Published in final edited form as:
Arthritis Care Res (Hoboken). 2014 October ; 66(10): 1438–1446. doi:10.1002/acr.22366.

Contributions of Familial Rheumatoid Arthritis or Lupus and Environmental Factors to Risk of Rheumatoid Arthritis in Women: a Prospective Cohort Study

Jeffrey A. Sparks, MD[1], **Chia-Yen Chen, ScD**[2], **Linda T. Hiraki, MD, SM, ScD**[3], **Susan Malspeis, SM**[1], **Karen H. Costenbader, MD, MPH**[1], and **Elizabeth W. Karlson, MD**[1]

[1]Department of Medicine, Division of Rheumatology, Immunology and Allergy, Brigham and Women's Hospital, Boston, MA

[2]Harvard School of Public Health and Department of Medicine, Division of Rheumatology, Immunology and Allergy, Brigham and Women's Hospital, Boston, MA

[3]Research Institute, Genetics and Genome Biology, Division of Rheumatology, The Hospital for Sick Children, Toronto, Canada

Abstract

Objective—We assessed the contributions of familial rheumatoid arthritis (RA) or lupus and environmental factors to risk of RA.

Methods—Among 121,700 women in the Nurses' Health Study, 65,457 provided data on familial RA/lupus. Among these, 493 RA cases (301 seropositive and 192 seronegative) were validated. We estimated hazard ratios (HR) for RA comparing those with and without familial RA/lupus, adjusting for environmental factors (smoking, alcohol, body mass index [BMI], parity, breastfeeding, menopause, hormone use, early menarche, and menstrual regularity) using Cox proportional hazards models. Population attributable risks (PAR) for RA within this cohort were calculated for familial RA/lupus, smoking, alcohol, BMI, parity, and breastfeeding.

Results—Familial RA/lupus was significantly associated with RA (HR 3.67), seropositive RA (HR 3.90) and seronegative RA (HR 3.95). After adjusting for environmental factors, familial RA/lupus was significantly associated with RA (HR 3.59, 95% confidence interval 2.94–4.37). Smoking >10 pack-years, alcohol intake 5–10 g/day, overweight, breastfeeding ≥12 months, and pre-menopausal status remained significantly associated with RA after adjusting for familial RA/lupus. For RA in this cohort, the PAR for smoking, BMI, alcohol, parity, or breastfeeding collectively was 41%; the PAR due to heredity from familial RA/lupus was 21%.

Correspondence: Jeffrey A. Sparks, MD, Department of Medicine, Division of Rheumatology, Allergy, and Immunology, Brigham and Women's Hospital, 45 Francis Street, Boston, MA 02115, Phone: 617-732-5325, Fax: 617-732-5766, jasparks@partners.org.

AUTHOR CONTRIBUTIONS: All authors were involved in drafting the article or revising it critically for important intellectual content, all authors approved the final version to be published. Dr. Sparks had full access to all of the data in the study and takes full responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Sparks, Chen, Hiraki, Costenbader, Karlson.

Acquisition of data. Sparks, Costenbader, Karlson.

Analysis and interpretation of data. Sparks, Chen, Hiraki, Malspeis, Costenbader, Karlson.

Conclusion—In this large, prospective cohort, women with familial RA/lupus had a four-fold increased risk for RA that remained significant after adjusting for environmental factors. A large proportion of RA risk was attributable to environmental factors even among those with familial RA/lupus.

Keywords

rheumatoid arthritis; family history; epidemiology; population attributable risk

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic autoimmune disease primarily affecting the joints often leading to disability.(1) RA risk is composed of inherited and environmental risk factors.(2–5) Prior studies have established RA as having a familial component, with about 15% concordance and heritability of 53–65% in twin studies.(6, 7)

Familial RA risk may be composed of shared environmental factors, such as cigarette smoking, which tend to occur in families.(8, 9) Environmental risk factors have been shown to be associated with the development of RA.(8) Cigarette smoking has been shown to be a strong risk factor for RA with a population attributable risk approaching 35% for seropositive RA.(10, 11) Obesity tends to occur within families, even among spouses and adopted children.(12–14) Other environmental risk factors, such as moderate alcohol intake and hormonal factors may also be correlated within families. These factors have been associated with RA, with higher risk of RA from increased body mass index (BMI), lower risk from moderate alcohol intake, and lower risk from breastfeeding.(3, 15–17)

Studies have previously estimated the personal risk of RA conferred by having an affected first-degree relative with RA.(18–20) A study compared RA cases identified by hospital discharge to a national registry with information on family history, and found that the standardized incidence ratios (SIR) of RA were 3.02 for an affected parent and 4.64 for an affected sibling.(20) This study also evaluated the association of family history of other autoimmune diseases with development of RA and found that family history of lupus in a first-degree relative was significantly associated with the personal development of RA (SIR 2.13).(20) RA and lupus have also been shown to aggregate in families.(21)

Whether the familial risk of RA is due to genetics alone or from shared environmental exposures is unknown. Prior studies have not examined the effect of environmental factors and familial RA or lupus for the development of RA. Moreover, most prior studies of familial RA have not investigated possible differences in RA risk based on seropositive and seronegative RA phenotypes.(19) A recent Swedish study suggested that anti-citrullinated protein antibody (ACPA)-positive RA has higher heritability (50%) compared to ACPA-negative RA (20%) and that ACPA-positive RA had higher familial risk than ACPA-negative RA.(22) Seropositive and seronegative RA may have different environmental risk factors.(23) In a prospective cohort study, the Nurses' Health Study, women completed a single question on familial RA or lupus in first-degree relatives. Since the prevalence of RA (1%) is twenty times higher than the prevalence of lupus (0.05%) in the United States most of these familial reports are likely due to RA.(20, 24)

We aimed to determine whether known environmental RA risk factors influence the association of familial RA or lupus with personal RA, according to serologic phenotypes in the Nurses' Health Study. We also aimed to evaluate the contributions of modifiable environmental risk factors and familial RA or lupus to the development of RA.

PATIENTS AND METHODS

Study Population

The Nurses' Health Study (NHS) is a prospective cohort of 121,700 female nurses in the United States aged 30 to 55 years in 1976, when the study began. Information was collected from subjects by biennial questionnaires regarding anthropometrics, medications, medical history, environmental factors, dietary factors, and family history of diseases. All aspects of this study were approved by the Partners Healthcare Institutional Review Board.

Identification of Rheumatoid Arthritis

The method for identification and validation of incident RA in NHS has been previously described.(25) Briefly, participants self-reported a diagnosis of connective tissues disease (CTD), such as RA or lupus. Potential cases were identified by self-report and the CTD screening questionnaire (CSQ) was then mailed to participants.(25, 26) For those whose CSQ was positive, medical records were requested and reviewed independently by two board-certified rheumatologists who confirmed RA according to the 1987 American College of Rheumatology RA classification criteria.(27)

Clinical RA characteristics, such as serologic status, symptom onset, and date of diagnosis were extracted from the participants' medical record review. Seropositive RA was defined as the presence of rheumatoid factor or ACPA (not clinically available during early during early years of NHS follow-up) on medical record review, or the presence of ACPA among those who provided plasma samples (n = 12 cases).(28, 29) All other RA cases were classified as seronegative, including those without available antibody testing. For all analyses, we excluded prevalent cases of RA diagnosed before the start of NHS. We censored non-responders and women who reported CTD that were not subsequently confirmed to be RA by medical record review. Participants who did not answer the 2008 questionnaire concerning familial RA or lupus were excluded for all analyses.

Assessment of Familial and Environmental Factors

In 2008, women in NHS were asked, "Have any of the following biological relatives had rheumatoid arthritis or lupus (SLE)?" RA and lupus were combined into a single question due to space constraints. Possible answers were: "no," "parent," "sibling," or "offspring." Participants could choose more than one type of relative but were instructed not to include half siblings for their answer. Categories of parent, sibling, and offspring were not mutually exclusive. Familial RA or lupus was defined as a positive response to at least one relative. For these analyses, all women provided information on family history of RA or lupus. In NHS, family history of Hashimoto's thyroiditis, type 1 diabetes mellitus, and other rheumatic autoimmune diseases was not assessed.

All environmental exposure information was self-reported on mailed questionnaires administered every two years since 1976. Cigarette smoking was categorized as: never to ≤10 pack-years, >10 to ≤20 pack-years, and >20 pack-years. Alcohol intake was measured as drinks of beer, wine, and liquor per day by the food frequency questionnaire assessed every four years since 1980. This was converted into grams per day based on alcohol content in each beverage; cumulative average intake was calculated based on all assessments prior to RA development or until last follow-up for non-cases.(30) A validation study of alcohol intake comparing assessment by food frequency questionnaire and dietary recall had a correlation coefficient of 0.9 for women.(31) Alcohol use (cumulative average daily intake) was defined as: never to <5 grams per day, 5 to <10 grams per day, and ≥10 grams per day. BMI was calculated from self-reported height and weight and categorized according to the World Health Organization (WHO): underweight (>14 to <18.5 kg/m^2) or normal (18.5 to 25 kg/m^2), overweight (25 to 30 kg/m^2), and obese (>30 kg/m^2).(32)

Reproductive covariates were chosen on the basis of previous findings of associations between reproductive factors and the risk of developing RA in NHS and other studies.(33, 34) We included covariates for parity and breastfeeding duration (nulliparous, parous and no breastfeeding, parous and 1–11 months breastfeeding, and parous and ≥12 months breastfeeding), menopause and hormone use (pre-menopausal, post-menopausal and no hormone use, and post-menopausal and hormone use), age at menarche (≤10 years or menarche at >10 years), and menstruation (regular or irregular).

Statistical Analysis

We estimated hazard ratios (HR) and 95% confidence intervals (CI) for the association between familial RA or lupus in a first-degree relative and the development of RA using age-adjusted and multivariate Cox proportional hazards models. All analyses were adjusted for age and questionnaire period. Last follow-up was defined as last questionnaire returned, death, or loss to follow-up. Women who died or were lost to follow-up were censored at the last questionnaire response.

We used age-adjusted Cox proportional hazards models to estimate the HR and 95% CI for dichotomous (any or none) familial RA and for each affected first-degree relative (parent, sibling, or offspring) with the reference of no RA or lupus in first-degree relatives. Those with familial RA or lupus other than the relative being analyzed were excluded for these analyses to provide a consistent reference group without familial RA or lupus. Separate models were performed to estimate HR for all RA, seropositive RA, and seronegative RA phenotypes. For seropositive and seronegative RA analyses, cases of the other serologic status were excluded.

Multivariate analyses were performed using Cox proportional hazards models for the association of familial RA or lupus with RA adjusting for environmental factors. Covariates that were cumulatively updated biennially at each NHS questionnaire included: smoking, alcohol intake, BMI, parity, breastfeeding, menopause and post-menopausal hormone use, and menstrual regularity. Cox proportional hazard models were initially performed for familial RA or lupus in first-degree relatives and development of RA, adjusting for age and questionnaire period. We then added each RA environmental risk factor separately to

estimate the effect of that environmental factor on the HR for familial RA or lupus. We performed a full multivariate Cox proportional hazard model that included familial RA or lupus, age, questionnaire period, smoking, alcohol intake, BMI, parity and breastfeeding duration, menopausal status and hormone use, early menarche, and menstrual regularity. We performed multivariate Cox proportional hazards models including only environmental RA risk factors to examine whether these were associated with RA in our study cohort. All multivariate analyses were performed for all, seropositive, and seronegative RA in separate models.

We calculated the population attributable risk (PAR) percent for RA from familial RA or lupus and environmental RA risk factors within our entire study cohort and among those that reported familial RA or lupus. We calculated PAR according to methods that have been previously described in detail.(35) We considered familial RA or lupus as a non-modifiable risk factor for the calculation of PAR for the entire study cohort. We considered cigarette smoking (>10 pack-years), low alcohol intake (<5 grams per day and no intake), increased BMI (overweight or obese by WHO category), nulliparity or breastfeeding <12 months as modifiable risk factors that all increase the risk of RA. PAR for modifiable risk factors were calculated separately for each factor and in combinations. All models for PAR for RA were adjusted for age, questionnaire period, familial RA or lupus, smoking, BMI, alcohol intake, parity, breastfeeding, menopausal status, hormone use, age at menarche, and menstrual regularity.

All *p* values were 2-sided, with values less than 0.05 considered statistically significant. Statistical analyses were conducted using SAS software version 9.2 (SAS Institute Inc., Cary, North Carolina).

RESULTS

Among 65,457 women who provided information on familial RA and lupus in 2008, we identified 493 RA cases that occurred after 1976 during 1,846,189 person-years of follow-up in NHS. Of these, 301 (61%) seropositive and 192 (39%) seronegative RA cases were identified. RA or lupus in first-degree relatives was self-reported in 143 (29%) cases and 6,856 (10.6%) non-cases, for a total of 6,999 (10.7%) women.

Table 1 summarizes the baseline characteristics in 1976 of women stratified by familial RA or lupus. Baseline characteristics at the start of NHS in 1976 were similar based on familial RA or lupus reported in 2008. The mean age at baseline for those with familial RA or lupus was 41.6 years (standard deviation, SD 6.8) and 41.3 (SD 6.8) for those with no familial RA or lupus. Among those with familial RA or lupus, 68% smoked for ≤10 pack-years, while 69% of those without familial RA or lupus had ≤10 pack-years.

Mean age at RA diagnosis was 57.9 years (SD 10.0) for those with familial RA or lupus and 58.5 years (SD 9.9) for those without familial RA or lupus (Table 2). Similar proportions of the participants with and without familial RA or lupus had seropositive RA (60% vs. 61%, respectively).

Familial RA or lupus in first-degree relatives was significantly associated with personal development of RA (HR 3.67, 95% CI 3.01–4.47) (Table 3). Familial RA or lupus was significantly associated with seropositive (HR 3.90, 95% CI 3.03–5.03) and seronegative RA (HR 3.95, 95% CI 2.88–5.40). The HR for RA from two or more first-degree relatives with RA or lupus was 6.83 (95% CI 4.43–10.53).

RA or lupus in a parent (HR 4.27, 95% CI 3.39–5.37), sibling (HR 3.35, 95% CI 2.45–4.58), and offspring (HR 4.12, 95% CI 2.76–6.14) were all significantly associated with RA. Familial RA or lupus according to each type of affected first-degree relative was significantly associated with both seropositive and seronegative RA.

Supplemental Table shows the HR for familial RA or lupus and RA phenotypes after adjusting for each individual environmental risk factor. When adjusted for smoking, familial RA or lupus remained significantly associated with all RA (HR 3.63, 95% CI 2.98–4.43), seropositive RA (HR 3.86, 95% CI 2.99–4.97), and seronegative RA (HR 3.92, 95% CI 2.87–5.37). Other environmental factors similarly had little effect in hazard ratios of positive family history and RA serologic phenotypes. There were no statistically significant interactions between familial RA or lupus and each environmental factor (data not shown).

Table 4 shows the HR for familial RA or lupus and RA after adjusting for all environmental factors. Familial RA or lupus was significantly associated with all RA (HR 3.59, 95% CI 2.94–4.37), seropositive RA (HR 3.81, 95% CI 2.95–4.92), and seronegative RA (HR 3.84, 95% CI 2.80–5.25) after adjustment for all environmental RA risk factors (Table 4). In addition, the HR for smoking (1.54, 95% CI 1.18–2.02, for >10 to 20 pack-years; 1.52, 95% CI 1.23–1.92, for >20 pack-years), overweight (1.23, 95% CI 1.01–1.51 compared to normal or underweight),, and pre-menopausal status (0.69, 95% CI 0.50–0.97, compared to post-menopause and no hormone use) remained significantly associated with RA (Table 4).

The PAR for RA based on risk factor profiles are shown in Table 5. Within the entire study cohort (n = 65,457), 21% of RA risk was attributable to familial RA or lupus. Smoking >10 pack-years accounted for 14% of RA risk, low alcohol intake (none or <5 g/day) accounted for 12% of RA risk, increased BMI (overweight or obese) accounted for 9% of RA risk, and nulliparity or breastfeeding <12 months accounted for 15% of RA risk. Collectively, 41% of RA risk could be attributed to modifiable factors (smoking, low alcohol intake, excess BMI, and nulliparity/low breastfeeding) in the study cohort.

Among those who reported familial RA or lupus in 2008 (n = 6,999), 18% of RA risk was attributable to cigarette smoking, 3% of RA risk was due to low or no alcohol intake, 11% of RA risk was attributable to increased BMI, and 25% of RA risk was due to nulliparity or breastfeeding <12 months (Table 5). Among women with self-reported familial RA or lupus, a similar proportion of RA risk (46%) was attributable to smoking, low alcohol intake, excess BMI, and nulliparity/low breastfeeding.

DISCUSSION

In this large, prospective cohort of women, there was a significant association between familial RA or lupus and development of RA. This association was significant with any

affected first-degree relative and for each type of relative (parent, sibling, or offspring). The association of familial RA or lupus with RA persisted after adjusting for known environmental RA risk factors, such as smoking, alcohol intake, overweight or obesity, and reproductive/hormonal factors, suggesting that the risk attributable to familial RA or lupus is not due to environmental factors. Smoking, alcohol intake, overweight, parity and breastfeeding, and menopausal status and post-menopausal hormone use were all significantly associated with RA within our study cohort after adjusting for familial RA or lupus suggesting that these factors are independent of family history (Table 4). Within our study cohort, a large proportion of RA risk was attributable to modifiable environmental risk factors, even among those with familial RA or lupus.

The effect size estimate of RA risk from familial RA or lupus in our study (HR 3.59) is similar to previous reports for risk from familiar RA, likely because lupus is less common than RA.(20, 24) Hemminki *et al*. reported a SIR of 3.02 for RA from a parent affected with RA and a SIR of 4.64 from an RA-affected sibling.(20) Family history of lupus in a first-degree relative was also significantly associated with the personal development of RA (SIR 2.13).(20) Grant *et al*. reported relative risks (λ) for RA of 3.88 for RA-affected parents and 4.38 for RA-affected siblings.(18) Koumantaki *et al*. reported an odds ratio for developing RA of 4.4 for a first-degree relative with RA. Somers *et al*. reported a HR of 2.7 for RA in female offspring with a maternal history of RA.(36) Frisell *et al*. recently reported an OR of 3.2 for RA from a first-degree relative with RA.(22)

We found that effect size estimates between different types of first-degree relatives were similar, as has been reported in other studies.(18–20, 22) In 2008, when familial RA or lupus data were collected in our study, most participants were advanced in age (age range 62–87 years), likely resulting in higher effect size estimates for affected children since these children were likely older compared to other studies.(18) We found that familial associations were similar for seropositive and seronegative RA. A study prior to the development of ACPA testing addressed rheumatoid factor and familial risk for RA and found no association with rheumatoid factor and familial RA, as our study also suggests.(19) However, a recent study showed higher familial risk for ACPA-positive RA (OR 3.7) compared to ACPA-negative RA (OR 2.1).(22) RA cases diagnosed prior to the adoption of ACPA testing had the potential to be misclassified as seronegative in our study. The inclusion of lupus in our familial estimate may have also affected our effect size estimates, especially for seronegative RA. Even though most environmental factors were more strongly associated with seropositive RA than seronegative RA (Table 4), inclusion of environment did not confound the risk conferred by history of familial RA or lupus for either RA serostatus.

Family history of a disease is thought to be a proxy for genetic risk, information that is easily obtained in clinical practice.(37) There are currently 101 alleles that have been associated with RA with genome-wide significance.(38) However, the total variance explained by validated genetic variants is estimated to be only 16%, so many genetic risk variants likely remain to be discovered which could explain some of the excess risk seen in familial RA.(39)

Family history is also likely composed of shared environmental factors.(3) Children who grow up with parents who smoked cigarettes are more likely to smoke themselves.(9) Previously, we were not able to show that secondhand smoke exposure was associated with RA risk. Smoking is thought to be an important risk factor in the development of seropositive RA among those who are at high genetic risk with significant gene-environment interactions.(10, 11) Excess body mass likely has both environmental and genetic components, with correlations of obesity among spouses and adopted children.(12–14) Previous studies examining familial risk of RA have not been able to include time-varying environmental risk factors, such as cigarette smoking, alcohol intake and BMI, which can be assessed in prospective, longitudinal cohort studies, such as NHS. However, we found that familial risk was not attenuated after adjusting for environmental factors, suggesting that shared environment does not contribute to familial risk.

In our study population, 21% of RA risk was attributable to familial RA or lupus, while 46% was attributable to environmental risk factors. These findings are similar to previous studies in which genetics were estimated to explain 16% of the variance in RA and cigarette smoking accounted for 20% of RA risk and 35% of ACPA-positive RA risk.(11, 39) The same PAR for modifiable risk factors (41%) was present within the subset of our study cohort who reported familial RA or lupus. This suggests that environmental RA risk factors and familial RA or lupus are independent and that RA risk may be modifiable even among those with familial RA or lupus. While the effect size estimates for familial RA or lupus are large in our studies and others, the PAR for environmental factors suggests that environmental factors have an important role in the pathogenesis and etiology of RA.(11) A recent study reported that, among a high-risk population with arthralgias and positive RA-related antibodies, those that smoked and were overweight were more likely to develop RA.(40) Identifying positive family history may be a powerful tool to motivate those at increased risk of RA to adopt healthy behaviors aimed at prevention.(37) We caution that our PAR estimates do not necessarily imply preventability since only smoking has strong evidence to support a causal role in the development of RA.

Our study has several strengths. We used a large, prospective cohort with data on environmental factors provided biennially prior to symptom onset and RA diagnosis with over two million patient-years of follow-up data. Environmental risk factors were collected prospectively without recall bias. Our study is the largest to examine the familial risk for RA phenotypes by serologic status. We were able to examine familial risk of RA at the level of each affected first-degree relative. This study is the first to adjust familial RA risk for known RA environmental risk factors. Ours is also the first to explore PAR for several RA risk factors in the context of familial RA or lupus.

Our study has limitations as well. While our study was large and lifestyle risk factor data were collected prospectively, only women in the United States were included in NHS. Data on familial RA or lupus were collected after RA diagnosis in 2008 and by self-report, which might have led to recall bias, or changes in behavior due to familial disease. Moreover, the timing of the diagnoses in the participants and their affected relatives is not known. Thus, these cross-sectional analyses of familial RA or lupus and RA risk should be interpreted as associations and not prospective risk analyses. As a compound question was used, we were

unable to distinguish whether the reported family member was affected with RA or lupus. Family history of lupus has a known association with RA, and the prevalence of RA (1%) is twenty times higher than the prevalence of lupus (0.05%) in the United States.(20, 24) We therefore expect that most of the familial diagnoses were RA, though acknowledge that some were lupus. The percentages of familial RA or lupus among RA cases (29%) and non-cases (10.6%) in this study were higher than those of a previous Dutch study, in which 10% of RA patients had a sibling with RA, and in a Colombian study, in which 7% of RA patients had a first-degree relative with RA.(41, 42) Despite these limitations, the effect size of familial RA or lupus was very similar to previous reports. Data on multiple affected relatives of the same type (e.g., two siblings vs. two parents) were unavailable. However, the HR for RA in our study for two or more first-degree relatives affected with RA or lupus (6.83) is similar to the recent study by Frisell *et al*. that reported an OR of 7.0 for RA with two or more first-degree relatives with RA.(22) Participants who were adopted or had complicated family structures may have been misclassified according to familial RA or lupus. However, these are similar limitations to the practical ascertainment of family history in clinical practice.(37) Additionally, future studies may identify environmental factors other than those analyzed that could be important to the familial component of RA risk and also might affect our PAR estimate. Finally, the PAR estimation assumes that environmental factors are causal, and that, if they could all be eliminated, then 41% of RA cases would be prevented. However, only for cigarette smoking is there evidence that risk is reduced after cessation.(25)

Our study quantified the association between familial RA or lupus, and RA among women. Familial associations with RA were similar for different first-degree relatives affected and for seropositive and seronegative RA. The familial association with RA was not accounted for by known environmental RA risk factors. Even among those who reported familial RA or lupus, a high proportion of RA may be preventable. Further studies are needed to establish the genetic and environmental contributions to familial risk in RA. Public health efforts encouraging healthy behaviors may have an important role in RA prevention, especially among those with familial RA or lupus.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

The authors would like to thank May Al-Daabil, MD for her assistance in reviewing medical records in addition to all the participants and staff of the Nurses' Health Studies for their contributions.

Financial disclosures: This work was supported by grants from the National Institutes of Health (grants CA087969, CA049449, CA050385, and CA067262) and the National Institute of Arthritis and Musculoskeletal and Skin Diseases (grants AR049880, AR052403, and AR047782). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

REFERENCES

1. Kirwan JR. Links between radiological change, disability, and pathology in rheumatoid arthritis. J Rheumatol. 2001; 28(4):881–886. [PubMed: 11327270]

2. Frisell T, Holmqvist M, Kallberg H, Klareskog L, Alfredsson L, Askling J. Familial risks and heritability of rheumatoid arthritis: role of rheumatoid factor/anti-citrullinated protein antibody status, number and type of affected relatives sex, and age. Arthritis Rheum. 2013; 65(11):2773–2782. [PubMed: 23897126]
3. Lahiri M, Morgan C, Symmons DP, Bruce IN. Modifiable risk factors for RA: prevention, better than cure? Rheumatology (Oxford). 2012; 51(3):499–512. [PubMed: 22120459]
4. Karlson EW, Deane K. Environmental and gene-environment interactions and risk of rheumatoid arthritis. Rheum Dis Clin North Am. 2012; 38(2):405–426. [PubMed: 22819092]
5. Deane KD, Norris JM, Holers VM. Preclinical rheumatoid arthritis: identification, evaluation, and future directions for investigation. Rheum Dis Clin North Am. 2010; 36(2):213–241. [PubMed: 20510231]
6. Silman AJ, MacGregor AJ, Thomson W, Holligan S, Carthy D, Farhan A, et al. Twin concordance rates for rheumatoid arthritis: results from a nationwide study. Br J Rheumatol. 1993; 32(10):903–907. [PubMed: 8402000]
7. MacGregor AJ, Snieder H, Rigby AS, Koskenvuo M, Kaprio J, Aho K, et al. Characterizing the quantitative genetic contribution to rheumatoid arthritis using data from twins. Arthritis Rheum. 2000; 43(1):30–37. [PubMed: 10643697]
8. Karlson EW, Ding B, Keenan BT, Liao K, Costenbader KH, Klareskog L, et al. Association of environmental and genetic factors and gene-environment interactions with risk of developing rheumatoid arthritis. Arthritis Care Res (Hoboken). 2013
9. Arillo-Santillan E, Lazcano-Ponce E, Hernandez-Avila M, Fernandez E, Allen B, Valdes R, et al. Associations between individual and contextual factors and smoking in 13,293 Mexican students. Am J Prev Med. 2005; 28(1):41–51. [PubMed: 15626554]
10. Sugiyama D, Nishimura K, Tamaki K, Tsuji G, Nakazawa T, Morinobu A, et al. Impact of smoking as a risk factor for developing rheumatoid arthritis: a meta-analysis of observational studies. Ann Rheum Dis. 2010; 69(1):70–81. [PubMed: 19174392]
11. Kallberg H, Ding B, Padyukov L, Bengtsson C, Ronnelid J, Klareskog L, et al. Smoking is a major preventable risk factor for rheumatoid arthritis: estimations of risks after various exposures to cigarette smoke. Ann Rheum Dis. 2011; 70(3):508–511. [PubMed: 21149499]
12. Llewellyn CH, Trzaskowski M, Plomin R, Wardle J. Finding the missing heritability in pediatric obesity: the contribution of genome-wide complex trait analysis. Int J Obes (Lond). 2013
13. Maes HH, Neale MC, Eaves LJ. Genetic and environmental factors in relative body weight and human adiposity. Behav Genet. 1997; 27(4):325–351. [PubMed: 9519560]
14. Garn SM, Cole PE, Bailey SM. Living together as a factor in family-line resemblances. Hum Biol. 1979; 51(4):565–587. [PubMed: 527953]
15. Kallberg H, Jacobsen S, Bengtsson C, Pedersen M, Padyukov L, Garred P, et al. Alcohol consumption is associated with decreased risk of rheumatoid arthritis: results from two Scandinavian case-control studies. Ann Rheum Dis. 2009; 68(2):222–227. [PubMed: 18535114]
16. Wesley A, Bengtsson C, Elkan AC, Klareskog L, Alfredsson L, Wedren S. Association between body mass index and anti-citrullinated protein antibody-positive and anti-citrullinated protein antibody-negative rheumatoid arthritis: results from a population-based case-control study. Arthritis Care Res (Hoboken). 2013; 65(1):107–112. [PubMed: 22674870]
17. Jorgensen C, Picot MC, Bologna C, Sany J. Oral contraception, parity, breast feeding, and severity of rheumatoid arthritis. Ann Rheum Dis. 1996; 55(2):94–98. [PubMed: 8712873]
18. Grant SF, Thorleifsson G, Frigge ML, Thorsteinsson J, Gunnlaugsdottir B, Geirsson AJ, et al. The inheritance of rheumatoid arthritis in Iceland. Arthritis Rheum. 2001; 44(10):2247–2254. [PubMed: 11665965]
19. del Junco D, Luthra HS, Annegers JF, Worthington JW, Kurland LT. The familial aggregation of rheumatoid arthritis and its relationship to the HLA-DR4 association. Am J Epidemiol. 1984; 119(5):813–829. [PubMed: 6609637]
20. Hemminki K, Li X, Sundquist J, Sundquist K. Familial associations of rheumatoid arthritis with autoimmune diseases and related conditions. Arthritis Rheum. 2009; 60(3):661–668. [PubMed: 19248111]

21. Alarcon-Segovia D, Alarcon-Riquelme ME, Cardiel MH, Caeiro F, Massardo L, Villa AR, et al. Familial aggregation of systemic lupus erythematosus, rheumatoid arthritis, and other autoimmune diseases in 1,177 lupus patients from the GLADEL cohort. Arthritis Rheum. 2005; 52(4):1138–1147. [PubMed: 15818688]
22. Frisell T, Holmqvist M, Kallberg H, Klareskog L, Alfredsson L, Askling J. Familial risks and heritability of RA in relation to RF/ACPA status, number and type of affected relatives sex, and age. Arthritis Rheum. 2013
23. Pedersen M, Jacobsen S, Klarlund M, Pedersen BV, Wiik A, Wohlfahrt J, et al. Environmental risk factors differ between rheumatoid arthritis with and without auto-antibodies against cyclic citrullinated peptides. Arthritis Res Ther. 2006; 8(4):R133. [PubMed: 16872514]
24. Danchenko N, Satia JA, Anthony MS. Epidemiology of systemic lupus erythematosus: a comparison of worldwide disease burden. Lupus. 2006; 15(5):308–318. [PubMed: 16761508]
25. Costenbader KH, Feskanich D, Mandl LA, Karlson EW. Smoking intensity, duration, and cessation, and the risk of rheumatoid arthritis in women. Am J Med. 2006; 119(6):e1–e9. 503. [PubMed: 16750964]
26. Karlson EW, Sanchez-Guerrero J, Wright EA, Lew RA, Daltroy LH, Katz JN, et al. A connective tissue disease screening questionnaire for population studies. Ann Epidemiol. 1995; 5(4):297–302. [PubMed: 8520712]
27. Arnett FC, Edworthy SM, Bloch DA, McShane DJ, Fries JF, Cooper NS, et al. The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. Arthritis Rheum. 1988; 31(3):315–324. [PubMed: 3358796]
28. Chibnik LB, Mandl LA, Costenbader KH, Schur PH, Karlson EW. Comparison of threshold cutpoints and continuous measures of anti-cyclic citrullinated peptide antibodies in predicting future rheumatoid arthritis. J Rheumatol. 2009; 36(4):706–711. [PubMed: 19228654]
29. Arkema EV, Goldstein BL, Robinson W, Sokolove J, Wagner CA, Malspeis S, et al. Anti-citrullinated peptide autoantibodies, human leukocyte antigen shared epitope and risk of future rheumatoid arthritis: a nested case-control study. Arthritis Res Ther. 2013; 15(5):R159. [PubMed: 24286474]
30. Lu B, Solomon DH, Costenbader KH, Keenan BT, Chibnik LB, Karlson EW. Alcohol consumption and markers of inflammation in women with preclinical rheumatoid arthritis. Arthritis Rheum. 2010; 62(12):3554–3559. [PubMed: 20827783]
31. Giovannucci E, Colditz G, Stampfer MJ, Rimm EB, Litin L, Sampson L, et al. The assessment of alcohol consumption by a simple self-administered questionnaire. Am J Epidemiol. 1991; 133(8): 810–817. [PubMed: 2021148]
32. de Onis M, Habicht JP. Anthropometric reference data for international use: recommendations from a World Health Organization Expert Committee. Am J Clin Nutr. 1996; 64(4):650–658. [PubMed: 8839517]
33. Karlson EW, Mandl LA, Hankinson SE, Grodstein F. Do breast-feeding and other reproductive factors influence future risk of rheumatoid arthritis? Results from the Nurses' Health Study. Arthritis Rheum. 2004; 50(11):3458–3467. [PubMed: 15529351]
34. Pikwer M, Bergstrom U, Nilsson JA, Jacobsson L, Berglund G, Turesson C. Breast feeding, but not use of oral contraceptives, is associated with a reduced risk of rheumatoid arthritis. Ann Rheum Dis. 2009; 68(4):526–530. [PubMed: 18477739]
35. Spiegelman D, Hertzmark E, Wand HC. Point and interval estimates of partial population attributable risks in cohort studies: examples and software. Cancer Causes Control. 2007; 18(5): 571–579. [PubMed: 17387622]
36. Somers EC, Antonsen S, Pedersen L, Sorensen HT. Parental history of lupus and rheumatoid arthritis and risk in offspring in a nationwide cohort study: does sex matter? Ann Rheum Dis. 2013; 72(4):525–529. [PubMed: 22586159]
37. Valdez R, Yoon PW, Qureshi N, Green RF, Khoury MJ. Family history in public health practice: a genomic tool for disease prevention and health promotion. Annu Rev Public Health. 2010; 31:69–87. 1 p following. [PubMed: 20070206]

38. Okada Y, Wu D, Trynka G, Raj T, Terao C, Ikari K, et al. Genetics of rheumatoid arthritis contributes to biology and drug discovery. Nature. 2014; 506(7488):376–381. [PubMed: 24390342]

39. Stahl EA, Raychaudhuri S, Remmers EF, Xie G, Eyre S, Thomson BP, et al. Genome-wide association study meta-analysis identifies seven new rheumatoid arthritis risk loci. Nat Genet. 2010; 42(6):508–514. [PubMed: 20453842]

40. de Hair MJ, Landewe RB, van de Sande MG, van Schaardenburg D, van Baarsen LG, Gerlag DM, et al. Smoking and overweight determine the likelihood of developing rheumatoid arthritis. Ann Rheum Dis. 2012

41. Barrera P, Radstake TR, Albers JM, van Riel PL, van de Putte LB. Familial aggregation of rheumatoid arthritis in The Netherlands: a cross-sectional hospital-based survey. European Consortium on Rheumatoid Arthritis families (ECRAF). Rheumatology (Oxford). 1999; 38(5): 415–422. [PubMed: 10371279]

42. Rojas-Villarraga A, Diaz FJ, Calvo-Paramo E, Salazar JC, Iglesias-Gamarra A, Mantilla RD, et al. Familial disease, the HLA-DRB1 shared epitope and anti-CCP antibodies influence time at appearance of substantial joint damage in rheumatoid arthritis. J Autoimmun. 2009; 32(1):64–69. [PubMed: 19117726]

Significance & Innovations

- We investigated the contributions of familial RA or lupus and known RA environmental risk factors (smoking, alcohol, excess body weight, and female reproductive factors) to RA risk.
- We found that familial RA or lupus and environmental risk factors were independently associated with RA; the hazard ratio of RA from a first-degree relative with RA or lupus was 3.59 after adjusting for environmental factors.
- The population attributable risk (PAR) for RA from familial RA or lupus was 21%, while the PAR from smoking, alcohol, body weight, nulliparity, or breastfeeding collectively was 41%.
- These results suggest that environmental risk factors are responsible for a large proportion of RA risk, even among those with familial RA or lupus.

Table 1

Baseline characteristics in 1976 of women who answered the 2008 Nurses' Health Study questionnaire according to self-reported familial RA or lupus in first-degree relatives (FDR) (n = 65,457).

	No FDR (n = 58,458)	Any FDR (n = 6,999)
Mean age, years (SD)	41.3 (6.8)	41.6 (6.8)
Cigarette smoking pack-years (%)		
Never to ≤10	69	68
>10 to ≤20	14	15
>20	15	16
Alcohol intake (g/day) (%)		
None to <5	29	30
5 to <10	10	10
≥10	20	17
Body mass index by WHO category (%)		
Normal or Underweight	76	74
Overweight	18	19
Obese	6	7
Parity and breastfeeding duration (%)		
Nulliparous	6	6
Parous, <1 month	40	40
Parous, 1–11 months	30	30
Parous, ≥12 months	17	16
Menopausal status and post-menopausal hormone use (%)		
Pre	77	75
Post	12	13
Post	10	11
Age at menarche (%)		
≤10 years	6	7
>10 years	94	93
Menses (%)		
Regular	72	70
Irregular	12	14

Missing values were not included.

FDR = first-degree relative; RA = rheumatoid arthritis; SD = standard deviation; WHO = World Health Organization.

Table 2

Characteristics of RA cases (n = 493) who answered the 2008 Nurses' Health Study questionnaire according to self-reported familial RA or lupus in first-degree relatives (FDR).

RA case characteristics	No FDR (n = 350)	Any FDR (n = 143)
Age at RA diagnosis (mean, SD)	58.5 (9.9)	57.9 (10.0)
Age at RA symptoms (mean, SD)	57.7 (10.4)	57.0 (11.0)
Seropositive[1], no. (%)	215 (61)	86 (60)

[1] Seropositivity was defined as positive rheumatoid factor and/or anti-citrullinated protein antibody.

FDR = first-degree relative; RA = rheumatoid arthritis; SD = standard deviation.

Table 3

Hazard ratios for RA phenotypes (all, seropositive, and seronegative) according to familial RA or lupus by affected first-degree relative (FDR) in age-adjusted models for women in the Nurses' Health Study (n = 65,457).

	All RA (n = 493)			Seropositive RA (n = 301)			Seronegative RA (n = 192)		
Familial RA or lupus	**RA cases**	**HR**	**95% CI**	**RA cases**	**HR**	**95% CI**	**RA cases**	**HR**	**95% CI**
No FDR	350	1.0	Ref	215	1.0	Ref	135	1.0	Ref
Parent	95	4.27	3.39–5.37	61	5.08	3.80–6.78	34	4.23	2.89–6.19
No FDR	350	1.0	Ref	215	1.0	Ref	135	1.0	Ref
Sibling	46	3.35	2.45–4.58	25	3.10	1.03–4.73	21	4.19	2.62–6.70
No FDR	350	1.0	Ref	215	1.0	Ref	135	1.0	Ref
Offspring	27	4.12	2.76–6.14	14	3.65	2.11–6.33	13	5.19	2.90–9.28
No FDR	350	1.0	Ref	215	1.0	Ref	135	1.0	Ref
Any FDR	143	3.67	3.01–4.47	86	3.90	3.03–5.03	57	3.95	2.88–5.40
No FDR	350	1.0	Ref	215	1.0	Ref	135	1.0	Ref
1 FDR	120	3.37	2.73–4.16	73	3.60	2.75–4.71	47	3.53	2.52–4.94
≥2 FDRs	23	6.83	4.43–10.53	13	7.62	4.26–13.64	10	8.69	4.50–16.79

All models were adjusted for age and questionnaire period.

CI= confidence interval; FDR = first-degree relative; HR = hazard ratio; RA = rheumatoid arthritis; Ref = reference.

Table 4

Hazard ratios for RA phenotypes (all, seropositive, and seronegative) in multivariate analyses for familial RA or lupus in first-degree relatives and all environmental factors for women in the Nurses' Health Study (n = 65,457).

	All RA[1] (n=493)		Seropositive RA[2] (n=301)		Seronegative RA[3] (n=192)	
	HR (95% CI), Adjusted for environment*	HR (95% CI), Adjusted for familial RA or lupus and environment	HR (95% CI), Adjusted for environment	HR (95% CI), Adjusted for familial RA or lupus and environment	HR (95% CI), Adjusted for environment	HR (95% CI), Adjusted for familial RA or lupus and environment
Familial RA or lupus						
No FDR	-	1.0 (Ref)	-	1.0 (Ref)	-	1.0 (Ref)
Any FDR	-	3.59 (2.94– 4.37)#	-	3.81 (2.95–4.92)#	-	3.84 (2.80–5.25)#
Cigarette smoking pack-years						
Never to ≤10	1.0 (Ref)	1.0 (Ref)	1.0 (Ref)	1.0 (Ref)	1.0 (Ref)	1.0 (Ref)
>10 to ≤20	1.58 (1.21–2.06)#	1.54 (1.18–2.02)#	1.86 (1.34–2.60)#	1.82 (1.30–2.54)#	1.19 (0.75–1.88)	1.17 (0.74–1.86)
>20	1.56 (1.26–1.92)#	1.52 (1.23–1.88)#	1.77 (1.36–2.32)#	1.72 (1.32–2.26)#	1.31 (0.93–1.85)	1.27 (0.90–1.80)
Alcohol intake (g/day)						
None to <5	1.0 (Ref)	1.0 (Ref)	1.0 (Ref)	1.0 (Ref)	1.0 (Ref)	1.0 (Ref)
5 to <10	0.75 (0.56–1.01)	0.76 (0.57–1.03)	0.69 (0.47–1.03)	0.71 (0.48–1.04)	0.85 (0.53–1.35)	0.86 (0.54–1.37)
≥10	0.85 (0.67–1.09)	0.89 (0.70–1.14)	0.82 (0.60–1.13)	0.86 (0.63–1.18)	0.88 (0.59–1.32)	0.92 (0.62–1.38)
Body mass index by WHO category						
Normal or underweight	1.0 (Ref)	1.0 (Ref)	1.0 (Ref)	1.0 (Ref)	1.0 (Ref)	1.0 (Ref)
Overweight	1.26 (1.03–1.54)#	1.23 (1.01–1.51)#	1.21 (0.93–1.56)	1.17 (0.90–1.52)	1.39 (1.00–1.93)#	1.36 (0.98–1.89)
Obese	1.11 (0.86–1.45)	1.09 (0.84–−1.42)	0.96 (0.67–1.36)	0.93 (0.66–1.32)	1.45 (0.97–2.17)	1.45 (0.97–2.17)
Parity and breastfeeding duration						
Parous, no breastfeeding	1.0 (Ref)	1.0 (Ref)	1.0 (Ref)	1.0 (Ref)	1.0 (Ref)	1.0 (Ref)
Parous, 1–11 months	0.97 (0.78–1.20)	0.98 (0.79–1.22)	1.06 (0.81–1.40)	1.07 (0.81–1.41)	0.84 (0.60–1.18)	0.85 (0.61–1.19)
Parous, ≥12 months	0.79 (0.60–1.05)	0.81 (0.61–1.07)	0.92 (0.64–1.31)	0.92 (0.64–1.31)	0.63 (0.40–1.00)#	0.65 (0.41–1.04)
Nulliparous	1.33 (0.93–1.91)	1.35 (0.94–1.94)	1.58 (1.02–2.47)#	1.60 (1.03–2.51)#	0.98 (0.52–1.85)	0.99 (0.53–1.87)
Menopausal status and post-menopausal hormone use						
Post-menopausal, no hormone use	1.0 (Ref)	1.0 (Ref)	1.0 (Ref)	1.0 (Ref)	1.0 (Ref)	1.0 (Ref)

	All RA[1] (n=493)		Seropositive RA[2] (n=301)		Seronegative RA[3] (n=192)	
	HR (95% CI), Adjusted for environment*	**HR (95% CI), Adjusted for familial RA or lupus and environment**	**HR (95% CI), Adjusted for environment**	**HR (95% CI), Adjusted for familial RA or lupus and environment**	**HR (95% CI), Adjusted for environment**	**HR (95% CI), Adjusted for familial RA or lupus and environment**
Pre-menopausal	0.69 (0.49–0.96)#	0.69 (0.50–0.97)#	0.73 (0.48–1.12)	0.74 (0.48–1.14)	0.60 (0.34–1.04)	0.61 (0.35–1.05)
Post-menopausal, hormone use	1.07 (0.86–1.34)	1.06 (0.85–1.33)	1.07 (0.80–1.42)	1.06 (0.79–1.41)	1.10 (0.78–1.57)	1.10 (0.78–1.57)
Age at menarche						
>10 years	1.0 (Ref)	1.0 (Ref)	1.0 (Ref)	1.0 (Ref)	1.0 (Ref)	1.0 (Ref)
≤10 years	0.93 (0.63–1.38)	0.91 (0.61–1.35)	1.27 (0.82–1.97)	1.22 (0.79–1.91)	0.44 (0.18–1.07)	0.44 (0.18–1.07)
Menstrual regularity						
Regular	1.0 (Ref)	1.0 (Ref)	1.0 (Ref)	1.0 (Ref)	1.0 (Ref)	1.0 (Ref)
Irregular	1.16 (0.90–1.50)	1.13 (0.87–1.46)	1.25 (0.90–1.73)	1.22 (0.88–1.69)	1.07 (0.71–1.62)	1.04 (0.69–1.58)

[1] A total of 1,846,189 person-years were included in the all RA model.

[2] A total of 1,708,858 person-years were included in the seropositive RA model.

[3] A total of 1,837,936 person-years were included in the seronegative RA model.

* Environment: cigarette smoking pack-years, alcohol intake, body mass index, parity and breastfeeding duration, menopausal status and post-menopausal hormone use, age at menarche, and menstrual regularity.

P value <0.05.

All models were adjusted for age, questionnaire period, cigarette smoking pack-years, body mass index, alcohol intake, parity, breastfeeding duration, menopausal status, post-menopausal hormone use, age at menarche, and menstrual regularity. Familial models were also adjusted for familial RA or lupus.

CI = confidence interval; FDR = first-degree relative; HR = hazard ratio; RA = rheumatoid arthritis; Ref = reference; WHO = World Health Organization.

Table 5

Population attributable risks (PAR) for RA according to specified profiles that increase RA risk within the Nurses' Health Study among all who answered the 2008 questionnaire (n = 65,457) and among those who reported familial RA or lupus (n = 6,999).

Risk factor profile[1]	PAR for RA (%) among all women (n = 65,457)[2]	PAR for RA (%) among women with familial RA or lupus in any first-degree relative (n = 6,999)[3]
Non-modifiable risk factor		
Familial RA or lupus in any first-degree relative	21	-
Modifiable risk factors		
Smoking (>10 pack-years)	14	18
Low alcohol intake (none or <5 g/day)	12	3
Increased BMI (overweight or obese)	9	11
Nulliparity/breastfeeding <12 months	15	25
Smoking, Low alcohol, and Increased BMI	31	29
Smoking, Low alcohol, Increased BMI, and Nulliparity /breastfeeding <12 months	41	46

[1] Each model calculates the percentage of RA risk that is attributed to the specified risk factor(s) within the specified cohort. All specified profiles confer increased risk of RA.

[2] A total of 1,846,189person-years with 493 RA cases were included in this model.

[3] A total of 186,764 person-years with 143 RA cases were included in this model.

All models were adjusted for age, questionnaire period, cigarette smoking pack-years, body mass index, alcohol intake, parity, breastfeeding duration, menopausal status, post-menopausal hormone use, age at menarche, and menstrual regularity. The model for all participants was also adjusted for familial RA or lupus.

BMI = body mass index; PAR = population attributable risk; RA = rheumatoid arthritis.