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Regional differences regarding risk of developing Rheumatoid Arthritis in Stockholm County, Sweden:

Results from the Swedish Epidemiological Investigation of Rheumatoid Arthritis (EIRA) study

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Abstract

Objectives—Rheumatoid arthritis (RA) is a complex disease that is associated with genetic and environmental factors. We have investigated geospatial variation in risk of developing RA within Stockholm County, with respect to established environmental risk factors for RA, as well as serologically-defined subgroups of RA.

Methods—Information regarding geographical location for 1432 cases and 2529 controls from the Epidemiological Investigation of Rheumatoid Arthritis (EIRA) study, living in Stockholm County at RA symptom onset, or matched date for controls, was used to estimate geospatial variation in risk. We used Generalized Additive Models (GAM) to create a risk surface, calculate odds ratios and adjust for potential confounding by smoking, educational level and RA within

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All authors approved the manuscript.

family. We performed a stratified analysis based on presence/absence of antibodies to citrullinated peptides (ACPA).

Results—We found significant spatial variation in the odds of developing RA in Stockholm County. After adjustment for smoking, educational level and family history of RA, this geospatial variation remained. The stratified analysis showed areas with higher odds ratios for ACPA-positive RA and ACPA-negative RA, after adjusting for smoking, educational level and having a family history of RA. Living in the city of Stockholm was associated with decreased risk of RA.

Conclusion—The risk of developing RA in Stockholm County is not evenly distributed and there are areas of increased risk that could not be explained by known factors. Further investigations of local exposures or social factors are warranted.

Keywords

Rheumatoid Arthritis; Epidemiologic methods; Antibodies; Geography; Risk; Smoking; ACPA; Stockholm

Introduction

Rheumatoid arthritis (RA) is a complex autoimmune disease thought to be caused by both genetic and environmental risk factors [1-6].

Past studies have shown that the RA prevalence varies between nations and that RA is more common in countries in Northern Europe and North America as compared to countries in Southern Europe [7]. There is also evidence for RA being a less common disease in Africa as compared to Northern Europe and North America [8].

Geographical investigation of the risk of RA in the US using The Nurses' Health Study (NHS) has demonstrated that women living in northeast US had increased risk of developing RA as compared to those in other parts of the US [9]. This geographical pattern regarding increased risks of RA was still present even after adjusting for potential confounding from smoking, which is the most established environmental risk factor for RA that is estimated to be responsible for a substantial proportion of incident RA [5-6, 10-13]. Smoking is primarily associated with RA characterized by the presence of anti-bodies toward citrullinated peptides (ACPA)[9-11]. The pathogenesis of RA characterized by presence of ACPA likely differs from that of RA without ACPA; cigarette smoking and the most established genetic risk factor, HLA-DRB1 shared epitope alleles, are primarily associated with ACPA positive RA [6,12-14]. In addition, lower educational level has been observed to be associated with an increased risk of RA [15]. Geographical differences with regard to RA risk may give rise to testable hypotheses concerning risk factors for the disease such as air pollution.

The aim of the present study was to investigate geographical variation in the risk of developing RA within Stockholm County, adjusting for risk factors such as smoking, educational level, family history of RA; and at the same time consider differences regarding disease phenotype as characterized by presence of antibodies toward citrullinated peptides.

We employed general additive models (GAM) to investigate potential geographical variation. The GAM model allows for the inclusion of a smoothing function for location as a variable in a logistic model and adjustment for potential confounders [16].

Methods

Study design

Cases and controls were recruited to the Swedish Epidemiological Investigation of Rheumatoid Arthritis (EIRA) study. EIRA is a population-based case control study with incident cases recruited between May 1996 and October 2009. All cases of RA were diagnosed by a rheumatologist, and the diagnosis was in almost all cases made at the first visit of the patient to a specialized rheumatology unit. Most (82%) of the cases were also diagnosed with RA within a year after the first subjective symptoms of the disease. Controls were matched to cases (between 1996 and 2006 with ratio 1:1 (individual matching), between 2006 and 2009 with ratio 2:1 (frequency matching)) based on age, sex and living area (based on County). In this study we only use cases and controls living in Stockholm County (area = 6 526,24 km²) at the time point of symptom onset (the participation rate for cases (n=1432) was 95 percent and 74 percent for the controls (n=2529). For each case and control, we retrieved information on geographical location from time points prior to study inclusion (from 1968 and forward annually). A nationwide register containing geographical residence information from a Swedish national dataset (Statistics Sweden) was linked to EIRA participants. We restricted the analysis to the geographic longitude and latitude coordinates for the residency in the year when RA symptoms began (index year). The matched control received the same index year. We also used geographic information regarding residency five years prior to the index year.

Information regarding smoking habits prior to RA onset in cases and during the same time period for controls was retrieved from the EIRA questionnaire. Family history of RA (first degree relative) was collected through the multigeneration register in Sweden [17].

Study participants provided a blood sample for biological measures. The presence of antibodies to citrullinated peptides (ACPA) was determined using a Euro Diagnostica assay (Malmö, Sweden) and the cut off for ACPA positivity was 25 units/micro liters.

Stockholm county ethical review board approved the study and all participants were contributing with data to the study on voluntarily basis with informed consent. More details on the study design of the EIRA study are available elsewhere [11-12, 14, 18].

Confounders

We considered education level, smoking and a family history of RA (using information from first degree relatives) as potential confounders in our analysis. Educational level was considered a proxy for socioeconomic status. We categorized education into having a university degree or not having a university degree. Higher education level has been observed to be associated with decreased risk of developing RA in earlier studies based on the EIRA data [15]. Smoking was categorized based on previous history of smoking (ever and never smokers). We adjusted for family history of RA through including a dichotomous variable in the models for having a family history of RA or not.

Statistical analysis

In order to study the relationship between geographical location and risk of developing RA, estimated through odds ratios, we used Generalized Additive Models (GAM) [19-20]. These models allow us to create a continuous surface of odds ratios for different locations that are adjusted for potential confounders. In our GAM model, the variable of interest is a bivariate smooth function of x and y coordinates in contrast to an ordinary regression model where the variable of interest is a value of exposure. GAMs are useful models for predicting disease risk when location is a proxy for environmental and/or social factors. One challenge

in using GAMs is to find the optimal span size for the specified smoothing function (location variable). In this study we used locally-weighted smoothing functions (LOESS) which weigh points within a neighborhood that is defined by the number of nearest (k -nearest) study participants. The LOESS function weight decreases to zero for the neighbor furthest away from the point of interest. LOESS also allow for smoothing in two dimensions. In order to choose the optimal span size (size of the resolution, small span size indicate higher resolution) for the LOESS function we calculated the Akaike information criterion (AIC) and chose the span size that minimized the AIC.

We tested whether location of residence was significantly associated with odds of RA by comparing the GAM model with the smoothing function and confounders, to a model with the same confounders but without the smoothing function for location, using a permutation test to generate a distribution of the deviance of the two models. We consider p -values < 0.05 as significant and employed point-wise permutations to determine regions with increased or decreased odds ratios. Based on the point-wise permutation test, we plotted contour lines on the Stockholm County map for regions associated with statistically significant increased or decreased odds ratios as estimates for RA risks. Odds ratios for the different points in Stockholm County were calculated using the odds of disease in all of Stockholm County as the reference. We also ran the analysis for geographical location five years prior to the index year to investigate if there was a different pattern regarding odds ratios of developing RA.

We did a separate analysis for ACPA-positive RA cases and ACPA-negative RA cases compared to all controls. We adjusted for age and sex in all of the models and for potential confounding by education level, smoking and family history of RA for all RA, ACPA- RA and ACPA+ RA (Table 1). Participants with missing data regarding the variables used in the corresponding model were excluded from that specific analysis. For the analysis regarding geospatial variation we used the GAM function with scripts written for analyzing geospatial data [16, 18-19]. Additional information regarding the GAM analysis can be found in previous published work by Vieira et al. [16].

We also used the “map” function for making maps of the geospatial distribution of the odds ratios [21]. All functions and scripts that were used were written using the R software (version R 2.10.1), which is free software under license and terms issued by the GNU (GNU is not UNIX) organization [22].

Results

Our spatial analyses included geocoded information for 1432 cases and 2581 controls living in Stockholm County at the time of RA symptom onset. In the controls we were missing information on 52 individuals on all covariates.

Analysis based on all RA cases

We found significant spatial variation as estimated through odds ratios for risk of RA ($p < 0.01$, Figure 1A). The highest odds ratios were observed in the west of Stockholm County (Figure 1) delineated by the dashed line. Significantly decreased odds ratios were observed in parts of the city of Stockholm and in northern regions of Stockholm County. Analysis based on geospatial data five years (data not shown) prior to symptoms onset showed the same pattern as the analysis based on data during the year of symptoms onset.

The spatial variation increased somewhat after adjusting for potential confounding from education level, family history of RA or smoking (Table 2). In the fully adjusted model (including educational level, smoking and family history of RA), the western region

remained with significantly increased odds ratios and Stockholm city with the northern region was still decreased odds (Figure 1B).

Stratified analysis regarding risk of ACPA-positive or ACPA-negative RA

The stratified analysis for ACPA positive RA cases ($n = 876$, Figure 1C, 1E) resulted in maps that were similar to maps based on all RA cases regarding areas associated with increased or decreased risk of RA. We observed increased odds ratios in the northwestern, southwestern regions and decreased odds ratios in Stockholm city with an extension to the northeast of the city (Figure 1C). The geospatial variation remained significant after we adjusted for potential confounding from ever smoking, educational level and family history of RA (Table 2, Figure 1E). After adjusting for all potential confounders there were one area in the northwest with significantly increased odds ratios and one area including parts of the city of Stockholm and a northern area proximal of the city with decreased odds ratios. There was still an area in southwest that was associated with increased odds ratio after adjusting for all the factors (Figure 1E).

In the analysis based on the ACPA-negative subset of RA cases ($n = 484$, Figure 2D), we found an area in the northwest and an area including parts of the city of Stockholm with an outreach including the archipelago in the east of the city with increased odds ratios of ACPA-negative RA. Adjustment for smoking in the ACPA-negative RA group did not change the map results regarding areas with increased or decreased odds ratios. When we adjusted for educational level, the odds ratios in the northwest increased and the area associated with decreased odds shifted to include most of the city of Stockholm and most of the northern parts of Stockholm County. In the fully adjusted model (adjusted for age, sex, education level, family history of RA and smoking), the area in the west still showed increased risk of developing ACPA- RA and the city and one area north of the city showed decreased odds ratios of developing ACPA- RA (Figure 1F).

Discussion

In this study we investigated geospatial variation regarding risk of developing RA in Stockholm County through odds ratios estimated by general additive models. We found areas of increased RA risk in the northwestern and western parts of the county and areas of decreased RA risk in the city of Stockholm and northeast region of the county. Previous studies in the US using a similar methodology have suggested that one potential explanation of geospatial variation in RA risk may be lower levels of vitamin D due to lack of sunlight in the northern parts of US, which could affect the function of the immune system [7]. This reasoning is probably not applicable in our study because of the comparable smaller area of Stockholm County. Using the relatively small area of Stockholm County for analysis provide the opportunity to detect areas that are associated with local exposures or local characteristics. One obvious source of confounding in a city is air pollution. In a recent study also restricted to Stockholm County we did not find any association between air pollution and risk of developing RA [23]. We adjusted for socioeconomic status through education level. This is a crude measure of socioeconomic status that does not differentiate between potential confounding from different occupational exposures in people with lower levels of education. Some occupational exposures have been observed to be associated with increased risk of RA [24]. Our maps with the geospatial distribution of increased odds ratios of RA are partly overlapping with areas with low income level in Stockholm County [25]. Adjusting for education level (university degree) in addition to smoking, sex and age decreased the odds ratios marginally for the areas in the northwest and in the south of Stockholm county but did attenuate the results in Stockholm city. Smoking is both associated with RA and lower socioeconomic status [1-6, 26]. Adjustment for smoking did not change the pattern of the risk areas as compared to the crude analysis without adjustment

for smoking, indicating that smoking is not a spatial confounder in our study. The lack of information regarding smoking and education due to data administration is unlikely to be associated with any selection. Finally we adjusted for potential confounding from family history of RA as one way to handle confounding from inheritance of RA. Adjusting for family history of RA did not change the estimates despite the strong association between having a family history of RA and having RA (Table 1). The geospatial risk patterns did not fluctuate much for different combinations of the confounders (education level, smoking and/or family history of RA).

Regarding ACPA status and geospatial variation, spatial patterns in the ACPA-positive RA map resembled the patterns in the analysis of all RA. We did not adjust for HLA-DRB1 alleles because lack of genetic information in many controls. However, adjustment for family history of RA did not change the geospatial risk pattern in Stockholm County which might indicate that there is no geospatial confounding from genetic factors such as HLA-DRB1 alleles.

In our analysis we used binary variables (for instance was smoking classified into the categories never or ever smoking). Unfortunately we did not have large enough sample size to include additional categories of smoking in the analysis. This means that we cannot exclude potential residual confounding but it is unlikely that residual confounding from smoking or education level would change the geospatial risk pattern much and there are no major differences between the crude and the adjusted map (Figure 1) concerning risk of RA.

In order to investigate demographic changes over time we also used the living location five years prior to symptoms onset. The geospatial risk pattern five years prior to symptoms onset was similar to the time point when symptoms occurred which indicate that there is no temporal differences between five years before symptoms onset and when symptoms occurred. The locations was the same for most of the cases and controls for the time of symptoms onset (index year for controls) and the time point five years before. This indicates that there is no major change in location for cases and controls over a five year period. However, we cannot exclude that there are other factors that have a long latency period and are correlated with location and that can cause RA that we have not adjusted for.

One potential source of bias is potential geospatial differences in terms of referral to rheumatology clinics from the general health care services. This problem should not be a major issue because of the established early arthritis clinics in Sweden, which aims to catch individuals with rheumatic diseases and start treatment early.

Despite our high participation rate, the discrepancy between participation rate in cases and controls is a potential source of bias. If the majority of non-participating controls is located within a certain area than the geospatial pattern can be affected. This is one limitation with our investigation that could explain parts of the results.

In the analysis of the ACPA-negative RA subgroup, only one area in the Northwest was associated with increased odds ratios. This area partly overlaps with the area of increased odds ratios for ACPA-positive RA. The pattern of the ACPA-negative RA map did not change when we adjusted for smoking. This is not surprising since earlier articles point out that smoking is primarily associated with ACPA-positive RA [6, 27]. After adjusting for education level, the odds ratios increased slightly. It is possible that the remaining geospatial variation is due to additional environmental or social factors, such as stress, occupational exposures or hormonal factors affecting the immune system [15, 25, 27].

The small geospatial differences between ACPA-positive and ACPA-negative RA, in terms of risk areas could be explained by differences in amount of smoking or some other

confounder that was included in the analysis. However, it cannot be excluded that differences regarding number of ACPA-negative cases and ACPA-positive cases (implying larger span size for ACPA-negative RA) in some regions have an impact on the model and hence the geospatial distribution regarding odds ratios on the Stockholm County map and therefore explain the differences between the ACPA positive and the ACPA negative RA map.

Conclusions

We observed a geographical variation in risk of developing RA, even after adjustment for potential confounding from previous known risk factors such as education level, smoking, and family history of RA. The geospatial variation was evident both regarding risk of ACPA positive and risk of ACPA negative RA, respectively, with slightly different patterns of distribution for these two subtypes of RA. Our findings indicate that there are additional risk factors that are correlated to the living area and that further explorative investigation is needed.

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List of abbreviations

RA	Rheumatoid Arthritis
GAM	Generalized additive models
ACPA	Antibodies toward citrullinated peptides
AIC	Akaike Information Criterion
LOESS	Locally weighted smoothing functions

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A (ACPA+,- RA ,
Crude model)

B (ACPA+,- RA, Fully Adjusted for Smoking,
education and family history of RA)

C (ACPA+ RA, CRUDE)

D (ACPA- RA, CRUDE)

E (ACPA+ RA, adjusted for Smoking, education and family history of RA)

F (ACPA- RA, adjusted for Smoking, education and family history of RA)

Figure 1.

Maps of Stockholm County regarding geographical distribution of odds ratios for all RA adjusted for age and sex (Figure 1A), all RA adjusted for age, sex, smoking, Family history of RA and educational status (Figure 1B), of ACPA+, adjusted for age and sex (Figure 1C), and of ACPA-adjusted for age and sex (Figure 1D), of ACPA+ RA, adjusted for age, sex, smoking, Family history of RA and educational status (Figure 1E), and of ACPA- adjusted for age, sex, smoking, Family history of RA and educational status (Figure 1F). Dotted lines indicate areas with $p < 0.05$.

Table 1

Background characteristics for cases with Rheumatoid Arthritis and controls in Stockholm County

Characteristics	Cases (n = 1432)	Controls (n = 2529)	p-value
ACPA + (%)	876 (64.4) [‡]	19 (3.5)	<0.001
Never smokers (%)	408 (29.7) [‡]	903 (39.9) [‡]	<0.001
Women (%)	1036 (72.3)	1802 (71.3)	0.5
RA in family (%)	174 (12.5) [‡]	105(4.6) [‡]	<0.001
Age (sd)	50.8 (12.8)	51.0(12.9)	0.63
University degree (%)	462 (33.5) [§]	1058 (45.5) [§]	<0.001

[‡]Lack of information regarding ACPA status on 72 cases

[‡]Missing information on smoking on 57 cases and 265 controls

[§]Lack of information regarding university degree on 108 cases and 204 controls

[‡]Lack of information from 43 cases and 256 controls.

Global p-values regarding geographical variation associated with different phenotypes of RA with adjustment for potential confounding from smoking and education level.

Table 2

ACPA status	Adjustment	Span size	Global p-value (Geospatial variation)
All RA	Sex, Age ^A	0.25	<0.001
All RA	Sex, Age, Educational level	0.25	<0.001
All RA	Sex, Age, Smoke	0.3	<0.001
All RA	Sex, Age, Educational level, Smoke, RA in family ^B	0.2	<0.001
ACPA+ RA	Sex, Age ^C	0.3	<0.001
ACPA+ RA	Sex, Age, Educational level	0.3	0.001
ACPA+ RA	Sex, Age, Smoke	0.3	<0.001
ACPA+ RA	Sex, Age, RA in family	0.3	<0.001
ACPA+ RA	Sex, Age, Educational status, Smoke, RA in family ^E	0.3	<0.001
ACPA- RA	Sex, Age ^D	0.65	<0.001
ACPA- RA	Sex, Age, Educational status	0.25	<0.001
ACPA- RA	Sex, Age, Smoke	0.65	<0.001
ACPA- RA	Sex, Age, RA in family	0.25	<0.001
ACPA- RA	Sex, Age, Educational status, family history of RA, Smoke ^F	0.25	<0.001

^a All analysis are displayed in figure 1 corresponding to the superscripted letter.

^b All analysis are displayed in figure 1 corresponding to the superscripted letter.

^c All analysis are displayed in figure 1 corresponding to the superscripted letter.

^d All analysis are displayed in figure 1 corresponding to the superscripted letter.

^e All analysis are displayed in figure 1 corresponding to the superscripted letter.

^f All analysis are displayed in figure 1 corresponding to the superscripted letter.