Published in final edited form as:
Arch Intern Med. 2008 August 11; 168(15): 1664–1670. doi:10.1001/archinte.168.15.1664.

Geographic Variation in Rheumatoid Arthritis Incidence among Women in the United States

Karen H. Costenbader, MD, MPH, **Shun-Chiao Chang, MS**, **Francine Laden, PhD**, **Robin Puett, PhD**, and **Elizabeth W. Karlson, MD**
From the Division of Rheumatology, Immunology, and Allergy, Section of Clinical Sciences, Robert B. Brigham Arthritis and Musculoskeletal Diseases Clinical Research Center, and the Channing Laboratory, Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, and Department of Epidemiology, Harvard School of Public Health, Boston, MA, 02115

Abstract

Background—Geographic variation in RA incidence in the United States is unknown.

Methods—We studied residential region from 1921–1976 and RA risk in a prospective cohort of women, the Nurses' Health Study. Information on state of residence was collected at baseline in 1976 (ages 30–55), and on state at birth, at age 15, and at age 30 in 1992. Among 83,546 subjects reporting residence for all 4 time points, 706 incident RA cases from 1976–2004 were confirmed by screening questionnaire and record review for American College of Rheumatology criteria. Residential region was classified as: West, Midwest, Mid-Atlantic, New England, and Southeast. Multivariate cox proportional hazard models were used to assess relationships between region and RA risk, adjusting for age and smoking, body mass index, parity, breastfeeding, postmenopausal status, postmenopausal hormone use, father's occupation, race, and physical activity. Analyses were performed in subjects who lived in the same regions, or moved, over time.

Results—Compared to those in the West, women in New England had a 37–45% elevated risk of RA in multivariable models at each time point (eg. state in 1976: RR 1.42; 95% CI 1.10, 1.82). In analyses of women who lived in the same region at birth, age 15, and age 30, living in the Midwest was associated with greater risk (RR 1.47; 95% CI 1.05, 2.05), as was living in New England (RR 1.40; 95%CI 0.98, 2.00). Compared to living in the West at birth, age 15, and age 30, RA risk was higher in the East.

Conclusion—In this large cohort of American women, there was significant geographic variation in incident RA after controlling for confounders. Potential explanations include regional variation in behavioral factors, climate, environmental exposures, RA diagnosis, or genetic factors.

Keywords

rheumatoid arthritis; risk factors; incidence; geography; air pollution

Rheumatoid arthritis (RA) is an autoimmune disease of unknown etiology, characterized by chronic, destructive, debilitating arthritis, that affects approximately 1% of the adult population[1]. Both environmental and genetic factors appear to be important in determining RA susceptibility and it is likely that they interact[2, 3]. Epidemiologic research points to environmental risk factors, including cigarette smoking[4–16], exogenous hormone use[17–25],

Address for correspondence and reprints: Karen H. Costenbader, MD, MPH, 75 Francis St., Boston, MA 02115, telephone (617)-732-5158, FAX (617) 731-9032, KCostenbader@partners.org.

female reproductive factors[26, 27], occupational silica[28] and mineral oil[29], as likely influences of RA risk.

Little is known about geographic distribution in RA in the United States or worldwide. A recent systematic review of the existing studies suggests that RA is more common in Northern Europe and North America than Southern Europe, Africa and the developing world[30]. There is also some evidence that the incidence of RA has declined in recent years in the United States and Northern Europe[31, 32].

Our goal was to investigate the geographic variation in RA incidence in women living in the United States, using the Harvard-based Nurses' Health Study, and to assess for epidemiologic clues to exposures that may be related to RA risk. Begun in 1976, when 121,700 registered female nurses from 11 large U.S. states were initially enrolled, the NHS is now the largest prospective cohort study of women used for the study of rheumatic disease. Participants have lived in every U.S. state, with the bulk of their numbers in the most populated U.S. states, and there have been more than 800 incident validated cases of RA since the start of the cohort. With a wide range of high quality data concerning health behaviors, exposures and disease, this study offered a unique opportunity to investigate the relationship between geographic area of residence and risk of RA.

Methods

Study Population

The Nurses' Health Study (NHS) is a prospective cohort of 121,700 female nurses, aged 30–55 years in 1976 when the study began. Nurses were originally recruited from the 11 most populated U.S. states (CA, CT, FL, MD, MA, MI, NJ, NY, OH, PA, and TX), but lived in much more geographically dispersed areas before this, including all 50 states. Ninety-four percent of the NHS participants have remained in active follow-up (6% no longer respond to questionnaires and have not been confirmed as dead). Information is prospectively collected via biennial questionnaires regarding diseases, lifestyle, and health practices. The Brigham and Women's Hospital Institutional Review Board approved all aspects of this study. For the purposes of this study, we included all women who had reported their U.S. state of residence in 1976, and in 1976 as well as at birth, and at ages 15 and 30 on the 1992 questionnaire for analyses of those time points. Women were censored after their last response to the biennial questionnaires as incident RA cases could not be identified. Thus, the final group included 105,754 women followed 1976–2004 for the 1976 state of residence analyses and 83,546 women followed from 1976–2004 with residential data for all 4 time points

Identification of RA

As previously described[16, 26], we employed a two-stage procedure in which all nurses who self-reported any connective tissue disease underwent received a screening questionnaire for connective tissue disease symptoms[33], and, if positive, a detailed medical record review for American College of Rheumatology (ACR) diagnostic criteria for RA.[34] We excluded subjects who self-reported but subsequently denied the diagnosis of RA, had prevalent RA (diagnosed before the start of the cohort), denied permission for record review, or had a negative connective tissue diseases screening questionnaire. Since NHS inception, the annual incidence of RA has ranged from 26–56 cases/100,000 persons per year, with an overall incidence rate of 40/100,000 persons per year. This is quite similar to that reported by Doran and colleagues in Rochester, Minnesota, where the overall annual incidence of RA among those age 18 or older was 44.6/100,000 population[31].

State of Residence

At enrollment in 1976, participants were asked for their home mailing address. On the 1992 questionnaire, NHS participants were asked for their state of birth and state of residence at ages 15 and 30 (82% response rate in NHS). We divided the continental United States into six geographic regions: Pacific, Mountain, Mid-West, Mid-Atlantic, New England, and Southeast. We combined Pacific and Mountain regions into a referent group for West (due to low numbers of subjects living in Mountain regions). For moving pattern analyses, Mid-West, Mid-Atlantic, New England, and Southeast were further grouped into East category, as compared to the West area.

Covariate Information

Age was updated in each cycle. Based on our past findings[16, 26, 35], risk factors for RA in these cohorts that could potentially vary by geographic region, including cigarette smoking, parity and breast feeding history, menopausal status and postmenopausal hormone use were included as potential confounders of the relationship between geographic state of residence and incident RA. Questions concerning passive cigarette smoke exposure were asked once in 1982. Participants were asked whether neither of their parents, their mother only, their father only, or both parents had smoked at home. Subjects were also asked to report the number of years they had lived with a smoker (including as a child and as an adult) and whether they were never, occasionally, or regularly exposed to cigarette smoke at work. Body mass index (BMI), computed for each two-year time interval using the most recent weight in kilograms divided by height in meters squared, was also include in multivariable models. Father's occupation was assessed in 1992 in NHS and served as a proxy for socioeconomic level in childhood. In 1992, participants in NHS were asked to report their racial and ethnic ancestry as African, Asian, Hispanic, Caucasian, or other. Ninety-eight percent of participants reported Caucasian ancestry, reflecting the racial background of women trained as nurses in the United States in the years of cohort enrollment. Hours per week spent in physical activities was assessed seven times in NHS. A validation study conducted by Li et al found a correlation of 0.79 between one week exercise recall and exercise reported on the NHS questionnaire[36].

Statistical analysis

We compared the characteristics of RA cases at diagnosis according to their current residence (East vs. West) using t- tests for continuous variables and χ^2 tests for categorical variables. Person-years of follow-up accrued from the date of return of the baseline questionnaire until the date of diagnosis of RA as defined in the medical record or report of any connective tissue disease that was not confirmed RA, death, or loss-to-follow-up, defined as no further return of questionnaires. Age-adjusted relative risks were calculated using age in months. Cox proportional hazards regression models were employed to study the association between U.S. state of residence since birth in years 1921–1946) and incident RA (developing from ages 33–81), while adjusting simultaneously for covariates of interest. We used time-varying information for covariates from each two-year questionnaire to analyze the risk of RA in the next two-year cycle. Final multivariable models included age, as well as pack-years of cigarette smoking, BMI, physical activity, parity, total duration of breastfeeding, postmenopausal status, postmenopausal hormone use, father's occupation, and race. Further adjustment for BMI at age 18, age at menarche, menstrual regularity, childhood exposure to smoke and exposure to cigarette smoke in the workplace did not affect risk estimates and thus these covariates were not included in the final models.

In stratified analyses, we examined the relative risks of RA associated with living in each geographical region over time separately among ever-smokers and non-smokers. To assess effects of geographic residence at different ages, we performed analyses of region of residence at each of the time points (birth, age 15, age 30 and 1976). We also performed analyses

including women living in the same and different geographic regions over time to assess the effects of moving between regions. SAS version 9 was employed for all analyses[37].

Results

The characteristics of the NHS participants in 1976 are shown in Table 1 according to geographic area of residence. Fewer women were smokers in the West and Mid-West than in the other regions, and participants living in New England and the Southeast had the highest numbers of pack years of smoking and the highest rates of regular exposure to cigarette smoke in the workplace. While the majority of NHS participants are Caucasian, the West had the highest proportion of non-Caucasians and New England had the lowest. Among parous women, slightly higher proportions of those living in the West had breastfed for a total of 12 or more months (21.6%), and among postmenopausal women, more in the West were currently receiving postmenopausal hormones (56.1%). No important differences in the characteristics (listed in Table 1) of participants who responded to our additional mailings compared to those who did not respond were found (data not shown).

Characteristics at diagnosis of the 706 RA cases included in these analyses, according to their residential location in the East vs. West at that time, are shown in Table 2. The mean (±SD) age at RA diagnosis among the cases was 57.6 (±9.4) years. The mean age at RA diagnosis was three years older among participants currently living in the West (60.1 years compared to 57.3 years in the East, $p = 0.01$) and a higher percentage of the cases were documented to be rheumatoid factor positive at diagnosis in the East than in the West (60.9% compared to 50.5% in the West, p=0.06). Most cases were diagnosed by a physician who was a member of the ACR.

Table 3 shows the relative risks of RA by geographic region of residence at each of the time points (birth, age 15, age 30 and 1976), both in age-adjusted models and multivariable models. Adjustment for all the potential confounders included did not substantially affect relative risk estimates in most cases. In both models, compared to those who lived in the West, the relative risk of RA was the most significantly elevated among residents of New England at all time points (multivariable RR 1.41; 95%CI 1.03, 1.93 at birth and 1.42; 95%CI 1.10, 1.82 in 1976). The relative risk of RA was also significantly elevated for residents of the Midwest and Mid-Atlantic states at age 30.

In analyses stratified by never versus ever smoking, there was some suggestion that the increased risk of RA associated with living in the East at multiple time points may have been confined to women who had ever smoked, but these analyses included smaller numbers of participants and thus the point estimates have wide confidence intervals. There was no evidence of statistically significant interaction between smoking status and residence in each geographic region at each of the time points(results not shown).

Table 4 shows the results of analyses of geographic area of residence among women who did not move for at least two of the time points. Residents of New England and the MidWest who stayed in the same area from birth though ages 15 and 30 had the highest relative risks of developing RA, compared to women who stayed in the West (multivariable RR for New England 1.40; 95%CI 0.98, 2.00 and for the MidWest 1.47; 95%CI 1.02, 2.05). Relative risks of RA were also non-significantly elevated among women who lived in the Mid-Atlantic states from birth to age 30 (multivariable RR 1.32; 95%CI 0.97, 1.81).

The results of analyses of staying in the East, staying in the West, or migrating between the two regions between birth and ages 15 and 30 are shown in Table 5. Those who lived in the East at all three time points had the highest relative risk compared to women who lived in the West at all three times points (multivariable RR 1.36; 95%CI 1.01, 1.84). However, those who

were born in the West and moved to the East before age 30 acquired a risk closer to those who had lived in the East at all three time points (multivariable RR 1.35; 95%CI 0.71, 2.56). Women who were born in the East but moved to the West before age 30 had a risk similar to those who lived in the West at all three time points (multivariable RR 0.99; 95%CI 0.65, 1.52).

Discussion

In this large cohort of American women followed prospectively for the development of RA over 28 years, we have demonstrated increased risk of RA for those women who lived in the Eastern and Mid-Western United States, compared to living in the West, in particular at earlier time points in their lives. Furthermore, our analyses of moving patterns within the United States, between birth, age 15 and age 30 suggested that those who consistently lived in the West had lower risk, even after adjusting for potential confounding lifestyle factors, and that moving to the East was associated with an increase in risk, however power was limited by the small numbers of women in this analysis. Relative risks among women in the Southeast were similar to those in other Eastern states at most time points, although not significantly elevated compared to those in the West, given smaller numbers of participants living in these states. These results suggest that exposure to an environmental factor or factors may influence the risk of developing RA during adolescence or early adulthood.

Several potential explanations for the geographic variation in RA incidence observed in this study should be considered. Regional environmental exposures, including ultraviolet light, infectious diseases, climatic differences, soil composition such as silica, lifestyle factors such as diet and exercise, and socioeconomic factors may be important in RA susceptibility. Access to rheumatology specialists and differences in RA diagnostic proclivity by region are important potential explanations that are difficult to investigate. We did find some evidence of differences in the RA cases at diagnosis according to region: the mean age at RA diagnosis was older and the percent of rheumatoid factor positive cases was lower in the in the West.

We hypothesize that the increased risk of RA among women living in the Midwest and Eastern U.S. during the years 1921 to 1976 could be attributable to an environmental exposure. Cigarette smoking is a well-established risk factor for RA, increasing the risk of seropositive RA in particular, with evidence for dose-dependent effects and prolonged increased risk after smoking cessation[4, 6–9, 11, 13–15]. A gene-environment interaction appears to exist with the HLA-DRB1 shared epitope, the strongest genetic risk factor for RA, such that individuals who carry two copies of the shared epitope and are smokers are much increased risk of developing anti-cyclic citrullinated peptide(CCP) positive RA[2, 3]. Exposure to silica dust though the respiratory tract in occupations such as rock drilling, mining and sand blasting, has been linked to risk of RA in several epidemiologic studies[38–41] with effect modification by cigarette smoking[28]. Silica dust exposure, like cigarette smoke exposure, appears to be a risk factor only for rheumatoid factor (RF)/anti-CCP seropositive RA and not for seronegative RA. Our stratified analyses suggested that the increased RA risk may have been primarily among the ever smokers, although this was based on smaller numbers of participants and formal tests for interaction between smoking and geographic region of residence at each of the time points were non-significant.

The associations of cigarette smoke and silica with increased risk of RA suggest that respiratory exposures may activate the immune system to trigger an autoimmune disease such as RA. Particulate matter in the air is a mixture of inorganic and organic components of varied size, origin, and composition. Respiratory exposure to particulate air pollution is associated with increased systemic inflammation[42, 43] and could possibly be involved in the pathogenesis of RA. Geographic variation in the incidence of lung cancer, cardiovascular disease, and overall mortality has been linked with air pollution levels in past epidemiologic studies[44–47].

Nationwide air pollution data does not exist for most of the years examined in this study (1921–1976), but, not surprisingly, heavily industrial areas of the Northeast and Midwest did have high concentrations of particulate air pollution when such monitoring began in the 1970s with the first of the Environmental Protection Agency's annual reports[48–50]. Recent studies continue to show much higher levels of airborne particulate matter in the Midwest and Northeast, compared to the rest of the United States, the Los Angeles area excepted, probably exacerbated by meteorologic patterns[51, 52]. Given the greater risk of RA among those who lived in more polluted industrial regions, our data may suggest a potential ecological association between living in states with higher air pollution and risk of RA.

The majority of NHS participants are Caucasian, but the racial composition of the cohort varies with respect to geographic location. We controlled for race in our multivariable models, the contribution of genetic risk factors to RA susceptibility may have varied by geographic region. While based on small numbers of participants, our analyses of migration patterns and the risk of RA, suggested that not only that women living in the West had lower risks of developing RA, but also that migration into or out of the West changed the risk of RA. Women who were born in the West and moved to the East before age 30 did not have reduced risk, a result not compatible with an entirely genetic explanation.

The NHS has detailed data on physical activity, cigarette smoking, and reproductive factors, but it is possible that residual confounding may contribute to our findings. Women in the NHS were originally recruited from the 11 most populated U.S. states, but moved widely, throughout all 50 states, and abroad, during the 28-year follow-up period. The relative risks reported reflect the incidence of RA among study participants living in each of the geographic regions at each time point, and thus take the population denominators into account. Despite having a large nationwide cohort, our analyses are limited by the residential and migration patterns of cohort participants and, in some cases, results are based on small numbers of individuals. One possibility is again genetics, as persons more likely to move may be of more genetically admixed heritage than those who remain in the same area for their entire lives.

Despite its limitations, this study represents the most detailed analysis of the differences in RA incidence rates in American women between geographic regions to date. These preliminary findings are hypothesis-generating and deserving of further study. Regional differences in one or more factors not considered in this study could be responsible for the differences, including exposures to environmental factors. We are currently engaged in extending these observations using updated geocoding of residential addresses and assessments of environmental air pollution at geocoded locations.

Acknowledgments

The authors gratefully acknowledge the participants in the NHS for their continuing cooperation. The authors also thank Frank Speizer and Walter Willett. We are grateful to Joel Schwartz for his expert advice, and to Karen Corsano for her technical assistance.

Supported by NIH grants Supported by NIH grants CA87969, P60 AR047782, R01 AR49880, K24 AR0524-01 and BIRCWH K12 HD051959 (supported by NIMH, NIAID, NICHD, and OD). Dr. Costenbader is the recipient of an Arthritis Foundation/American College of Rheumatology Arthritis Investigator Award and a Katherine Swan Ginsburg Memorial Award.

References

1. Gabriel SE, Crowson CS, O'Fallon WM. The epidemiology of rheumatoid arthritis in Rochester, Minnesota, 1955–1985. Arthritis Rheum JID - 0370605 1999;42:415–420.

2. Klareskog L, Stolt P, Lundberg K, et al. A new model for an etiology of rheumatoid arthritis: Smoking may trigger HLA-DR (shared epitope)-restricted immune reactions to autoantigens modified by citrullination. Arthritis Rheum 2006;54:38–46. [PubMed: 16385494]

3. Lee HS, Irigoyen P, Kern M, et al. Interaction between smoking, the shared epitope, and anti-cyclic citrullinated peptide: a mixed picture in three large North American rheumatoid arthritis cohorts. Arthritis Rheum 2007;56:1745–1753. [PubMed: 17530703]

4. Vessey MP, Villard-Mackintosh L, Yeates D. Oral contraceptives, cigarette smoking and other factors in relation to arthritis. Contraception 1987;35:457–464. [PubMed: 3621942]

5. Hernandez Avila M, Liang MH, Willett WC, et al. Reproductive factors, smoking, and the risk for rheumatoid arthritis. Epidemiology 1990;1:285–291. [PubMed: 2083305]

6. Hazes JM, Dijkmans BA, Vandenbroucke JP, de Vries RR, Cats A. Lifestyle and the risk of rheumatoid arthritis: cigarette smoking and alcohol consumption. Ann.Rheum.Dis 1990;49:980–982. [PubMed: 2270970]

7. Heliovaara M, Aho K, Aromaa A, Knekt P, Reunanen A. Smoking and risk of rheumatoid arthritis [see comments]. J.Rheumatol 1993;20:1830–1835. [PubMed: 8308766]

8. Voigt LF, Koepsell TD, Nelson JL, Dugowson CE, Daling JR. Smoking, obesity, alcohol consumption, and the risk of rheumatoid arthritis. Epidemiology 1994;5:525–532. [PubMed: 7986867]

9. Symmons DP, Bankhead CR, Harrison BJ, et al. Blood transfusion, smoking, and obesity as risk factors for the development of rheumatoid arthritis: Results from a primary care-based incident case-control study in Norfolk, England. Arthritis Rheum 1997;40:1955–1961. [PubMed: 9365083]

10. Karlson EW, Lee IM, Cook NR, Manson JE, Buring JE, Hennekens CH. A retrospective cohort study of cigarette smoking and risk of rheumatoid arthritis in female health professionals. Arthritis & Rheumatism 1999;42:910–917. [PubMed: 10323446]

11. Uhlig T, Hagen KB, Kvien TK. Current tobacco smoking, formal education, and the risk of rheumatoid arthritis. J Rheumatol 1999;26:47–54. [PubMed: 9918239]

12. Criswell LA, Merlino LA, Cerhan JR, et al. Cigarette smoking and the risk of rheumatoid arthritis among postmenopausal women: results from the Iowa Women's Health Study. Am J Med JID - 0267200 2002;112:465–471.

13. Krishnan E, Sokka T, Hannonen P. Smoking-gender interaction and risk for rheumatoid arthritis. Arthritis Res Ther 2003;5:R158–R162. [PubMed: 12723987]

14. Stolt P, Bengtsson C, Nordmark B, et al. Quantification of the influence of cigarette smoking on rheumatoid arthritis: results from a population based case-control study, using incident cases. Ann Rheum Dis 2003;62:835–841. [PubMed: 12922955]

15. Padyukov L, Silva C, Stolt P, Alfredsson L, Klareskog L. A gene-environment interaction between smoking and shared epitope genes in HLA-DR provides a high risk of seropositive rheumatoid arthritis. Arthritis Rheum 2004;50:3085–3092. [PubMed: 15476204]

16. 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(503):e1–e9. [PubMed: 16750964]

17. Doran MF, Crowson CS, O'Fallon WM, Gabriel SE. The effect of oral contraceptives and estrogen replacement therapy on the risk of rheumatoid arthritis: a population based study. J Rheumatol 2004;31:207–213. [PubMed: 14760786]

18. Spector TD, Roman E, Silman AJ. The pill, parity, and rheumatoid arthritis. Arthritis Rheum 1990;33:782–789. [PubMed: 2363734]

19. Brennan P, Bankhead C, Silman A, Symmons D. Oral contraceptives and rheumatoid arthritis: results from a primary care-based incident case-control study. Semin.Arthritis Rheum 1997;26:817–823. [PubMed: 9213380]

20. Hazes JM, Dijkmans BC, Vandenbroucke JP, de Vries RR, Cats A. Reduction of the risk of rheumatoid arthritis among women who take oral contraceptives [see comments]. Arthritis Rheum 1990;33:173–179. [PubMed: 2306289]

21. Jorgensen C, Picot MC, Bologna C, Sany J. Oral contraception, parity, breast feeding, and severity of rheumatoid arthritis. Ann.Rheum.Dis 1996;55:94–98. [PubMed: 8712873]

22. Vandenbroucke JP, Witteman JC, Valkenburg HA, et al. Noncontraceptive hormones and rheumatoid arthritis in perimenopausal and postmenopausal women. JAMA 1986;255:1299–1303. [PubMed: 3944948]

23. Allebeck P, Ahlbom A, Ljungstrom K, Allander E. Do oral contraceptives reduce the incidence of rheumatoid arthritis? A pilot study using the Stockholm County medical information system. Scand.J.Rheumatol 1984;13:140–146. [PubMed: 6740269]
24. Vandenbroucke JP, Valkenburg HA, Boersma JW, et al. Oral contraceptives and rheumatoid arthritis: further evidence for a preventive effect. Lancet 1982;2:839–842. [PubMed: 6126710]
25. Wingrave SJ, Kay CR. Reduction in incidence of rheumatoid arthritis associated with oral contraceptives. Lancet 1978;1:569–571. [PubMed: 76118]
26. 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;50:3458–3467. [PubMed: 15529351]
27. Merlino LA, Cerhan JR, Criswell LA, Mikuls TR, Saag KG. Estrogen and other female reproductive risk factors are not strongly associated with the development of rheumatoid arthritis in elderly women. Semin Arthritis Rheum 2003;33:72–82. [PubMed: 14625816]
28. Stolt P, Kallberg H, Lundberg I, Sjogren B, Klareskog L, Alfredsson L. Silica exposure is associated with increased risk of developing rheumatoid arthritis: results from the Swedish EIRA study. Ann Rheum Dis 2005;64:582–586. [PubMed: 15319232]
29. Sverdrup B, Kallberg H, Bengtsson C, et al. Association between occupational exposure to mineral oil and rheumatoid arthritis: results from the Swedish EIRA case-control study. Arthritis Res Ther 2005;7:R1296–R1303. [PubMed: 16277683]
30. Alamanos Y, Voulgari PV, Drosos AA. Incidence and prevalence of rheumatoid arthritis, based on the 1987 American College of Rheumatology criteria: a systematic review. Semin Arthritis Rheum 2006;36:182–188. [PubMed: 17045630]
31. Doran MF, Pond GR, Crowson CS, O'Fallon WM, Gabriel SE. Trends in incidence and mortality in rheumatoid arthritis in Rochester, Minnesota, over a forty-year period. Arthritis Rheum 2002;46:625–631. [PubMed: 11920397]
32. Drosos AA, Alamanos I, Voulgari PV, et al. Epidemiology of adult rheumatoid arthritis in northwest Greece 1987–1995. J Rheumatol 1997;24:2129–2133. [PubMed: 9375871]
33. Karlson EW, Sanchez-Guerrero J, Wright EA, et al. A connective tissue disease screening questionnaire for population studies. Ann.Epidemiol 1995;5:297–302. [PubMed: 8520712]
34. Arnett FC, Edworthy SM, Bloch DA, et al. The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. Arthritis Rheum 1988;31:315–324. [PubMed: 3358796]
35. Karlson EW, Mandl LA, Aweh GN, Grodstein F. Coffee consumption and risk of rheumatoid arthritis. Arthritis Rheum 2003;48:3055–3060. [PubMed: 14613266]
36. Li TY, Rana JS, Manson JE, et al. Obesity as compared with physical activity in predicting risk of coronary heart disease in women. Circulation 2006;113:499–506. [PubMed: 16449729]
37. SAS/STAT User's Guide. Vol. Fourth Edition. Vol. Version 6. Cary, NC: SAS Institute, Inc.; 1990.
38. Sluis-Cremer GK, Hessel PA, Hnizdo E, Churchill AR. Relationship between silicosis and rheumatoid arthritis. Thorax 1986;41:596–601. [PubMed: 3787543]
39. Turner S, Cherry N. Rheumatoid arthritis in workers exposed to silica in the pottery industry. Occup Environ Med 2000;57:443–447. [PubMed: 10854495]
40. Klockars M, Koskela RS, Jarvinen E, Kolari PJ, Rossi A. Silica exposure and rheumatoid arthritis: a follow up study of granite workers 1940–81. Br Med J (Clin Res Ed) 1987;294:997–1000.
41. Steenland K, Sanderson W, Calvert GM. Kidney disease and arthritis in a cohort study of workers exposed to silica. Epidemiology 2001;12:405–412. [PubMed: 11416778]
42. van Eeden SF, Yeung A, Quinlam K, Hogg JC. Systemic response to ambient particulate matter: relevance to chronic obstructive pulmonary disease. Proc Am Thorac Soc 2005;2:61–67. [PubMed: 16113470]
43. Jimenez LA, Drost EM, Gilmour PS, et al. PM(10)-exposed macrophages stimulate a proinflammatory response in lung epithelial cells via TNF-alpha. Am J Physiol Lung Cell Mol Physiol 2002;282:L237–L248. [PubMed: 11792628]
44. Parodi S, Stagnaro E, Casella C, et al. Lung cancer in an urban area in Northern Italy near a coke oven plant. Lung Cancer 2005;47:155–164. [PubMed: 15639714]

45. Dominici F, McDermott A, Zeger SL, Samet JM. National maps of the effects of particulate matter on mortality: exploring geographical variation. Environ Health Perspect 2003;111:39–44. [PubMed: 12515677]

46. Dominici F, Peng RD, Bell ML, et al. Fine particulate air pollution and hospital admission for cardiovascular and respiratory diseases. Jama 2006;295:1127–1134. [PubMed: 16522832]

47. Laden F, Neas LM, Dockery DW, Schwartz J. Association of fine particulate matter from different sources with daily mortality in six U.S. cities. Environ Health Perspect 2000;108:941–947. [PubMed: 11049813]

48. Environmental Protection Agency Monitoring and Air Quality Trends Report. N.C.: Research Triangle Park; 1972.

49. State of the Environment Report: The Conservation Foundation. Washington, D.D.: 1982.

50. Crandall, RW. Controlling Industrial Pollution: The Economics and Politics of Clean Air. Washington, D.C.: The Brookings Institute; 1983.

51. A Special Report of the Institute's Particle Epidemiology Reanalysis Project. National Institute of Environmental Health Sciences; 2000. Reanalysis of the Harvard Six Cities Study and the American Cancer Society Study of Particulate Air Pollution and Mortality.

52. Environmental Protection Agency. Office of Air Quality Planning and Research. N.C.: National Air Pollution Emissions Trends, 1900–1998 Research Triangle Park; 2000.

Table 1

Age-standardized characteristics of the Nurses' Health Study women by geographic regions at cohort baseline in 1976

Characteristics	West N=21,553	Midwest N=22,280	Mid-Atlantic N=57,385	New England N=17,094	Southeast N=3,262
Age, mean (SD)	44.4 (6.9)	42.7 (7.3)	42.6 (7.2)	42.2 (7.2)	44.0 (7.4)
Age at menarche years, mean	12.6	12.6	12.5	12.5	12.6
BMI, mean	23.4	24.0	23.9	23.7	23.2
BMI ≥ 30 (%)	6.8	9.3	8.5	7.5	6.4
Never smokers (%)	48.3	48.2	42.2	36.0	41.0
Pack years of cigarette smoking*, mean	18.7	18.1	19.0	19.5	19.8
Non-Caucasian ethnicity (%)	6.7	1.8	2.1	0.7	2.9
Either or both parents smoked in home (%)	47.9	51.3	51.5	56.8	49.4
Regular exposure to smoke at work (%)	17.9	23.9	22.1	25.9	23.3
Father non-professional occupation (%)	61.7	67.8	65.5	64.0	59.1
Irregular menses at age 20–35 (%)	10.9	11.9	11.7	12.4	11.3
Nulliparous (%)	8.8	6.4	6.9	6.1	8.6
Breastfeeding > 12 months† (%)	21.8	20.7	17.3	16.5	14.4
Premenopausal (%)	69.2	71.0	71.5	70.5	68.4
Past postmenopausal hormone use‡ (%)	15.0	14.0	16.8	17.3	17.9
Current postmenopausal hormone use‡ (%)	56.1	50.0	38.9	47.7	51.8
No strenuous physical activity§ (%)	31.9	34.1	31.9	34.1	28.2
High strenuous physical activity§ (%)	5.6	4.5	4.5	4.4	6.1

*Mean pack years of cigarette smoking among ever smokers

†% of breastfeeding > 12 months among parous women only

‡% of postmenopausal hormone use among postmenopausal women BMI = body mass index

§% of strenuous physical activity between age 18 and 22 years asked in NHS 1988 questionnaire

Table 2

Characteristics of the RA cases at diagnosis according to current residential location (N=706)

	West (N=95)	East (N=611)	p*
Mean age at RA dx, years (SD)	60.1 (± 8.9)	57.3 (± 9.4)	**0.01**
Rheumatoid factor positive, N (%)	48 (50.5%)	372 (60.9%)	0.06
Rheumatoid nodules, N (%)	13 (13.7%)	87 (14.2%)	0.89
Radiographic changes, N (%)	27 (28.4%)	182 (29.8%)	0.79
Mean number of ACR criteria (SD)**	4.7 (± 0.8)	4.7 (± 0.8)	0.37
Diagnosed by ACR member (%)	73 (82.0%)	516 (85.9%)	0.34

* t- tests for continuous variables, χ^2 tests for categorical variables

** 4/7 criteria required for diagnosis of RA by American College of Rheumatology criteria[34]

Table 3

Relative risk of RA by geographic region of residence at single time point among women in the Nurses' Health Study, 1976–2004

Geographic regions	Cases	Person-years observation	Age-adjusted[α] RR (95% CI)		Multivariable[β] RR (95% CI)	
At Birth[*]						
West	61	207,734	1.00	(ref)	1.00	(ref)
Midwest	164	458,725	1.24	(0.92–1.67)	1.25	(0.92–1.68)
Mid-Atlantic	341	976,753	1.25	(0.95–1.64)	1.22	(0.92–1.61)
New England	120	291,777	**1.46**	**(1.07–1.99)**	**1.41**	**(1.03–1.93)**
Southeast	20	49,347	1.45	(0.87–2.41)	1.40	(0.84–2.33)
At Age 15 [*]						
West	64	219,185	1.00	(ref)	1.00	(ref)
Midwest	162	447,363	1.26	(0.94–1.69)	1.26	(0.94–1.69)
Mid-Atlantic	334	973,570	1.23	(0.94–1.60)	1.20	(0.91–1.57)
New England	126	297,261	**1.51**	**(1.11–2.04)**	**1.45**	**(1.07–1.98)**
Southeast	20	46,957	1.51	(0.91–2.51)	1.47	(0.88–2.44)
At Age 30 [*]						
West	89	321,175	1.00	(ref)	1.00	(ref)
Midwest	160	399,231	**1.47**	**(1.13–1.91)**	**1.49**	**(1.14–1.94)**
Mid-Atlantic	332	923,854	**1.35**	**(1.07–1.71)**	**1.33**	**(1.05–1.70)**
New England	108	286,470	**1.41**	**(1.06–1.87)**	**1.37**	**(1.03–1.83)**
Southeast	17	53,605	1.19	(0.71–2.00)	1.16	(0.69–1.95)
At NHS cohort baseline in 1976[**]						
West	121	466,292	1.00	(ref)	1.00	(ref)
Midwest	161	489,859	**1.33**	**(1.05–1.68)**	**1.33**	**(1.05–1.69)**
Mid-Atlantic	392	1,244,441	**1.29**	**(1.05–1.58)**	**1.30**	**(1.05–1.60)**
New England	137	384,174	**1.45**	**(1.13–1.86)**	**1.42**	**(1.10–1.82)**
Southeast	21	69,780	1.21	(0.76–1.93)	1.20	(0.75–1.91)

[α] Adjusted for age in months.

[β] Also adjusted for pack-years of cigarette smoking, BMI, parity, duration of breastfeeding, post-menopausal status, postmenopausal hormone use, father's occupation, race, and physical activity

[*] 83,546 women followed from 1976–2004 and 706 confirmed incident cases of RA.

** 105,754 women followed 1976–2004 for the state of residence in 1976 analyses and 832 confirmed incident cases of RA..

RR = rate ratio; CI = confidence interval

Table 4

Relative risk of RA by migration status at multiple time points among women in the Nurses' Health Study, 1976–2004

Geographic regions	Cases	Person-years observation	Age-adjusted* RR (95% CI)		Multivariable† RR (95% CI)	
Both at Birth and Age 15						
Stay West	54	189,016	1.00	(ref)	1.00	(ref)
Stay Midwest	155	419,073	1.32	(0.97–1.81)	1.33	(0.97–1.82)
Stay Mid-Atlantic	326	936,821	1.28	(0.96–1.72)	1.25	(0.93–1.68)
Stay New England	117	278,634	**1.54**	**(1.11–2.12)**	**1.48**	**(1.06–2.06)**
Stay Southeast	15	33,373	1.61	(0.90–2.88)	1.55	(0.87–2.78)
Both at Age 15 and Age 30						
Stay West	56	196,141	1.00	(ref)	1.00	(ref)
Stay Midwest	137	344,305	**1.42**	**(1.04–1.94)**	**1.43**	**(1.04–1.96)**
Stay Mid-Atlantic	303	854,440	1.29	(0.97–1.72)	1.27	(0.95–1.70)
Stay New England	100	247,903	**1.46**	**(1.05–2.03)**	**1.41**	**(1.01–1.97)**
Stay Southeast	8	19,672	1.58	(0.75–3.31)	1.53	(0.73–3.22)
Both at Age 30 and 1976‡						
Stay West	81	298,465	1.00	(ref)	1.00	(ref)
Stay Midwest	137	366,171	**1.41**	**(1.07–1.86)**	**1.43**	**(1.08–1.89)**
Stay Mid-Atlantic	321	891,267	**1.38**	**(1.08–1.77)**	**1.37**	**(1.07–1.76)**
Stay New England	106	271,886	**1.50**	**(1.12–2.00)**	**1.46**	**(1.08–1.96)**
Stay Southeast	12	36,927	1.28	(0.70–2.35)	1.25	(0.68–2.29)
From Birth to Age 30						
Stay West	48	170,897	1.00	(ref)	1.00	(ref)
Stay Midwest	130	325,683	**1.46**	**(1.04–2.03)**	**1.47**	**(1.05–2.05)**
Stay Mid-Atlantic	297	827,224	1.35	(0.99–1.83)	1.32	(0.97–1.81)
Stay New England	92	234,938	**1.46**	**(1.03–2.07)**	1.40	(0.98–2.00)
Stay Southeast	7	14,080	1.93	(0.87–4.27)	1.87	(0.84–4.15)
From Birth to 1976 ‡						
Stay West	48	168,033	1.00	(ref)	1.00	(ref)
Stay Midwest	121	311,983	**1.40**	**(1.00–1.96)**	**1.41**	**(1.00–1.98)**
Stay Mid-Atlantic	292	809,909	1.33	(0.98–1.81)	1.31	(0.96–1.79)
Stay New England	91	229,927	**1.45**	**(1.02–2.07)**	1.40	(0.98–2.00)

Geographic regions	Cases	Person-years observation	Age-adjusted* RR (95% CI)		Multivariable† RR (95% CI)	
Stay Southeast	5	11,861	1.67	(0.66–4.21)	1.64	(0.65–4.14)

*Adjusted for age in months

†Also adjusted for pack-years of cigarette smoking, BMI, parity, duration of breastfeeding, post-menopausal status, postmenopausal hormone use, father's occupation, race, and physical activity

≠Nurses' Health Study cohort baseline in 1976

RR = rate ratio; CI = confidence interval

Table 5

Relative risk of RA by moving pattern from birth to age 30 years among women in the Nurses' Health Study, 1976–2004

Geographic regions	Cases	Person-years observation	Age-adjusted* RR (95% CI)		Multivariable† RR (95% CI)	
From Birth to Age 30						
Stay West at all 3 time points	48	170,897	1.00	(ref)	1.00	(ref)
Born in West and move to East ‡ at age 15 or age 30	12	32,052	1.34	(0.71–2.53)	1.35	(0.71–2.56)
Stay East at all 3 time points	603	1,626,183	**1.38**	**(1.03–1.85)**	**1.36**	**(1.01–1.84)**
Born in East and move to West at age 15 or 30	40	145,492	1.00	(0.65–1.52)	0.99	(0.65–1.52)
Other moving patterns	3	9,711	1.14	(0.35–3.66)	1.09	(0.34–3.53)

*Adjusted for years in months

†Also adjusted for pack-years of cigarette smoking, BMI, parity, duration of breastfeeding, postmenopausal status, postmenopausal hormone use, father's occupation, and race, and physical activity

‡Combine Midwest, Mid-Atlantic, New England, and Southeast into East.