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Airborne occupational exposures and risk of developing rheumatoid arthritis

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AIRBORNE OCCUPATIONAL EXPOSURES AND RISK OF DEVELOPING RHEUMATOID ARTHRITIS

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”Min farbror disputerade för en månad sedan, coolt!
Det skulle jag också vilja göra en vacker dag.”

Anna Ilar, Facebook 13 april 2008

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Most of all, I'm grateful towards all the RA patients who have contributed to the EIRA study. You have always been in my mind. This book is my humble gift back to you.

ABSTRACT

Background: Rheumatoid Arthritis (RA) is an autoimmune, inflammatory disease with multifaceted aetiology. Cigarette smoke is the strongest environmental risk factor of RA, and research suggests that airborne exposures may trigger RA among genetically susceptible individuals. The aim of this thesis was to investigate the influence of airborne, occupational exposures on the risk of developing RA. The purpose of Study I was to explore whether there was any association between occupation and risk of developing RA. The airborne occupational exposures later studied were textile dust (Study II), asbestos and crystalline silica dust (Study III) and five types of organic dusts (Study IV).

Methods: All four PhD projects are case-control studies. Study I is based on the Swedish Eipidemiological Investigation of Rheumatoid Arthritis (EIRA) study. In Study I we identified newly diagnosed RA cases from the age of 18 in the southern and central parts of Sweden from May 1996 until September 2014. 1-2 controls per case were randomly selected from the population register, matched on age, sex and residential area. Data on occupational titles and environmental risk factors were collected through an extensive questionnaire.

Study II is based on the Malaysian EIRA (MyEIRA) study. We identified newly diagnosed female RA cases from 18 to 70 years of age from Peninsular Malaysia between August 2005 and December 2009. One control per case was selected and matched on age and residential area. Data on occupational titles and environmental risk factors were collected through an interview, based on an extensive questionnaire.

In Study III and IV the study base comprised of men and women in Sweden from 1996 until 2013. RA patients were selected based on the information from EIRA, the national patient register, the Swedish Rheumatology Quality Register (SRQ) and the Swedish Prescribed Drug Register. Apart fom the EIRA controls, ten additional controls per case were randomly selected from the total population register. For Study III and IV the occupational titles were retrieved from the national Population and Housing censuses (1960-1990) and from Statistics Sweden's LISA-register (2001-2010). We assessed the occupational exposure to the inorganic dusts asbestos, silica and five organic dusts by applying job-exposure matrices (JEMs) to the occupations of the participants.

In all four studies, we calculated odds ratios (ORs) and corresponding 95 % confidence intervals (CIs) by means of logistic regression analysis to assess the association between the main exposure and risk of RA.

Results: Among men the production-related occupations bricklayers and concrete workers, electrical and electronics workers and material handling operators were associated with an increased risk of RA compared to workers within the professional, administrative and technical sectors after adjustment for potential confounding from cigarette pack-years, alcohol use, education and body mass index (BMI). Among women, we observed an increased risk of RA among assistant nurses and attendants. Men working with crystalline silica or asbestos had an increased risk of developing RA compared to unexposed workers.

This finding may partly explain the increased risk among men working in production related occupations. The highest risk estimates for both asbestos and crystalline silica were observed among male workers with the longest duration of exposure, and for seropositive RA there was a significant dose-response trend for both agents. We could not detect an increased risk among women from asbestos or crystalline silica exposure. But fewer women than men had been working in occupations where they had been exposed to inorganic dusts and they also tended to have been exposed for a shorter period of time and to lower intensities.

For the organic dusts wood, animal, paper, textile and flour, the risk estimates were more similar for men and women. Among these five types of dust, animal dust showed the most solid association with an increased risk of RA. The OR also increased with duration of exposure to animal dust. We observed an increased risk of RA among women from exposure to textile dust in Malaysia. There was also an interaction between textile dust exposure and HLA-DRB1 shared epitope (SE) alleles, predominantly for the risk of developing Anti-Citrullinated Protein/Peptide Antibody (ACPA) + RA. Also in the Swedish population there were signs of an association between textile dust and seropositive RA.

Conclusions: This thesis demonstrates that your occupation may be associated with an increased risk of developing both seropositive and seronegative RA, where exposures to inorganic but also organic dusts play a role. Duration of exposure to organic and inorganic dusts is associated mainly with seropositive RA. These findings support the notion that the lung plays an important role in the pathogenesis of RA. The results can contribute to preventive measures at workplaces where workers are associated with an increased risk. This doctoral thesis highlights the importance to study inorganic and organic airborne exposures in countries with high or long-term exposure.

SAMMANFATTNING

Bakgrund: Reumatoid Artrit (RA) är en autoimmun inflammatorisk sjukdom med mångfacetterad etiologi. Cigarettrök är den mest kända riskfaktorn i miljön för att utveckla RA, och forskning tyder på att luftburna exponeringar kan utlösa RA bland genetiskt mottagliga individer. Syftet med denna avhandling var att undersöka påverkan av luftburna, yrkesmässiga exponeringar och risken för att utveckla RA. Studie I undersökte om det fanns någon koppling mellan yrke och risk för att utveckla RA. De luftburna yrkesmässiga exponeringar som senare studerades var textildamm (Studie II), asbest och kvartsdamm (Studie III) och fem olika sorters organiska damm (Studie IV).

Metoder: Samtliga fyra doktorandprojekt är baserade på fall-kontroll studier. Studie I är baserad på EIRA-studien (Epidemiologisk Undersökning av Riskfaktorer för Reumatoid Artrit). Nydiagnostiserade fall av RA, minst 18 år gamla, inkluderades på kliniker i delar av södra och mellersta Sverige under maj 1996 till september 2014. En till två kontroller per fall valdes slumpmässigt ut från folkbokföringsregistret och matchade på ålder, kön och boendeort. För studie I samlades uppgifter om yrkeshistorik, livsstil och miljöfaktorer in via ett omfattande frågeformulär.

Studie II är baserad på en malaysisk motsvarighet till EIRA kallad MyEIRA. Nydiagnostiserade fall av RA, 18-70 år, från Peninsular Malaysia, inkluderades mellan 2005 och 2009. En kontroll per fall valdes ut och matchades på ålder och boendeort. För studie II samlades uppgifter om yrkeshistorik, livsstil och miljöfaktorer in via intervjuer som baserades på ett omfattande frågeformulär.

I studie III och IV består studiebasen av män och kvinnor i Sverige från 1996 till 2013. RA-patienter valdes ut baserat på information från EIRA, det nationella patientregistret, Svensk Reumatologis Kvalitetsregister (SRQ) och det svenska läkemedelsregistret. Utöver kontroller från EIRA valdes tio ytterligare kontroller per fall slumpmässigt ut från registret över totalbefolkningen. För studierna III och IV kom deltagarnas yrkeshistorik från de nationella befolknings- och bostadsräkningarna som utfördes mellan 1960 och 1990 samt från SCB:s LISA- register för åren 2001 och 2010. Vi estimerade den yrkesmässiga exponeringen för de olika oorganiska och organiska damm-sorterna genom att använda jobb-exponeringsmatriser som applicerades på studiedeltagares yrkesinformation.

I alla fyra studierna beräknade vi oddskvoter och 95 % konfidensintervall med hjälp av logistisk regressionsanalys för att bedöma sambandet mellan exponering och risken för att utveckla RA.

Resultat: Bland män var de produktionsrelaterade yrkena murare och betongarbetare, el- och elektronikarbetare och materialhanteringsoperatörer associerade med en ökad risk för RA, jämfört med arbetstagare inom administrativa och naturvetenskapliga yrken, efter justering för cigarettvanor, alkoholanvändning, utbildning och kroppsmasseindex (BMI). Bland kvinnor observerades en ökad risk för RA bland undersköterskor och vårdbiträden. Män som

arbetade med kvartsdamm eller asbest, hade en ökad risk att utveckla RA jämfört med oexponerade män. Detta kan potentiellt förklara den ökade risken hos män som arbetar med produktionsrelaterade yrken. Risken för RA var som högst bland de män som varit exponerade för asbest eller kvartsdamm under längst tid, och för seropositiv RA observerade vi ett signifikant dos-responssamband för både asbest och kvartsdamm. Vi kunde inte upptäcka någon ökad risk bland kvinnor som exponerats för asbest- eller kvartsdammsexponering. Det bör dock påpekas att färre kvinnor än män hade arbetat i yrken där de hade blivit exponerade för oorganiskt damm som asbest och kvartsdamm, och bland dem som varit exponerade så hade de varit exponerade under en kortare tid och för lägre halter än sina manliga kollegor.

För det organiska dammet; trä, djur, papper, textil och mjöl var riskestimaten mer lika mellan män och kvinnor. Bland dessa fem typer av damm var det huvudsakligen djurdamm som visade en association med RA. Risken ökade med exponeringens varaktighet. Beträffande textildamm, observerade vi en ökad risk för RA hos textildammsexponerade kvinnor i Malaysia. Där observerades också en interaktion mellan textildammsexponering och HLA-DRB1 shared epitope (SE) alleler, främst för risken att utveckla Anti-Citrullinated Protein/Peptide Antibody (ACPA) + RA. Även i den svenska populationen fanns tecken på en association mellan textildamm och seropositiv RA.

Slutsatser: Denna avhandling visar att ditt yrke kan vara förenat med en ökad risk att utveckla både seropositiv och seronegativ RA, där exponering för oorganiska men också organiska exponeringar ökar risken för RA. Med ökad exponeringstid finns det en ökad risk för huvudsakligen seropositiv RA. Dessa fynd stöder teorin om att lungan spelar en viktig roll för uppkomsten av RA. Resultaten kan bidra till förebyggande åtgärder på arbetsplatser där det föreligger en ökad risk för sjukdomen. Denna doktorsavhandling belyser också vikten av att studera oorganiska och organiska luftburna exponeringar i länder med hög eller långvarig exponering.

POPULÄRVETENSKAPLIG SAMMANFATTNING

Ledgångsreumatism är den vanligaste ledsjukdomen i Sverige, som drabbar ca 0,5–1,0 % av befolkningen. Sjukdomen är vanligare bland kvinnor och risken att insjukna ökar med stigande ålder. Sjukdomen är kronisk och är förknippad med stort fysiskt och psykiskt lidande. Ledgångsreumatism beror på en samverkan mellan arv och faktorer i miljön. Den mest kända riskfaktorn från miljön är cigarrettrökning. Eftersom vi vet att rökning kan öka risken för ledgångsreumatism är det av betydelse att undersöka om olika luftföroreningar vi andas in också kan påverka sjukdomsrisken. Sådana ämnen skulle kunna vara olika typer av damm eller kemikalier, som individen i huvudsak andas in under sitt arbetsliv. Denna avhandling bygger på fyra doktorandprojekt, med det övergripande syftet att undersöka om yrke och yrkesrelaterade, luftburna ämnen kan öka risken för ledgångsreumatism.

I det första doktorandprojektet undersökte vi om det fanns någon koppling mellan olika yrken och risken att utveckla ledgångsreumatism. Att studera yrke kan visa på riskyrken för sjukdomen, och därmed öka vår förståelse för bakomliggande, yrkesrelaterade luftburna exponeringar. Projektet är baserat på den världsunika EIRA-studien. EIRA, som står för epidemiologisk undersökning av riskfaktorer för reumatoid artrit, undersöker orsakerna till varför människor drabbas av ledgångsreumatism. Det är den hittills mest ambitiösa studien om ledgångsreumatism som studerar både miljöns och genetikens påverkan på sjukdomens uppkomst och förlopp. Studiedeltagarna har lämnat information om sina tidigare yrken och olika livsstilsvanor via en enkät. Analyserna gjordes på över 3 500 patienter och 5 500 friska kontroller i södra och mellersta Sverige med information insamlad mellan 1996 och 2014.

Resultaten visade att det bland män kan finnas en ökad risk hos elektriker, murare och betongarbetare och arbetare inom godshantering och maskinkörning jämfört med personer som arbetar med kontorsrelaterade arbeten. Hos kvinnor såg vi en ökad risk bland undersköterskor. Bland kvinnorna kunde vi inte bevisa att det förekom någon ökad risk inom tillverknings- eller maskinskötselrelaterade yrken. Det kan bero på att det är ovanligt för kvinnor att arbeta inom dessa yrken. Betydelsen av inandning av farliga ämnen hos kvinnor är därför en viktig fråga att undersöka.

I det andra projektet undersökte vi om kvinnor i Malaysia som var exponerade för textildamm hade en ökad risk för ledgångsreumatism. Projektet baserades på MyEIRA studien, som har ett liknande studieupplägg som den svenska EIRA studien, men är utförd i Malaysia. Analyserna gjordes på 910 kvinnliga patienter och 910 friska kvinnliga kontroller med information insamlad mellan 2005 och 2009. Resultaten visade att kvinnor som ansett sig vara exponerade för textildamm under sitt arbetsliv hade en ökad risk för ledgångsreumatism. Risken var extra stor hos dem som också bar på den mest kända genetiska riskfaktorn för ledgångsreumatism.

För det tredje och fjärde doktorandprojektet samlade vi in registerdata från ett flertal nationella myndighetsregister och kvalitetsregister angående sjukdomsstatus och yrkeshistorisk hos patienter och motsvarande friska kontroller från den svenska

befolkningen. Patienter med ledgångsreumatism valdes ut från EIRA, det nationella patientregistret, Svensk Reumatologis Kvalitetsregister (SRQ) och det svenska läkemedelsregistret. Kontroller valdes ut från EIRA-studien och tio ytterligare kontroller per fall valdes slumpmässigt ut från registret över totalbefolkningen. Deltagarnas yrkeshistorik erhölls från de nationella folk- och bostadsräkningarna som utfördes mellan 1960 och 1990 och från Longitudinell integrationsdatabas för sjukförsäkrings- och arbetsmarknadsstudier (LISA) för åren 2001 och 2010. Vi utvärderade den yrkesmässiga exponeringen för asbest, kvartsdamm och organiskt damm genom att använda jobb-exponeringsmatriser som applicerades på alla studiedeltagarnas yrkeshistorik.

I det tredje doktorandprojektet undersöktes om personer som arbetat med kvartsdamm eller asbest hade en ökad risk för ledgångsreumatism. Analyserna gjordes på över 11 000 patienter med ledgångsreumatism och över 115 000 slumpmässigt valda kontroller med information insamlad mellan 1996 och 2013. Resultaten visade att män som arbetade med kvartsdamm och asbest hade en ökad risk för ledgångsreumatism. Detta kan potentiellt förklara den ökade risken hos män som arbetar med produktionsrelaterade yrken. Risken ökade i takt med antalet jobb som personen varit exponerad i. Vi kunde inte upptäcka en ökad risk bland kvinnor. Men färre kvinnor än män hade arbetat i yrken där de hade blivit exponerade för oorganiskt damm som asbest och kvartsdamm, och bland dem som varit exponerade så hade de varit det under en kortare tid och för lägre halter än sina manliga kollegor.

I det fjärde projektet undersöktes om personer som arbetat med olika typer av organiskt damm hade en ökad risk att drabbas av ledgångsreumatism. Analyserna utfördes på över 12 000 patienter och mer än 129 000 kontroller med information insamlad mellan 1996 och 2013. För de organiska damm-sorterna (trä, djur, papper, textil och mjöl) var riskestimaten mer lika mellan män och kvinnor. Bland dessa fem typer av damm var det huvudsakligen djurdamm som visade på en association med ledgångsreumatism. Risken ökade också med exponeringens varaktighet. Även i den svenska populationen fanns tecken på en association mellan textildamm och ledgångsreumatism.

Denna avhandling visar att ditt yrke kan vara förenat med en ökad risk för att utveckla ledgångsreumatism, där exponering för både oorganiska och organiska exponeringar spelar en roll. Risken att utveckla den vanligaste typen av ledgångsreumatism; seropositiv RA, ökade med tiden som en arbetare varit exponerad. Det faktum att män i större utsträckning än kvinnor tenderar att utveckla ledgångsreumatism på grund av sitt val av yrke kan förklaras av att män är överrepresenterade i produktionsrelaterade yrken, där de dessutom har utsatts för skadliga luftburna exponeringar i större utsträckning än deras kvinnliga kollegor med samma yrke.

Resultaten kan bidra till förebyggande åtgärder på arbetsplatser där det föreligger en ökad risk för sjukdomen. Men doktorsavhandlingen belyser också vikten av att studera luftburna ämnen i länder där exponeringsnivåerna är högre än i Sverige. Slutligen visade resultaten i denna avhandling att rökning fortfarande är relativt vanligt bland arbetare i industrier där det

finns ökad risk för ledgångsreumatism. Detta innebär att arbetare i industrier där det finns en ökad risk för ledgångsreumatism är viktiga målgrupper när det gäller interventioner för rökavvänjning.

LIST OF SCIENTIFIC PAPERS

I. **Ilar A**, Alfredsson L, Wiebert P, Klareskog P, Bengtsson C. *Occupation and Risk of Developing Rheumatoid Arthritis: Results From a Population-Based Case-Control Study*. Arthritis Care & Research. 2018;70(4):499-509.

II. Too Cl, Muhamad Na, **Ilar A**, Padyukov L, Alfredsson L, Klareskog L, Murad S, Bengtsson C. *Occupational exposure to textile dust increases the risk of rheumatoid arthritis: results from a Malaysian population-based case-control study*. Annals of the rheumatic diseases. 2016;75(6):997-1002.

III. **Ilar A**, Klareskog L, Saevarsdottir S, Wiebert P, Askling J, Gustavsson P, Alfredsson L. *Occupational Exposure to Asbestos and Silica and Risk of Developing Rheumatoid Arthritis: Findings from a Swedish Population-Based Case-Control Study*. Submitted.

IV. **Ilar A**, Gustavsson P, Wiebert P, Alfredsson L. *Occupational exposure to organic dusts and risk of developing rheumatoid arthritis*. Manuscript.

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LIST OF PUBLISHED CONFERENCE PAPERS

I. **Ilar**, **A**, Wiebert, P, Klareskog, L, Alfredsson, L, Bengtsson, C. *Occupation and Risk of Developing Rheumatoid Arthritis*. Arthritis & Rheumatology. 2014;66:S885-S885.

II. **Ilar A**, Bengtsson C, Klareskog L, Alfredsson, L. *THU0417 Occupation and Risk of Developing Rheumatoid Arthritis*. Annals of the Rheumatic Diseases. 2014;73(Suppl 2):326.

III. **Ilar A**, Alfredsson L, Wiebert P, Klareskog L, Bengtsson C. *AB0081 Occupation and Risk of Developing Rheumatoid Arth*ritis. Annals of the Rheumatic Diseases. 2016;75:924.

IV. **Ilar A**, Gustavsson P, Wiebert P, Bengtsson C, Klareskog L Alfredsson L. *THU0124 Occupational exposure to asbestos and risk of rheumatoid arthritis*. Annals of the Rheumatic Diseases. 2017;76:248.

V. **Ilar A**, Gustavsson P, Wiebert P, Bengtsson C, Klareskog L, Alfredsson L. *0297 Occupational exposure to organic dust and risk of developing rheumatoid arthritis*. Occup Environ Med. 2017;74:A93.

VI. **Ilar A**, Gustavsson P, Wiebert P, Bengtsson C, Klareskog L, Alfredsson L. *Occupational Exposure to Asbestos and Risk of Rheumatoid Arthritis*. Arthritis Rheumatol. 2017; 69 (suppl 10).

VII. **Ilar A**, Wiebert P, Saevarsdottir S, Askling J, Gustavsson P, Alfredsson L. *Occupational Exposure to Combustion Products and Risk of Developing Rheumatoid Arthritis*. Arthritis Rheumatol. 2017; 69 (suppl 10).

VIII. **Ilar A**, Wiebert P, Saevarsdottir S, Askling J, Gustavsson P, Alfredsson L. *774 Occupational exposure to combustion products and risk of developing rheumatoid arthritis*. Occup Environ Med. 2018;75:A391.

CONTENTS

LIST OF ABBREVIATIONS

ACPA	Anti-Citrullinated Protein/Peptide Antibody
ACR	American College of Rheumatology
Anti-CarP	Anti-Carbamylated Protein
AP	Attributable Proportion
APC	Antigen-Presenting Cell
ARTIS	Anti Reumatisk Terapi I Sverige
ATC	Anatomic Therapeutic Chemical classification system
BAL	Bronchoalveolar Lavage
BMI	Body Mass Index
CI	Confidence Interval
CRP	C-reactive protein
EIRA	Epidemiological Investigation of Rheumatoid Arthritis
ESR	Erythrocyte Sedimentation Rate
FAIR	Foetal air pollution exposure
FINJEM	Finnish Information System on Occupational Exposure
FoB	Folk- och Bostadsräkningen
GDPR	General Data Protection Regulation
HLA	Human Leukocyte Antigen
ICD-10	International Classification of Disease (Tenth Revision)
ILO	International Labour Organization
ISCO	International Standard Classification of Occupations
JEM	Job-Exposure Matrix
LISA	Longitudinal Integration Database for Health Insurance and Labour Market Studies
MyEIRA	Malaysian Epidemiological Investigation of Rheumatoid Arthritis
NF-kB	Nuclear Factor Kappa-Light-Chain-Enhancer of Activated B Cells
NO2	Nitrogen Dioxide
NOCCA	Nordic Occupational Cancer Study
NSAID	Non-steroid Anti-inflammatory Drugs

NYK	Nordisk Yrkesklassificering / Nordic Standard Classification of Occupations
OEL	Occupational Exposure Limit
OR	Odds Ratio
PAMP	Pathogen-Associated Molecular Patterns
PARCC	PARticles and Cardio- and Cerebrovascular diseases
PM	Particulate Matter
RA	Rheumatoid Arthritis
RF	Rheumatoid Factor
ROS	Reactive Oxygen Species
SE	Shared Epitope
SO2	Sulphur Dioxide
SRQ	The Swedish Rheumatology Quality Register
SSYK	Standard för svensk yrkesklassificering / Swedish Standard Classification of Occupations
SUN	the Swedish Educational Terminology
TLR	Toll-Like Receptors

1 PREFACE

Epidemiology is the study of how varying exposures are associated with health-related outcomes in well-defined populations. Sweden is an excellent country to perform epidemiological research. The Swedish Personal identification numbers is a unique personal identifier. It allows researchers in Sweden to conduct large-scale population-based studies by linking data on sociodemographic characteristics from national registers or other sources of data with data on medical care or death.

I attended my first epidemiology course during my bachelor program in public health at Gävle University and was so intrigued by this research area that I decided to pursue a master program specialized in epidemiology at Karolinska Institutet, starting August 2011. At the end of my master program in Epidemiology I was given the opportunity to write my master thesis on the Epidemiological Investigation of Rheumatoid Arthritis (EIRA) study material. The purpose was to explore whether there was any association between what occupation you had and your risk of developing rheumatoid arthritis (RA).

The neighbourhood I have walked by to reach Karolinska Institutet for the past eight years is one where many changes have occurred during the last decade. A new city area is on the rise, the new Karolinska Hospital is built and Karolinska Institutet is expanding its premises. The construction area stretches from Vasastan in the South to Karolinska Institutet and the newly built Karolinska Hospital in the North. With its 96 hectares, the new city area Hagastaden will hold 6 000 new homes and 50 000 workplaces. Hence, right next to the Karolinska Hospital and one of the world's most prestigious medical universities, lies one of Europe's largest construction sites. Every day, thousands of construction workers come here to work, and thereby being at risk of being exposed to harmful, airborne exposures.

The results of my master thesis indicated that this same group of workers that I was passing by every day appeared to have an increased risk of the disease my research group was studying; RA. Why was it that some groups of workers had an increased risk of RA? I wanted to find an answer to this question. Consequently, I was enrolled as a PhD candidate by the end of January 2014. You now hold the result of several years of research on this subject in your hands.

1.1 OVERALL AIM OF THE THESIS

The overall aim of this doctoral thesis was to explore if different airborne occupational exposures were associated with an increased risk of developing RA. Specifically, the aim was to study these exposures in relation to immunologically defined subtypes of RA, and to investigate gene-environment interaction between these exposures and the genetic risk factor Human Leukocyte Antigen (HLA)-DRB1 Shared Epitope (SE).

1.1.1 Specific aims

Study I: The aim of the study was to explore the association between occupation and the risk of developing RA. Which occupations were associated with the risk of RA among men and women? Were occupations differently associated with the risk of Anti-Citrullinated Protein/Peptide Antibodies + RA and ACPA- RA?

Study II: The aim of the study was to study occupational exposure to textile dust and risk of developing ACPA+ and ACPA- RA in Malaysian women.

Study III: The aim of this study was to explore the associations between occupational exposure to asbestos and crystalline silica exposure and risk of seropositive or seronegative RA in men and women.

Study IV: The aim of the study was to estimate the risk of seropositive or seronegative RA in men and women in relation to organic dust exposure.

1.2 THESIS OUTLINE

This doctoral thesis is a compilation thesis, which means that it consists of a compilation of scientific papers and a kappa. Paper I and II have been published in scientific, peer-reviewed journals. Paper III has been submitted and is currently on peer-review. Paper IV is yet to be submitted.

The kappa is the thesis' summarizing introductory section clarifying the collected scientific contribution of the research. The kappa in this thesis consists of seven chapters. The first chapter consist of a brief motivation to why the research is conducted and the aim of the thesis. The second chapter of this thesis conclude a background to the research area. It will provide knowledge about RA and how occupational airborne exposures may induce the disease onset. Chapter three provide the reader with the research approach undertaken to conduct the four papers, including the materials used in the research and the methods for how the four studies have been conducted.

Chapter four; Results, will provide the reader with a summary of the main findings from the four studies. Chapter five will discuss the main research findings with regards to previous literature in the research area, as well as review strengths and limitations of the research conducted. Chapter six will conclude the main research findings and link them to the research questions in the introductory chapter. The seventh and final chapter provides the reader with references.

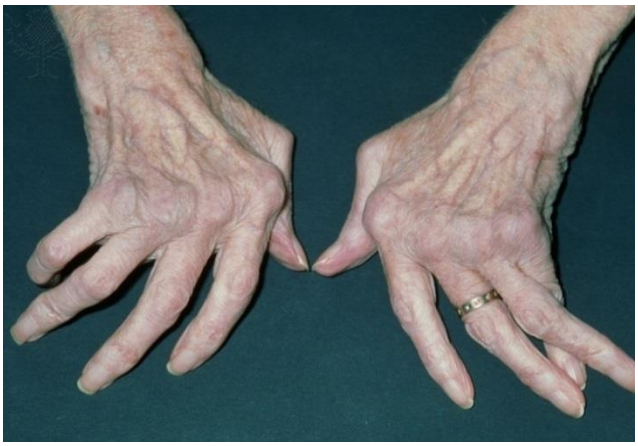
2 BACKGROUND

2.1 RHEUMATOID ARTHRITIS

RA is a rheumatic, chronic disease known for causing swollen and hurting joints in the hands and feet. Prior to today's advancements in medication, RA patients were primarily known for their heavily deformed hands and feet. Up until the nineteenth century, RA was still considered a form of gout. The first modern description of RA was provided by the French medical surgeon Augustin Jacob Landré-Beauvais, published in his doctoral thesis from the year 1800 [1]. Landré-Beauvais believed that he had identified a new form of gout (asthenic gout), with predominance in women. This disease had a chronic disease course and joint involvement at an early disease stage. The term RA was later introduced by Sir Alfred Garrod. In his book *The Nature and Treatment of Gout and Rheumatic Gout*, published in 1859 [2], he states that:

> *"Perhaps Rheumatoid Arthritis would answer the object by which term I should wish to imply an inflammatory affection of the joints, not unlike rheumatism in some of its characters but differing materially from it. (…) "The term Rheumatic Gout is applied to so many different forms of disease that it is exceedingly difficult to define what it is intended to be understood by it."*

The word *rheumatoid* comes from the Greek stem rheuma and means "a discharge from the body". *Arthritis* is derived from the Greek *arthron* (joint) and *itis* (inflammation). RA is an autoimmune disease, meaning that the body´s immune system attacks and destroys healthy tissue, because it fails to recognize the difference between self and non-self-antigens. The attack on healthy tissues causes inflammation in the synovial membranes and the joints [3]. Several joints can be affected by the inflammation and RA is therefore to be considered a polyarthritis. The patient often initially experiences joint pain followed by swollen and stiff joints due to the inflammation. Usually the inflammation is symmetric, which means that it affects the left and right body half equivalently. If untreated the inflammation will damage the bones, the articular joint cartilage and adjacent structures including tendons [3].



Woman's hands crippled with rheumatoid arthritis.
Source: Encyclopædia Britannica ImageQuest. Accessed May 12, 2019.

The subsequent musculoskeletal deficits and impaired functional capacity of the patient can lead to severe disability [4] and the inflammation may lead to cardiovascular disease [5]. RA leads to both direct and indirect societal costs. The direct costs are due to the continuous treatment of the disease and required surgeries whereas the indirect costs are related to the productivity loss at

the workplace and the effect on the mental health of the patients and their families [6, 7]. The annual total cost per patient in Sweden (including drug use, hospital care and productivity loss) is estimated to be 23 147 euro [8].

The incidence and prevalence of RA differs worldwide, with variations mainly due to sex and geographical area. The disease is more common in northern Europe than southern Europe, and a systematic review estimated that the median annual incidence rate in northern Europe is 29 cases per 100 000 inhabitants [9]. However, several countries worldwide do not have national data on the incidence of disease, which complicates international comparisons. In Sweden, the mean annual incidence rate was 56 per 100 000 among women and 25 per 100 000 among men during 2006-2008 [10]. RA is thereby the most prevalent joint disease in Sweden, and in 2008 the prevalence of RA was 0.4 % among men and 1.1 % among women [11]. The risk of RA increases with age and for women above 60 years of age the prevalence of RA during 2008 was approximately 2-3 % [11]. Figure 1 shows the trend in number of RA diagnoses in outpatient specialized care since 2001 in Sweden.

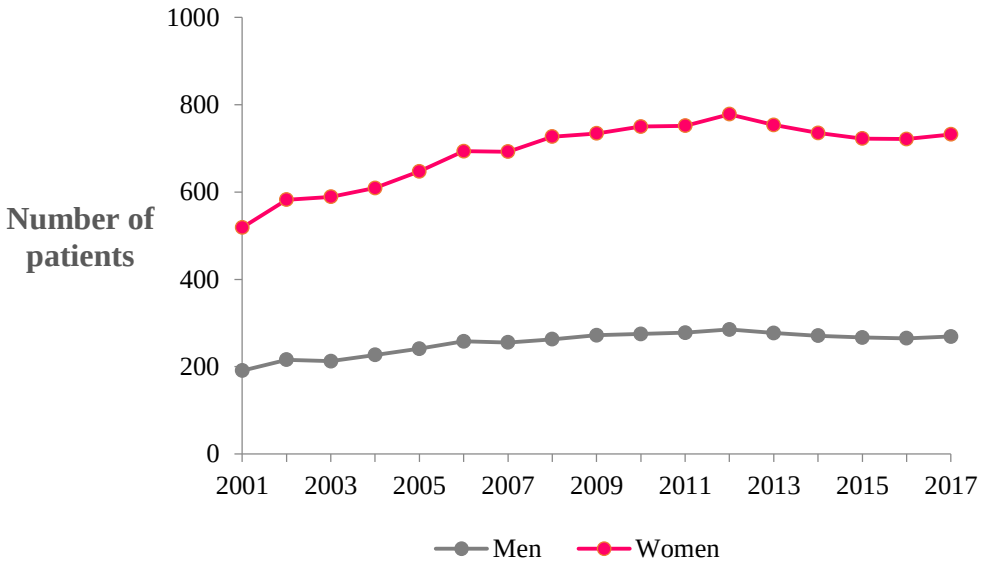


Figure 1. Annual number of unique diagnoses of RA in outpatient specialized care per 100 000 inhabitants in Sweden (age: 20-85 +).

Source: The National Board of Health and Welfare Statistical database. RA defined as ICD-10 M05 and M06.

2.1.1 Diagnostic criteria

Several autoantibodies function as diagnostic markers of RA today, such as the Rheumatoid Factor (RF), ACPA, Anti-carbamylated protein (anti-CarP) antibodies and antiperinuclear factor. The latter two are not used often because of the strict technical requirements needed to detect them [12]. Elevated levels of ACPA, RF and anti-CarP have been found in RA patients before onset of the symptoms [13-15]. ACPA is believed to have the best

diagnostic accuracy because of a higher specificity for RA. A review including 86 studies found that the pooled specificity and sensitivity were 95% (95 % CI: 94-97) and 67% (95% CI, 62-72) for ACPA and 85% (95 % CI: 82-88) and 69% (95 % CI: 65-73), for lgM RF [12]. Approximately 70 % of all prevalent RA cases are ACPA+ [16].

According to the commonly applied 1987 American College of Rheumatology (ACR; formerly, the American Rheumatism Association) classification criteria for RA [17], the patients need to show at least four out of these seven criteria to be classified with RA:
1) Morning stiffness lasting at least one hour
2) Arthritis of three or more joint areas
3) Arthritis of hand joints
4) Symmetric arthritis
5) Rheumatoid nodules
6) Abnormal amounts of serum RF
7) Radiographic changes

(Criteria 1 to 4 must have been present for at least six weeks)

In 2010, the ACR classification criteria were revised to better be able to detect early cases of RA. Because of this, symptoms associated with long-lasting disease, e.g. joint damage and rheumatoid nodules were removed. Patients with at least 1 joint with definite clinical synovitis (swelling), where the synovitis is not better explained by another disease, are classified with RA if they have a score of 6 or more [18]:

		Score
1.	Joint involvement	
	a. 1 large joint	0
	a. 2-10 large joints	1
	b. 1-3 small joints (with or without involvement of large joints)	2
	c. 4-10 small joints (with or without involvement of large joints)	3
	d. >10 joints (at least 1 small joint)	5
2.	Serology (at least 1 test result is needed for classification)	
	a. Negative RF and negative ACPA	0
	b. Low-positive RF or low-positive ACPA	2
	c. High-positive RF or high-positive ACPA	3
3.	Acute-phase reactants (at least 1 test result is needed for classification)	
	a. Normal C-reactive protein (CRP) and normal Erythrocyte Sedimentation Rate (ESR)	0
	b. Abnormal CRP or abnormal ESR	1

4. Duration of symptoms
    a. <6 weeks 0
    b. ≥6 weeks 1

For the 2010 diagnostic criteria of RA, RF and ACPA are the accepted markers used for serological testing of the disease [19]. A patient is defined as seropositive if he/she is either RF+ or ACPA+. A seronegative patient is both RF- and ACPA-. Increasing evidence suggest that ACPA+ RA and ACPA- RA have different etiologies and partly different pathogenesis [16, 20, 21].

2.1.2 Genetic risk factors

Genetic factors contribute to roughly 50 % of the disease development of RA overall [22, 23] with heritability for ACPA+ RA being higher than for ACPA- RA [24]. More than 100 different loci have been identified [25] and the major genetic risk factor for RA is the Human Leukocyte Antigen D-Related (HLA-DR) [26] gene. HLA-DR is the one genetic risk factor which has been shown to be a risk factor for populations worldwide, and it may account for up to half of the genetic risk of RA [23]. The part of the HLA-DR molecule most recognised to be associated to ACPA+ RA is the SE region located in the HLA-DRβ1 gene [26], and recent research has identified the precise amino acids in the antigen-binding groove of the MHC molecules that contribute to the disease risk [27]. The second major genetic determinant of RA is the PTPN22 polymorphism. As for the HLA region, PTPN22 only increase the risk of ACPA+ RA [21, 28].

2.1.3 Environmental risk factors

Environmental risk factors represent exposures external of the individual, such as lifestyle behaviours, biological exposures, occupational exposures, residential factors and socio-economic status. Environmental exposures have been shown to both cause and affect the disease progression of RA. Cigarette smoking is the environmental factor most strongly associated with RA, and mostly to the seropositive subtype [29]. The risk increases with increasing number of cigarette pack-years and is lower among former smokers as compared to current smokers [30-32]. Snuff does not appear to increase the risk of RA [33, 34], suggesting the importance of other airborne components rather than nicotine.

The second strongest behavioural lifestyle factor associated to RA is alcohol consumption. Ever use of alcohol has been shown to decrease the risk of RA, with an inverse exposure-response relation [35-37]. The potential mechanism of this association is still unclear, but potential explanations are confounding due to healthier lifestyle choices of ever drinkers, the anti-inflammatory effects of alcohol [38-40] or the immune-regulatory aspects [41-43]. Another proposed risk factor for RA is vitamin D deficiency, although findings are inconclusive [44-46].

Socio-economic status has been associated with risk of RA within different study settings. It can be described as a social hierarchical system within a society that places individuals

on a social gradient based on their education, income or occupational class [47], which may affect the ability to access and engage in healthy lifestyle behaviours [48]. Socio-economic status could be seen as a proxy for a number of lifestyle and occupational exposures. Level of education appears to be the best socio-economic status measure in predicting RA, with high educational level being inversely associated with risk of RA [47, 49, 50], even after adjustments for smoking [47]. Occupational class, as a measure of socio-economic status, has also been found to be related with onset of RA [47].

Several studies have found an association between occupation and risk of RA. Findings reveal that workers within industries related to production, transport and the mining industry appear to be at higher risk of RA, whereas occupations within administrative or technical fields are at less risk [49, 51-55]. The occupational exposures that have been associated with RA come from a broad spectrum of mainly chemical, physical and physiological exposures. Considering chemical exposures, crystalline silica dust is so far the occupational exposure most strongly associated with risk of RA [56-64]. The association between crystalline silica and RA was first reported by Colinet [65] and Caplan [66] in the early fifties. In Sweden, men who reported that they had been working with stone crushing, rock drilling or had exposure to stone dust have an almost two-fold risk of RA [60].

It has been suggested that there might be an association between traffic pollutants and risk of RA. So far, findings from the literature are inconclusive, and no convincing relation between ambient exposure to Sulphur Dioxide (SO_2), ozone, Nitrogen Dioxide (NO_2), Particulate Matter $(PM)_{2.5}$ or PM_{10} has been presented [67-70], although living close to a road has turned out to be associated with an increased risk of RA [68, 70].

2.1.4 Environmental and gene-environment interactions

Additive interaction between two risk factors takes place when their joint effect exceeds the sum of their independent effects, e.g. deviation from additivity [71]. For the development of RA, airborne exposures and genetic risk factors have been shown to interact [29, 72]. There is a particularly strong interaction between cigarette smoking and HLA-DRB1 SE and development of ACPA+ RA [32]. This is illustrated in Figure 2, where individuals in the EIRA study who are both smokers and born with the HLA-DRB1 SE risk gene have an increased risk of ACPA+ RA, which is larger than the sum of the two risk factors.

Figure 2 below was adjusted for the matching variables sex, age group and residential area. As the figure illustrates, having both risk factors elicit a greater risk than the mere sum of their independent effects, i.e. they display interaction on the additive scale. The EIRA research group established this gene-environment interaction between HLA-DRB1 SE and smoking in the development of ACPA+ RA in 2006 [29]. The odds ratio (OR) of ACPA+ RA among ever smokers carrying two copies of the HLA-DRB1 SE allele was 21.0 (95 % CI = 11.0-40.2) compared with never smokers without SE genes. Among smokers carrying one copy of the SE, the AP due to interaction was 0.4 (95 % CI = 0.2-0.7). With two copies of the SE, the AP increased to 0.7 (95 % CI = 0.5-0.9).

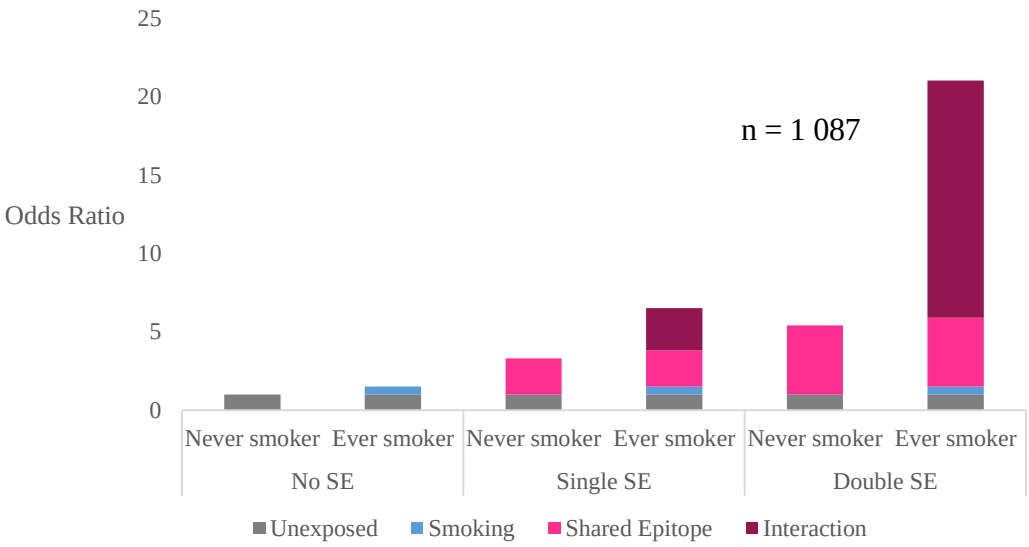


Figure 2. Gene–environment interaction between smoking and shared epitope (SE) genes regarding the risk of developing anticitrulline antibody–positive RA in the EIRA study

Source: Figure based on numbers presented in Table 2, Klareskog et al [29].

An interaction between current smokers and silica exposure for ACPA+ RA has also been observed, with an observed attributable proportion (AP) due to interaction of 0.60 (95% CI 0.26-0.95) [61]. The AP due to interaction between smoking and crystalline silica has also been shown to increase with number of pack-years [73].

2.2 OCCUPATIONAL EPIDEMIOLOGY

Occupational epidemiology can be described as a research area focusing on the risk factors present in the work environment, and their effect on exposed workers. Apart from work, harmful agents may affect persons at their home and outdoors, although levels at work for certain exposures tend to be higher in the workplace than in other settings.

2.2.1 Occupational exposures

An occupational exposure is an external factor present in the work environment which comes in contact with any surface of the human body. Exposure levels change over time due to technological advancements within industries, updated legislations, newly introduced products and international trade [74]. There are several different types of exposures to which humans may be exposed to during their work life. These exposures can be [75]:

- Mechanical — Work posture, heavy loads, repetitive work, etc
- Psychosocial — Work load, demands, control, lack of social support, threats, etc
- Physical — Cold, heat, noise, vibrations, radiation, etc
- Biological — Viruses, mold, bacteria, etc
- Chemical — Solvents, dusts, metals, etc

A chemical agent can be defined as a natural or synthetic compound or element in liquid, solid or gaseous form which exerts its effect on the human tissue. Chemical agents can be synthetically made but can also be found naturally in soil and sand. They are released into the air through natural events like forest fires, or through different commonly work-related activities such as crushing, cutting, grinding, drilling or explosions. As many chemical agents are airborne, inhalation is considered the main route of exposure in occupational settings [76].

There are several sources of data for assessing occupational exposures, such as personnel records with work task descriptions, occupational hygiene monitoring data, inspection reports, protective equipment documentation, biological monitoring reports and individual measurements [76]. A common approach to assess historical occupational exposures is with a job-exposure matrix (JEM). A JEM is usually constructed by a team of industrial hygienists and it contains assessments of exposure intensity and probability of exposure for each occupation during different time periods, which can be applied to the study participants´ work histories. The exposure estimates can be based on different sources of data such as monitoring data and collections of personal exposure measurements conducted at workplaces. JEM's are considered a cost-efficient tool to assess retrospective exposures in large study populations. Table 1 provides an example of how a JEM can look like for the two exposures asbestos and crystalline silica for the year 1960.

Table 1. Part of the job-exposure matrix PARCC with estimates on 4 occupational codes in the Population and Housing Census 1960, time period 1955-1964.

Occupational code	**Work title**	**Asbestos (**fiber/cm^3**)**		**Crystalline silica (**mg/m^3**)**	
		P	**N**	**P**	**N**
791	Bricklayers	40	0.30	95	0.12
792	Masons	-	-	95	0.30
793	Construction workers	40	1.00	95	0.10
794	Insulators	90	2.00	-	-

Abbreviations: PARCC, Particles and Cardio- and Cerebrovascular diseases
P = Prevalence of the exposure in % in the occupation
N = Air concentration of occupational exposure expressed as 8-hour time-weighted average among those in the occupation actually exposed

2.2.2 Occupational classification systems

Occupational classification systems are ways of categorizing and coding occupations based on common characteristics of the job, such as the work tasks involved. Classification systems are used to group information on the population's jobs or work tasks, and they are a useful tool in many statistical applications. Most countries have their own classification systems, although it is common to use the International Standard Classification of Occupations (ISCO) [77] as a basis when creating a national standard. The International Labour Organization (ILO) launched the first ISCO in 1958, and new versions were released in 1968, 1988 and 2008. The purpose of ISCO is primarily to serve as a model for national and regional classification systems, be applicable for countries that do not develop their own national

classification system and provide a current and relevant basis for international reporting, comparisons and exchange of work information.

Sweden's first national classification system was the Nordic Standard Classification of Occupations (Nordisk Yrkesklassificering; NYK), based on ISCO-58. Different versions of NYK were used to code occupations in the Population and Housing Censuses (Folk- och Bostadsräkningen; FoB) carried out between 1960 and 1990. Due to the changes in the labour market this classification system was replaced with a new one called The Swedish Standard Classification of Occupations (SSYK) in 1996. SSYK is currently used to code occupations in the Swedish Occupational Register. Table 2 gives an overview of NYK and SSYK.

Table 2. Comparison of the two occupational classification systems NYK and SSYK.

	NYK	SSYK
Based on	ISCO 1958	ISCO 1988 or ISCO 2008
Grounds for classification	Occupations are divided based on business-oriented functions, i.e. that everyone who accomplishes the same result belongs to the same occupation. The placement of occupations normally takes place without regard to the requirements for education, employment or occupational position.	Occupations are divided on the basis of the tasks that are performed, and on the qualifications normally required to perform the work. The qualifications have two dimensions, level and specialization.
Versions	5 (1964, 1965, 1974, 1978, 1983)	2 (1996, 2012)
Major groups		
0	Professional, technical and related work	Armed forces
1	Health and nursing work, social work	Legislators, senior officials and managers
2	Administrative, managerial and clerical work	Professionals
3	Sales work	Technicians and associate professionals
4	Agricultural, forestry and fishing work	Clerks
5	Mining, quarrying and petroleum extraction work	Service workers and retail workers
6	Transport and communications work	Skilled agricultural and fishery workers
7	Production work	Craft and related trades workers
8		Plant and machine operators and assemblers
9	Service work	Elementary occupations

Abbreviations: ISCO, International Standard Classification of Occupations; NYK, Nordic Classification of Occupations; SSYK, Swedish Standard Classification of Occupations

2.3 AIRBORNE EXPOSURES AND INITIATION OF RA

Since autoantibodies like ACPA have been found in blood of patients prior to inflammation in the joints [14], there is reason to believe that the immunity against citrullinated peptides is initially triggered outside of the joint [78]. Increasing evidence suggests that the lungs are the site where RA-specific autoimmunity can be initiated [79, 80]. This section will describe the deposition of airborne exposures in the lungs and hypothesize about the biological mechanisms involved in them causing RA.

2.3.1 Respiratory deposition of airborne particles

An aerosol can be defined as a solid or liquid substance suspended in a gas. The substance part of the aerosol is referred to as PM. Both short- and long-term exposure to PM have for many decades been known to cause diseases in the respiratory and cardiovascular systems [81, 82]. The properties of the agent, the chemical composition and characteristics of the individual affect the influence of the body's defence mechanisms and thereby the fraction of PM reaching the lung. If the body's capability to dispose of airborne pollutants is damaged by inhalation of excessive amounts of pollution, a larger fraction of these pollutants will reach the alveoli.

To understand how exposure to an airborne agent causes disease, we have to know its chemical composition, but also where it will deposit in the respiratory system. Particles have to deposit to cause biological effects. The deposition of particles will depend on the agent's physical properties, its interaction with other exposures as well as genetically and environmental characteristics of the host. These different aspects are covered briefly below.

Considering respiratory deposition, the respiratory system in humans can be divided into three regions:
1) the nasopharyngeal region consisting of the mouth, nose, pharynx and larynx;
2) the tracheobronchial region, including the trachea, bronchi and bronchioles, and finally
3) the alveolar region, which is where the gas exchange occurs [83].

Each of these regions has its own clearance mechanisms against airborne particles. The main clearance mechanism in the nasopharyngeal region and the tracheobronchial region is the mucociliary transport, which will cause the aerosols to be either swallowed or expectorated. The alveolar region is not covered with cilia, and here the main defense instead consists of macrophages that engulf the aerosols and transport them to the cilia-covered regions of the airways [83]. Cigarette smoking will affect the fraction of PM depositing in the lung, since smoking impairs the self-clearing mechanism of the bronchi [84]. PM will accumulate in the lung if the clearance mechanisms fail to dispose them.

The main physical properties of PM which will affect where it deposits are size, shape, density and solubility. The size of PM is defined by its aerodynamic diameter. PM is usually referred to as $PM_{2.5}$ or PM_{10} in the literature depending on the aerodynamic diameter measured in micrometres. The aerodynamic diameter of a particle is an estimation of the

diameter of a spherical particle with the same settling velocity as the particle of interest but with the density as water (1 g/cm3) [83]. Hence, $PM_{2.5}$ and PM_{10} is the mass of particles in the air with an aerodynamic diameter of less than 2.5 and 10 μm respectively, independent of the particles´ shapes.

The fraction of PM reaching down the respiratory tract will depend on the aerodynamic diameter; therefore, a greater fraction of particles with small aerodynamic diameter will reach the lung compared to particles with larger aerodynamic sizes [85, 86]. Hence, it follows that the aerodynamic diameter is strongly linked to which type of respiratory disease that will occur. Particles with an aerodynamic size larger size than 10 μm - like organic dusts - seldom pass through the nose or throat, and only about 20 % of 10 μm particles can reach into the lower respiratory tract in the case of nasal breathing [86]. The respirable fraction is the fraction of PM that penetrates beyond the bronchioles into the alveolar region of the lungs. For 4 μm particles the respirable fraction is 50 % [87]. It is the aerodynamic diameter rather than the length of the particle that determines where it will deposit in the airways. This is why fibrous dusts such as asbestos - which are characterized by their length – still can deposit in the lungs where they are known to cause great harm, instead of higher up in the airways [88, 89].

To understand how an airborne agent causes disease we also have to consider certain properties and behaviours of the host. Physical workload will for instance affect the breathing pattern in terms of tidal volume, breathing frequency and whether you breathe in with your nose or mouth. The amount of air breathed in during an 8 hour work day may increase from 2 800 litres to 10 000 litres for an individual involved in hard physical work [90]. Another factor affecting the fraction being deposited is if you already have a respiratory disease, such as asthma [91]. The dose can additionally be affected by external factors in the work environment, such as proper safety equipment used by the worker and the ventilation system.

Cigarette smoke has a harmful effect on the body's defense system against airborne agents, since it damages the protecting effect of the cilia in the airway region [84]. If an individual is smoking and additionally exposed to other noxious agents, we speculate that this would lead to a greater fraction of that agent reaching the lung, as compared to the situation in a never smoker. This would be one explanation for the synergistic effects observed for smoking and other airborne exposures. Exposure to asbestos is of special interest as such exposures are well known to cause other types of inflammatory reactions in the lung, resulting in for example fibrosis [92, 93].

2.3.2 Biological mechanisms

Toll-like receptors (TLRs) are receptors found on the membrane of immune cells. They play an important role in the innate immune response since they help to immediate the immune response against pathogenic invasions. When TLRs recognize foreign components - pathogen-associated molecular patterns (PAMP) - they become activated, which will lead to an activation of different transcription factors, such as nuclear factor kappa-light-chain-enhancer of activated B cells (NF-kB). NF-kB further stimulates the production of pro-inflammatory cytokines.

As is illustrated in Figure 3, our research group's hypothesis is that hazardous airborne agents like crystalline silica and cigarette smoke modifies the activity of TLR [94, 95], which can lead to an activation of the citrullinating enzymes Peptidylarginine deiminases (PADs). PAD-mediated citrullination plays a central role in the development of autoimmune diseases, as it generates neoantigens that may become targets of autoantibodies originally produced in the lung. This hypothesis is supported by research showing that cigarette smoke increases the expression of the PAD2 enzyme in the bronchial mucosal and alveolar compartment [79, 96-98]. Hence, airborne exposures activate PADs and this leads to citrullination of autoantigens. TLR can additionally cause production of pro-inflammatory cytokines [94, 95] and activation of antigen-presenting cells (APCs) [99] in the lung, leading to local activation of T cells and subsequent production of autoantibodies [100, 101].

Another potential mechanism for how airborne exposures can cause RA involves oxidative stress. Silica [102, 103], smoking [104] and PM [105] have been shown to generate reactive oxygen species (ROS) and can thereby cause oxidative stress. ROS can trigger an immune response in the lung by activating the protein-complex NF-kB [106-108], which regulates the transcription of several genes related to immune functions. NF-kB activate lymphocyte T-helper cell (Th1), which stimulates the production of pro-inflammatory cytokines like TNF-alfa and IL1 [109]. This chain of events will trigger and contribute to the local pulmonary inflammation and systemic inflammation observed in the lungs.

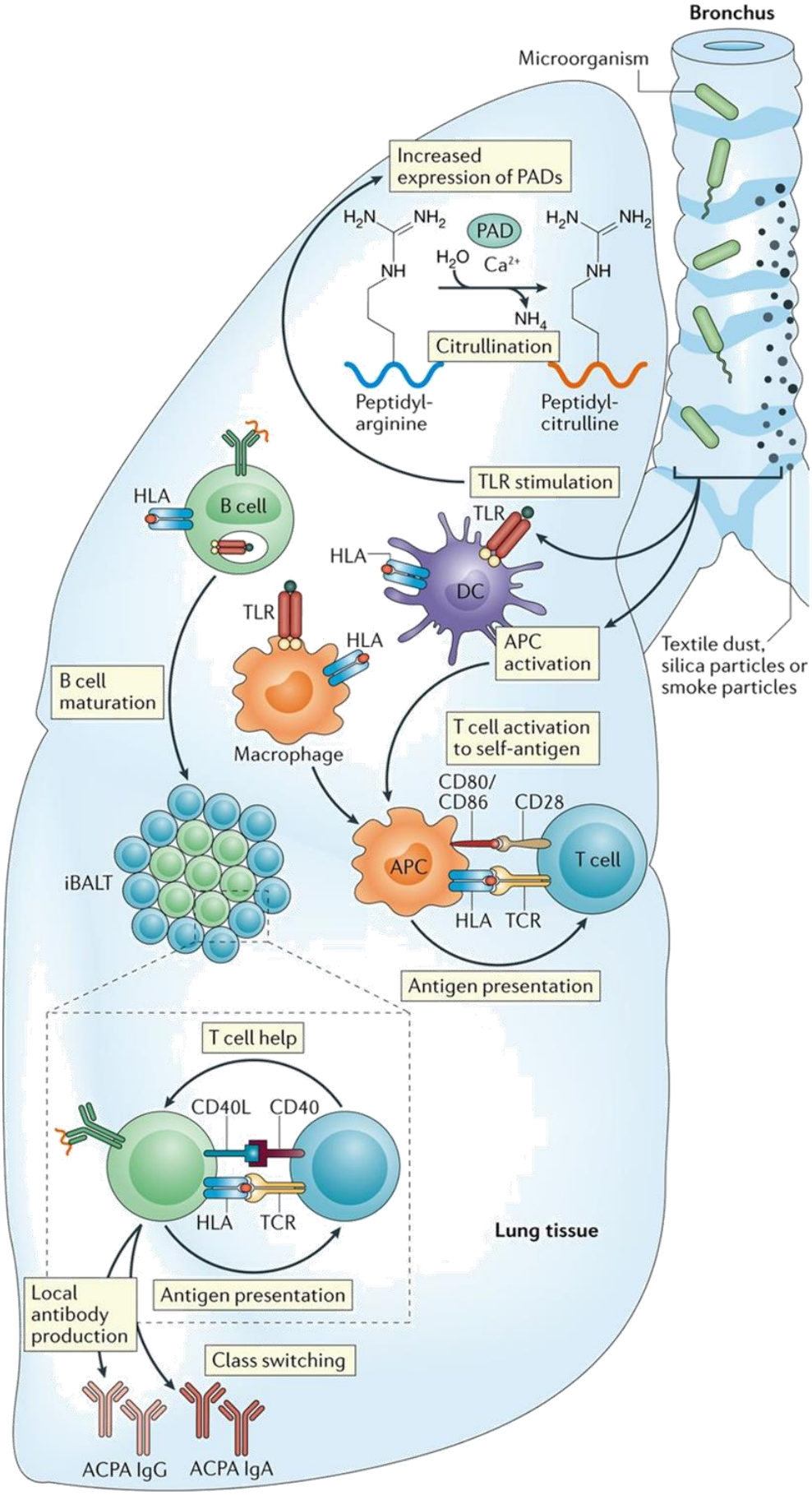


Figure 3. Local early immune activation in the lungs.
Source: Malmström et al. The immunopathogenesis of seropositive rheumatoid arthritis: from triggering to targeting. Nature Reviews Immunology. 2017;17:60–75. [110] Reprinted with permission from Springer Nature.

3 RESEARCH APPROACH

This chapter will provide the reader with details of the data collection and the statistical analysis. An overview of the materials and methods used for all studies in the doctoral thesis is presented in Table 3. A description of all variables used in the studies is provided in Appendix A.

3.1 MATERIALS

Study I is based on the case-control study EIRA and Study II on the case-control study Malaysian Epidemiological Investigation of Rheumatoid Arthritis (MyEIRA). For these two papers, the exposures of interest were self-reported and exposure data were collected with questionnaires.

For Study III and IV, apart from the cases from the EIRA study, we included participants from three national public authority registers and one quality register. Figure 4 is a Venn diagram showing the overlap between the five sources of data. Incident RA cases were enrolled from EIRA from 1996, whereas the registers were used to identify incident RA cases from 2006. The reason for this is that data from the prescribed drug register was used in order to classify RA patients as incident, and data from this register was only available from 2005 and onwards. See Paper III for a detailed definition of how we defined an incident RA case.

Occupational titles were collected from the Population and Housing Censuses 1960-1990. JEM's provided exposure data for inorganic and organic dust types. Study IV had a slightly larger study population than Study III, since the inclusion of another JEM with more recent exposure data allowed for more participants to be classified as workers. Occupational titles from 2001 and onwards from The Longitudinal integration database for health insurance and labor market studies (LISA) was therefore also used in Study IV.

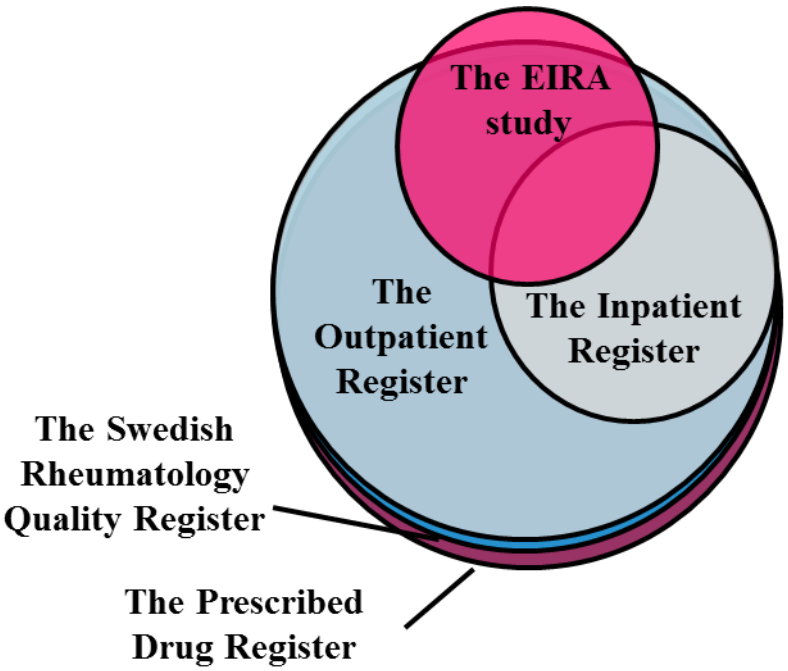


Figure 4. Analyzed cases in Study III represented in the five sources of data (n = 11 285)

A flow chart is provided to show the inclusion and exclusion of participants in Study IV (Figure 5).

Table 3. Overview of materials and methods applied in Study I-IV.

Paper	Study I: Occupation	Study II: Textile dust	Study III: Asbestos and silica	Study IV: Organic dusts
Study design	Case-control	Case-control	Case-control	Case-control
Data materials	The EIRA study	The MyEIRA study	The National Patient Register, The SRQ Register, The Prescribed Drug Register, The EIRA study, The National Population Registers, The Population and Housing Censuses, The LISA register, PARCC-JEM	The National Patient Register, The SRQ Register, The Prescribed Drug Register, The EIRA study, The National Population Registers, The Population and Housing Censuses, The LISA register, PARCC-JEM, FAIR-JEM
Study base	Men and women from 18 years of age recruited between 1996-2014 from the southern and middle parts of Sweden	Women, 18 to 70 years old recruited between 2005-2009 from Peninsular Malaysia	Men and women in Sweden from 1996-2013	Men and women in Sweden from 1996-2013
Main exposure	Self-reported occupation	Self-reported exposure to textile dust	Occupational exposure to asbestos and crystalline silica based on JEM	Occupational exposure to wood, animal, paper, textile, and flour dust based on JEM
Main outcome	ACPA+, ACPA-, RF+ and RF- RA	ACPA+ and ACPA- RA	Seropositive and seronegative RA	Seropositive and seronegative RA
Confounders	Age group, residential area, sex, study design (EIRA I or EIRA II), education, BMI, pack-years of smoking, alcohol consumption	Age group, residential area, education, ethnicity	Age, county, sex, education, pack-years of smoking, alcohol consumption, asbestos or crystalline silica exposure	Age, county , sex, education, crystalline silica
Measures of association and other measures reported	OR (95 % CI)	OR (95 % CI) AP due to interaction	OR (95 % CI)	OR (95 % CI)
Statistical analysis	Unconditional logistic regression Complete case analysis	Unconditional logistic regression Complete case analysis	Unconditional logistic regression Multiple imputation	Unconditional logistic regression Complete case analysis
Progress	Published in Arthritis Care & Research.	Published in Annals of the rheumatic diseases.	Submitted manuscript	In manuscript

Abbreviations: ACPA, Anti-Citrullinated Protein/Peptide Antibody; AP, Attributable Proportion; BMI, Body Mass Index; EIRA, Epidemiological Investigation of Rheumatoid Arthritis; FAIR, Foetal air pollution exposure; JEM, Job Exposure Matrix; LISA, Longitudinal Integration Database for Health Insurance and Labour Market Studies; MyEIRA, Malaysian Epidemiological Investigation of Rheumatoid Arthritis; OR, Odds Ratio; PARCC, Particles and Cardio- and Cerebrovascular diseases; RF, Rheumatoid Factor

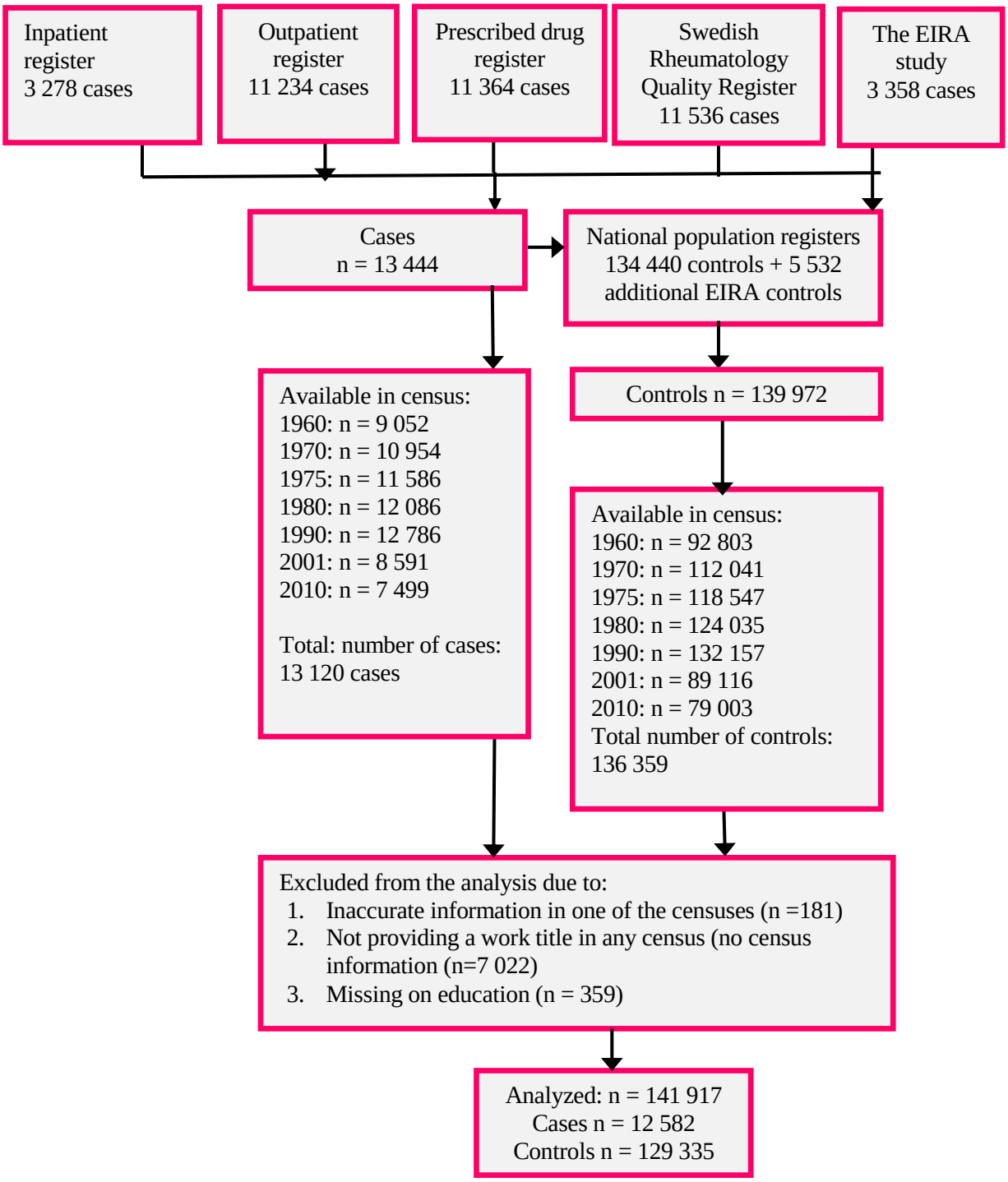


Figure 5. Inclusion and exclusion of participants in Study IV.

3.1.1 The EIRA study

The EIRA study logo

For study I, we used data from the EIRA study. EIRA is an ongoing population-based case-control study based on incident cases of RA in Sweden. The study base comprises adult men and women in areas from the southern and central parts of Sweden from May 1996 and onwards. The current dataset used in Study I, III and IV includes participants up until September 2014. The age limit was initially 18 to 70 years of age, but after April 2011 participants older than 70 were also included.

Newly diagnosed cases were recruited to the EIRA study through rheumatology clinics. The mean and median time between symptom onset and RA diagnose were 301 and 195 days respectively. In EIRA the time of symptom onset is treated as the onset of RA. Almost all RA cases are referred to rheumatology clinics in Sweden, and almost all clinics in the study area recruited cases to EIRA [111]. Rheumatologists identified cases based on the ACR 1987 diagnostic criteria [17] at participating rheumatology clinics. As of October 2011, the new ACR 2010 diagnostic criterion was implemented by participating clinics. Patients were defined as cases if they fulfilled either the ACR 1987 and/or the ACR 2010 criteria.

For each case, 1-2 controls were randomly selected from the population register shortly after case identification, matched to the case on age, sex and residential area. From January 2006, two controls instead of one were collected for the EIRA study. A modified version of the questionnaire was also launched. Hence, the time period May 1996 until May 2006 is referred to as EIRA I and March 2006 until September 2014 is referred to as EIRA II. In this thesis, and in Study I, III and IV, we refer to these different time periods as EIRA study design. A flow chart in Study I shows the inclusion and exclusion of study participants [112].

Blood samples were collected and assayed for ACPA-status among participants using the Immunoscan-RA Mark2 ELISA test (Euro-Diagnostica, Malmö, Sweden) [113]. 96 % of participating cases provided blood samples and 60 % of participating controls.

Cases and controls were invited to answer an extensive questionnaire including questions about heredity and demographic-, socioeconomic- and psychosocial factors, lifestyle, occupational history and occupational exposures. Cases received the questionnaire at the clinic, whereas it was sent by post to controls. If a case or control did not answer the questionnaire within 3 or 2 weeks respectively, a first reminder was sent out with mail. A second reminder was done over the phone two weeks later, a third reminder was done by sending out the questionnaire again through mail and finally a fourth reminder was done by calling. The median time it took to fill in the questionnaire was 90 minutes among cases and 70 minutes among controls. Almost all questionnaires need to be complemented due to missing or incorrect information. When this was needed, an EIRA staff member would try

to call the participant at least five times. If the participant did not answer, a letter was sent out.

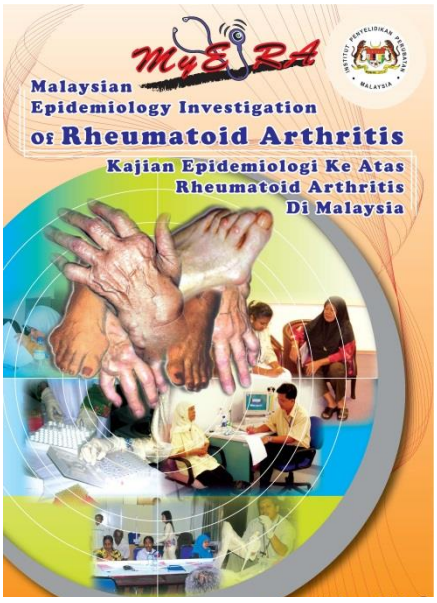
Participants were asked to fill in their occupational history in the questionnaire and could provide up to 14 employments. For each employment, the participant could add information about when they started and ended, working time in %, job title, employer's name, employer's city and activity or production (see Figure 6). The occupations were coded according to the occupational classification system used in the Population and Housing census 1985 (largely identical to NYK-83) and the Population and Housing census 1980 (NYK-78). For Study I we merged all occupations into 76 occupational groups (See Appendix B).

The EIRA study questionnaire

Participants were also asked whether they had been exposed to a wide range of occupational exposures, or work tasks believed to be related to certain exposures. For each exposure or work task, the participant was asked to report which years the exposure had occurred and for how many hours per week (see Figure 7).

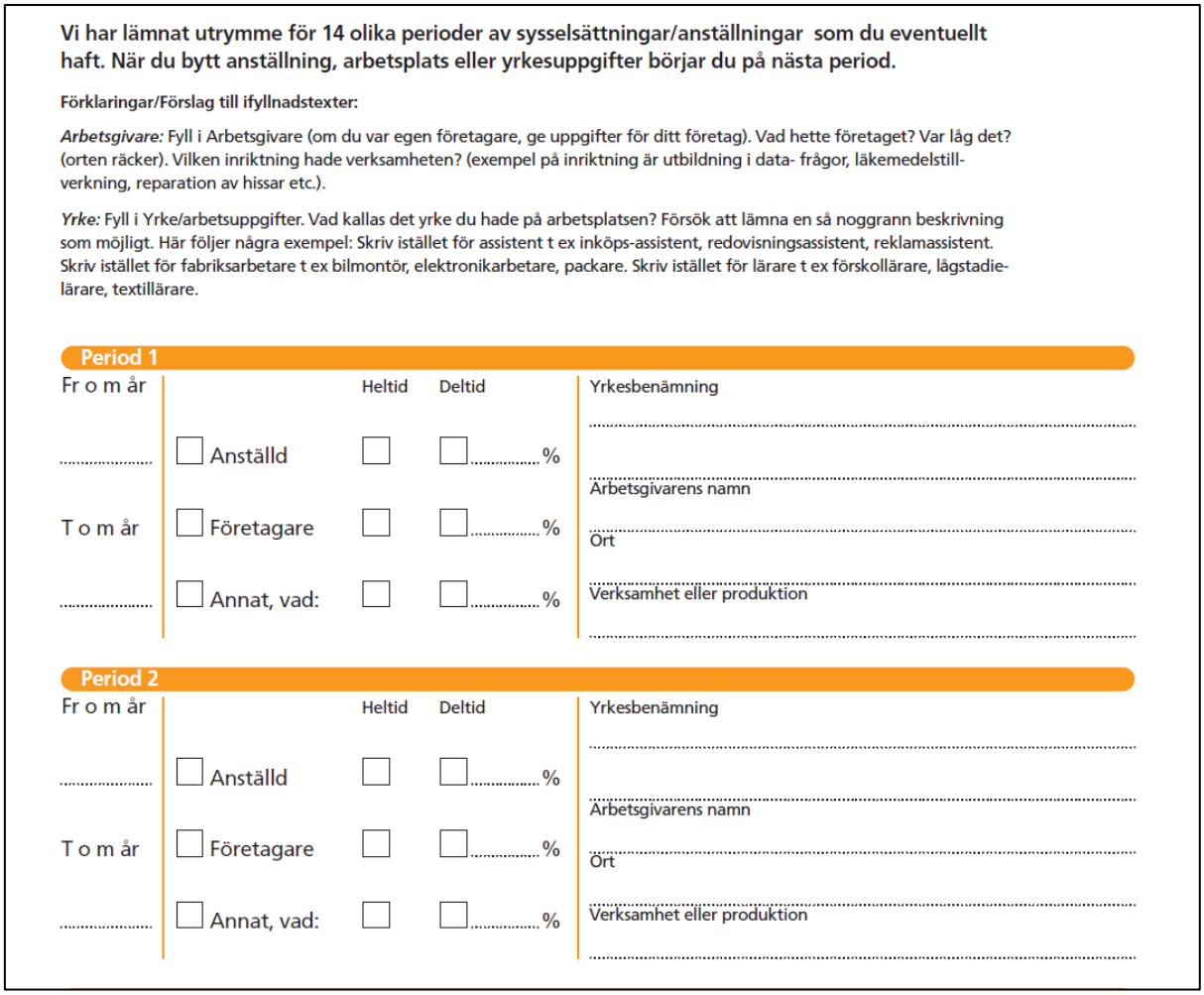
3.1.2 The MyEIRA study

For study II, we used data from the MyEIRA study. MyEIRA is a Malaysian case-control study run by the Institute for Medical Research (Kuala Lumpur). It is a sister study to EIRA with a similar design as described for EIRA but adapted to local conditions. Newly diagnosed cases were gathered from nine rheumatology clinics in Peninsular Malaysia (West Malaysia) between August 2005 and December 2009. Participants were 18-70 years old. For each case, one control was selected and matched to the case with regard to age (2 year age groups), sex and residential area. During the study's first two years, hospital-based controls were selected at the same hospital where the case was located. These controls consisted of patients without an underlying autoimmune disease, patients' visitors and hospital staff. During the study's last two years, controls were selected from the same neighborhood which had generated the cases. MyEIRA staff went to the same neighborhood which had generated the case and asked people to volunteer in the study. Information from 1 056 cases and 1 416 controls is included and approximately one fourth is hospital-based controls. In MyEIRA, 86 % of the cases and 85 % of the controls are women.



The MyEIRA study questionnaire

The questionnaire in MyEIRA is similar to the one in EIRA but was filled in by a trained research assistant during an interview with the participant. Fewer questions on occupational exposures were asked in MyEIRA than in the EIRA study. For instance, the only organic dust covered by the questionnaire was textile dust. All cases and controls provided blood samples.



Vi har lämnat utrymme för 14 olika perioder av sysselsättningar/anställningar som du eventuellt haft. När du bytt anställning, arbetsplats eller yrkesuppgifter börjar du på nästa period.

Förklaringar/Förslag till ifyllnadstexter:

Arbetsgivare: Fyll i Arbetsgivare (om du var egen företagare, ge uppgifter för ditt företag). Vad hette företaget? Var låg det? (orten räcker). Vilken inriktning hade verksamheten? (exempel på inriktning är utbildning i data- frågor, läkemedelstillverkning, reparation av hissar etc.).

Yrke: Fyll i Yrke/arbetsuppgifter. Vad kallas det yrke du hade på arbetsplatsen? Försök att lämna en så noggrann beskrivning som möjligt. Här följer några exempel: Skriv istället för assistent t ex inköps-assistent, redovisningsassistent, reklamassistent. Skriv istället för fabriksarbetare t ex bilmontör, elektronikarbetare, packare. Skriv istället för lärare t ex förskollärare, lågstadielärare, textillärare.

Period 1

Fr o m år ..... T o m år .....

☐ Anställd ☐ Företagare ☐ Annat, vad:

Heltid ☐ Deltid ☐ ..... %

Yrkesbenämning .....

Arbetsgivarens namn .....

Ort .....

Verksamhet eller produktion .....

Period 2

Fr o m år ..... T o m år .....

☐ Anställd ☐ Företagare ☐ Annat, vad:

Heltid ☐ Deltid ☐ ..... %

Yrkesbenämning .....

Arbetsgivarens namn .....

Ort .....

Verksamhet eller produktion .....

Figure 6. Occupational history in the EIRA questionnaire.

L. Arbetsmiljöförhållanden och kemiska exponeringar

1 Ange om du i ditt arbete har kommit i kontakt med någon av följande arbetsuppgifter, hanteringar eller kemiska produkter och i så fall under vilket/vilka år? Du kan ange två tidsperioder om du kommit i kontakt med det efterfrågade flera gånger.

	Nej	Ja	Tidsperiod 1: From – t o m år	Tidsperiod 1: Antal nätter/mån	Tidsperiod 2: From – t o m år	Tidsperiod 2: Antal nätter/mån
1. Nattarbete (Allt nattarbete mellan kl 22.00-07.00, även som del av skiftarbete, enstaka pass vid nattjour etc.)	☐	☐	..... –	.....	..... –	.....

	Nej	Ja	From – t o m år	Antal tim/vecka	From – t o m år	Antal tim/vecka
2. Utomhusarbete	☐	☐	..... –	.....	..... –	.....
3. Arbete i kyla	☐	☐	..... –	.....	..... –	.....
4. Arbete med händerna i vatten	☐	☐	..... –	.....	..... –	.....
5. Desinfektionsmedel	☐	☐	..... –	.....	..... –	.....
6. Rengöringsmedel	☐	☐	..... –	.....	..... –	.....

	Nej	Ja	From – t o m år	Antal tim/vecka	From – t o m år	Antal tim/vecka
7. Textildamm	☐	☐	..... –	.....	..... –	.....
8. Kosmetika och kroppsvårdsprodukter	☐	☐	..... –	.....	..... –	.....
9. Frisörkemikalier (hårvårdsprodukter)	☐	☐	..... –	.....	..... –	.....

	Nej	Ja	From – t o m år	Antal tim/vecka	From – t o m år	Antal tim/vecka
10. Matolja	☐	☐	..... –	.....	..... –	.....
11. Mjöl	☐	☐	..... –	.....	..... –	.....
12. Spannmål	☐	☐	..... –	.....	..... –	.....
13. Fiskrensning	☐	☐	..... –	.....	..... –	.....
14. Kött och inälvor	☐	☐	..... –	.....	..... –	.....

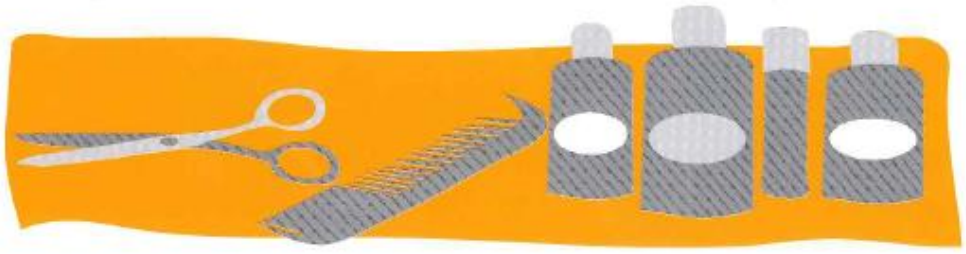


Figure 7. Occupational exposures in the EIRA questionnaire.

3.1.3 The National Patient Register

The National Patient Register was founded in 1964, but have national coverage since 1987 [114]. It is handled by the National Board of Health and Welfare and is the largest of the national public authority health registers. It contains patient information on all medical visits in inpatient care and outpatient specialized health care. The patient register does not contain information about primary care or information about care occasions or visits that medical doctors have not been involved in. The register mainly provides data on main and secondary diagnosis, date of admission and discharge, name of hospital/clinic and department. Data on all specialist care visits has been collected since 2001.

In the current thesis, the National Patient Register was used to identify RA cases in Study III and IV. We identified all RA patients ever hospitalized from 1964 until 2013 or received specialist care due to their RA diagnosis 2001-2013. RA was diagnosed by physicians using the International Classification of Disease (Tenth Revision) ICD-10. ICD-10 has been used since 1996, and the following codes were used to identify RA patients: M05, M06.0, M06.2, M06.3, M06.8, M06.9 and M12.3.

3.1.4 The Swedish Rheumatology Quality Register

The Swedish Rheumatology Quality Register (SRQ) is a national quality register founded in 1995 by the Swedish Rheumatology Society [115]. Its purpose is to improve the treatment and follow-up of patients with rheumatic diseases at rheumatology clinics as part of standard care. SRQ has approximately 85 % coverage, based on a comparison between SRQ data and data from the National Patient Register [116]. SRQ collects clinical data on disease activity, disability, drug initiation, drug discontinuation and reason for discontinuation. Both patients and caregivers enter information in the register and make a joint decision on continued care based on the patient's health data. An important integrated part of the SRQ is the Anti Reumatisk Terapi I Sverige (ARTIS) register. ARTIS includes RA patients since 1999 who have received biologic anti-rheumatic drugs. This is a biological treatment register with the purpose of monitoring the safety and efficacy of new drugs.

Through the SRQ we could identify and get additional information on RA patients diagnosed according to ICD-10 between 2006 and 2013. From this register we got information on date of debut symptoms and seropositive status, used in Paper III and IV.

3.1.5 The Prescribed Drug Register

The Prescribed Drug Register was founded in July 2005 and is a national public authority register handled by the National Board of Health and Welfare [117]. The register contains all dispensed prescription drugs, and we used it to identify biologics, non-biologic treatment, gold, prescription Non-steroid Anti-inflammatory Drugs (NSAIDs) and glucocorticoids used to treat RA.

The purpose of the register is to increase patient safety in the pharmaceutical field by continuously monitoring the health effects and health economic effects from drug use.

Information is collected about the dispensed drug (for example, Anatomic Therapeutic Chemical classification (ATC) code, drug name, strength, packaging size), the prescription (for example, prescribed amount, date of prescribing and dispensing), costs (county council cost and personal fee) and which profession and education the prescriber at the pharmacy has [117].

Through the Prescribed Drug Register we could identify and get additional information on RA patients between 2006 and 2013 in relation to papers III and IV.

3.1.6 The National Population Registers

Sweden has two national population registers; The Population Register (Folkbokföringsregistret) which is handled by the Swedish National Tax Agency, and the Total Population Register (Registret över totalbefolkningen), controlled by Statistics Sweden. The Swedish National Tax Agency took over the responsibility of the registration of the population from the Swedish church in 1991. The total population register was founded in 1968 [118].

Our national population registers monitor the composition of the entire Swedish population and life events, such as birth, citizenship, sex, age, address, immigration, emigration, marital status, family relations and death. The Total Population Register is an excerpt from the Population Register and unlike the Population register Statistics Sweden usually link data in the Total Population Register to other registers they are responsible for [118].

For Study I, based on the EIRA study, we collected 1-2 controls per case from the Population Register and matched them on age, sex and geographical area. For Study III and IV, we collected ten controls per case from the Total Population Register and matched them on age, sex and geographical area.

3.1.7 The Population and Housing Censuses

There are many different uses for occupational statistics, including research, health care planning and forecasts. Sweden has a long tradition of systematically collecting data on the population through censuses. During the first half of the 20th century, population and housing censuses were carried out with the help of postal surveys every tenth year in Sweden, and since 1960 every fifth year. It was mandatory for everyone 15 years and older to fill in the form. The census data collected information on education, occupation and housing status. The main purpose of the census was to produce statistics on the population and the households for use in planning, research and general information. The population and housing census in 1990 became the last in the line of traditional population and housing censuses to collect data from all adult persons in Sweden.

In Study III and IV we used data from the Population and Housing Censuses carried out in 1960, 1970, 1975, 1980 and 1990. The data of interest was primarily on occupational title, coded with different versions of NYK.

3.1.8 The LISA register

The Longitudinal Integration Database for Health Insurance and Labour Market Studies (LISA) is a longitudinal database that is managed by Statistics Sweden and is updated annually with information from other registers controlled by Statistics Sweden and register data from other authorities [119]. The purpose of LISA is to follow a person's transitions between, for example, work, unemployment and illness over time. Data are currently available from the 1990s onwards for all persons aged 16 and older who have been registered in Sweden on 31 December the year for which the data is collected. As of 2010 there are also data for 15 year olds.

The database contains information from a number of different registers for which Statistics Sweden or other authorities are responsible. In particular, detailed information is gathered about the individual regarding sickness, parental and unemployment insurance. Information about companies and workplaces is also collected. From LISA we used variables on an individual's highest level of education, income and occupational titles.

In 1999 the Swedish Parliament decided that a register of the working population in Sweden should be created. The new register (the Swedish Occupational Register) replaced the population and housing censuses, and collects data from about twenty different sources on an annual basis [120]. The Swedish Occupational Register includes all persons aged 16 and older, who are registered in Sweden on 31 December the year the data is collected for. Occupations are coded with the occupational classification system SSYK and data are available from the year 2001 and forward. The data in this register is included in LISA.

From LISA we also received information about the participants' education. Information on completed education is continuously reported to Statistics Sweden from schools and educational providers. Other sources of data are the Population and Housing censuses carried out in 1970 and 1990. It contains information about an individual's highest level of education, education area, completion year and place of education. Educations are coded with the Swedish Educational Terminology (SUN). Information on immigrants' education comes primarily from questionnaires aimed at immigrants, as well as from the Population and Housing censuses.

We also had variables from LISA on income. Information on household disposable income during the years 1990, 2000 and 2010 were used for the imputation model in Study III.

3.1.9 Job Exposure Matrices

Estimates on occupational exposures applied to the work histories of participants in Paper III and IV came from the JEM's PARticles and Cardio- and Cerebrovascular diseases (PARCC) and Foetal air pollution exposure (FAIR). Both PARCC and FAIR JEM are based on the Nordic Occupational Cancer Study (NOCCA) JEM [121] and Finnish Information System on Occupational Exposure (FinJEM) [122], but adapted to Swedish circumstances.

PARCC is a semi-quantitative JEM estimating the exposure to 17 airborne agents between 1955 and 1995 [123]. The 8 exposures used in Paper III and IV are described in detail in Table 4. The PARCC JEM is based on occupational titles from Population and Housing Census 1960, 1970, 1975, 1980 and 1990 coded on three-digit level. The corresponding five historical time periods for the occupational titles were 1955-1964, 1965-1972, 1973-1977, 1978-1984 and 1985-1995. For each agent, occupation and historical time, the prevalence of exposure is stated as % and air concentration of the exposure within the occupational group expressed as an 8-hour time-weighted average. The product of the prevalence and the value for air concentration can be seen as an average of the exposure in the group.

FAIR JEM is an update of PARCC where two time periods have been added: 1995-2004 and 2005-2014. The occupational classification system was NYK 83 (Population and Housing Census 1985) for these two time periods. FAIR contains updated estimates for organic dusts, but not for asbestos and crystalline silica. Since the occupational titles for 2001 and 2010 were coded based on the occupational classification system SSYK 96, these titles were recoded to NYK 83 based on a translational key from Statistics Sweden [120].

In order to make estimations about the exposure duration in Study III and IV, we made the assumption that having an occupation reported in a census corresponds to ten years of exposure (or five years of exposure, for the census carried out in 1975). In Study III, we removed exposed participants who had been exposed to asbestos and/or crystalline silica, but where none of the reported occupations had a probability of exposure reaching 50 % (n = 545). In Study IV, the same logic was applied and no participants had to be removed.

Table 4. Description of exposures in the PARCC and FAIR JEM used in Study III and IV.

Agent	Unit	Swedish OEL	Description
Inorganic dusts			
Asbestos	fiber/cm3	0.1 fiber/cm3	Occupational, inhalatory exposure to any form of asbestos (chrysotile, crocidolite, tremolite, antophyllite etc.) or asbestos-containing material.
Quartz	mg/m^3	Respirable 0.1 mg/m3	Occupational, inhalatory exposure to respirable (aerodynamic diameter <5um) quartz or crystalline silica containing dusts (e.g., granite). Does not include amorhous silica dust.
Organic dusts			
Wood dust	mg/m^3	Inhalable 2 mg/m3	Occupational, inhalatory exposure to wood dust (pine, spruce, birch, other softwoods and hardwoods, cane, wood bark etc.).
Animal dust	mg/m^3	Total dust 5 mg/m3	Occupational, inhalatory exposure to dust from living animals (cows, horses, cats, dogs, reindeer etc.), or hairs of animals (raw wool, furs of minks, foxes etc.). Does not include treated wool dust or leather dust.
Paper dust	mg/m^3	Total dust 2 mg/m3	Occupational, inhalatory exposure to pulp or paper dust (pulp, newsprint, printing paper, soft papers, cardboard etc.).
Textile dust	mg/m^3	Total dust 1 mg/m3	Occupational, inhalatory exposure to dust from treated cotton, treated wool or other treated, natural materials used in fabrics, other textiles or garments. Does not include raw cotton, raw wool or synthetic textiles.
Flour dust	mg/m^3	Inhalable 3 mg/m3	Occupational, inhalatory exposure to flour dust (from wheat, oat, barley, rye), milk powder, potato powder, starch powder or fish powder.

Abbreviations: FAIR, Foetal air pollution exposure; JEM, Job-Exposure Matrix; OEL, Occupational Exposure Limit; PARCC, PARticles and Cardio- and Cerebrovascular diseases

3.2 STATISTICAL ANALYSES

Unconditional logistic regression analysis was the statistical method used in all studies. We calculated the AP due to interaction in study II and III in order to assess interaction between genetic and/or environmental factors. Missing data was handled using either complete case analysis or multiple imputation. All statistical analyses were performed using SAS 9.4. Figures 9-11 were produced using Prism 8.

3.2.1 Logistic regression

A regression analysis will tell you the likelihood of developing RA, given a specific value of your exposure and additional covariates. Logistic regression is a type of regression commonly used when the dependent variable is binary (e.g., "RA" versus "no RA"), as compared to the linear regression where the dependent variable is continuous. Binary data does not have a normal distribution, which is a condition needed for linear regression analysis [124].

When using the logistic regression model, an OR with 95 % confidence intervals (CIs) is calculated. The OR is a measure of association used to determine whether an exposure is related to a disease. The OR represents how the odds of having RA change with a one unit increase of our independent variable, holding all other covariates in the model constant. It is calculated by comparing the odds of exposure (or disease) in the cases to the odds of exposure (or disease) in the controls. If the odds of exposure is higher in cases than in controls, that suggests that there is a relationship between the exposure and the disease. An OR higher than 1.0 means that the analyzed exposure is associated with higher odds of developing the outcome RA, whereas an OR of less than 1.0 means that the exposure is associated with a decreased risk of developing the disease.

In this doctoral thesis, an OR was considered statistically significant if the lower CI bound was larger than 1.0 or the upper bound was less than 1.0. In the first study on occupation and risk of developing RA, 99 % CI's were additionally performed in order to account for multiple testing. In paper III and IV the p-value for trend was assessed by running the main exposure (number of censuses exposed) as a continuous variable (i.e., we estimated the incrementally increased log-odds for RA with each additional census exposed), and $p < 0.05$ was considered statistically significant.

3.2.2 Additive interaction analysis

There is additive interaction if the joint effect from two risk factors on a disease outcome is greater than the sum of the effects from the two risk factors combined. Rothman [71] argues that the assessment of interaction should be done on an additive scale, since this is considered more indicative of the causal mechanism. When the analysis is logistic regression, biological interaction between two risk factors is measured as the deviation from additivity. This is calculated by the formula below, where P is the probability of the outcome when two exposures (A and B) are either unexposed (0) or exposed (1):

$$(p_{A1B1} - p_{A0B0}) - [(p_{A1B0} - p_{A0B0}) + (p_{A0B1} - p_{A0B0})] = p_{A1B1} - p_{A1B0} - p_{A0B1} + p_{A0B0} \quad [71]$$

There are three commonly used measures to assess additive interaction, as proposed by Rothman [71]; the relative excess risk due to interaction (RERI), the AP due to interaction (AP) or the synergy index (S). They are calculated as:

$$\begin{aligned} \text{RERI} &= \text{RR}_{\text{A+B+}} - \text{RR}_{\text{A+B−}} - \text{RR}_{\text{A−B+}} + 1 \\ \text{AP} &= \frac{\text{RERI}}{\text{RR}_{\text{A+B+}}} \\ \text{S} &= \frac{\text{RR}_{\text{A+B+}} - 1}{(\text{RR}_{\text{A+B−}} - 1) + (\text{RR}_{\text{A−B+}} - 1)} \end{aligned} \quad [71]$$

In all four studies and in this thesis, the AP has been used as the measure of interaction. AP = 0 means that there is no interaction, AP < 0 indicates negative interaction and AP > 0 point toward positive interaction.

3.2.3 Handling of missing data

Missing data can be handled with either deletion or imputation techniques. The reason why the data is missing, and the proportion of data missing, are the main things to consider when deciding how to handle the missing data.

In Study I, II and IV we deleted missing data based on a method called complete case analysis, also referred to as list-wise deletion. All participants with missing data on any of the variables in the analysis were deleted. In study I, II and IV, 99.2 %, 93.4 %[1] and 99.7 % of the participants eligible for analysis had complete data on all variables included in the analyses.

In the third study, 6 % of study participants had complete data on all variables in the analysis. We handled missing data by multiple imputation. One of the data sources (EIRA) contained self-reported information on cigarette and alcohol consumption. Missing values for cigarette pack-years and alcohol consumption were imputed according to the fully conditional specification (FCS) method (24) under the missing at random assumption. Briefly, for each variable with missing data a model is specified based on that variable's distribution (different models depending on whether the imputed variable is categorical or continuous). Variables used to predict missing values should consist of all variables in the analysis model, auxiliary variables which are predictors of the missing values and variables which are predictors of having missing data. Our imputation model included case status, seropositive status, age, birth year, index year, sex, whether participants had belonged to the EIRA study or not, crystalline silica exposure, asbestos exposure, alcohol consumption, disposable household income during 1990, 2000 and 2010. Squared terms were added for the continuous variables. We generated 20 imputed datasets with the PROC MI command in SAS version 9.4 and

[1] In the published paper, it has not been mentioned that women exposed to textile dust during leisure time have been excluded (n=407). The number of missing is here calculated as 88 / 1325 = 6.6 %.

performed the analysis in each dataset. In order to obtain a single point estimate we pooled the results by averaging the parameter estimates across the 20 datasets using the command PROC MIANALYZE.

3.3 ETHICAL CONSIDERATIONS

3.3.1 Study I: EIRA

Ethical approval for the EIRA study has been granted by the ethics committee at Karolinska Institutet and the Regional Stockholm ethics committee (Dnr 96-174, Dnr 2006/476-31/4). Participation in EIRA was voluntary and participants consented to participate by answering the questionnaire. Almost all rheumatology units within the study area participated and thereby the EIRA study provided a majority of all new cases of RA the same opportunity to participate. Participants received information about the EIRA study at the RA clinic before oral consent was sought.

The EIRA study follows the General Data Protection Regulation (GDPR). GDPR is a European Union regulation for protecting data privacy, in particular the participants' right to protection and control of their personal data. All participants in the EIRA study have therefore been informed about their specific rights, the aim of the study and that all personal data is handled in a secure way. To preserve confidentiality, the EIRA study follows The Swedish Privacy Protection Law. When the database was created, the Swedish personal identity number was replaced with a unique ID number for each participant, and individuals in the database could therefore not be identified by researchers during the analysis.

An issue to consider is whether the patients felt obliged to participate in the study since they may have perceived themselves to be in a dependent relationship with their doctor at the rheumatology clinic. Additionally, recruiting cases at clinics might be considered unethical, since the patients might be in a vulnerable and emotional situation. This aspect was, however, handled carefully within the EIRA study since the patients brought the questionnaires to their homes and could inform the EIRA staff (who work at an office separated from the clinics) that they wanted to stop their participation. The hospital staff was not informed of interrupted participations. Furthermore, the health care staff had to respect the patients' autonomy and thereby their right to refuse or withdraw from the study. Participants were informed that their decision to participate in the study or not would not affect the continued healthcare.

3.3.2 Study II: MyEIRA

The MyEIRA study was approved by the Medical Research and Ethics Committee of the Ministry of Health in Malaysia (KKM/JEPP/02 Jld.1 (86);(14)dlm.KKM/NIHSEC/08/0804/ MRG-2005-12). Participation in MyEIRA was voluntary and all participants gave written informed consent.

3.3.3 Study III and IV: Register data

Ethical approval for linking the RA register linkage was granted by the regional Stockholm ethics committee (Dnr 2009/2005-31/3) March 17 2010, and approval to add data related to work was granted June 9 2010 (Dnr 2010/939-32).

The clinical information in the registers that formed the basis for RA diagnosis came from patient records in health care, collected according to their routines. Each individual in the register linkage was assigned a unique serial number by the National Board of Health and Welfare, and we only got access to anonymized data containing the unique serial number.

There is a risk that the collection of information through the registry can be seen as a privacy intrusion. This risk is minimized by the fact that the linking of register data takes place at the National Board of Health and Welfare, whereby we only have access to anonymized data. Our study will in itself not generate any information that will be recorded in the hospital records. Since all data comes from already existing information in registers there is no risk that the participants are harmed in any way from our study. At the individual level, we see no direct benefit from participating, but the results from our study can be implemented in preventive health and safety measures, and thereby indirectly favors the healthy population still at risk of RA.

Data have been stored in accordance with the regulations issued by the Personal Data Act (PUL), controlled by the Swedish Data Inspection Authority. All information is confidential under the Public Access to Information and Secrecy Act (Offentlighets- och sekretesslagen) 2009:400 and the Public Access to Information and Secrecy Ordinance (Swedish Code of Statutes 2009:641) (Offentlighets- och sekretessförordningen). Both the Clinical Epidemiology Unit and Institute for Environmental Medicine have well developed procedures to protect digital information. Acquired information is stored on password protected computers kept locked up at the Unit of Clinical Epidemiology and the Unit of Translational Epidemiology at the Karolinska Institutet.

4 RESULTS

In this chapter I will present the main findings with regards to the specific aims of the thesis. More detailed results are available in each paper. Some additional results not included in any of the papers are also presented. Table 5, 8-12, 14, 16-17 and Figure 8, contain new or partly new data not published in any of the four papers.

4.1 OCCUPATION

We analyzed the association between occupation and the risk of developing RA among 3 522 cases and 5 580 controls. Figure 8 shows the distribution of different professional areas among men and women. 71 % among analyzed study participants were women, and women constituted a majority in all professional areas except for Production work and Agricultural, forestry and fishing work. Almost as many men as women were working in transport and communications work. When comparing professional areas between cases and controls, it was more common among cases to have worked in the production industry.

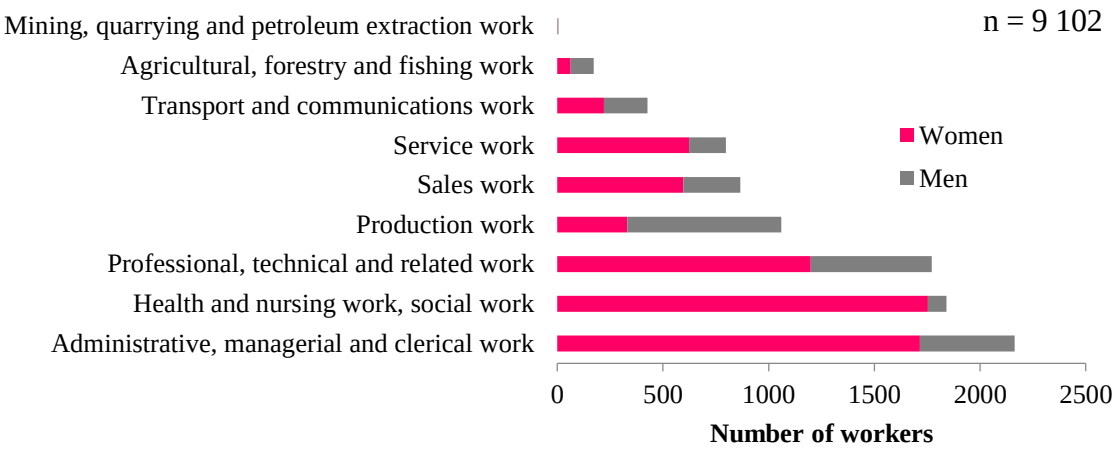


Figure 8. Number of workers by professional area and sex in the EIRA study

Apart from what was presented in the results of Study I, I present the risk of RA by professional area in table 5. Among men the highest risks for both ACPA+ RA and ACPA- RA were observed among men having production work after adjustment for confounding from pack-years of smoking, alcohol use, university degree and body mass index (BMI) (OR = 1.6, 95 % CI = 1.1-2.1 and OR = 1.9, 95 % CI = 1.3-2.6). Among women, the highest risk estimates for both disease subtypes were noted for workers in the Agricultural, forestry and fishing field (OR = 1.4 (0.8-2.5 and 1.3, 95 % CI = 0.6-2.8). For neither men nor women did the results differ substantially between ACPA+ and ACPA- RA, hence in table 6 and 7 results for occupations are presented for men and women with ACPA+ and ACPA- RA combined.

Among men, Table 6 shows that the five occupations which had a lower bound of the 95 % CI of at least 1.0 all belonged to the professional area Production work. These occupations

were Mechanics, iron and metalware workers (OR = 1.5, 95 % CI = 1.0-2.2), Electrical and electronics workers (OR = 2.2, 95 % CI = 1.3-3.6), Wood workers (OR = 1.5 (1.0-2.4), Bricklayers and concrete workers (OR: 2.7, 95 % CI: 1.5-5.1) and Material handling operators (OR: 1.8, 95 % CI: 1.0-3.1). Among women, the one occupation which was associated with a significantly increased risk was Assistant nurses and attendants (OR = 1.2, 95 % CI = 1.1-1.5).

Table 5. ORs of developing ACPA+ or ACPA- RA with 95 % CIs, among men or women according to what professional area they belonged to prior to being enrolled into the EIRA study (n=9 102).

Professional area	Exposed cases / controls	ACPA+ RA		Exposed cases / controls	ACPA- RA	
		OR (95 % CI)[a]	OR (95 % CI)[b]		OR (95 % CI)[a]	OR (95 % CI)[b]
Men						
Reference [c]	209/703	1.0	1.0	120/703	1.0	1.0
Health and nursing work, social work	14/50	0.9 (0.5-1.8)	0.9 (0.5-1.8)	9/50	1.0 (0.5-2.2)	1.0 (0.5-2.2)
Sales work	53/176	1.0 (0.7-1.4)	0.9 (0.6-1.3)	40/176	1.4 (0.9-2.2)	1.2 (0.8-1.9)
Agricultural, forestry and fishing work	25/66	1.2 (0.7-2.1)	1.2 (0.7-2.2)	20/66	1.5 (0.8-2.7)	1.3 (0.7-2.4)
Transport and communications work	59/119	1.6 (1.1-2.3)	1.3 (0.8-1.9)	33/119	1.6 (1.0-2.5)	1.3 (0.8-2.1)
Production work	163/261	2.1 (1.6-2.7)	1.6 (1.1-2.1)	101/261	2.3 (1.7-3.1)	1.9 (1.3-2.6)
Service work	110/214	1.7 (1.3-2.3)	1.4 (1.0-1.9)	45/214	1.2 (0.8-1.8)	0.9 (0.6-1.4)
Women						
Reference [c]	707/1932	1.0	1.0	373/1932	1.0	1.0
Health and nursing work, social work	446/968	1.3 (1.1-1.5)	1.1 (1.0-1.3)	220/968	1.2 (1.0-1.4)	1.1 (0.9-1.4)
Sales work	171/359	1.3 (1.1-1.6)	1.2 (0.9-1.5)	67/359	1.0 (0.8-1.4)	0.9 (0.7-1.3)
Agricultural, forestry and fishing work	21/37	1.6 (0.9-2.8)	1.4 (0.8-2.5)	10/37	1.3 (0.6-2.8)	1.3 (0.6-2.8)
Transport and communications work	60/154	1.1 (0.8-1.5)	0.9 (0.7-1.3)	27/154	0.9 (0.6-1.4)	0.8 (0.5-1.3)
Production work	60/105	1.6 (1.1-2.2)	1.1 (0.8-1.7)	24/105	1.1 (0.7-1.8)	1.0 (0.6-1.6)
Service work	215/430	1.4 (1.1-1.7)	1.1 (0.9-1.4)	116/430	1.3 (1.0-1.6)	1.1 (0.9-1.5)

Abbreviations: ACPA, Anti-Citrullinated Protein/Peptide Antibody; BMI, Body Mass Index; CI, Confidence Interval; EIRA, Epidemiological Investigation of Rheumatoid Arthritis; OR, Odds Ratio; RA, Rheumatoid Arthritis

[a] Adjusted for age group, geographical area and study design.

[b] Additionally adjusted for cigarette smoking (pack-years: 0, >0-10, >10-20, >20), alcohol use (low, non-drinkers, moderate, high), BMI (<20, 20-25, >25) and education (primary education, secondary education, university degree).

[c] Professional, technical and related work and administrative, managerial and clerical work.

Table 6. ORs of developing RA with 95 % CIs among men according to their last occupation before index year in the EIRA study (n=2 596).

Occupation	Exposed cases / controls	OR (95 % CI)[a]	OR (95 % CI)[b]
Reference [c]	329/703	1.0	1.0
HEALTH AND NURSING WORK, SOCIAL WORK			
Assistant nurses and attendants	9/18	1.1 (0.5-2.6)	0.9 (0.4-2.2)
SALES WORK			
Sales agents and salesmen	70/149	1.0 (0.7-1.4)	0.9 (0.7-1.3)
Shop assistants	23/27	2.0 (1.1-3.7)	1.7 (0.9-3.2)
AGRICULTURAL, FORESTRY AND FISHING WORK			
Farmers	22/29	1.3 (0.7-2.3)	1.3 (0.7-2.5)
Horticultural workers	10/16	1.4 (0.6-3.2)	1.2 (0.5-2.8)
Forestry workers	10/14	1.5 (0.6-3.6)	1.4 (0.6-3.3)
TRANSPORT AND COMMUNICATIONS WORK			
Motor vehicle drivers	65/76	1.8 (1.3-2.6)	1.4 (0.9-2.1)
Postal and communication workers	12/23	1.0 (0.5-2.0)	0.9 (0.4-1.8)
PRODUCTION WORK			
Mechanics, iron and metalware workers	68/71	2.1 (1.4-3.0)	1.5 (1.0-2.2)
Plumbers	11/17	1.0 (0.4-2.1)	0.7 (0.3-1.7)
Welders	8/11	1.8 (0.7-4.8)	1.6 (0.6-4.2)
Electrical and electronics workers	44/36	2.8 (1.7-4.5)	2.2 (1.3-3.6)
Wood workers	49/57	1.8 (1.2-2.8)	1.5 (1.0-2.4)
Painting and floor laying workers	17/20	1.8 (0.9-3.6)	1.5 (0.7-3.1)
Bricklayers and concrete workers	34/20	3.4 (1.9-6.2)	2.7 (1.5-5.1)
Other construction and production workers	10/12	2.0 (0.8-4.8)	1.5 (0.6-3.6)
Food manufacture workers	6/14	0.9 (0.3-2.4)	0.8 (0.3-2.3)
Material handling operators	34/31	2.3 (1.3-3.9)	1.8 (1.0-3.1)
Packing and storage workers	23/32	1.6 (0.9-2.9)	1.3 (0.7-2.4)
SERVICE WORK			
Caretakers and cleaners	24/41	1.2 (0.7-2.2)	1.0 (0.6-1.8)
Policemen and other protective service workers	13/19	1.6 (0.7-3.3)	1.6 (0.7-3.4)

Abbreviations: BMI, Body Mass Index; CI, Confidence Interval; EIRA, Epidemiological Investigation of Rheumatoid Arthritis; OR, Odds Ratio; RA, Rheumatoid Arthritis

[a] Adjusted for age group, geographical area and study design.

[b] Additionally adjusted for cigarette smoking (0, <10, 10-19, ≥20 pack-years and smoking other tobacco than cigarettes), alcohol use (non-drinkers, low, moderate, high), BMI (<20, 20-25, >25) and education (primary education, secondary education, university degree).

[c] Professional, technical and related work and administrative, managerial and clerical work.

Table 7. ORs of developing RA with 95 % CIs among women according to their last occupation before index year in the EIRA study (n=6 506).

Occupation	Exposed cases / controls	OR (95 % CI)[a]	OR (95 % CI)[b]
Reference [c]	1080/1932	1.0	1.0
HEALTH AND NURSING WORK, SOCIAL WORK			
Physicians	12/35	0.6 (0.3-1.2)	0.7 (0.4-1.4)
Nurses	88/162	1.0 (0.7-1.3)	1.0 (0.7-1.3)
Assistant nurses and attendants	474/588	1.5 (1.3-1.7)	1.2 (1.1-1.5)
Dental workers	25/42	1.1 (0.7-1.8)	1.2 (0.7-2.0)
Medical technicians	7/12	1.2 (0.5-3.1)	1.0 (0.4-2.6)
Pharmaceutical workers	7/24	0.6 (0.2-1.3)	0.6 (0.2-1.4)
Physiotherapy and occupational therapy workers	26/44	1.0 (0.6-1.7)	1.1 (0.6-1.8)
Other health and medical workers	23/48	0.9 (0.5-1.4)	0.8 (0.5-1.3)
SALES WORK			
Sales agents and salesmen	105/180	1.1 (0.8-1.4)	1.1 (0.8-1.4)
Shop assistants	133/179	1.4 (1.1-1.8)	1.2 (0.9-1.5)
AGRICULTURAL, FORESTRY AND FISHING WORK			
Farmers	10/15	1.1 (0.5-2.5)	0.9 (0.4-2.1)
Animal workers	9/11	1.7 (0.7-4.3)	1.5 (0.6-3.8)
TRANSPORT AND COMMUNICATIONS WORK			
Transport assistants and supervisors	7/14	0.8 (0.3-2.1)	0.7 (0.3-1.9)
Motor vehicle drivers	12/17	1.2 (0.6-2.6)	0.9 (0.4-2.0)
Aircraft workers	2/17	0.2 (0.1-0.9)	0.3 (0.1-1.4)
Postal and communication workers	59/103	1.1 (0.8-1.5)	0.9 (0.6-1.3)
PRODUCTION WORK			
Textile workers	20/35	1.0 (0.6-1.7)	0.8 (0.5-1.5)
Mechanics, iron and metalware workers	21/18	2.0 (1.0-3.9)	1.5 (0.8-2.9)
Electrical and electronics workers	13/23	1.0 (0.5-2.0)	0.7 (0.3-1.4)
Wood workers	11/13	1.8 (0.8-4.2)	1.5 (0.6-3.5)
Engravers, bookbinders and photographic laboratory workers	6/12	0.7 (0.3-2.0)	0.7 (0.3-1.9)
Food manufacture workers	12/14	1.6 (0.7-3.6)	1.4 (0.6-3.1)
Packing and storage workers	30/29	1.8 (1.1-3.1)	1.4 (0.8-2.5)
SERVICE WORK			
Catering service workers	43/51	1.6 (1.0-2.4)	1.4 (0.9-2.1)
Cooks and kitchen assistants	77/97	1.4 (1.0-1.9)	1.1 (0.8-1.5)
Caretakers and cleaners	83/108	1.4 (1.0-1.8)	1.0 (0.7-1.4)
Hairdressers	14/29	0.9 (0.5-1.8)	0.7 (0.4-1.4)
Policemen and other protective service workers	10/26	0.7 (0.3-1.5)	0.6 (0.3-1.3)

Abbreviations: BMI, Body Mass Index; CI, Confidence Interval; EIRA, Epidemiological Investigation of Rheumatoid Arthritis; OR, Odds Ratio; RA, Rheumatoid Arthritis

[a] Adjusted for age group, geographical area and study design.

[b] Additionally adjusted for cigarette smoking (0, <10, 10-19, ≥20 pack-years and smoking other tobacco than cigarettes), alcohol use (non-drinkers, low, moderate, high), BMI (<20, 20-25, >25) and education (primary education, secondary education, university degree).

[c] Professional, technical and related work and administrative, managerial and clerical work.

4.2 ORGANIC DUSTS

We analyzed the association between different types of organic dusts and the risk of developing RA in Sweden and in Malaysia. In Sweden we studied wood dust, animal dust, paper dust, textile dust and flour dust among men and women (Study IV), and in Malaysia we examined textile dust and risk of developing RA among women (Study II).

The most common occupations in different censuses for men and women are displayed in Appendix C. In summary, the most common jobs among workers exposed to wood dust were bench carpenters and cabinet makers, construction carpenters and joiners and woodworking machine operators. For animal dust exposure, the most common jobs were working proprietors, livestock, dairy and poultry farm workers and agricultural, horticultural and forestry enterprises. Among workers exposed to paper dust, it was packers and typographers, lithographers and mail sorting clerks and postmen. For textile dust exposure, spinners, weavers, knitters and dyers, upholsterers and seamstresses, ready-made clothing and launderers and dry-cleaners were common occupations. For flour dust exposure, bakers and pastry cooks was the most common occupation among both sexes during all censuses.

Starting with presenting the findings from Study IV in the Swedish population, table 8 shows the proportion of workers being exposed to the different types of dust, and the proportion of workers additionally exposed to the other four dust types. Overall there was a low likelihood if you had been exposed to one of the dusts to also be exposed to one of the four other dust types.

Table 8. Proportion of participants ever exposed to any of seven types of organic dusts and correlation of exposure factors (n=141 917).

	Exposed participants n (%)	% of exposed also exposed to				
		Wood	Animal	Paper	Textile	Flour
Women						
Wood dust	611 (1)		2	17	19	0
Animal dust	2594 (3)	1		3	2	0
Paper dust	4480 (5)	2	2		7	2
Textile dust	3006 (3)	4	2	11		0
Flour dust	333 (0)	0	2	20	2	
Men						
Wood dust	3506 (8)		4	6	5	1
Animal dust	2133 (5)	7		3	0	0
Paper dust	3281 (7)	7	2		2	1
Textile dust	505 (1)	34	2	11		2
Flour dust	373 (1)	8	2	10	3	

Figure 9 shows the risk of developing RA among workers ever exposed to different types of organic dusts compared to never exposed workers after adjustment for county, age, index year, education and crystalline silica. (n=141 917). The main finding was that exposure to animal dust was associated with a minor increased risk of RA among both men and women. When combining men and women (and subsequently adjusting for sex), this finding was observed for both the seropositive and seronegative subtype. For overall RA, the adjusted OR was 1.2 (95 % CI = 1.1-1.4). Worth noting is also that there was an association between textile dust exposure and RA, resulting in an OR of 1.1 (95 % CI = 1.0-1.3) for overall RA among men and women combined.

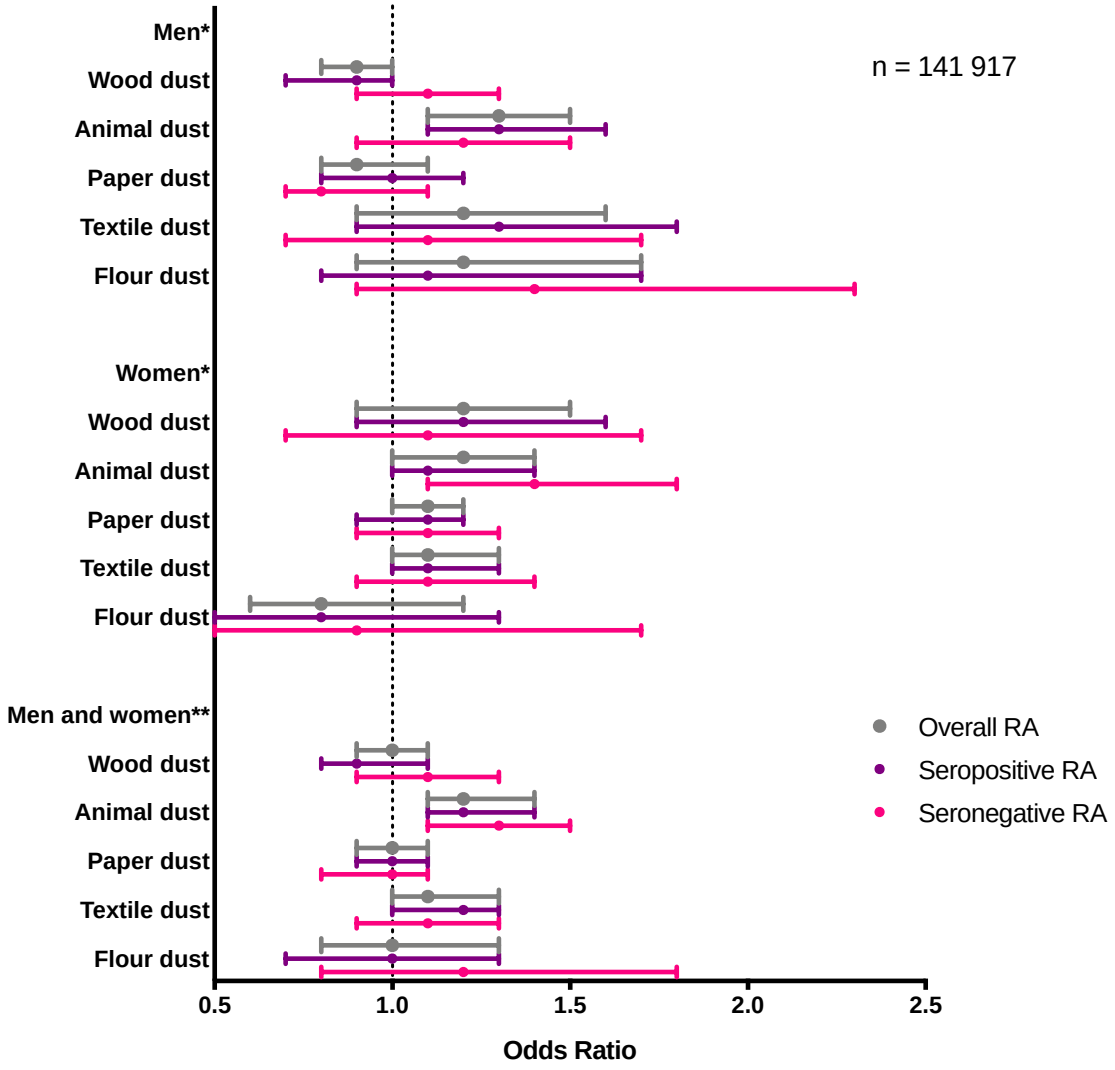


Figure 9: Odds ratios of overall RA, seropositive RA or seronegative RA among men and women exposed to different types of organic dust vs. unexposed workers

* Adjusted for county, age, index year, education and silica dust.
** Additionally adjusted for sex.

Whereas men and women working with organic dust overall had been exposed to the same intensity levels, men tended to have been working in more occupations where they had been exposed, and therefore likely had longer duration of exposure. For animal dust, the risk of seropositive RA was the highest among workers being exposed to animal dust in five to seven censuses (OR = 1.6, 95 % CI = 1.1-2.2, p for trend = 0.003) among men and women combined after adjusting for potential confounding from county, age, sex, index year, education and crystalline silica. For seronegative RA, the corresponding OR was 1.3 (0.8-2.0, p for trend = 0.016). Also for textile dust, the risk appeared to increase slightly with longer duration of exposure. Men and women exposed to textile dust in 5-7 censuses had an OR of 1.3 (0.6-3.1, p for trend = 0.014) for seropositive RA. Five to seven censuses correspond to a minimum of 45 years of exposure.

For a subset of participants being enrolled into the EIRA study we had information on HLA-DRB1 SE (n=3 826). We could not detect any sign of interaction between HLA-DRB1 SE and any of the five organic dust types (see Table 9). There was an association between HLADRB1-SE and an increased risk of seropositive RA, independent of whether these workers had been exposed to any of the five organic dust types or not. We did observe a significant interaction between occupational exposure to textile dust and HLA-DRB1 SE regarding the risk of developing ACPA+ RA in the Malaysian setting. The OR among female textile dust workers with two SE alleles versus females unexposed to both risk factors was 39.1 (95 % CI = 5.1-297.5. The AP due to interaction was 0.8 (95 % CI = 0.5-1.2).

For the subset of the study participants belonging to the EIRA study we had data on self-reported exposure to four of the five dust types (n=8 506). Table 10 shows a comparison of the proportion of exposed when comparing self-reported estimates and JEM-based estimates. A larger proportion of participants classified themselves as exposed to animal dust, textile dust and flour dust as compared to the JEM.

Table 11 provides a comparison between self-reported or JEM-estimated exposure to organic dusts. The ORs from Table 2 in Study IV (where work titles come from census data instead of the EIRA study questionnaire) has been added in the right column as a comparison. Apart from being adjusted for the matching variables (age, geographical area) and EIRA study design, the estimates were also adjusted for potential confounding from pack-years of cigarette smoking and crystalline silica dust. Overall the ORs for JEM-based or self-reported exposure show similarities for wood dust, animal dust and textile dust. However, there is a difference when comparing the ORs between the EIRA study and the entire register linkage for flour dust, where estimates are higher among women in the restricted data material. The agents with the highest agreement between self-reported and JEM-classified exposure also showed the highest potential risk of RA among men and women; animal dust exposure and flour dust exposure.

Table 9. Additive interaction of HLA-DRB1 SE and organic dust and risk of developing RA among participants in the EIRA study with complete data on all variables included in the analysis (n=3 826).

	All RA cases		Seropositive RA	Seronegative RA
	Cases / Controls	OR (95 % CI)[a]	OR (95 % CI)[a]	OR (95 % CI)[a]
Wood dust				
No SE / No wood dust	573/875	1.0	1.0	1.0
No SE / wood dust	20/30	0.8 (0.4-1.5)	0.7 (0.3-1.6)	0.9 (0.4-2.1)
SE / No wood dust	1592/887	2.7 (2.3-3.0)	3.9 (3.3-4.6)	1.1 (0.9-1.3)
SE / wood dust	58/37	2.0 (1.3-3.3)	2.8 (1.7-4.7)	0.9 (0.4-2.1)
AP		-0.2 (-0.8-0.4)	-0.3 (-0.9-0.4)	-0.1 (-1.1-1.0)
Animal dust				
No SE / No animal dust	576/887	1.0	1.0	1.0
No SE / animal dust	18/27	1.1 (0.6-2.1)	1.0 (0.5-2.3)	1.1 (0.5-2.5)
SE / No animal dust	1617/918	2.6 (2.3-3.0)	3.9 (3.3-4.6)	1.1 (0.9-1.3)
SE / animal dust	38/16	3.7 (2.0-6.8)	5.2 (2.7-10.0)	1.8 (0.7-4.6)
AP		0.2 (-0.3-0.7)	0.2 (-0.3-0.8)	0.3 (-0.5-1.1)
Paper dust				
No SE / No paper dust	559/865	1.0	1.0	1.0
No SE / paper dust	20/39	0.8 (0.4-1.4)	0.6 (0.3-1.3)	1.1 (0.5-2.2)
SE / No paper dust	1542/880	2.6 (2.3-3.0)	3.8 (3.3-4.5)	1.1 (0.9-1.4)
SE / paper dust	81/36	3.4 (2.2-5.2)	4.9 (3.2-7.7)	1.2 (0.6-2.5)
AP		0.3 (0.0-0.6)	0.3 (0.0-0.6)	0.0 (-0.9-1.0)
Textile dust				
No SE / No textile dust	576/883	1.0	1.0	1.0
No SE / textile dust	16/23	1.0 (0.5-2.0)	0.9 (0.4-2.1)	1.1 (0.5-2.5)
SE / No textile dust	1608/900	2.7 (2.3-3.1)	3.9 (3.3-4.6)	1.1 (0.9-1.3)
SE / textile dust	43/24	2.4 (1.4-4.0)	3.8 (2.2-6.5)	-
AP		-0.1 (-0.8-0.5)	0.0 (-0.6-0.6)	-1.0 (-3.8-1.7)
Flour dust				
No SE / No flour dust	591/914	1.0	1.0	1.0
No SE / flour dust	5/4	-	-	-
SE / No flour dust	1654/933	2.7 (2.3-3.1)	3.9 (3.3-4.6)	1.1 (0.9-1.3)
SE / flour dust	10/3	-	-	-
AP		-	-	-

Abbreviations: AP, Attributable Proportion; CI, Confidence Interval; EIRA, Epidemiological Investigation of Rheumatoid Arthritis; HLA, Human Leukocyte Antigen; OR, Odds Ratio; RA, Rheumatoid; SE, Shared Epitope

[a] Adjusted for county, age, sex, EIRA study design, index year, pack-years of smoking, alcohol consumption and ever exposure to crystalline silica.

Table 10. Prevalence of organic dusts using JEM or self/reported estimation among participants in the EIRA study with complete data on all variables included in the analysis (n=8 506).

	Prevalence JEM	Prevalence self-reported exposure
Wood dust	3	5
Animal dust	2	6
Textile dust	3	7
Flour dust	1	6

Abbreviations: EIRA, Epidemiological Investigation of Rheumatoid Arthritis; JEM, Job-Exposure Matrix

Table 11. ORs of developing RA in the EIRA study and the register linkage from self-reported or JEM-estimated exposure to organic dusts vs unexposed.

	EIRA data n=8 506			Register linkage n=141 917
	Self-reported exposure vs. unexposed	JEM-classified exposure vs. unexposed	Self-reported and JEM-classified exposure vs. unexposed according to both	JEM classified exposure vs. unexposed
	OR (95 % CI)[a]	OR (95 % CI)[a]	OR (95 % CI)[a]	OR (95 % CI)[b]
Men				
Wood dust	0.8 (0.6-1.1)	1.1 (0.7-1.5)	0.8 (0.5-1.2)	0.9 (0.8-1.0)
Animal dust	1.2 (0.9-1.7)	1.1 (0.7-1.8)	1.2 (0.7-2.0)	1.3 (1.1-1.5)
Textile dust	1.3 (0.8-2.3)	1.2 (0.6-2.7)	-	1.2 (0.9-1.6)
Flour dust	1.5 (1.0–2.1)	1.3 (0.7-2.7)	1.5 (0.7-3.5)	1.2 (0.9-1.7)
Women				
Wood dust	0.8 (0.5-1.2)	1.0 (0.5-1.9)	0.6 (0.3-1.5)	1.2 (0.9-1.5)
Animal dust	1.1 (0.9-1.4)	1.1 (0.7-1.7)	1.2 (0.8-1.9)	1.2 (1.0-1.4)
Textile dust	1.1 (0.9-1.4)	1.0 (0.7-1.3)	0.9 (0.7-1.4)	1.1 (1.0-1.3)
Flour dust	1.3 (1.1-1.6)	1.4 (0.6-3.3)	1.9 (0.7-5.4)	0.8 (0.6-1.2)
Men and women [c]				
Wood dust	0.8 (0.6-1.1)	1.0 (0.8-1.4)	0.8 (0.5-1.1)	1.0 (0.9-1.1)
Animal dust	1.2 (1.0-1.4)	1.1 (0.8-1.5)	1.2 (0.9-1.7)	1.2 (1.1-1.4)
Textile dust	1.1 (1.0-1.4)	1.0 (0.8-1.3)	1.0 (0.7-1.4)	1.1 (1.0-1.3)
Flour dust	1.3 (1.1-1.6)	1.4 (0.8-2.3)	1.7 (0.9-3.1)	1.0 (0.8-1.3)

Abbreviations: CI, Confidence Interval; EIRA, Epidemiological Investigation of Rheumatoid Arthritis; JEM, Job-Exposure Matrix; OR, Odds Ratio

[a] Adjusted for matching variables (age, sex, geographical area), EIRA study design, smoking (pack-years) and crystalline silica (JEM-based).

[b] Adjusted for matching variables (county, age and index year), education and crystalline silica (JEM-based).

[c] Additionally adjusted for sex.

Our findings in the Malaysian setting indicated that self-reported exposure to textile dust was associated with an increased risk of RA. Table 12 displays the risk of developing RA among female workers ever exposed to textile dust compared to never exposed workers. Swedish men and women from the EIRA study have been added as a comparison. Occupational exposure to textile dust was significantly associated with an increased risk of developing both ACPA+ and ACPA- RA in the Malaysian female population, and the OR for overall RA was 2.8 (95 % CI = 1.6-5.2). The corresponding OR was 1.1 (95 % CI = 0.9–1.3) among Swedish women and 1.5 (95 % CI = 0.9-2.7) among Swedish men.

Table 12. ORs of developing RA among female workers ever exposed to textile dust compared to never exposed workers (MyEIRA: n=1 325, EIRA: n=8 073).

	Ever exposed cases/controls	Never exposed cases/controls	OR (95 % CI)[a]
All RA cases			
MyEIRA: Women exposed to textile dust	41/15	622/647	2.8 (1.6-5.2)
EIRA: Women exposed to textile dust	218/300	2094/3171	1.1 (0.9–1.3)
EIRA: Men exposed to textile dust	25/25	884/1356	1.5 (0.9-2.7)
ACPA+ RA			
MyEIRA: Women exposed to textile dust	23/15	399/647	2.5 (1.3-4.8)
EIRA: Women exposed to textile dust	130/300	1379/3171	1.0 (0.8–1.2)
EIRA: Men exposed to textile dust	17/25	561/1356	1.7 (0.9-3.1)
ACPA- RA			
MyEIRA: Women exposed to textile dust	18/15	223/647	3.5 (1.7-7.0)
EIRA: Women exposed to textile dust	88/300	715/3,171	1.2 (0.9–1.6)
EIRA: Men exposed to textile dust	8/25	323/1356	1.4 (0.6-3.2)

Abbreviations: ACPA, Anti-Citrullinated Protein/Peptide Antibody; CI, Confidence Interval; EIRA, Epidemiological Investigation of Rheumatoid Arthritis; MyEIRA, Malaysian Epidemiological Investigation of Rheumatoid Arthritis; OR, Odds Ratio; RA, Rheumatoid Arthritis

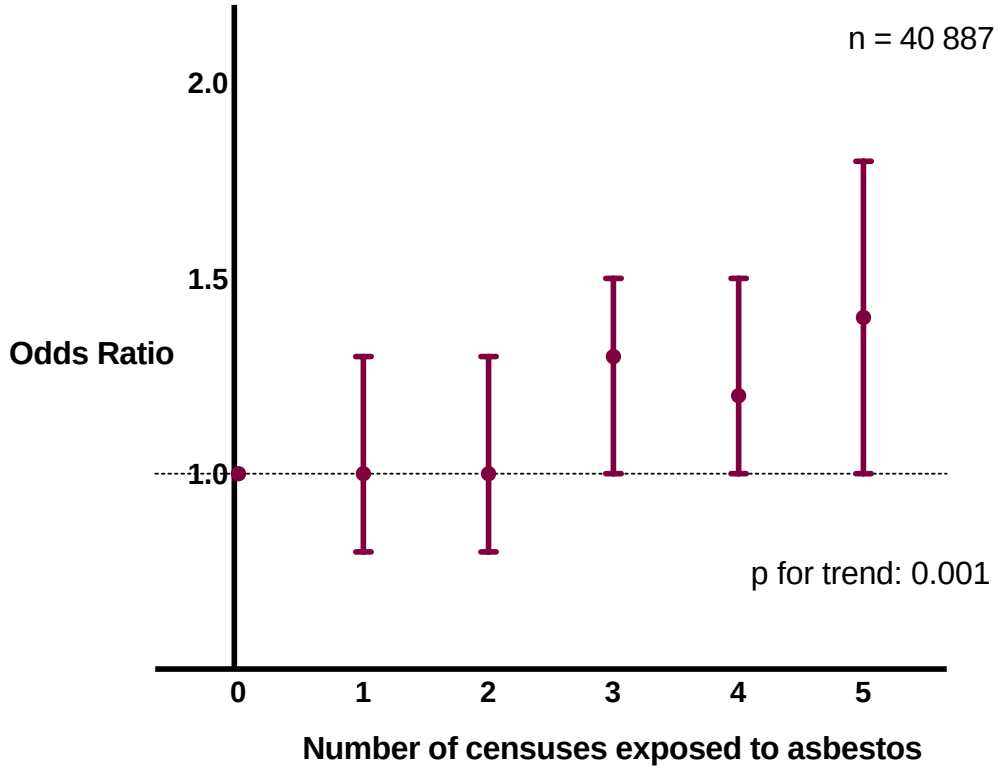
[a] Adjusted for age group, geographical area and educational level. Malaysian estimates adjusted for ethnicity.

4.3 INORGANIC DUSTS

The aim of Study III was to explore the associations between occupational exposure to asbestos and crystalline silica and risk of developing seropositive or seronegative RA among men and women. The most common exposed occupations in different censuses are displayed in Appendix C. In summary, among both male and female workers exposed to asbestos, the most common occupations were Engine mechanics, Electrical fitters and wiremen, Chimney sweeps and Insulators. For crystalline silica exposure, the most common occupations among male

workers were Unskilled manual workers and Construction carpenters and joiners. Female workers had worked as Unskilled manual workers and Metal casters and moulders.

We detected an increased risk among male workers exposed to asbestos compared to unexposed workers. This risk was similar for seropositive and seronegative RA. There was a 20 % increased risk of overall RA among men after adjustments for county, sex, age, index year, pack-years of smoking, alcohol consumption and crystalline silica. As shown in Figure 10, the OR for overall RA was the highest among men who had been exposed to asbestos in all five censuses. The test for trend showed a p-value of 0.001. For seropositive RA the p for trend was 0.002, whereas it was 0.065 for the seronegative subtype.



Adjusted for county, age, index year, pack-years of smoking, alcohol consumption and crystalline silica dust.

Figure 10: Number of censuses classified as exposed to asbestos vs. unexposed workers and risk of overall RA among men

There were indications that male workers exposed to asbestos prior to it being banned in Sweden were at a higher risk than those whose exposure started after the ban had been implemented.

Table 13 shows the risk among workers classified as exposed to different combinations of cigarette smoking and asbestos compared with workers classified as never exposed. The highest risk estimates were found among ever smokers, independent of whether these workers had been

exposed to asbestos or not. Compared with those unexposed to both smoking and asbestos, the adjusted OR was 1.6 (95 % CI = 0.8-3.2) among never smokers exposed to asbestos, 3.3 (95 % CI = 2.4-4.4) among workers who had a history of smoking and had not been exposed to asbestos, and finally 3.8 (95 % CI = 2.4-6.1) among workers exposed to both asbestos and smoking. For seronegative RA, only male ever smokers who had also been exposed to asbestos had an increased risk (OR = 2.0 (95 % CI = 1.1-3.5). The median number of pack-years was higher among asbestos exposed workers than workers who had never been exposed to asbestos.

There was no increased risk of RA among women exposed to asbestos after adjustments made for potential confounding from pack-years of smoking, alcohol consumption and crystalline silica. However, fewer women than men had been exposed to asbestos, and exposed female workers had been exposed in fewer jobs than men and to lower exposure intensities. The adjusted OR of overall RA among women exposed to asbestos versus women unexposed to asbestos was 1.0 (95 % CI = 0.6-1.7). Few female workers had been exposed to asbestos and among those who had been exposed, most of them had been classified as ever smokers. As was noted among men, the median number of pack-years was higher among female asbestos exposed workers than workers who had never been exposed to asbestos.

For a subset of participants being enrolled into the EIRA study we had information on HLA-DRB1 SE (n=3 506). There was an interaction between being exposed to asbestos and carrying the HLA-DRB1 SE risk gene for seropositive RA (see table 14). Male exposed to asbestos carrying the risk gene had an OR of 9.0 (4.3-18.7) for seropositive RA, even after adjustments made for cigarette smoking and crystalline silica. The AP due to interaction was 0.5 (95 % CI = 0.2-0.8).

Table 13. ORs of developing RA together with 95% CIs among workers classified as exposed to different combinations of cigarette smoking and asbestos compared with workers classified as never exposed (n=126 534).

	All RA cases					Seropositive RA	Seronegative RA
	Cases / Controls	Median intensity (fiber/cm^3)	Median years since exposure cessation	Median pack-years	OR (95 % CI)[a]	OR (95 % CI)[a]	OR (95 % CI)[a]
Men							
Never smoker / No asbestos exposure	671/9583				1.0	1.0	1.0
Never smoker / Exposed to asbestos	124/1250	0.10	35	0	1.2 (0.7-2.2)	1.6 (0.8-3.2)	0.8 (0.3-2.1)
Smoker / No asbestos exposure	1480/14450	0.00	-	16	2.2 (1.7-2.9)	3.3 (2.4-4.4)	1.0 (0.7-1.5)
Smoker / Exposed to asbestos	479/3375	0.10	35	20	3.0 (2.0-4.4)	3.8 (2.4-6.1)	2.0 (1.1-3.5)
Women							
Never smoker / No asbestos exposure	2725/35680				1.0	1.0	1.0
Never smoker / Exposed to asbestos	5/32	0.02	33	0	4.4 (0.4-48.8)	-	-
Smoker / No asbestos exposure	4634/39846	0.00	-	13	1.7 (1.5-1.9)	2.0 (1.7-2.3)	1.1 (0.9-1.3)
Smoker / Exposed to asbestos	12/107	0.02	32	21	0.8 (0.2-3.2)	1.2 (0.3-4.7)	-
Men and women [b]							
Never smoker / No asbestos exposure	3396/45263				1.0	1.0	1.0
Never smoker / Exposed to asbestos	129/1281	0.10	35	0	1.1 (0.6-1.9)	1.2 (0.6-2.2)	0.9 (0.4-2.3)
Smoker / No asbestos exposure	6114/54296	0.00	-	13	1.8 (1.6-2.0)	2.2 (1.9-2.4)	1.0 (0.9-1.3)
Smoker / Exposed to asbestos	491/3482	0.10	35	20	2.4 (1.7-3.4)	2.6 (1.8-3.8)	2.0 (1.2-3.3)

Abbreviations: CI, Confidence Interval; OR, Odds Ratio; RA, Rheumatoid Arthritis

[a]Adjusted for county, age, index year, pack-years of smoking and alcohol consumption. Asbestos and crystalline silica were adjusted for each other.

[b] Additionally adjusted for sex.

CI, confidence interval; OR, odds ratio; RA, rheumatoid arthritis.

Table 14. Additive interaction of HLA-DRB1 SE and asbestos and risk of developing RA among participants in the EIRA study with complete data on all variables included in the analysis (n=3 506).

	All RA cases		Seropositive RA	Seronegative RA
	Cases / Controls	OR (95 % CI)[a]	OR (95 % CI)[a]	OR (95 % CI)[a]
Men				
No SE / No asbestos	90/159	1.0	1.0	1.0
No SE / asbestos	25/38	1.1 (0.6-2.0)	1.0 (0.4-2.2)	1.5 (0.7-3.6)
SE / No asbestos	266/151	2.9 (2.1-4.1)	4.4 (2.9-6.6)	1.4 (0.8-2.2)
SE / asbestos	75/24	5.7 (3.0-10.9)	9.0 (4.3-18.7)	2.7 (1.1-6.9)
AP		0.5 (0.1-0.8)	0.5 (0.2-0.8)	0.3 (-0.4-1.0)
Women				
No SE / No asbestos	383/592	1.0	1.0	1.0
No SE / asbestos	1/1	-	-	-
SE / No asbestos	1053/643	2.5 (2.1-2.9)	3.6 (3.0-4.4)	0.9 (0.7-1.2)
SE / asbestos	3/2	-	-	-
AP		-	-	-
Men and women[b]				
No SE / No asbestos	473/751	1.0	1.0	1.0
No SE / asbestos	26/39	1.0 (0.6-1.8)	0.9 (0.5-1.9)	1.3 (0.6-2.7)
SE / No asbestos	1319/794	2.6 (2.2-3.0)	3.8 (3.2-4.5)	1.0 (0.8-1.2)
SE / asbestos	78/26	4.9 (2.8-8.6)	6.9 (3.8-12.6)	2.7 (1.2-6.1)
AP		0.5 (0.2-0.8)	0.5 (0.1-0.8)	0.5 (0.1-1.0)

Abbreviations: AP, Attributable Proportion; CI, Confidence Interval; EIRA, Epidemiological Investigation of Rheumatoid Arthritis; HLA, Human Leukocyte Antigen; OR, Odds Ratio; RA, Rheumatoid; SE, Shared Epitope

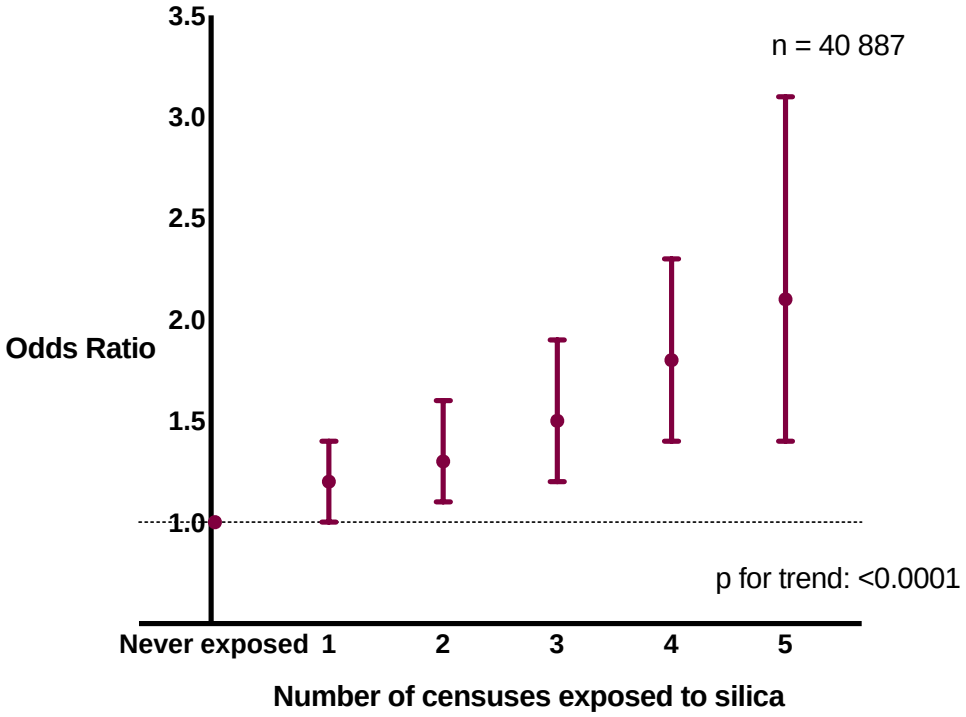
[a] Adjusted for county, age, EIRA study design, index year, pack-years of smoking, alcohol consumption and ever exposure to crystalline silica.

[b] Additionally adjusted for sex.

We detected an increased risk of RA among male workers exposed to crystalline silica. The risk estimates were similar for seropositive and seronegative RA. The OR went from 1.6 (1.4-1.7) to 1.3 (1.2-1.5) after we adjusted for potential confounding from pack-years of smoking, alcohol consumption and asbestos exposure. As was noted for asbestos, there was no significant association among women exposed to crystalline silica and RA. The adjusted OR's were 1.2 (95 % CI = 0.8-1.7) for seropositive RA and 0.8 (95 % CI = 0.4-1.5) for seronegative RA.

As shown in Figure 11, the risk of overall RA increased in an exposure-response manner with regard to duration of exposure among male workers exposed to crystalline silica. Men

exposed to crystalline silica in five censuses had an adjusted OR of 2.3 (95 % CI = 1.4-3.8) and 1.7 (95 % CI = 0.9-3.1) for seropositive and seronegative RA respectively. The p for trend was significant for both seropositive (p<0.0001) and seronegative (p = 0.0016) RA.



Adjusted for county, age, index year, pack-years of smoking, alcohol consumption and asbestos.

Figure 11: Number of censuses classified as exposed to crystalline silica vs. unexposed workers and risk of overall RA among men

As was noted for asbestos, fewer women than men had been exposed to silica, and exposed female workers had been exposed in fewer jobs than men and to lower exposure intensities.

Table 15 shows the risk among workers classified as exposed to different combinations of cigarette smoking and crystalline silica compared with workers classified as never exposed. The highest ORs were found among ever smokers, independent of whether these workers had been exposed to crystalline silica or not. The adjusted OR was 1.3 (95 % CI = 0.7-2.6) among never smokers exposed to crystalline silica, 3.0 (95 % CI = 2.3-4.0) among workers who had a history of smoking and had not been exposed to crystalline silica, and finally 4.1 (95 % CI = 2.7-6.4) among workers exposed to both crystalline silica and smoking. For seronegative RA, no significantly increased risk among male workers was detected. The median number of pack-years of smoking was higher among crystalline silica exposed workers than workers who had never been exposed to crystalline silica.

Table 15. ORs of developing RA together with 95% CIs among workers classified as exposed to different combinations of cigarette smoking and crystalline silica compared with workers classified as never exposed (n=126 534).

	All RA cases					Seropositive RA	Seronegative RA
	Cases / Controls	Median intensity (fiber/cm^3)	Median years since exposure cessation	Median pack-years	OR (95 % CI)[*]	OR (95 % CI)[a]	OR (95 % CI)[a]
Men							
Never smoker / No silica exposure	870/12245				1.0	1.0	1.0
Never smoker / Exposed to silica	151/1399	0.07	21	0	1.1 (0.6-1.9)	1.3 (0.7-2.6)	0.7 (0.3-1.7)
Smoker / No silica exposure	2086/20116	0.00	-	17	2.1 (1.7-2.6)	3.0 (2.3-4.0)	1.0 (0.7-1.4)
Smoker / Exposed to silica	527/3304	0.08	26	20	2.9 (2.0-4.3)	4.1 (2.7-6.4)	1.4 (0.8-2.5)
Women							
Never smoker / No silica exposure	2769/36286				1.0	1.0	1.0
Never smoker / Exposed to silica	13/166	0.10	29	0	-	-	-
Smoker / No silica exposure	4789/41084	0.00	-	13	1.7 (1.5-2.0)	2.0 (1.8-2.3)	1.1 (0.9-1.4)
Smoker / Exposed to silica	51/366	0.10	29	19	2.2 (0.9-5.4)	2.7 (1.0-6.9)	1.3 (0.3-6.3)
Men and women[b]							
Never smoker / No silica exposure	3640/48532				1.0	1.0	1.0
Never smoker / Exposed to silica	164/1565	0.07	25	0	0.8 (0.5-1.4)	0.9 (0.5-1.7)	0.7 (0.3-1.6)
Smoker / No silica exposure	6874/61199	0.00	-	14	1.8 (1.6-2.0)	2.2 (1.9-2.5)	1.1 (0.9-1.3)
Smoker / Exposed to silica	578/3670	0.08	26	20	2.5 (1.8-3.5)	3.1 (2.2-4.4)	1.4 (0.9-2.4)

Abbreviations: CI, confidence interval; OR, odds ratio; RA, rheumatoid arthritis.

[a] Adjusted for county, age, index year, pack-years of smoking and alcohol consumption. Asbestos and crystalline silica were adjusted for each other.

[b] Additionally adjusted for sex.

For a subset of participants being enrolled into the EIRA study we had information on HLA-DRB1 SE and crystalline silica (n = 3 809). We could not detect any additive interaction between HLA-DRB1 SE and occupational exposure to crystalline silica (see Table 16).

Table 16. Additive interaction of HLA-DRB1 SE and crystalline silica and risk of developing RA among participants in the EIRA study with complete data on all variables included in the analysis (n=3 809).

	All RA cases		Seropositive RA	Seronegative RA
	Cases / Controls	OR (95 % CI)[a]	OR (95 % CI)[a]	OR (95 % CI)[a]
Men				
No SE / No silica	134/210	1.0	1.0	1.0
No SE / silica	26/32	0.9 (0.5-1.6)	1.1 (0.5-2.3)	0.7 (0.3-1.5)
SE / No silica	363/191	2.8 (2.1-3.8)	4.3 (3.0-6.1)	1.4 (0.9-2.1)
SE / silica	68/28	2.7 (1.6-4.8)	4.6 (2.5-8.6)	1.1 (0.5-2.4)
AP		0.0 (-0.5-0.6)	0.0 (-0.5-0.6)	0.0 (-0.9-1.0)
Women				
No SE / No silica	391/608	1.0	1.0	1.0
No SE / silica	3/1	-	-	-
SE / No silica	1088/653	2.5 (2.1-3.0)	3.7 (3.0-4.4)	0.9 (0.7-1.2)
SE / silica	6/7	1.0 (0.3-3.3)	1.4 (0.4-4.9)	-
AP		-3.0 (-10.6-4.5)	-2.9 (-9.9-4.0)	-
Men and women [b]				
No SE / No silica	525/818	1.0	1.0	1.0
No SE / silica	29/33	0.9 (0.5-1.7)	1.1 (0.6-2.1)	0.7 (0.3-1.6)
SE / No silica	1451/844	2.6 (2.2-3.0)	3.8 (3.2-4.5)	1.1 (0.9-1.3)
SE / silica	74/35	2.4 (1.5-3.9)	3.7 (2.2-6.2)	1.0 (0.5-2.0)
AP		-0.1 (-0.6-0.5)	-0.1 (-0.6-0.5)	0.2 (-0.6-1.0)

Abbreviations: AP, Attributable Proportion; CI, Confidence Interval; EIRA, Epidemiological Investigation of Rheumatoid Arthritis; HLA, Human Leukocyte Antigen; OR, Odds Ratio; RA, Rheumatoid; SE, Shared Epitope

[a] Adjusted for county, age, EIRA study design, index year, pack-years of smoking, alcohol consumption and ever exposure to asbestos.

[b] Additionally adjusted for sex.

For the subset of the study participants belonging to the EIRA study we additionally had data on self-reported exposure to both asbestos exposure and crystalline silica (n=8 410). For asbestos, 3 % of the study participants were classified as exposed according to the JEM, whereas 2 % classified themselves as exposed. For crystalline silica, the corresponding numbers were 4 % and 3 %. 31 % of those classified as exposed to asbestos by the JEM classified themselves as exposed. For crystalline silica, 42 % of those classified as exposed

by the JEM considered themselves exposed. Table 17 provides a comparison of the ORs of RA from either self-reported or JEM-estimated exposure to asbestos or crystalline silica. Apart from being adjusted for the matching variables (age, geographical area) and EIRA study design, the estimates were also adjusted for potential confounding from pack-years of cigarette smoking and crystalline silica dust. The central finding in this table is that ORs were higher for crystalline silica exposure among both men and women when comparing the EIRA study to the register linkage.

Table 17. ORs of developing RA in the EIRA study and the register linkage from self-reported or JEM-estimated exposure to organic dusts vs unexposed.

	EIRA data n=8 410			Register linkage n= 126 534
	Self-reported exposure vs. unexposed [a]	JEM-classified exposure vs. unexposed [a]	Self-reported and JEM-classified exposure vs. unexposed according to both [a]	JEM classified exposure vs. unexposed [b]
Men				
Asbestos	0.9 (0.6-1.3)	1.3 (0.9-1.9)	1.1 (0.7-1.9)	1.2 (1.0-1.3)
Crystalline silica	1.4 (1.1-1.8)	1.4 (1.0-1.9)	1.8 (1.2-2.6)	1.3 (1.2-1.5)
Women				
Asbestos	1.3 (0.7-2.5)	-	-	1.0 (0.6-1.7)
Crystalline silica	2.5 (1.1-5.8)	1.3 (0.6-2.7)	-	1.1 (0.8-1.5)
Men and women [c]				
Asbestos	0.9 (0.7-1.3)	1.3 (0.9-1.8)	1.1 (0.7-1.8)	1.1 (1.0-1.2)
Crystalline silica	1.5 (1.1-1.9)	1.4 (1.0-1.8)	1.8 (1.2-2.6)	1.3 (1.2-1.5)

Abbreviations: CI, Confidence Interval; EIRA, Epidemiological Investigation of Rheumatoid Arthritis; JEM, Job-Exposure Matrix; OR, Odds Ratio

[a] Adjusted for matching variables (age, sex, geographical area), EIRA study design and smoking (pack-years). Asbestos and silica adjusted for each other (JEM-based).

[b] Adjusted for matching variables (age, sex, geographical area), EIRA study design and smoking (pack-years).

[c] Adjusted for county, age and index year and education. Asbestos and crystalline silica adjusted for each other (JEM-based).

[d] Additionally adjusted for sex.

5 DISCUSSION

The motive behind this doctoral thesis was to find out to what extent there is a risk that airborne exposures at work will affect the risk of developing RA. The four papers sought to shed light on the following:

1) Explore if different airborne occupational exposures are associated with RA risk.
    a. Occupation and risk of RA
    b. Exposure to organic dusts (wood, animal, paper, textile, flour)
    c. Exposure to inorganic dusts (asbestos, crystalline silica)
2) Study the occupational exposures in relation to immunologically defined subtypes of RA
3) Analyze gene-environment interaction between these occupational exposures and the genetic risk factor HLA-DRB1 SE

This chapter will discuss these three aspects first in relation to previous known literature and secondly consider methodological issues with regards to the research approach.

5.1 COMPARISON WITH PREVIOUS RESEARCH

5.1.1 Airborne occupational exposures

Study I showed that men with occupations related to production and construction were associated with a higher risk of developing RA. Women were less represented in these occupations. Previous studies had already indicated that occupations within the production sector were associated with an increased risk of RA [49, 51, 52, 54, 55]. The novelty of our findings is that we showed that workers within this sector are associated with an increased risk of RA even after controlling for the life-style related factors smoking, alcohol use, education and BMI. Previous studies had not taken these potential risk factors into account to the same extent, so it was uncertain whether the risks seen were related to the lifestyle of the workers rather than the work environment per se. Our findings indicate that work-related factors, such as airborne harmful exposures, most likely contribute to the disease development.

When taking a closer look at organic dust types, animal dust and textile dust were associated with an increased risk of developing RA. Our finding of an increased risk of RA from exposure to textile dust is new and has not been shown in other RA studies. More studies would have to be conducted in order to investigate different types of textile dusts, and look further into potential confounding from factors such as other organic dust types or inorganic dusts. We also propose that a potential explanation may be exposure to endotoxin, which has previously been linked to respiratory diseases in textile workers [125-128].

Animal dust has previously been associated with an increased risk of RA, mainly because of studies finding elevated risks among agricultural workers, where higher ORs have been shown in studies conducted in Sweden [49, 51, 52] and the US [54, 55] A majority of studies

specifically investigating animal dust and risk of RA found no association [52, 129, 130], whereas one study showed that exposure to animal dust was associated with the risk of death from RA (OR = 1.26, 95 % CI = 1.19-1.34) [55].

Several occupational exposures could explain the observed increased risk of RA in the agricultural industry or among workers exposed to animal dust, one of them being crystalline silica. Other studies finding a link between workers within the agriculture industry and risk of autoimmune diseases have brought up crystalline silica among farmers as a potential underlying explanation [131, 132]. In Sweden, the crystalline silica content in the bedrock varies between 20-70 %. In some quarries in south of Sweden the content is extremely high, which increases the risk of high exposure.

However, exposure to crystalline silica cannot explain the observed increased risks from animal dust in Paper IV, given that we not only adjusted our estimates for crystalline silica, but also because Swedish farmers are usually not considered exposed to respirable crystalline silica dust. Swedish farmers generally have small-scale agriculture (compared to the US) and therefore have more varied tasks, which results in lower exposure levels. Although exposure to crystalline silica does occur in the farming industry, it is the newly broken stone dust that is most reactive [133]. Older particles become less dangerous to inhale. Among farmers, only indoor management of potatoes and other root crops that are grown in the soil are counted as work exposed to crystalline silica by the Swedish Work Environment authority. Workers exposed to animal dust may also be exposed to endotoxins, pesticides, fertilizers and solvents.

Our findings from the third study showed that workers exposed to crystalline silica were associated with an increased risk of RA. The association between crystalline silica and RA was first reported by E Colinet [65] and A Caplan [66] in the early fifties, and has since then been shown in multiple studies [56, 61, 62]. Study III showed that among men there was a dose-response relation between number of censuses exposed to crystalline silica and risk of RA. This finding that the risk increases with duration of exposure among male workers has, to our knowledge, only been briefly tested by two studies previously [52, 134]. In a prospective cohort study among male foundry workers, Blanc et al. showed that the risk of RA was present only among workers exposed during at least 7.5 years [134]. According to the third paper in this doctoral thesis, the risk of RA from crystalline silica was apparent already after being classified as exposed in two censuses, corresponding to at least 15 years of exposure (OR = 1.3 (95 % CI = 1.1-1.6). In a Swedish case-control study, men exposed to stone and/or silica dust during 11-20 years or at least 20 years had a smoking-adjusted OR of 2.3 0.9-5.9 and 2.6 (0.4-19.5) respectively [52]. In our paper, a doubled risk of RA was apparent first after being considered exposed in five censuses, corresponding to at least 45 years of exposure (OR = 2.1 (95 % CI = 1.4-3.1). The fact that we observed lower estimates than the two previous studies can be explained by a more thorough adjustment for potential confounders and a larger study size. Lastly, our results indicate that the reason why the

associations are stronger in men than among women is because men are exposed to higher intensities and during longer time than women.

Our findings from Paper III showed that workers exposed to asbestos were associated with an increased risk of RA. The associations were again stronger in men than among women, but this can probably be explained by the fact that men are exposed to higher intensities and during longer time. A Swedish case-control study observed a smoking-adjusted OR of 2.5 (95 % CI = 1.0-6.8) for incident RA among workers exposed to asbestos [52]. A nested case-control study conducted in Montana detected an OR of 3.23 (95% CI: 1.31-7.96) for RA among 65 year old male workers exposed to asbestos-contaminated vermiculite [135]. However, none of these studies adjusted their findings for crystalline silica.

Asbestos is not a single compound but the name of a group of different fibers. It is commonly divided where into the two subgroups amphibole and serpentine asbestos, where chrysotile is the most common form of the latter group. A study by Ferro et al. [136] suggests that amphibole but not chrysotile is associated with the production of autoantibodies. The Montana study [135] mentioned above also found an increased risk among workers exposed to asbestos-contaminated vermiculite. Vermiculite is a crystalline silicate mineral where amphibole forms of asbestos occur as contaminants. Chrysotile is, however, a much more common type of asbestos used in the construction industry and is considered the dominating form of asbestos in Sweden. However, as asbestos was banned in the eighties in Sweden, one can question whether the exposure duration and intensity of the participants was sufficient to develop RA.

5.1.2 Seropositive and seronegative RA

There was no major difference in ORs between seropositive and seronegative RA in any of the studies when studying ever exposure to either occupation or occupational exposures. E.g., occupations and occupational exposures which were associated with an increased risk of RA were in general similar for the seropositive and the seronegative disease subtype.

Our findings show some differences to what has previously been described for exposures to cigarette smoking. Thus, smoking is mainly associated with the seropositive subtype of RA, but there is also a less pronounced risk of seronegative RA [31, 137].

It has further been shown that smoking duration is more strongly associated with risk of RA than the intensity [30, 31, 137, 138], which is similar to what was observed in Study III and IV. When exposure duration was taken into account in Study III and IV, the dose-response association was stronger for the seropositive subtype. Duration of smoking is more strongly related with ACPA+ RA than ACPA- RA, although when RF status is also taken into account the risk is most pronounced in the RF+ subsets of RA [31, 32].

Few studies exploring the association between occupational exposures and risk of RA have assessed the risk of both seropositive and seronegative RA. But a recent prospective cohort study conducted in Sweden detected a difference between seropositive and seronegative RA

among male workers exposed to crystalline silica [56]. The ORs were 1.28 (1.02-1.61) and 1.46 (1.03-2.07) for seropositive and seronegative RA respectively, after adjustments made for age, smoking, and other inorganic dusts. Self-reported exposure to crystalline silica has also showed differences between ACPA+ and ACPA- RA, but these ORs were not adjusted for cigarette smoking [61]. In another recent study published by the EIRA research group, an increased risk between physical workload was found for both ACPA+ RA and ACPA- RA after adjustments made for pack-years of smoking [139].

To summarize, our findings taken together with previous research indicate that airborne occupational exposures increase the risk of both seropositive and seronegative RA, but that the risk is stronger for seropositive RA when duration is taken into account. The etiology of seronegative RA is still fairly unknown, although it is believed to represent a more heterogeneous population of patients. One explanation to the increased risk from smoking and other airborne exposures could be that a subset of RA seronegative RA patients also has reactivity against citrullinated proteins not measured by the CCP2 assay [140, 141]. Hence, the same disease mechanism which has been proposed for seropositive RA patients may also be involved for a subset of seronegative RA. A disadvantage with the register data used in Study III and IV was that we were not able to consider different subsets of ACPA and RF patients in order to explore whether occupational airborne exposures are mainly a driver for the RF+ subsets.

5.1.3 Gene-environment interaction

We could detect an interaction between HLA-DRB1 and textile dust in MyEIRA (AP = 0.8, 95 % CI = 0.4-1.2, $p<0.0001$). However, there was only one control in the group of participants being exposed to textile dust and having any SE. We could not find any interaction between any of the studied organic dusts and workers carrying SE alleles in the Swedish EIRA study.

For crystalline silica there was no interaction with HLA-DRB1-SE in the EIRA study. The AP did not increase with an increasing number of censuses the workers had been exposed to crystalline silica. We have previously investigated interaction between HLA-DRB1-SE, with self-reported silica exposure [61]. Although a highly increased OR of 11.4 (95 % CI = 5.1-22.1) for ACPA+ RA was detected, there was no statistically significant interaction between the two exposures (AP: 0.2, 95 % CI = -0.3-0.7).

Among asbestos-exposed male workers carrying any SE allele we observed an increased risk for seropositive RA and the AP due to interaction was 0.5 (95 % CI = 0.2-0.8). This is the first observation of an interaction between asbestos and HLA-DRB1 SE and should be interpreted with caution since this is preliminary results. The mechanism between asbestos and HLA-DRB1 SE may have similarities to what is known for smoking, and the reason why we did not observe an interaction for silica can be due to differences in the biology between asbestos and crystalline silica.

5.2 SYSTEMATIC AND RANDOM ERRORS

Errors in epidemiological studies are either systematic or due to chance (random). Systematic errors can result from confounding, selection bias or misclassification.

5.2.1 Random errors

Random errors are errors due to chance, caused by sampling error, biological variation, or measurement error, and they occur because the study population is merely a sample of the source population. Random errors will result in point estimates that are different from the underlying population parameter, and the CI is a way of trying to quantify how much. Wide CIs indicate that the random error can be substantial, whereas narrow CIs indicate less random error. An increase in study size will reduce the random error. In the studies included in this thesis, the impact of sampling error was minimized by using large study populations. However, stratifying the analysis on several variables (sex, seropositive status and HLA-DRB1 SE) give rise to multiple testing, which increase the risk of a chance finding (Type 1 error).

5.2.2 Selection bias

Selection bias arises from a non-random selection of participants into the study or study analysis. In a case-control study, selection bias can occur if study participants are different from non-selected participants in terms of characteristics associated with the exposure of interest. This will lead to biased results. In other words, selection bias in a case-control study is an issue if the participating cases are not a representative sample out of all potential cases, or if selected controls not a representative sample of the population generating the cases.

In the Swedish studies in this doctoral thesis, the source population generating the cases could be enumerated and random samples of controls within these groups were generated, minimizing the risk of bias related to the selection of controls. However, in Malaysia there are no population-registers, hence the source population could not be enumerated. This makes it difficult to carry out random sampling of controls. Controls were therefore either hospital-based or neighbourhood controls. The hospital-based controls are not sampled from the source population which generated the cases; hence the exposure distribution might be different. It could be that people already ill from other diseases are likely to have a higher proportion of the exposure than the population which generated the cases. The MyEIRA study did not include controls with other autoimmune diseases, but it could have been wise to also exclude patients who had diseases where textile dust may be a risk factor.

In both Study I and II cases and controls decided for themselves if they wanted to participate in the study or not after being identified. A low participation proportion in a case-control study may give rise to a type of selection bias referred to as self-selection bias, where participants and non-responders may differ on certain characteristics related to the exposure and outcome.

Figure 12 shows the participation proportion of cases and controls in the EIRA study until 2017. In Study I where EIRA was the sole study material, the participation was 94 % among cases and 76 % among controls. Female cases (96 %) and controls (81 %) had a higher participation proportion than male cases (89 %) and controls (66 %). A previous examination of non-participation among cases and controls in EIRA showed that both participating cases and controls had higher education than the non-participants. Assuming that responding controls are more likely to be highly educated - and therefore not work in construction related occupations - than non-responders, this would likely lead to an overestimation of the associations studied in this thesis. The same type of bias may have occurred in the MyEIRA study, where the participation was 92 % among cases and 76 % among controls.

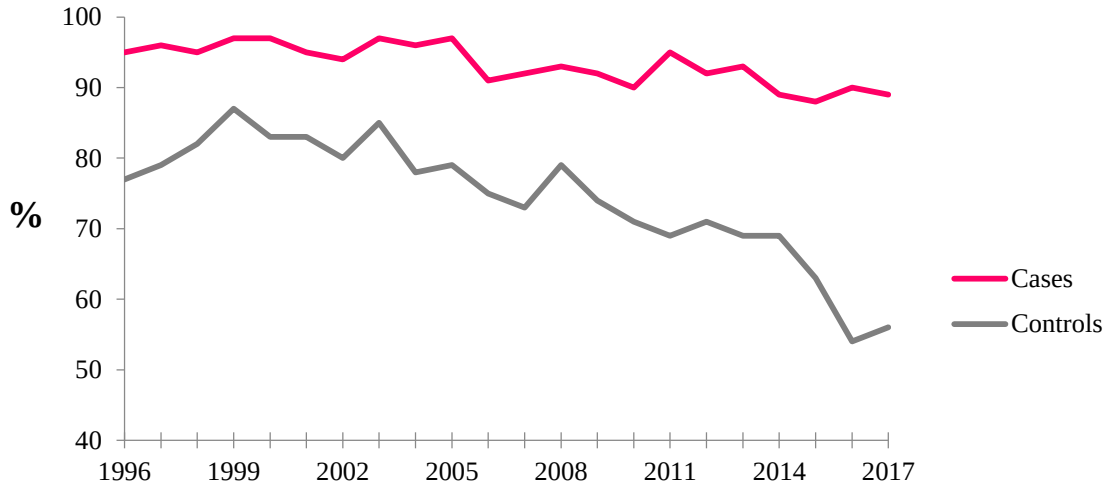


Figure 12. Participation proportion in the EIRA study

Another reason for selection bias is referred to as the healthy worker effect, which occurs in studies where the general population is used as a control group in studies where the main exposure and outcome is related to occupational health. Depending on how it is defined and used, it can be viewed both as selection bias or confounding [142]. The healthy worker effect can be depicted as the factors which enables a person to be part of and remain active in the workforce, and that these factors will lead to an overall better health than non-workers. Factors affecting whether a person is hireable could be disabilities and lifestyle behaviours, and beneficial factors of work, like improved access to healthcare, physical exercise at work [143]. We did in our studies not select participants from an industry or workplace, but both cases and controls were selected from the general population, which ought to have minimized this type of bias.

Study III and IV are based on national registers, limiting the risk of selection bias due to their large coverage. The National Patient register has an almost complete coverage of inpatient visits, whereas the outpatient visits vary due to year and speciality. We used data from the year 2006, in which the coverage for somatic diseases in the non-primary part of

the outpatient register was 78 % [144]. The SRQ register has an estimated 85 % coverage [116].

Another type of bias which might have affected Study III and IV is the one referred to as competing risk. Competing risks occur when an exposed patient is at risk of several different events and the occurrence of one of them will prevent the other(s) from happening. It could be that workers exposed to high levels or during a long time for organic or inorganic dusts have died from other causes and thereby not being eligible to be part of the study. A plausible example is that workers exposed to high levels of asbestos in Sweden prior to the sixties have been at risk for several different diseases, and the occurrence of for instance death from lung cancer could have preceded an RA diagnosis. For the present case-control studies, this would have led to less highly exposed participants in the study.

5.2.3 Confounding bias

A confounder is a common cause of both the exposure and outcome of interest. If not taken care of, the confounder will modify the true association between the main exposure and the outcome. Confounding can be controlled for in both the design of the study (by restriction, randomization, or matching) or in the statistical analysis (by restriction, adjustment, or stratification). In all four studies, confounding was both controlled for by matching controls to cases on sex, age, and residential area, and by performing restricted, adjusted, and stratified analyses.

RA is a disease where socio-economic and lifestyle-related factors are known to play a role in the disease aetiology. Having access to individual data from questionnaires and registers on these factors was a major advantage for the papers in this PhD project. In Study I, III and IV only participants who had ever reported at least one occupation were analyzed. The reason relates to the above described healthy worker effect; that the ORs can become biased if your unexposed group consist of participants who have never worked due to a reason related to RA.

The main environmental confounder to consider in all four studies was cigarette smoking. The second strongest environmental confounder known so far is alcohol consumption. In the EIRA study we adjusted for pack-years of cigarette smoking and for drinks of alcohol per week. In Study III, we imputed the information on smoking and alcohol from the EIRA study to the larger study material. To assess the validity of the imputation, we compared the distributions of imputed and observed values for cigarette smoking and alcohol consumption. There are several benefits with the multiple imputation approach. Firstly, only 6 % of the participants had complete information on all the variables in the analysis. If we only had done a complete case analysis, we would have omitted a large part of our study population and thereby lost information and widened the CIs. Secondly, participants with complete and incomplete information differed in terms of sex, age and education. An assumption you have to make when you conduct a complete case analysis is that the data is missing completely at

random. Hence, had we instead omitted a large part of the data that would likely have led to biased estimates.

In MyEIRA the analysis was restricted to females due to the low proportion of men being exposed to textile dust. Very few women in the study population reported being smokers, so adjusting for smoking had no effect on the estimates. In Study IV, we tried a different approach and adjusted risk estimates for education, as a proxy for life-style-related factors.

Because of the strong link between smoking and RA a potential confounder could be passive smoking at home or at the workplace. We did not have sufficient information in the studies to consider passive smoking. However, very few studies have evaluated the association between passive smoking on RA risk and findings are so far inconclusive [145, 146]. In a subpopulation of the EIRA study information on passive smoking is known, and there is no increased risk of ACPA+ or ACPA- RA from passive smoking [147].

Since the workplace may give rise to several types of occupational exposures, it is important to consider confounding also from such factors. Crystalline silica was adjusted for in Study III and IV, and to some extent in Study I. Our findings indicate that future research estimating associations between asbestos and autoimmune diseases ought to also take crystalline silica exposure into account. There are also other occupational exposures which might serve as potential confounders or effect modifiers that we have not considered in this thesis. Several organic dust types are known to absorb heavy metals [148]. One potential explanation could therefore be that the increased risks noted for animal dust and textile dust in our study are due to the fact that we have not adjusted for confounding from other unknown occupational risk factors, such as heavy metals [148], physical workload, organic solvents or other forms of inorganic or organic dusts.

A problem is that certain potential confounders are so strongly related to the main exposure of interest that they are difficult to study, because stratification will result in low precision and adjusting may result in over adjustment or results that are difficult to interpret. Self-reported physical workload is one such confounder, which was recently linked to an increased risk of RA in the EIRA study [139].

5.2.4 Misclassification bias

Misclassification bias, also known as information bias, is a measurement error where the main exposure, covariates or outcome status is being misclassified. We have data for the main exposures and covariates from three different sources: self-reported exposures, register-based exposure data and expert-assessed from JEM's. These sources are known to cause different types of exposure misclassification and are to varying degrees known to be differential between cases and controls.

In the EIRA study, we collected data through a questionnaire, where the section about work history and occupational agents comes at the end. In Study I, self-reported last occupation prior to inclusion in the study was used. Due to its retrospective nature, a case-control study

can be prone to recall bias. This type of recall bias might be differential between cases and controls, which could bias the estimates in our analyses. However, the time between ending their last year of working and being enrolled into the EIRA study was 10 years or less for 94 % of the study participants. Because of this we don't think there is any recall bias regarding occupation or that there is reason to believe this information is differential between cases and controls. Thus the potential misclassification of occupation can be viewed as non-differential, a bias that most likely will bias the strength of the associations towards the null-value.

For Study II, we used self-reported information on textile dust. Potentially this misclassification is different between cases and controls since cases are more eager to remember their exposure and understand why they became ill. In the MyEIRA study trained staff interviewed the participants face-to-face and filled in the questionnaire for them. This may give rise to social desirability bias, where participants state incorrect and healthier information about their lifestyle habits because they are ashamed or feel that the information is too private.

For Study III, occupational titles came from the population and housing censuses from 1960 until 1990 and exposures from JEM's. For the fourth study on organic dusts, additional work titles were collected from register data for 2001 and 2010. An advantage of using a JEM is that the exposure to asbestos and crystalline silica was assessed by industrial hygienists with knowledge about time-specific exposure levels. Since the exposure is not self-reported, there is no risk for differential misclassification between cases and controls. Albeit our JEM did not distinguish between different types of asbestos, it did still estimate exposure levels from the fifties and onwards, and exposure also occurs today in, for example, demolition or renovation of old buildings.

There are certain disadvantages to be aware of when using a JEM. First of all, the occupational classification systems are not primarily designed to study occupational exposure. The NYK codes on the 3-digit level sometimes consist of varying groups of workers, which make unusual exposures difficult to study. This leads to an increased risk of misclassification. Another disadvantage of using a JEM is that the JEM overestimate the proportion number of exposed workers. JEM's are known to overestimate the proportion of workers being exposed, since everyone with an occupation will be classified as exposed even if the likelihood of exposure within that occupation is low. This overestimation of number of exposed workers in the study population can lead to an underestimation of the studied association. To avoid this, we in paper III and IV analyzed participants who had reported at least one exposed occupation with a likelihood of exposure of at least 50 %. Figure 13 categorize participants in Study III and IV depending on if they have had at least one occupation classified as high probability or not. In Study III, 34 % of exposed female participants and 7 % of male exposed participants were excluded from the analysis since their likelihood of having an occupation exposed to asbestos and crystalline silica was classified as low. These 545 participants are not included in the bars for asbestos or crystalline silica in Figure 13.

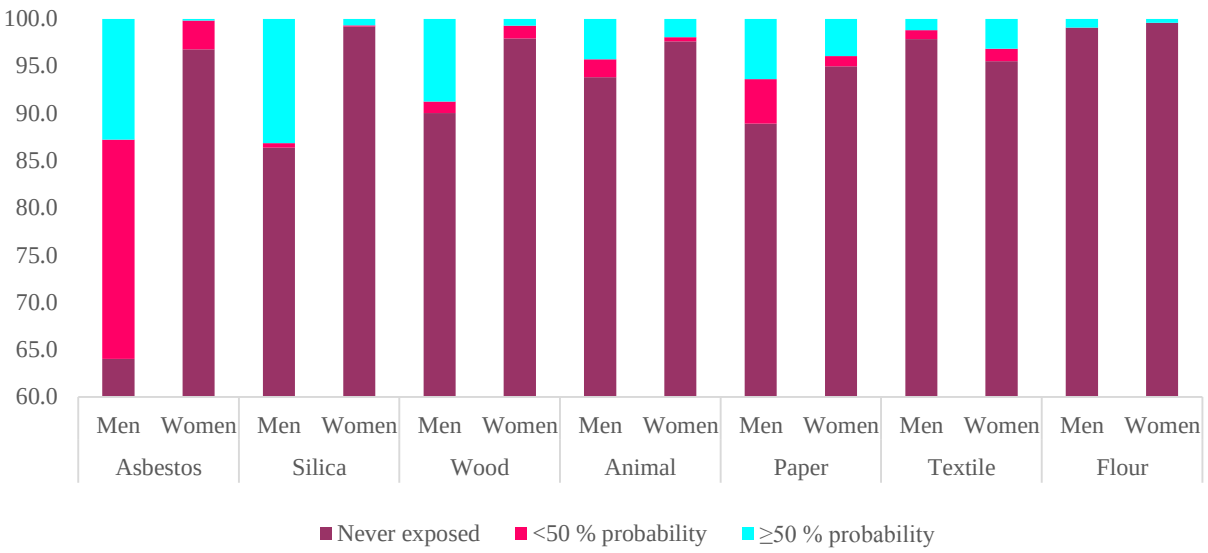


Figure 13. Participants in Study III and IV unexposed or classified as having at least one occupation with at least 50 % probability of being exposed.

Although misclassification of exposure is in general more common in observational studies, misclassification of the outcome can also occur. For Study I (EIRA) and Study II (MyEIRA), the RA diagnosis was set by a rheumatologist using the ACR criteria at a rheumatology clinic where patients were followed up. It is therefore unlikely that diagnostic errors had occurred. It was possible for a control in the EIRA and MyEIRA study to at a later stage develop RA. This person would then be entered as a case with a new unique id number and a new questionnaire would be filled in.

For Study III and IV, the definition of RA was based on multiple data sources, and data from blood tests. ICD-10 codes were used to identify patients in the National Patient Register, whereas ACR criteria were used for the SRQ register. Evaluations of more than 1 000 patients diagnosed with RA based on ICD-10 have found that 90 % of inpatient register patients and 85 % of patients with a non-primary outpatient care visit also fulfilled the ACR criteria [149-151].

In the EIRA study and for the SRQ register, blood samples were collected to measure antibodies as a diagnostic marker of RA. A value on a scale determines whether the patient is seropositive or not, where the cut-off for positivity is usually set at the 98th percentile. The values a patient have on RF and ACPA can vary over time, not least for RF where up to half of the patients become negative over time, while anti-CCP positive rarely become negative but can get much lower absolute levels when disease activity goes down. As these variations are due to disease activity, it is unlikely that a patient would be inaccurately classified as free from RA, however, it could be that some seropositive patients have been inaccurately classified as seronegative and vice versa.

In order to validate the RA diagnoses among cases in the SRQ register we compared the seropositive status to cases in the EIRA study. Among 2 623 seropositive cases (RF or ACPA positive in SRQ), 22 patients were classified as seronegative in EIRA. Among 1 021 seronegative cases (RF and ACPA negative in SRQ), 131 patients were classified as seropositive in EIRA. Among 19 unspecified cases in SRQ, 12 were seropositive and 7 were seronegative according to EIRA data. These 160 cases were recoded according to EIRA information. We considered the seropositive status in EIRA as more accurate, since we know exactly how the testing was done and are able to trace information about the test much better, e.g. with respect to the date of the sample and relation to inclusion in EIRA/SRQ.

6 CONCLUSIONS

6.1 MAIN FINDINGS

According to the findings in this doctoral thesis factors related to your occupation can increase your risk of developing RA, where exposure to inorganic and organic exposures plays a role.

The results showed that men working in construction and production industry have an increased risk of developing RA. Within these industries, exposure to crystalline silica dust and asbestos, are likely contributors to the disease development. This is the first study to extensively investigate the association between exposure to asbestos and risk of RA. For seropositive RA there is a significant dose-response trend and in the EIRA study there is additive interaction between asbestos and HLA-DRB1 SE for seropositive RA. For crystalline silica exposure, we added to previously conducted research that there is an exposure-response relation between duration to crystalline silica and risk of RA among men. The studies presented in this doctoral thesis are also the first to show that workers exposed to animal dust and textile dust are associated with an increased risk of developing RA. Significant p-values for trend were observed for duration of exposure for both animal dust and textile dust. In the Malaysian setting the observed association between exposure to textile dust and RA risk was stronger than in Sweden, and an interaction with HLA-DRB1 for ACPA+ RA was observed.

Study III and IV additionally examined duration of exposure to organic and inorganic dust types. Whereas ORs from ever exposure to different airborne exposures turned out similarly between the seropositive and seronegative disease subtype, duration of exposure was more strongly linked to seropositive RA. This finding is similar to what has been shown for cigarette smoking.

The studies in this doctoral thesis are unique in that they have studied airborne occupational exposures not just among men, but also among women. Women are much less represented in occupations at risk of being exposed to inorganic dusts, yet, seven out of ten RA patients in Sweden are women [11]. The fact that men to a greater extent than women tend to develop RA due to their choice of occupation may be explained by that men are overrepresented in production related occupations, where they additionally have been exposed to harmful airborne exposures to a greater extent than their female colleagues with the same occupation.

Lastly, the results in this thesis indicated that smoking is still relatively common among workers in industries where there is an increased risk of RA. This implies not only that smoking is an important confounder, but also that these are important target groups in terms of smoking prevention.

6.2 CLINICAL AND PUBLIC HEALTH IMPLICATIONS

One of the most famous concepts for causality in epidemiology is the causal pie model by Rothman [71]. What I have realized during my doctoral education is that for a disease like RA, where both genetic and environmental components are involved, there are endless different sufficient causes. Because, for a disease with genetic components, the complete induction time does not begin with onset of an environmental exposure, but already at conception of the fetus. Individual risk factors and contextual factors are both determinants of RA and they operate over the lifespan. This has to be acknowledged not only by researchers but maybe more importantly by decision-makers and medical doctors. The impact of the lifestyle among, for instance, construction workers, should be taken into account. One cannot analyze individual airborne exposures, without considering other risk factors at the workplace, such as smoking.

Workplaces with high levels of hazardous airborne exposures may lead to a greater risk of RA as well as other respiratory-related diseases. Crystalline silica exposure is very widespread and even though the levels have decreased since the 1960s, it is still an important occupational hazard and probably one of the most overlooked. RA is one of the most common autoimmune diseases worldwide and it is of great importance to find preventable risk factors. Findings on preventable work-related exposures are to be spread to employees, employers and decision-makers in order to prevent disease by reducing or eliminating known risk factors. The employer needs to ensure that the workplace is safe by complying with work environment laws and regulations. He or she also needs to ensure that workers have access and use appropriate tools and protective equipment. If we prevent or adequately control airborne exposures at the work-place fewer workers may be at risk of developing RA or other diseases caused by hazardous airborne exposures. An employer also has to be aware of the health impacts of cigarette smoking and passive smoking at the workplace.

Many patients try to find answers to why they have the disease. RA is a disease with a multifactorial background, so the patient's occupational history might only explain a small part of the disease picture, whereby genetic risk factors and lifestyle habits also have to be considered. It is important to point out to patients that they will not necessarily develop RA just because they have had a certain occupation or been exposed to potentially harmful exposures at work. The participants in our study reported their working history back in time. Hence, the increased risks of RA we see today may correspond to exposure levels of harmful exposures prevailing several decades ago. Hopefully today's workers within the production industry do not suffer the same risk of disease, since there is an increased awareness of the health implications of potential harmful hazards, which may have caused the exposure levels to decrease.

It is probably the case that the exposure levels have fallen over time in the larger construction companies, where employers have better control over work environment and legislation. But there is a risk that the exposures are considerably higher in smaller companies, which often get the dirtiest and heaviest jobs and where the knowledge about work environment is not as

high. This may apply to many start-ups, such as subcontractors in the construction industry, but also abroad where these exposures are more frequent or higher than they are in Sweden.

6.3 FUTURE PERSPECTIVES

The findings from this doctoral thesis strengthen our hypothesis that airborne exposures are associated with an increased risk of developing RA. This thesis covered seven different airborne exposures. The results provide a basis for future research in several areas. So, what are the next steps to take in the field of airborne exposures and risk of RA?

For the listed seven exposures, more research is needed on exposure to asbestos in countries where the probability of exposure is higher than in Sweden to establish the extent and nature of this association. Albeit asbestos was banned in Sweden several decades ago, this is not the case in many parts of the world. Study III established the association between crystalline silica and RA, and stresses that future research on asbestos need to take exposure to crystalline silica into account. More research is needed to confirm these associations, and whether they can be explained by other occupational exposures such as physical workload, or could be due to residual confounding from smoking or passive smoking.

Apart from the seven exposures covered in this thesis, there are many airborne exposures left to explore. Based on existing literature and the results in this thesis, airborne exposures of interests would be metals, welding fumes, nanoparticles, inorganic solvents and pesticides. These are all exposures existing in the production or agriculture industries, where associations to respiratory and/or autoimmune diseases have been suggested.

This doctoral thesis has been produced based on the hypothesis that the lung plays an important role in the development of RA. The findings show that airborne, occupational exposures increase the risk of both seropositive RA and seronegative RA. We know less about possible molecular mechanisms for seronegative RA, which needs to be explored further. Future epidemiological studies should take different subtypes of RA into account, but they are not sufficient to establish whether there is a biological plausibility between airborne exposures and risk of developing RA. The same disease mechanism which has been proposed for seropositive RA patients may also be involved for a subset of seronegative RA.

When I started my doctoral education, I wondered why certain workers were associated with an increased risk of RA. My research has greatly increased my understanding of which underlying factors that contribute to the disease development in certain professions. This knowledge should not be confined to the research community, but should be disseminated to relevant target groups in society, as well as to clinicians. Preventive measures should be taken in order to reduce the number of cases that develop RA from high risk occupations. It is now up to me and associated researchers within the field to make sure that the information and knowledge generated from this doctoral thesis is spread to relevant groups in society. The construction workers I pass by every day on my way to Karolinska Institutet are one such group.

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APPENDIX A: VARIABLE DEFINITIONS

Variable	Role	Data Source	Definition
Study I: Occupation and risk of developing RA			
Case	Outcome	The EIRA study The Population Register	0 = Control 1 = Case (based on the ACR 1987/2010 diagnostic criteria)
ACPA status	Outcome	The EIRA study	0 = ACPA+ 1 = ACPA-
RF status	Outcome	The EIRA study	0 = RF+ 1 = RF-
Sex	Matching variable	The EIRA study	0 = Woman 1 = Man
Geographical area	Matching variable	The EIRA study	The 13 involved counties in Sweden were grouped into 7 geographical areas: 1) Stockholm county 2) Kopparberg county and Uppsala county 3) Södermanland county, Östergötland county and Jönköping county 4) Kalmar county 5) Blekinge county and Malmöhus county 6) Halland county and Bohuslän county 7) Örebro county and Västmanland county
Age	Matching variable	The EIRA study	Age was categorized into 11 groups: 18–24 25–29 30-34 35-39 40-44 45-49 50-54 55-59 60-64 65–70 >70 years
Occupation	Main exposure	The EIRA study	Last occupation entered prior to study inclusion. For a list of occupations, see Appendix B
EIRA study design	Confounder	The EIRA study	1 = EIRA 1 2 = EIRA 2
Smoking	Confounder	The EIRA study	1 pack-year is 20 cigarettes smoked/day for 1 year 0=Never smoker 1= <10 pack-years 2= 10– 19 pack-years 3= ≥20 pack-years 4 = smoking tobacco other than cigarettes (e.g., cigarillos, cigars, or pipe tobacco).

Alcohol consumption	Confounder	The EIRA study	Consumption based on the sum of standard drinks (1 drink = 12 grams of alcohol) consumed the week prior to filling in the questionnaire. Cutoffs based on the controls' consumption. 0 = Low consumption of alcohol (>0-50th percentile) 1 = Nondrinkers (participants reporting no alcohol use for the last 12 months) 2 = Moderate consumption (>50-75th percentile) 3 = High consumption (>75th percentile)
BMI (kg/m^2)	Confounder	The EIRA study	0 = <20 1 = 20-25 2 = >25
Education	Confounder	The EIRA study	0 = University degree 1 = Secondary education 2 = Primary education
Crystalline silica	Confounder	The EIRA study	0 = Never exposed 1 = Workers reporting ever working with stone crushing, rock drilling, or being exposed to stone dust
Study II: Occupational exposure to textile dust increases the risk of RA			
Case	Outcome	The MyEIRA study	0 = Control 1 = Case (based on the ACR 1987 diagnostic critera)
ACPA status	Outcome	The MyEIRA study	0 = ACPA+ 1 = ACPA-
Residential area	Matching variable	The MyEIRA study	Unknown
Ethnicity	Confounder	The MyEIRA study	Malay Chinese Indian Others
Age	Matching variable	The MyEIRA study	Age group
HLA-DRB1 SE alleles	Main exposure	The MyEIRA study	0 = No alleles 1 = Single or double alleles
Occupational exposure to textile dust	Main exposure	The MyEIRA study	0 = Never exposed 1 = Reported ever being exposed to textile dust before or during the index year
Education	Confounder	The MyEIRA study	0 = College/university 1 = Secondary education 2 = Primary education 3 = No formal education
Smoking	Confounder	The MyEIRA study	0 = Never smoker 1 = Ever smoker
Study III: Occupational Exposure to Asbestos and Silica and Risk of Developing RA			
Case	Outcome Imputation	The National Patient Register,	0 = Control 1 = Case

	variable	The Swedish Rheumatology Quality Register, The Prescribed Drug Register, The EIRA study, The National Population Registers	
Seropositive status	Outcome Imputation variable	The Swedish Rheumatology Quality Register, The EIRA study	0 = RF+ and/or ACPA+ 1 = RF- and ACPA-
Sex	Matching variable Imputation variable	The National Population Registers	0 = Woman 1 = Man
Geographical area	Matching variable	The National Population Registers	21 counties: 01 Stockholms län 03 Uppsala län 04 Södermanlands län 05 Östergötlands län 06 Jönköpings län 07 Kronobergs län 08 Kalmar län 09 Gotlands län 10 Blekinge län 12 Skåne län 13 Hallands län 14 Västra Götalands län 17 Värmlands län 18 Örebro län 19 Västmanlands län 20 Dalarnas län 21 Gävleborgs län 22 Västernorrlands län 23 Jämtlands län 24 Västerbottens län 25 Norrbottens län
Age	Matching variable Imputation variable	The National Population Registers	Continuous variable (from 19 to 94)
Index year	Matching variable	The National Patient Register, The Swedish Rheumatology Quality Register, The Prescribed Drug Register, The EIRA study, The National	0 = 1996-2001 1 = 2002-2007 2 = 2008-2013

		Population Registers	
	Imputation variable	The National Patient Register, The Swedish Rheumatology Quality Register, The Prescribed Drug Register, The EIRA study, The National Population Registers	Continuous variable
Ever exposure to: Asbestos Crystalline silica	Main exposure	PARCC-JEM	Ever exposure: 0 = Never exposed 1 = Been exposed to ≥ 1 occupation with ≥ 50 % probability of being exposed
	Confounder	PARCC-JEM	0 = Never exposed 1 = Been exposed in occupations with < 50 % probability of being exposed 2 = Been exposed to ≥ 1 occupation with ≥ 50 % probability of being exposed
	Imputation variable	PARCC-JEM	0 = Never exposed 1 = Ever exposed
Number of jobs: Asbestos Crystalline silica	Main exposure	PARCC-JEM	0 = Unexposed worker 1 = Exposed in 1 census* 2 = Exposed in 2 census* 3 = Exposed in 3 census* 4 = Exposed in 4 census* 5 = Exposed in 5 census* * Been exposed to ≥ 1 occupation with ≥ 50 % probability of being exposed
	Imputation variable	PARCC-JEM	0 = Unexposed worker 1 = Exposed in 1 census 2 = Exposed in 2 census 3 = Exposed in 3 census 4 = Exposed in 4 census 5 = Exposed in 5 census
Smoking	Confounder Imputation variable	The EIRA study	1 pack-year is 20 cigarettes smoked/day for 1 year Continuous variable
Alcohol consumption	Confounder Imputation variable	The EIRA study	See Study I
Disposable household	Imputation variable	The LISA register	Continuous variable

income 1990			The disposable income includes all revenue: - Income from work (pay and income from business activities) - Taxable transfers (such as sickness allowance, parental benefit, A-kassa and pension) - Tax-free transfers (such as child allowance, housing allowance, study grants, maintenance support). - Capital income. From the sum of these amounts are deducted tax, repaid student funds and paid maintenance support.
Disposable household income 2000	Imputation variable	The LISA register	Continuous variable. See disposable household income 1990.
Disposable household income 2010	Imputation variable	The LISA register	Continuous variable See disposable household income 1990.
Educational level	Imputation variable	The LISA register	0 = >12 years of education 1 = 10–12 years 2 = ≤9 years
EIRA data	Imputation variable	The EIRA study	0 = Not in the EIRA study 1 = In the EIRA study
Birth year	Imputation variable	The National Population Registers	Continuous variable
Study IV: Occupational exposure to organic dusts and risk of developing RA			
Case	Outcome		See Study III
Seropositive status	Outcome	The SRQ register	See Study III
Sex	Matching variable	The National Population Registers	See Study III
Geographical area	Matching variable	The National Population Registers	See Study III
Age	Matching variable	The National Population Registers	See Study III
Index year	Matching variable	The National Patient Register, The Swedish Rheumatology Quality Register, The Prescribed Drug Register, The EIRA study, The National	See Study III

		Population Registers	
Ever exposed to: Wood dust Animal dust Paper dust Textile dust Flour dust	Main exposure	PARCC-JEM FAIR-JEM	0 = Never exposed 1 = Been exposed to ≥ 1 occupation with ≥ 50 % probability of being exposed
Number of jobs: Wood dust Animal dust Paper dust Textile dust Flour dust	Main exposure	PARCC-JEM FAIR-JEM	0 = Unexposed worker 1 = Exposed in 1-2 census* 2 = Exposed in 3-4 census* 3 = Exposed in 5-7 census* * Been exposed to ≥ 1 occupation with ≥ 50 % probability of being exposed
Highest average intensity to: Wood dust Animal dust Paper dust Textile dust Flour dust	Main exposure	PARCC-JEM FAIR-JEM	0 = Unexposed worker 1 = ≤50 percentiles* 2 = >50-≤75 percentiles* 3 = > 75 percentiles* * Been exposed to ≥ 1 occupation with ≥ 50 % probability of being exposed
Crystalline silica exposure	Confounder	PARCC-JEM FAIR-JEM	See Study III
Educational level	Confounder	The LISA register	0 = >12 years of education 1 = 10–12 years 2 = ≤9 years

Abbreviations: ACPA, Anti-Citrullinated Protein/Peptide Antibody; BMI, Body Mass Index; EIRA, Epidemiological Investigation of Rheumatoid Arthritis; FAIR, Foetal air pollution exposure; JEM, Job Exposure Matrix; LISA, Longitudinal Integration Database for Health Insurance and Labour Market Studies; MyEIRA, Malaysian Epidemiological Investigation of Rheumatoid Arthritis; PARCC, Particles and Cardio- and Cerebrovascular diseases; RF, Rheumatoid Factor

APPENDIX B: CLASSIFICATION OF OCCUPATIONS IN STUDY I

No	Occupational group	Occupational code (YK 85)
1	Technical, physical and biological workers	001 Architects, civil engineers and civil engineering technicians 002 Electrical engineers and technicians 003 Electronics and tele technical communications engineers and technicians 004 Mechanical engineers and technicians 005 Chemical engineers and technicians 006 Metallurgists, mining and petroleum engineers and technicians 007 Engineers and engineering technicians not elsewhere classified 008 Surveyors and cartographical engineers and technicians 009 Technical workers not elsewhere classified 014 Geologists 015 Meteorologists, hydrologists 019 Chemical and physical science workers not elsewhere classified 021 Biologists 022 Agricultural advisors 023 Forestry advisors 029 Biological workers not elsewhere classified
2	Laboratory workers	012 Laboratory technicians and assistants (not medical lab) 013 Laboratory assistants (medical lab) 016 Chemists, physicists, laboratory engineers
3	Teachers	030 Principals, headmasters 031 University and higher education teachers 032 Secondary education teachers (theoretical subjects) 033 Primary education teachers 034.70 Domestic science teachers 034.91 Drama teacher 034.92 Machine writing teacher, basic school 034.93 Drama pedagogue, eurhythmics teachers 034.94 Theater pedagogue 035 Technical education teachers 036 Pre-primary education teachers, recreation activities organizers 037 Educational methods advisors 039 Educational workers not elsewhere classified
4	Religious, juridical and other social science related workers	041 Ministers of religion 049 Religious workers not elsewhere classified 051 Judges and lawyers in courts of justice 052 Prosecutors, police commissioners 053 Jurists (private practice) et al. 054 Legal advisers (in enterprises or other organizations) 059 Law workers not elsewhere classified 091 Librarians 092 Archivists and museum curators 099 Professional, technical and related workers not elsewhere classified 151 Social and social welfare workers

		191 Psychologists 221 Personnel officers 222 Employment exchange officials 229 Personnel workers not elsewhere classified 261 Economists 262 Statisticians 269 Economics and statistics workers not elsewhere classified 971 Undertakers
5	Journalists	061 Journalists, authors 062 Public relations and publicity officers 063 Programme editors (radio, TV) 069 Literary and journalistic workers not elsewhere classified
6	Sculptors, painters and commercial artists	071 Sculptors, painters and commercial artists
7	Display artists and designers	034.10 Art teachers 072 Display artists 073.21 Interior design consultant, other 073.22 Interior Designer 073.31 Modelist, artist 073.32 Modelist, advertisement 073.33 Graphic designer 073.34 Designer, other 073.35 Industrial designer 073.50 Pattern designer 073.91 Metalsmith 073.92 Fashion Designer
8	Photographers	074 Photographers
9	Performing artist and producers	075 Performing artists 077 Producers, directors, stage managers (film, theatre) 079 Artistic workers not elsewhere classified
10	Composers and musicians	034.21 Singing teacher, musical consultant 034.22 Music teacher 034.23 Music director, teacher 034.24 Vocal pedagogue 076 Composers and musicians
11	Administrators and managers	201 Legislators and administrators (central government) 202 Legislators and administrators (county council administration) 203 Legislators and administrators (local government) 209 Government legislators and administrators not elsewhere classified 211 Business administrators 212 Organization administrators 219 Business administrative workers not elsewhere classified
12	Clerical workers	231 Auditors 232 Financial managers, accountants 239 Accounting workers not elsewhere classified 241 Secretaries, stenographers 242 Typists 249 Clerical and related workers not elsewhere classified 251 Systems analysts, programmers

		252 Computer operators 259 Computer processing workers (ADP) not elsewhere classified 291 Cost computing and estimating clerks 292 Bank tellers and finance clerks 293 Insurance clerks 294 National insurance clerks 295 Tourist- and travel agency clerks 296 Forwarders, transport planners 297 Property managers 299 Administrative, managerial and clerical workers not elsewhere classified
13	Physicians	101 Physicians and surgeons
14	Nurses	102 Nursing administrators 103 Registered nurses 104 Midwives
15	Assistant nurses and attendants	106 Attendants in psychiatric care 107 Assistant nurses and hospital aids 153 Children's nurses 154 Home helpers 155 Managers and assistants (for the mentally retarded)
16	Dental workers	121 Dentists 122 Dental hygienists 123 Dental assistants 129 Dental workers not elsewhere classified
17	Dental technicians	744 Dental technicians
18	Medical technicians	105 Medical technicians
19	Pharmaceutical workers	131 Pharmacists 139 Pharmaceutical workers not elsewhere classified
20	Physiotherapy and occupational therapy workers	111 Physiotherapists 112 Occupational therapists 119 Physiotherapy and occupational therapy workers not elsewhere classified
21	Environment and health protection workers	161 Occupational, safety and public health inspectors 162 Safety engineers, ergonomists 169 Environment and health protection workers not elsewhere classified
22	Other health and medical workers	109 Health and nursing workers not elsewhere classified 152 Managers of social welfare institutions 159 Social workers not elsewhere classified 192 Dietitians and nutritionists 199 Health, nursing and social workers not elsewhere classified
23	Sales agents and salesmen	311 Advertising salesmen 312 Real estate and securities brokers 313 Business services salesmen 319 Sales workers (business services and assets) not elsewhere classified 321 Buyers 331 Working proprietors, wholesale and retail trade 332 Salesmen (wholesale)

		339 Sales workers (goods) not elsewhere classified 399 Sales workers not elsewhere classified
24	Shop assistants	333 Shop assistants
25	Farmers	400.09 Farmer 400.19 Farmer 400.90 Other workers in 400 Working proprietors in agriculture and forestry 402 Farm managers and supervisors 409 Agriculture, horticulture and forestry managers not elsewhere classified 411 Agricultural workers 419.91 Harvesting estimator 419.92 Agricultural Surface Analyst 419.93 Sampler, households
26	Horticultural workers	401 Horticultural farmers 403 Horticultural managers and supervisors 413 Horticultural workers
27	Animal workers	141 Veterinarians 149 Veterinary workers not elsewhere classified 400.29 Piglet breeder, chicken breeder 400.49 Beekeeper, dog breeder 400.59 Breeders of animals 405 Reindeer farmers 406 Breeders of fur-bearing animals 412 Livestock, dairy and poultry farm workers 414 Fur-bearing animal farm workers and reindeer herdsmen 419.10 Zoo keeper 421 Game-keepers and hunters 961.40 Jockey 961.51 Dressage apprentice 961.52 Dressage trainer
28	Fishing workers	431 Fishermen 432 Fishfarmers 439 Fishing workers not elsewhere classified
29	Forestry workers	400.39 Forestry workers 404 Forestry managers and supervisors 441 Loggers 449 Forestry workers not elsewhere classified
30	Miners and quarrying workers	501 Miners, quarrymen 509 Mining and quarrying workers not elsewhere classified 511 Well and diamond drillers 521 Ore dressers 599 Mining and quarrying workers not elsewhere classified
31	Petroleum extraction workers	531 Petroleum extraction workers
32	Seamen	601 Ships' deck officers 602 Ship pilots 609 Ships' officers not elsewhere classified 611 Ships' deck ratings 619 Ships' deck- and engine-room ratings not elsewhere classified
33	Ships'	603 Ships' engineers

	engineers and engine-room ratings	612 Engine-room ratings
34	Transport assistants and supervisors	651 Air traffic controllers 653 Road transport assistants 659 Transport conductors and transport assistants not elsewhere classified 661 Harbormasters 662 Air-control officers, flight dispatchers 663 Railway station masters, train dispatchers 664 Road transport supervisors 669 Transport supervisors not elsewhere classified 691 Lighthouse and lock operators and harbor service assistants 699 Other transport and communications workers 916.30 Bus hostess
35	Motor vehicle drivers	640 Bus and taxi drivers 641 Lorry and pickup drivers 643 Delivery men 649 Motor vehicle drivers and delivery workers not elsewhere classified
36	Railway drivers	631 Railway engine drivers 642 Tram and underground drivers 652 Railway conductors and yardmen
37	Aircraft workers	621 Aircraft pilots, navigators and flight engineers 629 Aircraft officers not elsewhere classified 916.10 Purser 916.21 Cabin staff, air traffic 916.22 Flight attendant 916.23 Flight attendant 916.91 Train attendant 916.92 Cabin stewardess 916.93 Cabin boy
38	Postal and communication workers	671 Postmasters, post office clerks 673 Telecommunications clerks 674 Telephone operators 675 Telegraphers, radio communication operators 679 Postal service and telecommunications workers not elsewhere classified 681 Mail sorting clerks and postmen 682 Messengers 689 Mail distribution clerks and messengers not elsewhere classified
39	Textile workers	034.61 Textiles teacher 034.62 Textiles teacher 073.41 Textile artist 073.42 Textile caretaker, museum 701 Fibre processors 702 Spinners 703 Weavers, knitters 705 Weaving and knitting machine setters 706 Textile finishers, dyers 707 Fabrics inspectors and menders 709 Textile workers not elsewhere classified

		711 Tailors 712 Fur tailors 713 Milliners and hatmakers 714 Upholsterers 715 Patternmakers and cutters 716 Dressmakers and sewers 719 Tailoring and sewing workers not elsewhere classified
40	Shoe and leather workers	721 Shoemakers and shoe repairers 722 Shoe cutters, lasters and sewers 723 Leather goods makers 729 Shoe and leather goods workers not elsewhere classified 852 Tanners and fur dressers
41	Metal processing workers	731 Furnacemen 732 Metal annealers, temperers and case-hardeners 733 Rolling-mill workers 735 Wire and tube drawers 736 Blacksmiths, hammersmiths and forgers 737 Metal casters and moulders 739 Metal processing workers not elsewhere classified
42	Precision-instrument and precious metal manufacturing workers	741 Precision-instrument makers 742 Watchmakers 743 Opticians 745 Jewelry and precious metal workers 746 Engravers 749 Precision-tool manufacturing workers not elsewhere classified 853 Musical instrument makers and tuners
43	Mechanics, iron and metalware workers	751 Toolmakers, machine tool setters and operators 752 Machinery fitters 753 Machine assemblers and engine mechanics 754 Sheet-metal workers 757 Structural metal prepares and erectors 758 Metal platers and coaters 759 Metal machine workers and building metal workers not elsewhere classified
44	Plumbers	755 Plumbers and pipe fitters
45	Welders	756 Welders and flame cutters
46	Electrical and electronics workers	761 Electrical fitters and wiremen 762 Aircraft and vehicle electrician 763 Electrical machinery assemblers and repairmen 764 Tele- and electronic repairmen and fitters 766 Recording, sound and light equipment operators 769 Electrical and electronics workers not elsewhere classified
47	Electric linemen	765 Electric linemen
48	Wood workers	034.50 Woodwork teachers 771 Timberhandlers 772 Wood processing workers 773 Laminated wood and fibreboard workers 775 Wooden boat builders, coachbody builders 776 Cabinet makers and joiners 777 Woodworking machine operators 779 Wood workers not elsewhere classified

		794 Construction carpenters
49	Painting and floor laying workers	781 Building painters 782 Floor layers 783 Painters (others than building) 789 Painters and floor layers not elsewhere classified
50	Bricklayers and concrete workers	791 Bricklayers 793 Concrete workers 851 Cast concrete product makers 854 Stone cutters and carvers
51	Other construction and production workers	795 Insulators 796 Glaziers 799 Building and construction workers not elsewhere classified 859 Production and related workers not elsewhere classified
52	Type-setters	801 Type-setters
53	Engravers, bookbinders and photographic laboratory workers	802 Printing and photo engravers 804 Bookbinders 805 Photographic laboratory workers 809 Printing workers not elsewhere classified
54	Printing pressmen	803 Printing pressmen
55	Glass, ceramic and tile workers	073.10 Ceramic artist, glass artist 811 Glass formers and cutters 812 Potters 813 Glass and ceramics kiln men 814 Glass and ceramics painters and decorators 819 Glass, pottery and tile workers nee
56	Food manufacture workers	821 Grain mill and oil press workers 822 Bakers and pastry cooks 823 Chocolate and confectionary makers 824 Brewers and other beverage makers 825 Canning workers 826 Butchers and meat preparers 827 Dairy workers 828 Tobacco workers 829 Food processing and tobacco workers not elsewhere classified
57	Chemical process workers	831 Chemical process workers 832 Cookers and furnacemen (chemical process) 833 Crushers, grinders and calender operators (chemical products) 841 Paper pulp preparers
58	Rubber and plastic workers	834 Rubber products makers 835 Plastic products makers 839 Chemical processing workers not elsewhere classified
59	Pulp and paper making workers	842 Paper makers 843 Paper products makers 849 Pulp and paper makers not elsewhere classified
60	Stationery engine operation workers (energy and	861 Stationery engine and related equipment operators 869 Stationery engine and related equipment operators not elsewhere classified

	water supply)	
61	Material handling operators	871 Crane and hoist operators 872 Earth-moving and related machinery operators 873 Truck and conveyor operators 879 Material handling and related equipment operators not elsewhere classified
62	Packing and storage workers	881 Packers 882 Store and warehouse workers 889 Packing and storage workers not elsewhere classified
63	Firefighters	901 Firefighters
64	Chimney sweeps	902 Chimney sweeps
65	Catering service workers	911 Catering supervisors 914 Waiters 919.10 Matron, restaurant
66	Cooks and kitchen assistants	912 Cooks 913 Kitchen assistants, restaurants workers
67	Private household workers	921 Housekeepers, domestic helps 929 Private household workers not elsewhere classified
68	Hotel workers	915 Hotel managers, hotel receptionists 919.20 Matron, hotel 919.91 Restaurant hostess 919.92 Matron assistant
69	Caretakers and cleaners	931 Building caretakers 932 Cleaners 939 Caretakers and cleaners not elsewhere classified
70	Launderers	951 Launderers and dry-cleaners 952 Pressers 959 Launderers, dry-cleaners and related workers not elsewhere classified
71	Hairdressers	941.10 Ladies' hairdresser 941.19 Business holder, women’s hairdresser 941.20 Men's hairdresser, barber 941.29 Business holder, men’s hairdresser 941.50 Wigmaker 941.91 Hairdresser assistant 941.92 Hairdresser student, unspecified
72	Beauticians	941.30 Cosmetologist 941.40 Manicurist 949 Hygiene and personal care workers not elsewhere classified
73	Sports and physical training workers	034.31 Dance teacher, other 034.32 Ballet teacher 034.40 Gymnastics instructor, school 034.41 Gymnastics assistant, school 942 Bath attendants 961.10 Sports leader 961.11 Gymnastics Assistant 961.12 Gymnastics instructor, Sports manager 961.13 Stable manager, sports manager athletic club 961.20 Sports trainer

		961.21 Sports trainer 961.30 Professional athlete 961.90 Assistant, horse racing track
74	Policemen and other protective service workers	903 Policemen 904 Customs officials 905 Prison and reformatory officials 906 Watchmen 909 Civilian protective service workers not elsewhere classified
75	Military personnel	981 Officers 989 Members of the armed forces not elsewhere classified
76	Other economically active workers	891 Unskilled manual workers 979 Service workers not elsewhere classified 999 Workers reporting occupations unidentifiable or inadequately described

APPENDIX C: MOST COMMON OCCUPATIONS BY SEX, EXPOSURE AND CENSUS

The two most common occupations (with at least 50 % probability of exposure) per exposure and census in Study III and IV (n=142 276).

		Men			Women		
			Freq	%		Freq	%
Asbestos	**1960**	Engine mechanics	656	76	Chimney sweeps	1	100
		Plumbers and pipe fitters	174	20	-	-	-
	1970	Engine mechanics	1055	28	Engine mechanics	13	65
		Electrical fitters and wiremen	860	23	Electrical fitters and wiremen	4	20
	1975	Electrical fitters and wiremen	945	32	Electrical fitters and wiremen	120	92
		Construction carpenters and joiners	858	29	Construction carpenters and joiners	3	2
	1980	Chimney sweeps	32	58	Insulators	2	100
		Insulators	23	42	-	-	-
	1990	Insulators	26	100	Insulators	1	100
		-	-	-	-	-	-
Silica	**1960**	Unskilled manual workers	257	22	Other production and related work n.e.c	30	30
		Construction carpenters and joiners	242	21	Unskilled manual workers	28	28
	1970	Construction carpenters and joiners	776	35	Unskilled manual workers	29	33
		Concrete and construction workers	517	23	Metal casters and moulders	13	15
	1975	Construction carpenters and joiners	858	37	Unskilled manual workers	31	20
		Concrete and construction workers	557	24	Potters	26	17
	1980	Construction carpenters and joiners	958	36	Other production and related work n.e.c.	84	34
		Concrete and construction workers	639	24	Unskilled manual workers	38	16
	1990	Construction carpenters	849	36	Glass, pottery and tile workers n.e.c.	26	23

		Building and construction workers n.e.c.	615	26	Metal casters and moulders	19	17
Wood dust	**1960**	Bench carpenters and cabinet makers	271	35	Wood work n.e.c	11	42
		Construction carpenters and joiners	242	32	Bench carpenters and cabinet makers	8	31
	1970	Construction carpenters and joiners	776	52	Bench carpenters and cabinet makers	44	51
		Bench carpenters and cabinet makers	390	26	Wood work n e c	17	20
	1975	Construction carpenters and joiners	858	51	Bench carpenters and cabinet makers	84	54
		Bench carpenters and cabinet makers	447	27	Wood work n e c	31	20
	1980	Construction carpenters and joiners	958	55	Bench carpenters and cabinet makers	146	64
		Bench carpenters and cabinet makers	485	28	Frame and circular sawyers and planers	23	10
	1990	Construction carpenters	849	58	Wood workers n.e.c.	70	26
		Woodworking machine operators	182	12	Woodworking machine operators	57	21
	2001	Woodworking machine operators	337	55	Woodworking machine operators	167	94
		Cabinet makers and joiners	219	36	Cabinet makers and joiners	6	3
	2010	Cabinet makers and joiners	405	64	Woodworking machine operators	49	51
		Woodworking machine operators	129	20	Cabinet makers and joiners	22	23
Animal dust	**1960**	Working proprietors, agricultural, horticultural and forestry enterprises	253	84	Livestock workers	34	59
		Livestock workers	30	10	Working proprietors, agricultural, horticultural and forestry enterprises	18	31
	1970	Working proprietors, agricultural, horticultural and forestry enterprises	502	88	Livestock workers	94	60
		Livestock workers	43	8	Working proprietors, agricultural, horticultural and forestry enterprises	36	23
	1975	Working proprietors, agricultural, horticultural and forestry enterprises	665	65	Agricultural workers	549	66
		Agricultural workers	320	31	Working proprietors, agricultural, horticultural and forestry enterprises	226	27

	1980	Working proprietors, agricultural, horticultural and forestry enterprises	945	79	Working proprietors, agricultural, horticultural and forestry enterprises	895	76
		Agricultural and livestock workers	207	17	Agricultural and livestock workers	207	17
	1990	Working proprietors in agriculture and forestry	803	93	Working proprietors in agriculture and forestry	602	82
		Livestock, dairy and poultry farm workers	32	4	Livestock, dairy and poultry farm workers	90	12
	2001	Livestock, dairy and poultry farm workers	241	70	Livestock, dairy and poultry farm workers	68	57
		Working proprietors in agriculture and forestry	85	25	Working proprietors in agriculture and forestry	23	19
	2010	Livestock, dairy and poultry farm workers	196	75	Livestock, dairy and poultry farm workers	112	67
		Working proprietors in agriculture and forestry	52	20	Veterinarians	27	16
Paper dust	**1960**	Typographers, lithographers	276	46	Packers	141	43
		Soting clerks and postmen	149	25	Bookbinders	89	27
	1970	Typographers, lithographers	335	45	Typographers, lithographers	269	43
		Sorting clerks and postmen	195	26	Bookbinders	100	16
	1975	Typographers, lithographers	367	40	Packers	390	44
		Sorting clerks and postmen	259	28	Sorting clerks and postmen	179	20
	1980	Typographers, lithographers	349	37	Packers	324	34
		Sorting clerks and postmen	277	29	Sorting clerks and postmen	251	26
	1990	Mail sorting clerks and postmen	299	35	Packers	457	38
		Printing pressmen	209	24	Mail sorting clerks and postmen	441	37
	2001	Packers	459	59	Packers	718	67
		Mail sorting clerks and postmen	251	32	Mail sorting clerks and postmen	338	31
	2010	Packers	143	35	Packers	222	43

		Mail sorting clerks and postmen	142	34	Mail sorting clerks and postmen	197	38
Textile dust	**1960**	Spinners, weavers, knitters and dyers	51	32	Seamstresses, ready-made clothing	555	56
		Upholsterers	47	29	Spinners, weavers, knitters and dyers	177	18
	1970	Upholsterers	67	35	Seamstresses, ready-made clothing	459	49
		Spinners, weavers, knitters and dyers	55	29	Spinners, weavers, knitters and dyers	148	16
	1975	Upholsterers	79	39	Tailors and dressmakers	500	50
		Spinners, weavers, knitters and dyers	46	23	Spinners, weavers, knitters and dyers	172	17
	1980	Upholsterers	69	43	Tailors and dressmakers	344	50
		Spinners, weavers, knitters and dyers	38	23	Spinners, weavers, knitters and dyers	147	21
	1990	Upholsterers	41	33	Dressmakers and sewers	439	55
		Launderers and dry-cleaners	32	26	Launderers and dry-cleaners	154	19
	2001	Upholsterers	7	54	Launderers and dry-cleaners	39	51
		Weaving and knitting machine setters	2	15	Tailors	12	16
	2010	Textile workers n.e.c.	11	31	Launderers and dry-cleaners	47	39
		Launderers and dry-cleaners	8	23	Tailors	17	14
Flour dust	**1960**	Bakers and pastry cooks	178	96	Bakers and pastry cooks	58	100
		Grain mill and oil press workers	8	4	-	-	-
	1970	Bakers and pastry cooks	131	95	Bakers and pastry cooks	76	97
		Grain mill and oil press workers	7	5	Grain mill and oil press workers	2	3
	1975	Bakers and pastry cooks	120	94	Bakers and pastry cooks	73	97
		Grain mill and oil press workers	8	6	Grain mill and oil press workers	2	3
	1980	Bakers and pastry cooks	109	88	Bakers and pastry cooks	96	93
		Grain mill and oil press workers	15	12	Grain mill and oil press workers	7	7
	1990	Bakers and pastry cooks	116	90	Bakers and pastry cooks	126	98
		Grain mill and oil press workers	13	10	Grain mill and oil press workers	3	2

	2001	Bakers and pastry cooks	36	97		Bakers and pastry cooks	27	100
		Grain mill and oil press workers	1	3		-	-	-
	2010	Bakers and pastry cooks	45	96		Bakers and pastry cooks	80	99
		Grain mill and oil press workers	2	4		Grain mill and oil press workers	1	1

Abbreviations: NEC, Not Elsewhere Classified