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MS Increasingly a Woman's Disease

Steady Rise in Rates of Multiple Sclerosis Seen in Women

By Salynn Boyles
WebMD Medical News
Reviewed By Louise Chang, MD

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April 26, 2007 -- Women with multiple sclerosis (MS) now appear to outnumber men with the disease by a ratio of four to one in the U.S., new research shows.

The review of data from a voluntary MS registry suggests a steady increase in MS rates among women over time, while rates among men appear to have remained stable.

In 1940, twice as many women as men in the U.S. had multiple sclerosis. By 2000, four out of five cases were occurring among women, University of Alabama professor of biostatistics Gary Cutter, PhD, tells WebMD.

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That represents an increase in the ratio of women to men of nearly 50% per decade, and it mirrors recent findings from other countries with more comprehensive MS registries, including Canada, Norway, and Denmark.

It is not clear why MS rates seem to be increasing only among women, but the observation could help researchers searching for the cause or causes of the disease, Cutter says.

Some believe that environmental or viral influences early in life trigger the disease in people who are genetically predisposed toward getting it. Though there are many theories about what these triggers are, there is no proof that any of them cause MS.

MS is a disease that affects the brain and spinal cord. Experts believe that it is due to an abnormal response of the immune system attacking the myelin sheath that surrounds nerve fibers. Myelin is needed for sending nerve signals such as those that control movement. The National Multiple Sclerosis Society estimates that 400,000 Americans have MS.

Searching for Clues

"We have to ask ourselves, 'What has been going on over the last 50 years or so that would affect women more than men?'" Cutter says.

During that time, obesity and smoking rates have increased among women, the oral contraceptive was introduced, and there has been a trend toward earlier menstruation and later childbirth.

These factors influence levels of the sex hormones, and there is some evidence that sex hormones play a role in MS by suppressing the immune system.

Most women with MS have fewer symptoms of the disease during pregnancy. After delivery, symptoms often return.

The sex hormone connection is just one avenue that needs to be explored, Cutter says. He is scheduled to present findings from the study at next week's 59th Annual Meeting of the American Academy of Neurology in Boston.

Probably No Single Cause

"We also need to ask the general questions about what women do differently than men, such as use of hair dye and use of cosmetics that may block vitamin D absorption," he says in a news release. "At this point we are just speculating on avenues of research that could be pursued."

MS rates are highest among people living farthest from the equator, leading to speculation that vitamin D deficiency due to low sun exposure contributes to the disease.

MS researcher and clinician Gary Birnbaum, MD, tells WebMD that there probably isn't any single "smoking gun" that can explain all cases of MS.

Birnbaum directs the Multiple Sclerosis Treatment and Research Center at the Minneapolis Clinic of Neurology in Golden Valley, Minn. He is also a clinical professor of

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neurology at the University of Minnesota School of Medicine.

"If it were that simple we probably would have been able to figure it out by now," he says. "MS may not be a single disease. It may be a syndrome. The pathway may actually be very different for different people."

SOURCES: Cutter, G., early release of presentation, 59th Annual Meeting of the American Academy of Neurology, Boston, April 28-May 5, 2007. Gary Cutter, PhD, professor of biostatistics, University of Alabama at Birmingham School of Public Health. Gary Birnbaum, MD, director, Multiple Sclerosis Treatment and Research Center, Minneapolis Clinic of Neurology, Golden Valley, Minn.; clinical professor of neurology, University of Minnesota School of Medicine.

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59 Annual Meeting of the American Academy of Neurology Boston April 28 – May 5, 2007

[P04.068] Changes in the Sex Ratio over Time in Multiple Sclerosis

Gary Cutter, Rajani Yadavalli, Birmingham, AL, Ruth-Ann Marrie, Rocky River, OH, Tuula Tyry, Denise Campagnolo, Breanna Bullock, Timothy Vollmer, Phoenix, AZ

OBJECTIVE: To determine the change over time in the prevalence ratio of females to males in the NARCOMS MS population, and to assess whether this trend parallels that reported from Canada and if it appears to be continuing. **BACKGROUND:** A recently published study from Canada suggested that the sex ratio in the identified multiple sclerosis (MS) patients has increased for females compared to males over the last 60 years from about 1.9 females to males prior to 1940 to nearly 3.2 to 1 in 1976-1980. **DESIGN/METHODS:** Participants enrolled in the NARCOMS registry are predominantly from the US. They self-report demographic and clinical information regarding their MS at enrollment and semi-annually thereafter. Age, gender, age at diagnosis and age at onset were used to assess the female/male ratio in the year diagnosed adjusted for age at diagnosis. **RESULTS:** 32,414 participants were examined and 30,336 were available to assess the sex ratio adjusted for age at onset and year of diagnosis. Overall 72.5% were females and approximately 93% were white. The mean year of diagnosis was 1973 for males and 1975 for females. The ratio female/males increased from 1940 to 2000 adjusted for onset (from approximately 2 to 1 to over 4 to 1). The increase in the odds of being an MS female was 1.046 per year (95%CI 1.043-1.049) or slightly less than a 50% increase in the ratio per decade. This ratio has increased for all age groups with a larger increase for younger ages at onset. **CONCLUSIONS/RELEVANCE:** MS appears to be increasing in females compared to males confirming the Canadian observations. The changes appear to be more pronounced at younger ages of onset. These changing demographic patterns parallel a number of lifestyle changes over the past 50 years which may provide important clues for MS etiology. Supported by: Consortium of Multiple Sclerosis Centers (CMSC).

Category - MS and Related Diseases
SubCategory - Clinical Science

Wednesday, May 2, 2007 7:00 AM

Geographic variation of MS incidence in two prospective studies of US women

Miguel A. Hernán, MD, DPH; Michael J. Olek, DO; and Alberto Ascherio, MD, DPH

Article Abstract—*Objective:* To estimate the incidence of MS and its relation to latitude in two ongoing prospective studies of US women. *Background:* A higher incidence of MS has been found in northern areas compared with southern areas of the United States and other countries, but the attenuation of this gradient in Europe in the last few decades and the consideration of ethnic factors have led some authors to question the existence of a strong association between MS and latitude. *Methods:* The authors identified new cases of MS among participants in the Nurses' Health Study (NHS), which took place between 1976 and 1994, and in the Nurses' Health Study II (NHS II), which took place between 1989 and 1995. The NHS included women born between 1920 and 1946, and the NHS II included women born between 1947 and 1964. *Results:* The incidence of MS among NHS participants (181 definite/probable patients) increased significantly with latitude ($p = 0.03$, trend). Adjusted rate ratios were 3.5 (95% CI, 1.1, 11.3) for the north and 2.7 (95% CI, 0.8, 8.9) for the middle tiers relative to the southern tier. Among NHS II women (131 definite/probable patients), no association between latitude and MS was found ($p = 0.89$, trend). Adjusted rate ratios were 0.8 (95% CI, 0.4, 1.6) for the northern areas and 0.9 (95%, 0.4, 1.8) for the middle areas, relative to the southern areas. *Conclusions:* The association between latitude and risk of MS in the United States was corroborated, but there was an attenuation of the north–south gradient over time. If confirmed, this finding could provide new clues to identifying environmental causes of the disease. **Key words:** Multiple sclerosis—Cohort study—Geography—Ethnic groups—United States.

NEUROLOGY 1999;53:1711–1718

A south-to-north gradient of MS frequency has been observed in the United States,[1-4] western Europe,[5] and Australia.[6,7] Although several hypotheses have been proposed, this association of MS with latitude remains unexplained, and it has been challenged recently.[5,8] Population-based surveys conducted in southern Europe since 1990, based on improved case-finding procedures and standardized diagnostic criteria, have found a higher MS prevalence than believed previously.[9] Although a differential ascertainment of the disease does not seem to contribute to the observed differences within the United States, it has been argued that the latitude gradient reflects primarily genetic variation within the population.[10]

Besides the lack of recent studies on the association between risk of MS and latitude in the United States, there is also a lack of MS incidence data. Most MS surveys in the United States have used prevalence as the measure of frequency of the disease, probably due to the high costs required for conducting longitudinal studies and estimating directly the incidence rate of MS.

We present age-specific incidence rates of MS from two ongoing prospective cohort studies of US women—the Nurses' Health Study (NHS) and the Nurses' Health Study II (NHS II)—and compare them by ancestry and geographic region.

Methods. *Population.* The NHS was established in 1976, when 121,700 female registered nurses from 11 states (CA, CT, FL, MD, MA, MI, NJ, NY, OH, PA, TX), age 30 to 55 years, responded to a mailed questionnaire about disease history and lifestyle items. The NHS II was established in 1989, when 116,671 female registered nurses from 14 states (CA, CT, IN, IA, KY, MA, MI, MO, NY, NC, OH, PA, SC, TX), age 25 to 42 years, responded to a similar questionnaire. Every 2 years, follow-up questionnaires are mailed to the participants of both studies to update information on potential risk factors for chronic diseases and to ascertain whether major medical events have occurred. A specific question on the lifetime occurrence of MS was first included in the 1992 (the NHS) and 1991 (the NHS II) questionnaires. Before 1992, new diagnoses of MS in the NHS could be specified through an open-ended question regarding "Other major illness." For this analysis, we excluded women who had received a diagnosis of MS before they answered the baseline questionnaire. When using the date of first symptoms (described later), women who had symptoms of MS before the baseline questionnaire were also excluded.

Patient ascertainment. We requested permission to obtain relevant medical records from all participants who reported a new diagnosis of MS. After obtaining permission, we sent to the treating neurologists a questionnaire that included questions on the certainty of the diagnosis (definite, probable, possible, not MS) and questions regarding critical information from clinical history and laboratory

From the Departments of Epidemiology (Drs. Hernán and Ascherio) and Nutrition (Dr. Ascherio), Harvard School of Public Health; and the Center for Neurological Diseases–Multiple Sclerosis Unit (Dr. Olek), Brigham and Women's Hospital and Harvard Medical School, Boston, MA.

Supported by NIH grants CA40356, CA50385, and NS35624.

Received March 22, 1999. Accepted in final form June 11, 1999.

Address correspondence and reprint requests to Dr. Miguel Hernán, Department of Epidemiology, Harvard School of Public Health, 677 Huntington Avenue, Boston, MA 02115.

tests. If a neurologist was not involved or did not respond, we mailed the questionnaire to the patient's internist.

In a sample of 39 patients we also obtained their medical records for validation. These medical records were reviewed by the study neurologists, who classified the cases into definite, probable, or possible MS according to the criteria of Poser et al.[11] For all purposes, we considered the categories clinically definite or laboratory-supported definite as definite, and clinically probable or laboratory-supported probable as probable. No upper age limit was set for the diagnosis of MS. The study neurologists, who were blinded to the treating physicians' questionnaires and diagnoses, confirmed 62% of the cases classified as definite or probable MS by the treating physicians, and classified the remaining 38% as possible MS. Agreement on dates of diagnosis and first symptoms was complete within 1 year, except for three patients with a 2-year discrepancy. The lower degree of certainty of the diagnoses given by the study neurologists was most likely due to incompleteness of the medical records, because when the criteria of Poser et al.[11] for the diagnosis of MS were applied to the clinical and laboratory data provided by the treating physicians in the questionnaire, 93% of all definite and probable diagnoses were confirmed. Therefore, for the purpose of the investigation we confirmed the treating physicians' diagnoses.

Assessment of exposure. Participants reported their state of birth and state of residence at ages 15 and 30. To facilitate comparisons with previous studies, we divided the continental United States into northern, middle, and southern tiers, and into eastern, central, mountain, and Pacific zones. The northern tier includes states generally north of 41 to 42 deg north latitude in the east (CT, ME, MA, NH, NY, RI, VT), central (MI, MN, WI), mountain (ID, MT, NE, ND, SD, WY), and Pacific (OR, WA) zones. The southern tier consists of those states lying south of 37 deg south latitude in the east (FL, GA, NC, SC), central (AL, AR, LA, MS, TN), mountain (AZ, NM, OK, TX), and Pacific (southern CA) zones; and the middle tier consists of the remaining states in the east (DE, DC, MD, NJ, PA, VA, WV), central (IL, IN, IA, KY, MO), mountain (CO, KS, NV, UT), and Pacific (northern CA) zones. The results did not change when Hawaii and Puerto Rico were included in the southern tier, and Alaska in the northern tier. Information on state of residence at birth and at age 15 is available from 73% of women in the NHS and from 78% of women in the NHS II.

The participants were asked whether they had the following ancestries: African, Asian, Hispanic, Scandinavian, southern European/Mediterranean, other white, or other ancestry. Most of the women (93% in the NHS, 91% in the NHS II) reported only white ancestries, reflecting the ethnic background of women trained as registered nurses. More than 90% of the women reported a single ancestry. We categorized the participants as southern European/Mediterranean or as Scandinavian when that was the only ancestry reported, as Other White when a mixture of only white ancestries was reported, and as nonwhite when either African, Asian, or Hispanic ancestry was reported. The question on ancestry was asked in 1992 for the NHS, when most of the incident MS patients had already been diagnosed. In this cohort, 83% of women without MS and 98% of women diagnosed with MS by 1992 answered the question on ancestry. In the NHS II, ancestry data were collected at baseline and were available from 99% of the participants, regardless of whether they eventually developed MS. The mean number of ancestries reported was 1.1 for both MS patients and non-MS patients in both cohorts.

Statistical analysis. Each participant contributed person-time of follow-up from the month of return of the baseline questionnaire to the date of MS diagnosis, death from any cause, or end of follow-up, whichever came first. For the rates presented here, the end of follow-up was June 1994 for the NHS and June 1995 for the NHS II. Age-specific incidence rates were calculated as the number of MS cases (definite and probable only) divided by person-time of follow-up in each age group, and were summarized by calculating the corresponding lifetime probability of having an MS diagnosis.[12] We also performed separate analyses according to the date of first symptoms, defined as the earliest date at which neurologic symptoms attributable to MS were reported by the participant or her physician.

We used Cox proportional hazards regression to estimate rate ratios (RRs) and 95% confidence intervals (CIs) for geographic region and ancestry, adjusted for each other and for age. Separate regression models were used for incidence of MS diagnosis and incidence of MS first symptoms. Log relative risks from the two studies were weighted by the inverse of their variances to obtain a pooled estimate.

Results. In the NHS, 446 participants reported a new diagnosis of MS during the 18-year follow-up period (2,119,277 person-years). Of the 349 participants who we were able to contact and who confirmed their diagnoses, 83% gave us permission to contact their treating physicians. We obtained information from 249 physicians, who confirmed 98% of the self-reports as MS cases. Of these, 211 patients (127 definite, 54 probable, 30 possible) were diagnosed between enrollment in the study and June 1994. There were 129 physician-confirmed MS patients (79 definite, 29 probable, 21 possible) with first symptoms during the follow-up period.

In the NHS II, 324 participants reported a new diagnosis of MS during the 6-year follow-up (649,583 person-years). Of the 214 participants who we were able to contact and who confirmed the diagnosis, 88% gave us permission to contact their treating physicians. We obtained information from 170 physicians, who confirmed 97% of the self-reports as MS patients. Of these, 150 patients (102 definite, 29 probable, 19 possible) were diagnosed between enrollment in the study and June 1995. There were 94 physician-confirmed MS patients (62 definite, 18 probable, 14 possible) with first symptoms during the follow-up period.

Age-specific incidence rates of definite and probable MS for the NHS and the NHS II combined are shown in figures 1 and 2 according to date of diagnosis and date of first symptoms respectively. The highest incidence of diagnosis occurred among women in their 30s and 40s, whereas the incidence of first symptoms peaked before age 30. Based on these rates, the expected lifetime risk of having a diagnosis of definite or probable MS would be 4.89 per 1,000 women.

The percent of women with a Scandinavian ancestry was highest in the northern tier at birth, and in the southern tier at age 30 (table 1). The percent of Scandinavians was lowest, and that of southern Europeans was greatest, in the eastern zone at all ages, whereas the percent of

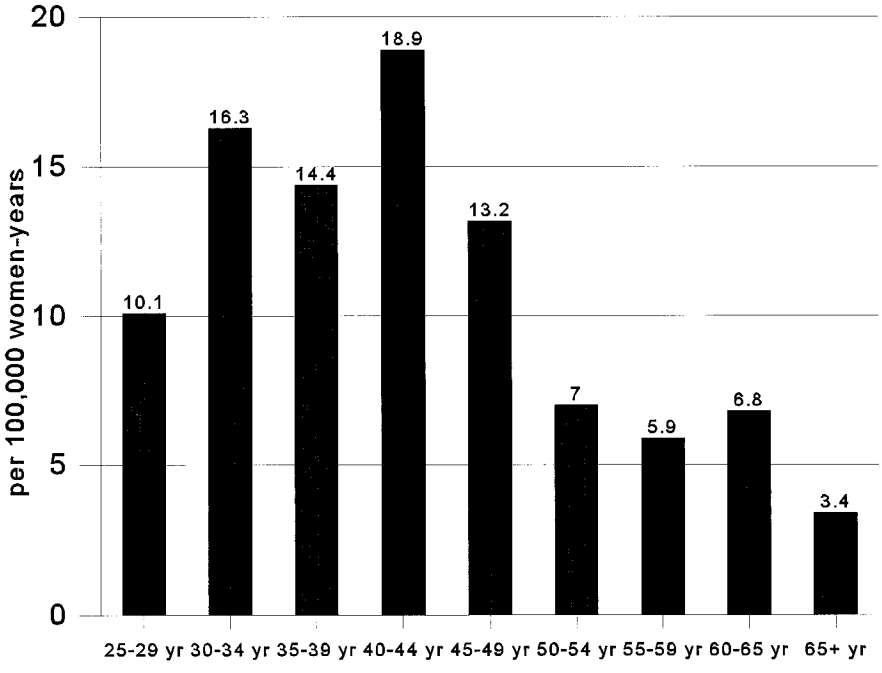

Figure 1. Incidence of MS diagnosis in the Nurses' Health Study (NHS) and the Nurses' Health Study II (NHS II).

nonwhites was greater in the Pacific and mountain zones at all ages.

In the NHS, incidence of MS appeared to increase with latitude of residence at age 15. The rate in the north was 3.5 times greater than in the south, after adjustment for age, ancestry, and longitude (table 2). In the NHS II, the rate in the north was not greater than in the south. The p value of a Wald test for the heterogeneity of the study-specific RRs was 0.05. The incidence of MS was not greater for those residing in the north at age 30. (The age-adjusted RR for the north compared with the south was 0.99 in the NHS and 0.95 in the NHS II). We could not study whether the north–south gradient was constant across longitude due to the small numbers of individuals in zones other than the eastern zone. When using date of first symptoms, the relative rates were qualitatively similar, but with broader CIs. A suggestion of a lower risk of MS was found among women born in the Pacific zone compared with the eastern zone: The multivariate RR was 0.7 (95% CI, 0.2, 2.3) in the NHS and was 0.3 (95% CI, 0.1, 1.2) in the NHS II, but these results are based on small numbers and are not significant (pooled RR, 0.5; 95% CI, 0.2, 1.2). After adjusting for latitude, the association between risk of MS and residing in the Pacific zone at age 15 was greatly attenuated.

When we restricted the analyses to NHS women born in the period 1920 to 1934, the age-adjusted relative rate for the northern tier versus the middle tier was 1.9. There were no patients in the southern tier (age-adjusted RR for north versus middle and south combined was 2.1). Among

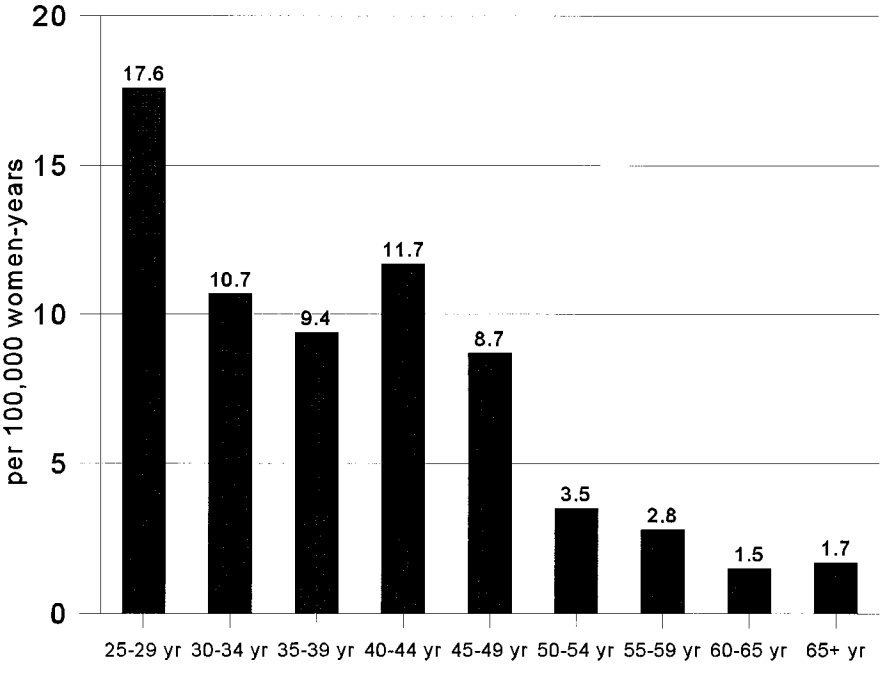

Figure 2. Incidence of MS clinical onset in the Nurses' Health Study (NHS) and the Nurses' Health Study II (NHS II).

Table 1 *Distribution of ancestry by geographic region at birth, age 15, and age 30 among women in the NHS/NHS II*

Study	Tier at birth			Tier at age 15			Tier at age 30		
	South	Middle	North	South	Middle	North	South	Middle	North
NHS									
Scandinavian, %	3.7	3.1	5.9	4.3	3.1	5.8	6.0	3.5	4.9
Southern European, %	12.0	16.0	15.7	13.0	16.1	15.5	13.7	15.8	15.6
Other white, %	70.0	75.8	73.7	70.5	75.6	73.6	71.6	74.9	73.7
Nonwhite, %	14.2	5.1	4.8	12.3	5.2	5.1	8.7	5.8	5.9
NHS II									
Scandinavian, %	4.2	4.0	5.3	4.4	4.2	4.9	5.4	4.3	4.1
Southern European, %	11.0	14.2	15.3	11.5	14.1	15.3	11.8	13.8	15.5
Other white, %	72.8	76.7	74.2	72.5	76.3	74.1	71.5	75.8	73.7
Nonwhite, %	11.9	5.1	5.3	11.6	5.4	5.7	11.3	6.0	6.7

NHS = Nurses' Health Study; NHS II = Nurses' Health Study II.

NHS women born from 1935 to 1946, the age-adjusted RRs were 1.3 for the middle and 1.5 for the north, compared with the south.

The relative rates of MS diagnosis by ancestry are shown in table 3. Although in the NHS women of southern European ancestry and other whites had a similar risk of being diagnosed, in the NHS II southern Europeans had the highest risk. Results for Scandinavians, although not significant, suggest an increased risk for Scandinavians compared with all others in the NHS, and a risk similar to other whites in the NHS II. The p value of the test of heterogeneity was 0.05. Note that the results for Scandinavians in the NHS II are based on a small number of participants. Relative risks for nonwhites are presented for completeness only and are not discussed further because the small sample size and the heterogeneity of the group (including a greater proportion of Hispanics, with mixed southern European descent, in NHS II) make difficult the interpretation of the estimates. The relative rates of MS first symptoms by ancestry are shown in table 4. Compared with the results in table 3, there is a marked increase in risk for Scandinavians.

Discussion. In these large prospective studies among US women, we found that the incidence of MS increased with latitude, as reported previously,[1-7] but the north–south gradient diminished over time. Women with Scandinavian ancestry had a higher risk of MS in the earlier cohort but not in the later cohort, in which the highest risk was associated with southern European ancestry.

The incidence of MS has been reported from several surveys conducted in North America,[13-18] but only one[3] reported age-specific incidence rates of MS in the United States. The risk of MS in the NHS and the NHS II is of similar magnitude to the one derived from this study (3.9 per 1,000 women).

Because we did not include the self-reported MS diagnoses that we were unable to confirm in the rate calculations (some participants denied us permission to contact their treating physician, others could not be contacted, and others may have not even reported their diagnosis to us), and because we assumed no cases occurred by age 25, the reported risk of MS in the NHS and the NHS II is probably an underestimate. On the other hand, this risk might have been overestimated if MS was overdiagnosed. Overdiagnosis seems unlikely, however, because the majority of the treating physicians were certified neurologists (89% NHS, 94% NHS II), and the proportion of definite and probable cases of MS (86% NHS, 87% NHS II) were similar to those reported in the literature.[19-22] Furthermore, none of the MS diagnoses made by the treating physicians was rejected by the study neurologists who reviewed medical records of a sample of patients, and the diagnoses made by the treating physicians were also consistent with the criteria of Poser et al.[11] applied to signs and symptoms reported in the questionnaire. Substantial agreement between observers in classifying MS according to these criteria has been reported before.[23] If women with undiagnosed MS had been more likely to join the study, we would have expected to find a greater incidence of MS diagnosis during the first years of follow-up, which did not occur (data not shown).

The NHS studies cover a period during which MRI was used increasingly as a diagnostic aid. Although the diagnosis of MS remains largely clinical,[11] MRI is the most sensitive test for demonstrating lesions that are not clinically detectable to satisfy the criterion of dissemination in space.[24] Also, MRI is the best test for predicting a future diagnosis of clinically definite MS.[25] Thus, generalized use of MRI would identify a larger proportion of patients in the earliest or mildest stages of the disease. Previously published incidence rates in European populations cover periods before the generalized use of MRI, which might contribute to their somewhat lower magnitude. This is also consistent with the increased incidence over time that we found in the NHS studies (data not shown).

Another intriguing possibility is that nurses might

Table 2 *Relative incidence of MS diagnosis by latitude tier in the NHS/NHS II**

Variable	Southern tier	Middle tier	Northern tier	*p* Value for trend
NHS				
n	4	65	72	—
Person-years of observation	99,500	708,724	592,115	—
RR (95% CI)				
Age adjusted	1.0	2.1 (0.8, 5.8)	2.8 (1.0, 7.7)	—
Age, ancestry adjusted†	1.0	2.0 (0.7, 5.6)	2.7 (1.0, 7.3)	—
Multivariate‡	1.0	2.7 (0.8, 8.9)	3.5 (1.1, 11.3)	0.03
NHS II				
n	14	54	43	—
Person-years of observation	59,499	231,850	159,075	—
RR (95% CI)				
Age adjusted	1.0	1.0 (0.5, 1.8)	1.2 (0.6, 2.1)	—
Age, ancestry adjusted†	1.0	1.0 (0.5, 1.7)	1.1 (0.6, 2.1)	—
Multivariate‡	1.0	0.8 (0.4, 1.6)	0.9 (0.4, 1.8)	0.89
Pooled analysis				
RR (95% CI) multivariate‡	1.0	1.1 (0.6, 2.0)	1.3 (0.7, 2.3)	—
p Value for heterogeneity	—	0.07	0.05	—

* Restricted to women who lived in the same tier at birth and at 15 years of age.
† Adjusted for age (5-year categories) and ancestry (Scandinavian, southern European, other white, nonwhite).
‡ Also adjusted for longitude zone (Pacific, mountain, central, eastern).

NHS = Nurses' Health Study; NHS II = Nurses' Health Study II; RR = rate ratio; CI = confidence interval.

actually have a higher incidence of MS than other women. An increased risk among nurses was reported in the Key West cluster of MS,[26] and in a survey in northeastern Scotland in 1973.[27] However, no increased risk among nurses was detected in a subsequent survey of the same Scottish area in 1980,[28] nor was MS listed as a cause of death more frequently than expected among British nurses and nursing administrators.[29] Our findings do not support an important excess risk of MS among NHS participants compared with US women in 1970 to 1975.[3] The slight elevation we found for MS diagnosis could be explained by the greater proportion of white women, and of women living in the north, along with an increased awareness of the disease and easier access to health care among nurses, so that even very mild MS cases would be detected. Higher MS rates have been found in two large epidemiologic studies of married British women, with duration of follow-up comparable with the NHS. In the Oxford/Family Planning Association study,[30] an expected lifetime risk of 5.4 per 1,000 women (including possible cases) was estimated among 17,032 women attending family planning clinics between 1968 and 1974, and followed through 1991.[31] In the Royal College of General Practitioners' Oral Contraception Study, an expected lifetime risk of 6.1 per 1,000 was estimated among a cohort of 46,000 women followed between 1968 and 1996.

Kurtzke et al.[1] found a north–south relative risk of 3.5 among white women (and 2.6 among white men) who served in the army during World War II or during the Korean conflict. In a national US survey, the relative incidence of MS during the period 1970 to 1975 was 2.7 for the northern tier relative to the south, both sexes combined (3.1 for women if the same proportions used in Kurtzke's study apply).[3] In the NHS, the incidence of MS was also 3.5 times greater among women residing in the northern tier by age 15 compared with those in the southern tier, after adjustment for age, ancestry, and longitude zone. The north–south difference was greater for women born from 1920 through 1934 than for those born from 1935 to 1946. For NHS II women, born between 1947 and 1964, no increase in the risk of MS was detected among those living in the north. Although borderline significant, these differences between cohorts are consistent with an attenuation over time of the north–south gradient of MS risk among women. If confirmed, this attenuation may provide an important clue to the etiology of MS because it suggests that the environmental factors that determined the north–south gradient of MS risk have also changed in the past few decades. This relatively rapid change is consistent with theories that involve infectious agents (e.g., viruses) in the etiology of MS, and suggests that genetic factors may have had a secondary role in the latitude gradient of the disease.

Since Davenport proposed that Scandinavians have a higher risk of MS and southern Europeans a lower risk than other whites living in North Ameri-

Table 3 *Relative incidence of MS diagnosis by ancestry in the NHS/NHS II*

Variable	Southern European	Scandinavian	Other white	Nonwhite
NHS				
n	27	11	131	7
Person-years of observation	271,026	75,974	1,331,646	123,038
RR (95% CI)				
Age adjusted	1.0	1.6 (0.8, 3.2)	1.0 (0.7, 1.5)	0.6 (0.3, 1.4)
Age, latitude adjusted*	1.0	1.8 (0.9, 3.8)	1.1 (0.7, 1.7)	0.7 (0.3, 1.8)
Multivariate†	1.0	1.9 (0.9, 3.9)	1.1 (0.7, 1.7)	0.7 (0.3, 1.8)
NHS II				
n	26	4	90	11
Person-years of observation	88,630	28,412	467,233	55,311
RR (95% CI)				
Age adjusted	1.0	0.5 (0.2, 1.4)	0.7 (0.4, 1.0)	0.7 (0.3, 1.4)
Age, latitude adjusted*	1.0	0.5 (0.2, 1.4)	0.6 (0.4, 1.0)	0.6 (0.3, 1.5)
Multivariate†	1.0	0.5 (0.2, 1.5)	0.6 (0.4, 1.0)	0.7 (0.3, 1.6)
Pooled analysis				
RR (95% CI) multivariate†	1.0	1.2 (0.7, 2.3)	0.8 (0.5, 1.4)	0.7 (0.4, 1.3)
p Value for heterogeneity	—	0.05	0.09	0.97

* Adjusted for age (5-year categories) and tier of birth (north, middle, south).
† Also adjusted for longitude zone (Pacific, mountain, central, eastern).

NHS = Nurses' Health Study; NHS II = Nurses' Health Study II; RR = rate ratio; CI = confidence interval.

Table 4 *Relative incidence of MS first symptoms by ancestry in the NHS II*

Variable	Southern European	Scandinavian	Other white	Nonwhite
NHS				
n	16	9	78	3
Person-years of observation	270,779	75,883	1,330,737	122,983
RR (95% CI)				
Age adjusted	1.0	2.2 (1.0, 4.9)	1.0 (0.6, 1.8)	0.5 (0.1, 1.6)
Age, latitude adjusted*	1.0	2.5 (1.0, 6.2)	1.3 (0.7, 2.3)	0.5 (0.1, 2.2)
Multivariate†	1.0	2.5 (1.1, 6.4)	1.3 (0.7, 2.3)	0.5 (0.1, 2.3)
NHS II				
n	11	4	56	8
Person-years of observation	88,546	28,401	467,047	55,300
RR (95% CI)				
Age adjusted	1.0	1.1 (0.4, 3.6)	1.0 (0.5, 1.8)	1.2 (0.5, 2.9)
Age, latitude adjusted*	1.0	1.1 (0.4, 3.5)	0.9 (0.5, 1.7)	0.8 (0.3, 2.6)
Multivariate†	1.0	1.1 (0.4, 3.6)	0.9 (0.5, 1.7)	0.9 (0.3, 2.8)
Pooled analysis				
RR (95% CI) multivariate†	1.0	1.9 (0.9, 3.8)	1.1 (0.7, 1.7)	0.7 (0.3, 1.8)
p Value for heterogeneity	—	0.26	0.42	0.57

* Multivariate RR and 95% CIs adjusted for age (5-year categories) and tier of birth (north, middle, south).
† Also adjusted for longitude zone (Pacific, mountain, central, eastern).

NHS = Nurses' Health Study; NHS II = Nurses' Health Study II; RR = rate ratio; CI = confidence interval.

ca,[32] others have looked into the same issue. An ecologic analysis found a positive association between MS and percent of population reporting Scandinavian ancestry in the state of residence of more than 5,000 US war veterans.[33] However, this association was not confirmed when the authors used an individual surname-derived ethnicity. Instead, individuals of southern European ethnicity were found to have a 1.25-fold higher risk of MS than those of other ethnicity.[34] Researchers in Alberta, Canada, also found a positive correlation between single Scandinavian ancestry and MS prevalence at the census division level, but again this correlation was not confirmed at the individual level.[35] Incidence rates of MS reported from Scandinavian countries[36-39] are of similar or lower magnitude than those from the United Kingdom.[19-22,40]

Our results suggest that US women of southern European ancestry do not have a significantly lower MS risk than other white women. In fact, in the NHS II, southern Europeans have the highest risk. The discrepancy between the two cohorts regarding the relative risk of Scandinavian women may simply reflect the uncertainty associated with the small number of participants of Scandinavian descent in the NHS II. Nonetheless, some methodologic differences between the two studies may also account for part of the difference.

A bias could exist if MS had an earlier onset among southern Europeans compared with the other white groups. Because women in the NHS were older at baseline than those in the NHS II, earlier cases might have been missed more frequently. The net result would be an apparent increased risk for Scandinavians. This is consistent with the observed drop in risk for southern Europeans when only patients with first symptoms during the follow-up are included in the analyses (see table 3).

Another factor that might contribute to the discrepancy is that NHS participants were asked to report their ancestry after most of the MS patients had been already diagnosed, and their responses may therefore be affected by the widespread belief that Scandinavians have a greater risk of MS. Interestingly, the response rate of MS patients to this question is higher than that of non-MS patients (98% versus 83%). The results would be biased if women of Scandinavian descent were more aware of their ancestry, or more likely to report it, after an MS diagnosis. On the other hand, ancestry data from the NHS II were obtained before any MS diagnosis was made, so the results are not subject to this potential bias. Self-reports on ancestry may have some degree of misclassification, but is probably not differential between cohorts. In any case, the NHS II appears to have a more appropriate design to study the association between risk of MS and ancestry. Unfortunately, it contains too few women of Scandinavian descent to permit a precise estimation of their risk.

Acknowledgment

The authors are indebted to the participants in the NHS and the NHS II for their continuing cooperation, and to Frank Speizer, principal investigator of the NHS. They thank Walter Willett, James Robins, and Marika Hohol for their expert advice; and Al Wing, Mark Shneyder, Karen Corsano, Lisa Li, Mary Louie, Lisa Dunn, Gary Chase, Barbara Egan, and Lori Ward for their technical help.

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Prevalence estimates for MS in the United States and evidence of an increasing trend for women

Abstract—The purpose of this study was to provide current age-, sex-, and region-specific MS prevalence estimates and to identify trends using the National Health Interview Survey. The overall prevalence estimate was 85/100,000 population, or approximately 211,000 (±20,000) persons. A 50% increase was observed in the number of women reporting MS for 1991 through 1994 vs 1982 through 1986. The observed trend in higher numbers of self-reported MS among women is consistent with recent observations of higher prevalence and incidence.

NEUROLOGY 2002;58:136–138

Curtis W. Noonan, PhD; Steven J. Kathman, PhD; and Mary C. White, ScD

Residents of several communities living near hazardous waste sites have expressed concerns about the perceived high prevalence of MS in their communities and the potential linkage with environmental contaminants. The ability of health agencies to respond to these concerns is limited because of a lack of reliable data on expected numbers of MS cases.

Prevalence figures from community-based studies in the United States range from 39 to 173 cases/100,000 population.[1] The only national data for MS prevalence by age groups and race/ethnicity are based on a 1976 survey sponsored by the National Institute of Neurologic and Communicative Disorders and Stroke.[2,3] Given the changes that have occurred in diagnostic criteria and the increasing use of laboratory methods for detection of MS, more current estimates are needed.

Methods. The National Health Interview Survey (NHIS) is conducted annually among a probability sample of the civilian, noninstitutionalized population of the United States by the National Center for Health Statistics (NCHS).[4] Our analysis was restricted to the years 1982 through 1996 because the sample design and core questionnaire remained relatively unchanged during these years, and, starting in 1997, MS was no longer included as a condition in the NHIS. Information was gathered through direct interview, or surrogate interview for some family members, about health conditions resulting in limitation of activity, doctor visits, or hospital visits.

Reports of limitation of activity caused by MS were used to reflect trends over time to lessen the impact that changes in media attention or public perception could have had on self-reporting of MS. Six recent years (1989 through 1994) of NHIS data were combined for analyses of overall prevalence and geographic, age, and race/ethnicity distributions of MS. Strata-specific prevalence estimates for the combined years 1989 through 1994 were based on reports among the one-sixth of the survey population that was specifically asked about the disease and the remainder who self-reported MS for other reasons. SUDAAN (RTI, Research Triangle Park, NC) and weights provided by the NCHS were used to determine prevalence and relative SE of the estimates (RSE). An estimate with an RSE greater than 30% was considered unstable and noted in the data presented below. Differences between strata-specific estimates were evaluated using pairwise χ^2 tests.

Results. Figure 1 shows a 15-year (1982 through 1996) trend in NHIS data in the estimated number of persons reporting MS as a cause of limitation of activity. Estimates for limitation of activity due to MS among women were approximately 50% higher in recent years, as compared with the earlier survey years. The estimates (per 100,000 women) were 75 for the grouped years 1982 through 1986, 102 for 1987 through 1990, and 113 for 1991 through 1994 ($p < 0.05$, pairwise χ^2 test for the years 1982 through 1986 vs 1987 through 1990 or 1991 through 1994). Similar trends over time were observed when evaluating MS prevalence estimates rather than limitation of activity (data not shown). There were no trends over time observed among men reporting MS as a cause for limitation of activity.

Based on reporting by participants who were specifically asked about MS, the overall combined prevalence estimate for MS (1989 through 1994) is 85/100,000 population, or approximately 211,000 (±20,000) persons with the disease among the civilian, noninstitutionalized population of the United States. The reporting of MS among those who were specifically asked about the condition and the remaining five-sixths of the sample was proportionally similar, thus all 609 reported cases of MS were used to achieve stable strata-specific estimates. The age and race/ethnicity distribution of MS are presented in the table. The ratio of women to men for the combined data are 2.6:1, but the ratio ranges from 1.9:1 to 3.6:1 for the specific age groups evaluated in this study. The MS prevalence estimates among both women and men were highest for the age groups 40 to 49 years and 50 to 59 years. White women had a higher prevalence estimate than women in other race/ethnicity groups (p value < 0.05, pairwise χ^2 tests). Figure 2 presents estimates of MS for each sex by the four geographic regions used in the NHIS. The estimate for women in the South was lower than for the other regions (p value < 0.05, pairwise χ^2 tests).

Discussion. This is the first use of a national probability sample combined over several years to estimate age- and sex-specific MS prevalence and to examine trends over time. The only previous age-

From the Health Investigations Branch, Division of Health Studies, Agency for Toxic Substances and Disease Registry, Atlanta, GA.

Received June 4, 2001. Accepted in final form September 26, 2001.

Address correspondence and reprint requests to Dr. Curtis W. Noonan, Agency for Toxic Substances and Disease Registry, 1600 Clifton Road NE, Atlanta, GA 30333; e-mail: cnoonan@cdc.gov

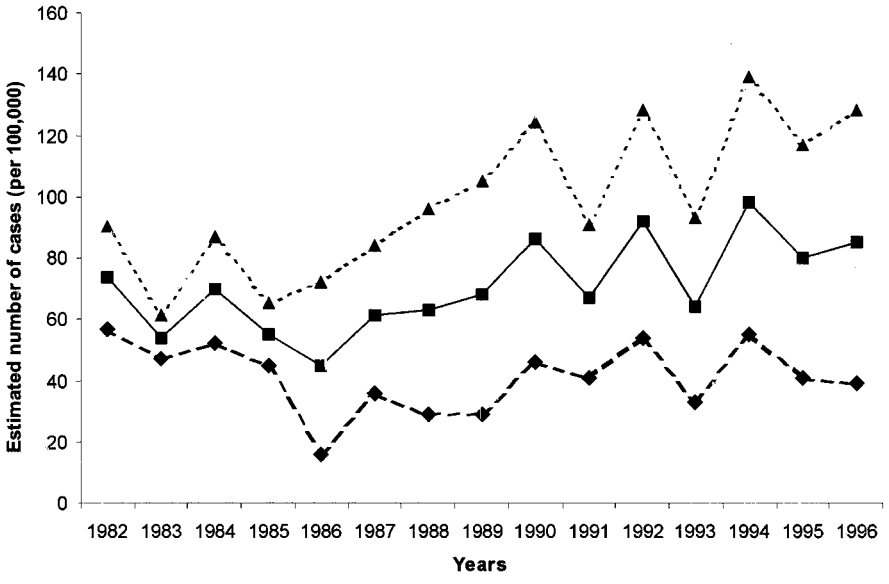

Figure 1. Estimated number of persons (per 100,000 civilian, noninstitutionalized US population) reporting MS as a cause for limitation of activity, according to the National Health Interview Survey, 1982 through 1996 (▲ = women, ◆ = men, ■ = total).

specific estimates were based on a 1976 survey of health care providers.[2,3] Our overall prevalence estimate of 85/100,000 population was higher than the 1976 estimate of 58/100,000 population; however, it is lower than the estimate 102 to 139/100,000, which was based on a revision of the 1976 data.[2,3] Alternative adjustments to the 1976 survey data result in prevalence estimates that are close to our estimate of approximately 211,000 people with MS in the United States.[5]

In agreement with previous studies,[1,2] a higher prevalence was observed among women and among those aged 40 to 59 years. These data also demonstrated an increasing trend over time in the numbers of women reporting MS as a cause for limitation of activity. This indication of increasing MS prevalence among women in the United States is consistent with recently observed increases in MS incidence.[6,7] In addition to changes in incidence, prevalence trends could be affected by diagnostic changes or treatments resulting in prolonged duration of disease. Men with MS may have poorer prognosis for disability and death and greater utilization of health care services than women,[8,9] but it is uncertain how these potential differences would influence prevalence trends. The observed variation in race/ethnicity-specific figures is in agreement with previous reports of a higher prevalence among white persons.[2] The estimates by geographic region agree with previous observations of a latitude gradient for MS, with the lowest prevalence in the South.[2]

Table *Estimated number of persons (per 100,000 civilian, noninstitutionalized US population) with MS by age, race/ethnicity, and sex, based on the National Health Interview Survey, 1989 through 1994*

Variable	Men	Women	Total
Race/ethnicity			
White	54 ± 4	137 ± 8	96 ± 5
Black/African American	25 ± 8*	68 ± 15	48 ± 9
All other races/ethnicities	19 ± 10*	67 ± 19	43 ± 11
Age group, y			
<30	5 ± 2*	25 ± 5	15 ± 2
30 –39	58 ± 11	145 ± 17	102 ± 11
40–49	110 ± 17	305 ± 27	209 ± 16
50–59	123 ± 20	237 ± 26	182 ± 16
60–69	98 ± 18	190 ± 26	148 ± 17
70+	33 ± 12*	105 ± 19	76 ± 12
Total	48 ± 4	123 ± 7	87 ± 4†

Values are expressed as estimated no. of persons ± SEM.

* Estimate is unstable. Standard error/estimate >0.30.

† This overall estimate differs slightly from the prevalence estimate of 85/100,000 presented in the text, because the table data is based on all reports of MS among those surveyed, not only those that were specifically asked about the condition.

Several limitations exist in the use of NHIS data to estimate chronic disease prevalence. First, proxy responses were used for family members who were not present at the time of the interview. Based on the 1976 survey, approximately 14% of participants with MS would be unaware of their diagnosis and unlikely to report the disease in a health interview.[2] Second, no medical records or laboratory results are available to confirm case diagnosis, so it must be assumed that MS cases identified from the NHIS could include definite, probable, and possible cases. Third, recent health care provider visits may not capture all respondents with MS who did not report the condition as a cause for limitation of activity.[8,10]

Finally, the age-, race/ethnicity-, and region-specific prevalence estimates in this study are based on self-reports of MS from all participants, regardless of whether or not they were specifically asked about the condition. NCHS does not recommend combining those who were specifically asked about a

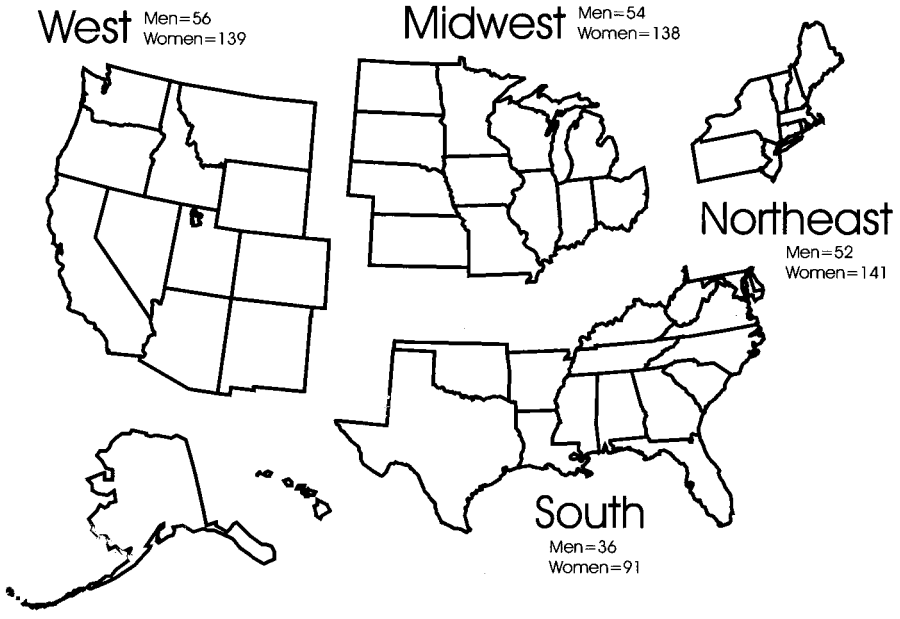

Figure 2. Estimated number of persons (per 100,000 civilian, noninstitutionalized U.S. population) with MS, by sex and geographic region, based on the National Health Interview Survey, 1989 through 1994.

condition and those who self-reported for other reasons, because individuals in the two groups have different opportunities for reporting the condition.[4] The reporting of MS among those specifically asked about the disease and others was proportionally similar, thus we do not expect this to be a major limitation. Indeed, for the years 1989 through 1994, our overall prevalence estimate based on those specifically asked about MS (approximately 211,000 people) was comparable to the estimate that was obtained when all reports of MS were included (approximately 217,000 people).

When conducting an assessment of a reported disease cluster, investigators must first determine whether or not an excess has occurred. The statistics presented here may be useful for assessing a suspected cluster of MS, assuming that appropriate consideration is given to the limitations discussed above.

Acknowledgment

The authors thank Roberta Hilsdon, Dhelia Williamson, and Laura Northen of the Agency for Toxic Substances and Disease Registry, and Matthew Zack, MD, of the Centers for Disease Control and Prevention, for assistance in compiling the data, technical guidance, and graphic support.

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