

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

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Background: The geographic variation in rheumatoid arthritis (RA) incidence in the United States is unknown.

Methods: We studied residential region from January 1, 1921, to May 31, 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 (when participants were aged 30-55 years) and on state of residence at birth, at age 15 years, and at age 30 years in 1992. Among 83 546 participants reporting residence for all 4 time points, 706 incident RA cases from June 1, 1976, to May 31, 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 hazards regression models were used to assess relationships between region and RA risk, adjusting for age, smoking, body mass index, parity, breastfeeding, postmenopausal status, postmenopausal hormone use, father's occupation, race, and physical activity. Analyses

were performed in participants who lived in the same regions, or moved, over time.

Results: Compared with those in the West, women in New England had a 37% to 45% elevated risk of RA in multivariate models at each time point (eg, state of residence in 1976: rate ratio [RR], 1.42; 95% confidence interval [CI], 1.10-1.82). In analyses of women who lived in the same region at birth, age 15 years, and age 30 years, 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 with living in the West at birth, age 15 years, and age 30 years, RA risk was higher in the East.

Conclusions: In this large cohort of US women, significant geographic variation in incident RA existed after controlling for confounders. Potential explanations include regional variation in behavioral factors, climate, environmental exposures, RA diagnosis, and genetic factors.

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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 seem 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 female reproductive factors,^{26,27} occupational silica,²⁸ and mineral oil²⁹ as likely influences of RA risk.

Little is known about geographic distribution of RA in the United States or worldwide. A recent systematic review³⁰ of the existing studies suggests that RA is more common in northern Europe and North America than southern Europe, Africa, and the developing world. Some evidence also indicates that the incidence of RA has de-

clined 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 (NHS), 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 US 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 US state, with the majority in the most populated US 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.

STUDY POPULATION

The NHS is a prospective cohort of 121 700 female nurses, aged 30 to 55 years in 1976 when the study began. Nurses were originally recruited from the 11 most populated US states (California, Connecticut, Florida, Maryland, Massachusetts, Michigan, New Jersey, New York, Ohio, Pennsylvania, and Texas) but lived in much more geographically dispersed areas before this, including all 50 states. Of the NHS participants, 94.4% have remained in active follow-up (either responding to questionnaires or 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 this study, we included all women who had reported their US state of residence in 1976 as well as at birth and at ages 15 and 30 years on the 1992 questionnaire for analyses of those time points. Women were censored after their last response to the biennial questionnaires because incident RA cases could not be identified. Thus, the final group included 105 754 women followed up from June 1, 1976, to May 31, 2004, for the 1976 state of residence analyses and 83 546 women followed up from 1976 to 2004 with residential data for all 4 time points.

IDENTIFICATION OF RA

As previously described,^{16,26} we used a 2-stage procedure in which all nurses who self-reported any connective tissue disease underwent a screening questionnaire for connective tissue disease symptoms³³ and, if positive for symptoms, a detailed medical record review for American College of Rheumatology diagnostic criteria for RA.³⁴ We excluded participants who self-reported but subsequently denied the diagnosis of RA, had prevalent RA (diagnosed before the start of the cohort), denied permission for medical record review, or had a negative connective tissue diseases screening questionnaire result. Since NHS inception, the annual incidence of RA has ranged from 26 to 56 cases per 100 000 persons per year, with an overall incidence of 40 cases per 100 000 persons per year. This is quite similar to that reported by Doran and colleagues³¹ in Rochester, Minnesota, where the overall annual incidence of RA among those 18 years or older was 44.6 per 100 000 population.

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 the ages of 15 and 30 years (73.4% response rate on the NHS). We divided the continental United States into 6 geographic regions: Pacific, Mountain, Midwest, mid-Atlantic, New England, and Southeast. We combined Pacific and Mountain regions into a reference group for West (owing to few participants living in Mountain regions). For moving pattern analyses, Midwest, mid-Atlantic, New England, and Southeast were further grouped into an East category compared with the West area.

COVARIATE INFORMATION

Age was updated in each cycle. Based on previous findings,^{16,26,35} risk factors for RA in these cohorts that could potentially vary by geographic region, including cigarette smoking, parity and breastfeeding history, menopausal status, and postmenopausal hormone use, were included as potential con-

founders 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. Participants 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 2-year interval using the most recent weight in kilograms divided by height in meters squared, was also included in multivariate models. Father's occupation was assessed in 1992 in the NHS and served as a proxy for socioeconomic level in childhood. In 1992, participants in the NHS were asked to report their racial and ethnic ancestry as African, Asian, Hispanic, white, or other. Of the participants, 97.7% reported white 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 7 times in the NHS. A validation study conducted by Li et al³⁶ found a correlation of 0.79 between 1-week exercise recall and exercise reported on the NHS questionnaire.

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 unavailability for 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 used to study the association between US state of residence since birth and incident RA (developing from ages 33-81 years), while adjusting simultaneously for covariates of interest. We used time-varying information for covariates from each 2-year questionnaire to analyze the risk of RA in the next 2-year cycle. Final multivariate models included age, 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 years, 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 nonsmokers. To assess the effects of geographic residence at different ages, we performed analyses of region of residence at each of the time points (birth, age 15 years, age 30 years, and in 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 statistical software, version 9, was used 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 Midwest than in the other regions, and regular exposure to cigarette smoke in the workplace was also lowest among

Table 1. Age-Standardized Characteristics of the NHS Women by Geographic Regions at Cohort Baseline in 1976

Characteristic	West (n=21 553)	Midwest (n=22 280)	Mid-Atlantic (n=57 385)	New England (n=17 094)	Southeast (n=3262)
Age, mean (SD), y	44.4 (6.9)	42.7 (7.3)	42.6 (7.2)	42.2 (7.2)	44.0 (7.4)
Age at menarche, mean, y	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 ^a	18.7	18.1	19.0	19.5	19.8
Nonwhite 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 has a nonprofessional occupation, %	61.7	67.8	65.5	64.0	59.1
Irregular menses at age 20-35 y, %	10.9	11.9	11.7	12.4	11.3
Nulliparous, %	8.8	6.4	6.9	6.1	8.6
Breastfeeding ≥12 mo, % ^b	21.8	20.7	17.3	16.5	14.4
Premenopausal, %	69.2	71.0	71.5	70.5	68.4
Postmenopausal hormone use, % ^c					
Past	15.0	14.0	16.8	17.3	17.9
Current	56.1	50.0	38.9	47.7	51.8
Strenuous physical activity, % ^d					
None	31.9	34.1	31.9	34.1	28.2
High	5.6	4.5	4.5	4.4	6.1

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); NHS, Nurses' Health Study.

^aAmong ever smokers.

^bAmong parous women only.

^cAmong postmenopausal women.

^dBetween age 18 and age 22 years, asked in the NHS 1988 questionnaire.

Table 2. Characteristics of the 706 RA Case Patients at Diagnosis According to Current Residential Location

Characteristics	West (n=95) ^a	East (n=611) ^a	P Value ^b
Age at RA diagnosis, mean (SD), y	60.1 (8.9)	57.3 (9.4)	.01
Rheumatoid factor positive	48 (50.5)	372 (60.9)	.06
Rheumatoid nodules	13 (13.7)	87 (14.2)	.89
Radiographic changes	27 (28.4)	182 (29.8)	.79
No. of ACR criteria, mean (SD) ^c	4.7 (0.8)	4.7 (0.8)	.37
Diagnosed by an ACR member	73 (82.0)	516 (85.9)	.34

Abbreviations: ACR, American College of Rheumatology; RA, rheumatoid arthritis.

^aData are given as number (percentage) of each group unless otherwise indicated.

^bt Tests were used for continuous variables, and χ^2 tests were used for categorical variables.

^cOf 7 criteria, 4 were required for the diagnosis of RA by the ACR criteria.³⁴

participants in the West. Although most NHS participants are white, the West had the most nonwhites and New England had the fewest nonwhites. Among parous women, slightly more of those living in the West had breastfed for 12 or more months, and among postmenopausal women, more in the West were receiving postmenopausal hormones. No important differences in the characteristics (listed in Table 1) of participants who responded to our additional mailings compared with those who did not respond were found (data not shown).

Characteristics at diagnosis of the 706 RA case patients 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 case patients was 57.6 (9.4) years. The mean age at RA diagnosis was 3 years older among participants living in the West vs the East and more case patients were documented as rheumatoid factor positive at diagnosis in the East than in the West. Most case patients were diagnosed as having RA by a physician who was a member of the American College of Rheumatology.

Table 3 shows the relative risks of RA by geographic region of residence at each of the time points (birth, age 15 years, age 30 years, and in 1976), both in age-adjusted and multivariate models. Adjustment for all the potential confounders included did not substantially affect relative risk estimates in most cases. In both models, compared with 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. The relative risk of RA was also significantly elevated for residents of the Midwest and mid-Atlantic states at age 30 years.

In analyses stratified by never vs 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 fewer participants and, thus, the point estimates have wide confidence intervals. No evidence existed of a statistically significant interaction between smoking status and residence in each geographic region at each of the time points (at birth, $P = .61$; at age 15 years, $P = .70$; at age 30 years, $P = .94$; and in 1976, $P = .64$).

Table 4 shows the results of analyses of geographic area of residence among women who did not move for

Table 3. Relative Risk of RA by Geographic Region of Residence at a Single Time Point Among Women in the NHS, 1976 to 2004

Geographic Region	No. of Cases	Person-Years of Observation	RR (95% CI)	
			Age Adjusted ^a	Multivariate ^b
At birth ^c				
West	61	207 734	1 [Reference]	1 [Reference]
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) ^d	1.41 (1.03-1.93) ^d
Southeast	20	49 347	1.45 (0.87-2.41)	1.40 (0.84-2.33)
At age 15 y ^c				
West	64	219 185	1 [Reference]	1 [Reference]
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) ^d	1.45 (1.07-1.98) ^d
Southeast	20	46 957	1.51 (0.91-2.51)	1.47 (0.88-2.44)
At age 30 y ^c				
West	89	321 175	1 [Reference]	1 [Reference]
Midwest	160	399 231	1.47 (1.13-1.91) ^d	1.49 (1.14-1.94) ^d
Mid-Atlantic	332	923 854	1.35 (1.07-1.71) ^d	1.33 (1.05-1.70) ^d
New England	108	286 470	1.41 (1.06-1.87) ^d	1.37 (1.03-1.83) ^d
Southeast	17	53 605	1.19 (0.71-2.00)	1.16 (0.69-1.95)
At NHS cohort baseline in 1976 ^e				
West	121	466 292	1 [Reference]	1 [Reference]
Midwest	161	489 859	1.33 (1.05-1.68) ^d	1.33 (1.05-1.69) ^d
Mid-Atlantic	392	1 244 441	1.29 (1.05-1.58) ^d	1.30 (1.05-1.60) ^d
New England	137	384 174	1.45 (1.13-1.86) ^d	1.42 (1.10-1.82) ^d
Southeast	21	69 780	1.21 (0.76-1.93)	1.20 (0.75-1.91)

Abbreviations: CI, confidence interval; NHS, Nurses' Health Study; RA, rheumatoid arthritis; RR, rate ratio.

^aAdjusted for age (in months).

^bAlso adjusted for pack-years of cigarette smoking, body mass index, parity, duration of breastfeeding, postmenopausal status, postmenopausal hormone use, father's occupation, race, and physical activity.

^cA total of 83 546 women were followed up from 1976 to 2004, and 706 confirmed incident cases of RA were found.

^dSignificant difference vs the reference.

^eA total of 105 754 women were followed up from 1976 to 2004 for the state of residence in 1976 analyses, and 832 confirmed incident cases of RA were found.

at least 2 of the time points. Residents of New England and the Midwest who stayed in the same area from birth through ages 15 and 30 years had the highest relative risks of developing RA compared with women who stayed in the West. Relative risks of RA were also nonsignificantly elevated among women who lived in the mid-Atlantic states from birth to age 30 years.

The results of analyses of staying in the East, staying in the West, or migrating between the 2 regions between birth and ages 15 and 30 years are shown in **Table 5**. Those who lived in the East at all 3 time points had the highest relative risk compared with women who lived in the West at all 3 time points. However, those who were born in the West and moved to the East before age 30 years acquired a risk closer to those who had lived in the East at all 3 time points. Women who were born in the East but moved to the West before age 30 years had a risk similar to those who lived in the West at all 3 time points.

COMMENT

In this large cohort of US women followed up 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 midwestern United States, com-

pared with those 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 years, and age 30 years, 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 few women in this analysis. Relative risks among women in southeastern states were similar to those in other eastern states at most time points, although not significantly elevated compared with those in the West, given fewer 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 UV 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

Table 4. Relative Risk of RA by Migration Status at Multiple Time Points Among Women in the NHS, 1976 to 2004

Geographic Region	No. of Cases	Person-Years of Observation	RR (95% CI)	
			Age Adjusted ^a	Multivariate ^b
Both at birth and at age 15 y				
Stay West	54	189 016	1 [Reference]	1 [Reference]
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) ^c	1.48 (1.06-2.06) ^c
Stay Southeast	15	33 373	1.61 (0.90-2.88)	1.55 (0.87-2.78)
Both at age 15 y and at age 30 y				
Stay West	56	196 141	1 [Reference]	1 [Reference]
Stay Midwest	137	344 305	1.42 (1.04-1.94) ^c	1.43 (1.04-1.96) ^c
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) ^c	1.41 (1.01-1.97) ^c
Stay Southeast	8	19 672	1.58 (0.75-3.31)	1.53 (0.73-3.22)
Both at age 30 y and in 1976 ^d				
Stay West	81	298 465	1 [Reference]	1 [Reference]
Stay Midwest	137	366 171	1.41 (1.07-1.86) ^c	1.43 (1.08-1.89) ^c
Stay mid-Atlantic	321	891 267	1.38 (1.08-1.77) ^c	1.37 (1.07-1.76) ^c
Stay New England	106	271 886	1.50 (1.12-2.00) ^c	1.46 (1.08-1.96) ^c
Stay Southeast	12	36 927	1.28 (0.70-2.35)	1.25 (0.68-2.29)
From birth to age 30 y				
Stay West	48	170 897	1 [Reference]	1 [Reference]
Stay Midwest	130	325 683	1.46 (1.04-2.03) ^c	1.47 (1.05-2.05) ^c
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) ^c	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 ^d				
Stay West	48	168 033	1 [Reference]	1 [Reference]
Stay Midwest	121	311 983	1.40 (1.00-1.96) ^c	1.41 (1.00-1.98) ^c
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) ^c	1.40 (0.98-2.00)
Stay Southeast	5	11 861	1.67 (0.66-4.21)	1.64 (0.65-4.14)

Abbreviations: See Table 3.

^aAdjusted for age (in months).

^bAlso adjusted for pack-years of cigarette smoking, body mass index, parity, duration of breastfeeding, postmenopausal status, postmenopausal hormone use, father's occupation, race, and physical activity.

^cSignificant difference vs the reference.

^dThe NHS cohort baseline in 1976.

Table 5. Relative Risk of RA by Moving Pattern From Birth to Age 30 Years Among Women in the NHS, 1976 to 2004

Geographic Region From Birth to Age 30 y	No. of Cases	Person-Years of Observation	RR (95% CI)	
			Age Adjusted ^a	Multivariate ^b
Stay West at all 3 time points (birth, age 15 y, and age 30 y)	48	170 897	1 [Reference]	1 [Reference]
Born in West and move to East at age 15 y or age 30 y ^c	12	32 052	1.34 (0.71-2.53)	1.35 (0.71-2.56)
Stay East at all 3 time points (birth, age 15 y, and age 30 y)	603	1 626 183	1.38 (1.03-1.85) ^d	1.36 (1.01-1.84) ^d
Born in East and move to West at age 15 y or age 30 y	40	145 492	1.00 (0.65-1.52)	0.99 (0.65-1.52)
Other moving patterns	3	9711	1.14 (0.35-3.66)	1.09 (0.34-3.53)

Abbreviations: See Table 3.

^aAdjusted for age (in months).

^bAlso adjusted for pack-years of cigarette smoking, body mass index, parity, duration of breastfeeding, postmenopausal status, postmenopausal hormone use, father's occupation, race, and physical activity.

^cMidwest, mid-Atlantic, New England, and Southeast were combined into East.

^dSignificant difference vs the reference.

RA cases at diagnosis according to region: the mean age at RA diagnosis was older and the percentage of rheumatoid factor–positive cases was lower in the West.

We hypothesize that the increased risk of RA among women living in the Midwest and eastern United States

from 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 cessa-

tion.^{4,6-9,11,13-15} A gene-environment interaction seems to exist with the HLA-DRB1 shared epitope, the strongest genetic risk factor for RA, such that individuals who carry 2 copies of the shared epitope and are smokers are at much increased risk of developing anti-cyclic citrullinated peptide-positive RA.^{2,3} Exposure to silica dust through the respiratory tract in occupations such as rock drilling, mining, and sandblasting 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, seems to be a risk factor only for rheumatoid factor/anti-cyclic citrullinated peptide-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 fewer participants, and formal test results for interaction between smoking and geographic region of residence at each of the time points were nonsignificant.

The associations of cigarette smoke and silica with increased risk of RA suggest that respiratory tract 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 tract 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 do 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 with the rest of the United States, except for the Los Angeles, California, area, where levels are 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.

Most NHS participants are white, but the racial composition of the cohort varies with respect to geographic location. We controlled for race in our multivariate models; the contribution of genetic risk factors to RA susceptibility may have varied by geographic region. Although based on few participants, our analyses of migration patterns and the risk of RA suggested 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 years 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 US states, but moved widely, throughout all 50 states, and abroad, during the 28-year follow-up. 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 few individuals. Again, one possibility is genetics because 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 US women between geographic regions to date. These preliminary findings are hypothesis generating and deserving of further study. Regional differences in 1 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.

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