatology unit to recruit cases to EIRA, or to an active decision from a case not to participate in EIRA. Based on informal discussions with collaborators from the participating unit, it appears that most of the discrepancy relates to logistics and workload issues at the rheumatology unit, rather than individual decisions of cases not to participate in EIRA. Furthermore, approximately the same proportion of the non-reported cases was diagnosed at rheumatology units in Stockholm (the capital) as the reported cases, indicating no selection according to rheumatology centres. However, the non-reported cases were older indicating selection of reported cases according to age. The proportion of rheumatoid factor positive/negative RA was approximately the same for reported and not reported cases, suggesting no selection according to biological measures.

Furthermore, both non-participating cases and controls were to a larger extent immigrants than the participants, and thus to a lesser extent Swedish-speaking (one of the inclusion criteria). According to practitioners at one large rheumatology unit, many of the cases at their unit that were included in the RA register but not in EIRA, were not Swedish-speaking. It is therefore reasonable to believe that some of the non-participating cases and controls did not belong to the study base and thus we have probably overestimated the non-participation among both cases and controls in the present thesis.

Another source of potential selection bias stems from the possibility that cases with RA who were diagnosed in primary care but never referred to a rheumatology unit, were not captured. The Swedish general welfare system provides universal access to medical care, and in the medical care system almost all RA cases are referred to rheumatology units[50]. It is therefore unlikely that the unidentified cases in primary care would have a significant impact on the results of this thesis. Moreover, a separate project was

performed to investigate this possibility. Medical records of a sample of primary health care units within the study base were reviewed and only a few, insignificant number of patients with a new diagnosis of RA, not referred to a rheumatology unit, were traced (Anita Berglund, Institute of Environmental Medicine, Karolinska Institutet, personal communication 2008).

The different socio-demography between participants and non-participants might have introduced selection bias in the present thesis. Demographic characteristics (i.e. male sex, slightly young age, single marital status, and being an urban resident) were associated with non-participation among controls, but not among cases (except for old age). However, markers of low socioeconomic status, i.e. low income, less education, low occupational class and not being born in Sweden, were associated with non-participation in both cases and controls**.** These similar patterns of socioeconomic characteristics among cases and controls reduce the risk and degree of selection bias in EIRA, which was reflected in the similarity in the odds ratios of the association between different socio-demographic characteristics and the risk of developing RA for participants alone as well as for participants and non-participants together. The relatively high participation in the study also makes it less vulnerable for selection bias.

In summary, the different types of observed selection, i.e. unidentified cases and different socio-demography between participants and non-participants, are only likely to have introduced bias in EIRA to a limited extent.

5.2.3 Misclassification of exposures

Besides being more cost-efficient, a case-control study using incident cases, such as EIRA, may provide better opportunities than a cohort study to obtain accurate exposure information before disease onset. The use of exposure information from baseline in a cohort study, with a long follow-up period, is sensitive to substantial bias regarding exposures that tend to vary with time, cigarette smoking being one example. Since smoking habits have declined during the latest decades, a prospective cohort study using only baseline data regarding smoking would tend to underestimate the effect of smoking with regard to RA incidence.

One disadvantage of a case-control study with retrospective collection of exposure data compared with a cohort study using prospectively collected exposure data, is the higher risk of differential misclassification of exposure due to recall bias, if the cases recalled their exposure differently from the controls. As the use of prevalent cases increases the risk of recall bias, only subjects from the study base that received a diagnosis of RA for the first time were included, which reduced the time gap between the aetiologically relevant exposure time and the time of response to the questionnaire. The mean duration of disease at inclusion in the study was ten months, and for 81% of the cases, disease duration was less than one year. It is most unlikely that the cases would recall their formal education, occupation or smoking habits differently from the controls. The increased risk for only one subgroup of RA, i.e. RF positive RA, also supports that recall bias is of minor importance, at least with regard to smoking. However, recall bias might have been a potential problem in classifying psychosocial work stress. The use of a job exposure matrix was an effort to avoid recall bias and the results of the matrix-derived data were, in general, in accordance with the self-reported data. Analyses were also performed using an external job exposure matrix[90] and even though the questions posed regarding job demands and decision latitude differed from the questions in present thesis, the results were overall in accordance with the results based on the self-

reported data. These agreements considerably strengthen the accuracy of the results of this thesis regarding an association between low decision latitude and an increased risk of developing RA.

5.2.4 Misclassification of disease

A set of adequate diagnostic criteria is an important precondition for an epidemiological study of RA. In the present thesis, cases were defined according to the ACR-criteria[8] which are fairly clear and easy to use in clinical practice but have the limitation of sometimes being inadequate in early cases of RA. If some early cases are not diagnosed as having RA and these cases more often are RF negative it means that the potential bias in estimated relative risks is towards an overestimation of RA overall in the analysis of socioeconomic status and smoking. This potential bias emphasizes the importance of analysing RF positive RA and RF negative RA separately.

5.2.5 Misclassification of rheumatoid factor

RF status was only determined once. Thus, some cases might have been misclassified with regard to RF status. This potential misclassification, however, would most likely be unrelated to the studied exposures, which in turn means that the potential bias in estimated relative risks is towards the null value with regard to RF positive RA and an overestimation of RF negative RA in the analyses of socioeconomic status and smoking.

5.3 FINAL REMARKS AND FUTURE RESEARCH

Socioeconomic status
We observed that high socioeconomic status, independent of smoking habits, is associated with lower risk of developing RA in Sweden, and also that this association may be different regarding RF positive RA as compared to RF negative RA, and among men and women. The results add to the likelihood that socioeconomic status indeed influences the risk of developing RA even today, including the highly egalitarian societies in Scandinavia[29,30,84]. It is thus of great interest to identify risk factors in the environment and/or in lifestyle that are responsible for the observed differences, but this was beyond the primary scope of the thesis. Explanations for social class differences in RA may possibly be found in the social structure (for example as variations in social capital between living areas), in the working environment as well as in the so-called lifestyle of the individual (e.g. smoking). They may also be found in conditions during youth and upbringing or in conditions closer to the onset of disease[91]. We hope to return to these questions later in the course of the EIRA project when the web of causation may be somewhat better elucidated.

Psychosocial stress at work
Low decision latitude was associated with an increased risk of developing RA, which adds to the likelihood that psychosocial factors in the work environment also influence the risk of developing RA. It is obviously difficult to determine which mechanisms might be involved in causing the association between low decision latitude and increased risk of RA. Low decision latitude has been associated with alterations in the immune system, i.e. both increased IL-6 levels[38] and increased fibrinogen levels[39], but little information is available on potential further mechanistic explanations for these findings. The present observation on a relationship between psychosocial stress and risk of RA, may provide an opportunity to further investigate these mechanisms, and in

particular which aspects of inflammation may be affected by different forms of psychosocial stress.

Smoking

In recent years it has been demonstrated that antibodies to citrullinated protein antigens (ACPA) precede development of RA by several years[92,93], and anti-citrulline immunity has increasingly been hypothesized to be causatively involved in the development of RA[94]. ACPA is a specific serological marker and the most specific autoimmunity known for RA. Furthermore, new identified genetic risk factors for RA, besides the HLA-DRB1 shared epitope alleles, i.e. the PTPN22 risk alleles[95-98], and the TRAF1/C5 locus[99-101] are all confined to the ACPA-positive subset of disease, whereas other genetic risk factors, notably IRF-5 appear to be mainly associated with ACPA-negative disease[102].

With this new information a possible gene-environment interaction between smoking and HLA-DRB1 shared epitope alleles with regard to ACPA-positive RA was subsequently analysed, using data from EIRA[103]. A strong gene-environment interaction between smoking and HLA-DR shared epitope alleles was evident for ACPA-positive RA, which has been confirmed in later studies[97,104,105]. Furthermore, smoking was associated with increased presence of citrulline-modified proteins in the lungs[103,106], and this new observation is related to possible biological mechanisms. With all these findings taken together, an aetiological hypothesis can thus be formulated that involves, genes, environment, and immunity to self-molecules made immunogenic (and possibly arthritogenic) through posttranslational modifications induced by the environmental agent. Notably, the components of this putative series of events are present in ACPA-positive RA, but not at all in ACPA-negative RA.[103] The new findings demonstrate that the criterion-based syndrome RA should be subdivided into at least two distinct subsets, i.e. ACPA-positive and ACPA-negative disease[107,108].

Future research

The aetiology of RA is multifactorial with both genes and environment involved in disease development, as seen from both concordance data in twins and from a number of epidemiological and genetic studies[11-13]. Knowledge about contribution of genetics is rapidly increasing[14] but there is still a lack of data on environmental factors that may cause RA.

The observation of differences in RA incidence between social classes, both in this thesis and in other studies, supports the evidence that environmental factors are involved in disease development. This observation is also of value in generating hypotheses about possible association between environmental factors and the risk of developing RA, as many lifestyle and environmental factors, such as smoking, differ between different socioeconomic strata. However, adjustment for smoking seemed to explain only a minor part of the association between social class and RA in this thesis. Another possible explanation for the observed social differences in RA may be found in the psychosocial work environment. In this thesis an increased risk of RA among those with low decision latitude was observed and when we subsequently adjusted the result from the social class analyses for low decision latitude some of the social class differences in RA was explained by psychosocial stress at work.

The strong gene-environment interaction between smoking and HLA-DRB1 genotypes that was observed in this thesis for RF positive RA, and in a later study for ACPA+

RA, emphasizes that we are only at the beginning of an era where it will be possible to disentangle the complex interactions between different environmental and genetic risk factors, and to understand what different pathology-associated immune reactions may be triggered in the context of various combinations of genes and environmental factors. It also emphasizes the importance of identifying risk factors in the environment and/or in lifestyle that are responsible for disease development.

6 CONCLUSIONS

- Low formal education and low occupational class were associated with higher risk of developing rheumatoid arthritis (RA) and this association may be different regarding rheumatoid factor (RF) positive RA as compared with RF negative RA, and among men and women. The results add to the likelihood that socioeconomic status influences the risk of developing RA.

- Low decision latitude was associated with an increased risk of developing RA, which adds to the likelihood that psychosocial factors of the work environment influence the risk of developing RA.

- Smoking was associated with an increased risk of developing RF positive RA, but not of developing RF negative RA. The finding that the increased risk required a long duration but merely a moderate intensity of smoking, and may remain for several years after smoking cessation, indicates that the mechanism behind the effect of smoking is complex, slow, or delayed.

- A striking gene-environment interaction between smoking and HLA-DRB1 genotypes was seen for RF positive RA but not for RF negative RA. This observation emphasizes that we are only at the beginning of an era where it will be possible to disentangle the complex interactions between different environmental and genetic risk factors and to understand what different pathology-associated immune reactions may be triggered in the context of various combinations of genes and environmental factors.

- The response proportion in EIRA was high (96% among cases and 82% among controls) and stable during the ten-year study period. This is in contrast to the decreasing participation in epidemiologic studies seen in recent years. According to both the high participation and results from a non-participation analysis, selection bias due to non-participation is probably of minor magnitude in EIRA and the results in the present thesis are likely to be only marginally biased by this source of systematic error. In a late response analysis, inclusion of smoking and occupational class data from late respondents did not alter the results compared with those of the early respondents only. Thus, it might not be worthwhile with several reminders to include reluctant or difficult-to-find study subjects in epidemiologic studies, if the costs and efforts to include these study subjects are high.

7 SAMMANFATTNING PÅ SVENSKA

Reumatoid artrit (RA) är en kronisk, inflammatorisk sjukdom. Kunskapen om genetiska orsaker ökar snabbt, men information om omgivningsfaktorer som orsakar RA är begränsad. Syftet med denna avhandling var att bidra till bättre kunskap om sjukdomens etiologi genom att undersöka sambandet mellan RA och socioekonomisk status, psykosocial stress i arbetet och rökning. Ett ytterligare syfte var att utreda deltagande/icke-deltagande samt sent deltagande i en stor befolkningsbaserad fall-kontrollstudie (1931 fall, 2214 kontroller) med incidenta RA-fall, kallad EIRA.

Avhandlingen baseras på data från EIRA, där befolkningen i åldern 18-70 år i delar av Sverige studerades. Ett fall definierades som en person i studiebasen med nydiagnosticerad RA enligt American College of Rheumatology kriterierna. Kontroller valdes slumpmässigt ur studiebasen, med hänsyn tagen till ålder, kön och bostadsort. Fall och kontroller besvarade ett frågeformulär avseende bland annat information om socioekonomisk status, psykosocial stress i arbetet och rökning. Svarsfrekvensen var 96% bland fallen och 82% bland kontrollerna. Dessutom togs ett blodprov för analyser av reumatoid faktor (RF) och HLA-DRB1 shared epitope (SE) alleler. För att kunna studera möjliga selektionsfel i EIRA, inhämtades sociodemografisk information från register hos Statistiska Centralbyrån för alla identifierade fall och kontroller.

Enligt resultaten i avhandlingen, var låg socioekonomisk status (låg formell utbildning respektive låg yrkesklass) associerat med ökad risk för RA. Denna ökade risk var mer uttalad för RF positiv RA jämfört med RF negativ RA. Vidare var låg kontroll, en markör för psykosocial stress i arbetet, associerat med en ökad risk att utveckla RA. Ingen större skillnad observerades avseende RF status. Cigarettrökare hade en ökad risk att utveckla RF positiv RA, men inte RF negativ RA. Denna ökade risk uppstod efter lång duration men efter måttlig intensitet av rökning, och kvarstod flera år efter avslutad rökning. Dessutom observerades en slående gen-miljöinteraktion mellan rökning och HLA-DRB1 SE alleler för RF positiv RA, men inte alls för RF negativ RA. En metodstudie visade att det höga deltagandet i EIRA varit stabilt under en tioårsperiod, vilket är i kontrast till det sjunkande deltagande som har noterats i epidemiologiska studier på senare tid. Både det höga deltagandet och resultaten från en bortfallsanalys, tyder på att selektionsfel på grund av icke-deltagande förmodligen är av mindre betydelse i EIRA och resultaten i denna avhandling är sannolikt endast marginellt påverkade till följd av denna källa till systematiska fel. Vidare observerades att inklusion av rök- och yrkesklassdata från dem som svarat sent inte förändrade resultaten jämfört med resultat baserade på enbart dem som svarat tidigt. Flera påminnelser för att inkludera dem som är motvilliga eller svåra att nå i epidemiologiska studier bör kanske därför vägas mot kostnader och ansträngningar för att inkludera dessa individer.

Sammanfattningsvis, visar resultaten i denna avhandling att socioekonomisk status och psykosocial stress i arbetet sannolikt påverkar risken att insjukna i RA. Analyserna av rökningen indikerar att effekten av rökningen är komplex, långsam eller försenad. Den slående gen-miljöinteraktionen mellan rökning och HLA-DRB1 genotyper för RF positiv RA, men inte RF negativ RA, antyder att vi endast är i början av en ny era där det är möjligt att utreda de komplexa interaktionerna mellan olika omgivnings- och genetiska riskfaktorer och dessutom att förstå vilka biologiska mekanismer som uppstår av olika gen-miljökombinationer.

8 APPENDIX

Questions about psychological job demands and decision latitude

Demands

	Often	Sometimes	Seldom	Never/ almost never
1. Do you have to work very fast?				
2. Do you have to work very intensively?				
3. Does your work demand too much effort?				
4. Do you have enough time to do everything?				
5. Does your work often involve conflicting demands?				

Decision latitude

	Often	Sometimes	Seldom	Never/ almost never
1. Do you have the opportunity of learning new things through your work?				
2. Does your work demand a high level of skill or expertise?				
3. Does your job require you to take the initiative?				
4. Do you have to do the same thing over and over again?				
5. Do you have a choice in deciding HOW you do your work?				
6. Do you have a choice in deciding WHAT you do at work?				

Values of quartiles

Self-reported data				
		Lower quartile	**Median**	**Upper quartile**
Psychological job demands	Women	11.0	14.0	16.0
	Men	12.0	13.0	15.5
Decision latitude	Women	17.0	19.0	21.0
	Men	18.0	20.0	21.0

Job-exposure-matrix derived data				
		Lower quartile	**Median**	**Upper quartile**
Psychological job demands	Women	13.0	13.4	14.0
	Men	12.8	13.5	14.0
Decision latitude	Women	17.4	18.9	20.5
	Men	18.0	20.0	20.8

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