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Personal and Family Medical History Correlates of Rheumatoid Arthritis

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Abstract

PURPOSE—Patients with rheumatoid arthritis (RA) often have comorbidities related to immune dysfunction, however, the timing of comorbidities relative to RA diagnosis and treatment is not clear. We studied personal and family medical history correlates of incident and prevalent RA in women.

METHODS—We used a nested case-control design including women in the Agricultural Health Study (AHS). Physician-confirmed cases of RA ($n = 135$) were matched to five controls each ($n = 675$) by birth date. We used logistic regression to examine associations between conditions listed in personal and family medical histories and both incident and prevalent RA, as estimated by odds ratios (ORs) and 95% confidence intervals (CIs).

RESULTS—The risk of incident RA was associated with personal medical history of nonmelanoma skin cancer (OR = 4.4, 95% CI: 1.4–14.1), asthma or reactive lung disease (OR = 3.7, 95% CI: 1.3–10.5), and cataract (OR = 3.3, 95% CI: 1.0–10.8). Personal history of herpes zoster was associated with prevalent RA (OR = 2.4, 95% CI: 1.2–4.8), but not with incident RA. There were no consistent associations between family medical history and RA.

CONCLUSIONS—Patients with medical conditions indicating compromised immunity are at increased risk of developing RA. These results may indicate common pathogenesis of an environmental or genetic nature between such diseases.

Keywords

Rheumatoid Arthritis; Autoimmune Diseases; Autoimmunity; Epidemiology; Medical History; Comorbidities; Family History

INTRODUCTION

Rheumatoid arthritis (RA) affects approximately 1% of the U.S. population and as many as 2% to 3% of persons over 60 years of age (1, 2). Women are more likely to be affected than men, for unknown reasons (1). The course of the disease varies widely, but it is generally

associated with progressive disability and early mortality (3). There have been previous reports of immune-related comorbidities occurring among RA patients (4, 5). Certain immune-related conditions may be sequelae of RA from immunosuppressive treatment regimens; alternatively, these conditions may share etiologic features with RA. However, few previous studies have investigated whether comorbid conditions preceded RA diagnosis, or whether there may be a familial environmental or genetic component contributing to both diseases.

We examined associations of various medical conditions with incident and prevalent RA among women enrolled in the Agricultural Health Study (AHS). Analyses of associations with conditions that predate incident RA may provide clues about diseases that contribute to the development of RA. Although the timing of diagnoses is not clear in associations of prevalent RA with coexisting medical conditions, these analyses can provide useful information about the frequencies of comorbid conditions, which may have related pathologies. In addition, we studied family history of medical conditions as a risk factor for RA to shed light on diseases which may have a familial shared environmental or genetic component to their causation.

MATERIAL AND METHODS

Study Population

The methods for the AHS and the confirmation of RA cases have been previously described (6, 7). The AHS is a prospective study of a cohort of licensed pesticide applicators ($n = 52,395$ private pesticide applicators; $n = 4916$ commercial pesticide applicators) and their spouses ($n = 32,347$) in Iowa and North Carolina, enrolled from 1993 to 1997. A baseline questionnaire was administered upon enrollment. The private applicators are primarily white (97.1%) and male (97.4%). More than 99% of spouses in the cohort are women, and their median age at enrollment was 46.6 years. Institutional Review Board (IRB) approval was obtained for the study at both the Division of Cancer Epidemiology and Genetics of the National Cancer Institute and the Epidemiology Branch of the National Institute for Environmental Health Sciences.

We validated RA diagnosis among women in the AHS who had self-reported RA during a telephone-administered Phase 2 (5-year follow-up) interview, administered to both applicators and spouses (24,514 women responded to this interview). The question in the interview read, "Has a doctor or other health professional ever told you that you had rheumatoid arthritis?", and 945 of 24,514 women responded 'yes'. The Phase 2 interview also contained several questions about RA symptoms, testing, and age at diagnosis. We targeted the RA validation effort to subgroups of women on the basis of criteria bearing on the feasibility of obtaining physician confirmation (e.g., time since diagnosis <10 years vs. longer), and issues reflecting the likelihood that the women truly had RA (e.g., reported ever having a positive 'blood test for RA' [i.e., rheumatoid factor], or reported more than one autoimmune disease). Women who did not report having ever had joint swelling for 6 or more weeks (a hallmark symptom of RA and one of the American College of Rheumatology (ACR) criteria for RA diagnosis) were infrequently selected unless they had another factor indicating probable RA (e.g., positive blood test). We did not include men in the initial validation because of the lack of information with which to target validation efforts, as men in the AHS were not asked specific questions about RA, such as symptoms and tests.

We attempted to re-contact 594 women with self-reported RA to obtain information about the diagnosis. For women who reconfirmed their RA diagnosis in the validation interview, we requested permission to contact their physician(s). Specific information from the woman's medical history pertaining to RA was elicited from physicians in the form of a

checklist, including information on the patient's diagnosis and presence of the ACR classification criteria for RA (8). A woman was classified as having 'physician-confirmed' RA if (a) any of her physicians indicated that she had RA by a 'yes/no' response or (b) her physicians indicated the presence of at least 4 of 7 ACR classification criteria (8).

Of the 594 women included in the validation process, 136 (23%) cases were physician confirmed (Table 1), a proportion similar to the 21% (9) and 22% (10) confirmation of self-reported RA in previous studies. Of the confirmed cases, 94.9% were confirmed according to the direct question about RA diagnosis (first classification criterion above), and 5.1% of cases were confirmed using the ACR criteria only. Of the women for whom we received information from any of their physicians ($n = 186$), RA diagnosis was confirmed for 73%. Women whose RA diagnoses were not confirmed by their physicians were less likely to have ever been treated by a rheumatologist, less likely to be currently taking prescription medications for RA, and were less likely to have certain symptoms, including testing positive for rheumatoid factor. The ages at the time of diagnosis for physician-confirmed cases ranged from 1 to 73 years. We excluded from further analyses the one confirmed case diagnosed when the patient was 1 year old; the remaining 135 cases were diagnosed at 16 years of age and older. Sixty-four percent of the physician-confirmed cases had tested positive for rheumatoid factor ([RF]; as reported by either the woman or her physician), similar to other populations (11, 12). Thirty-three of the physician-confirmed cases (24.4%) were incident between the baseline and Phase 2 interview, as indicated by the self-reported diagnosis date or, if not available, by the physician-reported date. The remaining 102 physician-confirmed cases (75.6%) were prevalent at the baseline interview.

Physician-confirmed RA cases formed the total case group for our case-control analysis. Cases ($n = 135$) were matched to five controls each ($n = 675$) by birth date, within 1 year. Controls were selected from among women in the AHS who had completed the Phase 2 interview ($N = 24,514$; the same group from which cases were validated); those who had reported RA that was not validated or other systemic autoimmune disease (scleroderma, systemic lupus erythematosus, or Sjögren's syndrome) at either the baseline or Phase 2 interview were excluded. The rationale behind this exclusion was based on the fact that we did not attempt to validate every participant who self-reported RA diagnosis (e.g., those with reported dates of diagnosis in the distant past), in addition to the difficulty of diagnosis and potential etiologic overlap of systemic autoimmune diseases.

Information on personal and family medical history was available from the AHS questionnaires administered at baseline (questionnaires are available at www.aghealth.org). The question about personal medical history asked about physician-diagnosed diseases. The question about family medical history asked about diseases in first-degree relatives (parents, brothers, sisters, or children related by blood). Both personal and family medical histories solicited yes/no responses to a list of conditions. We included in our analyses any personal or familial medical condition with a frequency of at least 3% among controls ($n = 20$ controls). In addition, we excluded from our presentation of results any condition with only one incident case, to avoid inadvertent participant identification. The versions of AHS data sets used for the current analysis were the Phase 1 release: P1REL0310 and the Phase 2 release: P2REL0312.02.

Statistical Analyses

Associations between personal and family medical history and the risk of RA were estimated using unconditional logistic regression to generate odds ratios (ORs) and 95% confidence intervals (CIs), adjusting for birth date (the matching factor) and state (Iowa or North Carolina). Analyses limited to incident cases ($n = 33$) or prevalent cases ($n = 103$) were conducted using all controls as the reference group. Because a previous analysis of the same

study population suggested associations between RA and smoking and RA and body mass index (BMI) (7), we also considered pack-years of cigarette smoking (0, 0.25–19.5, and ≥ 20 pack-years as indicator variables) and BMI (<25 , 25 to <30 , and ≥ 30 BMI as indicator variables) as potential confounders. We additionally explored potential confounding by demographic factors, including race (white vs. nonwhite) and education (did not finish high school, high school graduate, some college, college graduate or more). Lack of an association between RA and farming exposures such as pesticides or animals in our previous analysis (7) deemed adjustment for these factors unnecessary. Effect estimates from fully adjusted models were quite similar to models including only birth date and state (usually within 10%); however, there was considerable loss of precision upon inclusion of the additional covariates. For this reason, we present estimates adjusting for only birth date and state in our tables and refer to estimates with additional adjustment in the text, when they are notable. To evaluate the internal consistency of our results, we conducted analyses stratified by state (Iowa or North Carolina). We also conducted analyses specific to RF-positive or RF-negative RA, again using all controls as the reference group for each model.

RESULTS

Of the 135 physician-confirmed RA cases included in the nested case-control study, the median age at diagnosis was 47 years. There were few demographic differences between cases and controls (see Table 1), except that cases were slightly more likely than controls to be from North Carolina than from Iowa.

The risk of incident RA was associated with personal medical history conditions (Table 2), including nonmelanoma skin cancer (OR = 4.4, 95% CI: 1.4–14.1), asthma or reactive lung disease (OR = 3.7, 95% CI: 1.3–10.5), and cataract (OR = 3.3, 95% CI: 1.0–10.8). Among conditions reported in family histories (Table 3), nonmelanoma skin cancer was predictive of incident RA (OR = 2.4, 95% CI: 1.0–5.9), although this association was not present upon further adjustment for BMI and pack-years of smoking (OR = 1.1, 95% CI: 0.3–4.0).

The associations we observed with incident RA were present among both Iowa and North Carolina subjects (results not shown), with the exception that family history of nonmelanoma skin cancer was associated with incident RA among Iowa subjects (OR = 3.7, 95% CI: 1.3–10.9) but not North Carolina subjects (OR = 1.2, 95% CI: 0.2–5.9). Notable associations were also present for both RF-positive- and RF-negative cases, although the small case groups upon stratification made estimates imprecise (results not shown in the tables). For example, effect estimates for the association between personal history of nonmelanoma skin cancer and incident RA were elevated for both RF-positive cases (OR = 4.8, 95% CI: 1.2–18.3) and RF-negative cases (OR = 3.5, 95% CI: 0.4–29.7). For asthma or reactive lung disease and incident RA, associations were seen for RF-positive cases (OR = 3.7, 95% CI: 1.0–13.6) and RF-negative cases (OR = 3.5, 95% CI: 0.7–16.9), and the association with cataract was also seen for both case groups (OR = 2.8, 95% CI: 0.7–11.3 for RF-positive cases; OR = 3.7, 95% CI: 0.4–33.6 for RF-negative cases).

RA that was prevalent at the time of enrollment was associated with personal history of herpes zoster (OR = 2.4, 95% CI: 1.2–4.8). Personal history of arrhythmia was associated with prevalent RA (OR = 2.0, 95% CI: 1.0–4.2), and a borderline significant association with high blood pressure requiring medications was also observed (OR = 1.5, 95% CI: 0.9–2.5). There were no notable associations of medical conditions in the family history with prevalent RA.

DISCUSSION

Our results suggest that persons with certain medical conditions (nonmelanoma skin cancer, asthma, and cataract) are more likely to develop RA. These results may indicate common pathogenesis of an environmental or genetic nature between such diseases; alternatively, one disease may develop as an unintended result of treatment for the other condition. A family history of nonmelanoma skin cancer was associated with incident RA; nevertheless, this association was not present in all subanalyses and is therefore considered less robust than our other findings.

Increases in nonmelanoma skin cancer have been observed in immunocompromised patient populations including transplant recipients (13) and persons with lymphoma as a first cancer (14). Among RA patients, increased risk of nonmelanoma skin cancer has been observed among those treated with tumor necrosis factor (TNF) antagonists (15). Our results showing associations between personal history of nonmelanoma skin cancer with incident RA and family history of nonmelanoma skin cancer with RA suggest an inherited genetic component that contributes to both diseases, although the possibility of common environmental risk factors cannot be ruled out. The importance of genetic factors in the etiology of RA has long been recognized, supported by observations that concordance rates of RA are approximately four times higher among monozygotic than dizygotic twins (16) and are higher in dizygotic twins than in the general population (17). Most studies of genetic variation in relation to RA have focused on genes in the human leukocyte antigen (HLA) region—these genes are important in controlling innate immunity and may confer susceptibility to a variety of immune-related conditions (18); however, specific alleles contributing to both RA and non-melanoma skin cancer have not been identified.

RA is typically considered a T helper 1 cell (Th1)–mediated disease, and asthma is a Th2-related disorder. Previously, an inverse association between Th1 and Th2 diseases was postulated, under the assumption that an imbalance toward Th1 or Th2 with manifestation of one disease would thus confer protection against diseases in the other subset (19). Contrary to this hypothesis, several studies in addition to ours have reported links between asthma and RA (4, 5, 20–22), providing evidence of positive correlations between Th1- and Th2-mediated diseases. These findings suggest the possibility that common risk factors underlie autoimmune diseases and allergic conditions such as asthma.

Cataract is a known sequela of juvenile RA–related uveitis and is thought to result from chronic inflammation and corticosteroid use (23). To our knowledge, increased cataract frequency has not been reported in adult RA, although ocular inflammation is a common symptom of the disease (24). Ours is the first study to find an association between medical history of cataract and increased risk of incident RA, which may indicate common etiologies between the diseases. The four cataract patients with incident RA in our study were 39 to 67 years of age (mean, 59 years) at the study baseline. Although cataract is not usually considered an immune-related condition, it may have increased appearance among the immune compromised. For example, in a study of cancer survivors of all types, cataracts were most frequent among survivors of hematologic diseases (leukemia, myeloma, lymphoma), which are themselves associated with immune dysregulation (25). A unifying role of oxidative stress between cataract and RA has also been suggested (26).

Herpes zoster, or “shingles,” is a relatively common condition among the elderly, resulting from reactivation of varicella zoster virus (chickenpox). Outbreaks among patients with autoimmune disease occurring after typical immunosuppressive therapies (e.g., methotrexate) have been documented in case reports (27, 28). In addition, a study of systemic lupus erythematosus (SLE), another autoimmune disease, found that a history of

herpes zoster was associated with the risk of developing SLE (28). Another study of SLE observed that herpes zoster outbreaks were clustered just prior to or after diagnosis of SLE, compared to more temporally spaced outbreaks among controls (29). Whether herpes zoster precedes RA or results from an active RA disease state with associated therapies cannot be clearly discerned from our data; however, the stronger association of herpes zoster with prevalent RA seems to suggest the latter scenario.

Cardiovascular manifestations are common in RA and are associated with increased mortality in those persons with RA compared to the general population (30). Prevalent RA cases in our study had a two-fold increased prevalence of comorbid arrhythmia and 50% increased prevalence of high blood pressure requiring medications. While not a new finding, these associations speak to the representativeness of our case and control groups to the general population.

There are several limitations of our analysis, most notably a small sample size, particularly for analyses of incident cases. A further limitation is that the personal and family medical histories among study participants were based on self-report and were not validated using medical records (with the exception of RA). Self-reported medical history is typical in large, epidemiologic studies because of the expense associated with validation. The reliability of self-reported personal and family medical histories is likely to differ by condition. A previous validation study using medical chart documentation as the standard found that participants in a case-control study reported their nonmelanoma skin cancer status correctly in 91.8% of cases (31). In another validation study that evaluated multiple conditions, the differences between frequencies of self-reported and physician-reported medical conditions were small ($\leq 7\%$) for conditions such as diabetes, hypertension, and coronary heart disease, with the exception of a greater discrepancy between self- and physician-reported arthritis (15% difference) (32). Family medical history are less likely than self medical history to be accurately recalled, although a validation study did find that participants reported family histories of common cancers with fairly good sensitivity (>0.75) (33). We would expect misclassification of personal and medical histories collected at the baseline to be nondifferential with respect to prevalent RA status, since the conditions we studied were not autoimmune diseases. Misclassification was certainly nondifferential with respect to incident RA status, which was diagnosed after the baseline questionnaire. Such nondifferential misclassification would typically bias risk estimates toward the null value.

Despite limitations, our study provides intriguing data on preexisting and comorbid conditions associated with RA that may indicate shared environmental or genetic pathologies between immune-related diseases. Further investigation of these questions in studies with larger sample sizes and details on the timing of medical condition diagnoses in relation to RA diagnosis would help clarify comorbid risk factors and sequelae of RA.

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Selected Abbreviations and Acronyms

RA	rheumatoid arthritis
AHS	Agricultural Health Study
ACR	American College of Rheumatology
RF	rheumatoid factor
BMI	body mass index
SLE	systemic lupus erythematosus

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TABLE 1

Characteristics of female RA cases* in the Agricultural Health Study and controls

	Controls (n = 675)	Total cases (N = 135)	Incident cases (n = 33)	Prevalent cases (n = 102)
Characteristic	No. (%)	No. (%)	No. (%)	No. (%)
Age (yr) at diagnosis	N/A			
<25		7 (5.2)	0	7 (6.9)
25–39		39 (28.9)	4 (12.1)	35 (34.3)
40–54		53 (39.3)	14 (42.4)	39 (38.2)
55–69		33 (24.4)	12 (36.4)	21 (20.6)
≥70		3 (2.2)	3 (9.1)	0
Rheumatoid factor	N/A			
Positive		87 (64.4)	19 (57.6)	68 (66.7)
Negative		49 (35.6)	14 (42.4)	34 (33.3)
Age at enrollment in AHS				
<35	32 (4.7)	6 (4.4)	3 (9.1)	3 (2.9)
35 to <50	201 (29.8)	42 (30.4)	11 (33.3)	30 (29.4)
50 to <60	272 (40.3)	50 (37.0)	11 (33.3)	39 (38.2)
60 to <70	159 (23.6)	36 (26.7)	8 (24.2)	28 (27.5)
≥70	11 (1.6)	2 (1.5)	0	2 (2.0)
State				
Iowa	494 (73.2)	92 (68.2)	21 (63.6)	71 (69.6)
North Carolina	181 (26.8)	43 (31.9)	12 (36.4)	31 (30.4)
Race†				
White	649 (97.9)	131 (97.8)	32 (97.0)	99 (98.0)
Non-white	14 (2.1)	3 (2.2)	1 (3.0)	2 (2.0)
Education				
Did not finish high school	21 (3.6)	10 (8.3)	3 (10.0)	7 (7.8)
High school graduate	278 (47.4)	52 (43.3)	9 (30.0)	43 (47.8)
Some college	178 (30.4)	36 (30.0)	9 (30.0)	27 (30.0)
College graduate or higher	109 (18.6)	22 (18.3)	9 (30.0)	13 (14.4)

RA = rheumatoid arthritis; AHS = Agricultural Health Study; N/A = not applicable.

* Physician-confirmed cases.

† Frequencies of characteristics do not always add up to the total number of cases and controls because of missing data.

TABLE 2

Associations between personal medical history and rheumatoid arthritis

Personal medical condition	Controls (<i>n</i> = 675)		Incident cases (<i>n</i> = 33) [*]		Prevalent cases (<i>n</i> = 102) [†]	
	No. (%)	No. (%) [‡]	No. (%) [‡]	OR (95% CI) [§]	No. (%) [‡]	OR (95% CI) [§]
Nonmelanoma skin cancer	20 (3.1)	4 (12.1)	4 (12.1)	4.4 (1.4–14.1)	4 (4.0)	1.2 (0.4–3.6)
Other solid cancer	30 (4.6)	2 (6.5)	2 (6.5)	1.6 (0.4–7.4)	6 (6.0)	1.3 (0.5–3.3)
Arrhythmia	35 (5.4)	2 (6.5)	2 (6.5)	1.1 (0.3–5.0)	11 (11.0)	2.0 (1.0–4.2)
High blood pressure requiring medication	121 (18.9)	7 (22.6)	7 (22.6)	1.4 (0.6–3.5)	26 (26.0)	1.5 (0.9–2.5)
Asthma or reactive lung disease	29 (4.4)	5 (15.2)	5 (15.2)	3.7 (1.3–10.5)	5 (4.9)	1.1 (0.4–2.9)
Chronic bronchitis	31 (4.8)	2 (6.5)	2 (6.5)	1.3 (0.3–5.7)	4 (4.0)	0.8 (0.3–2.2)
Hay fever	59 (9.1)	4 (12.9)	4 (12.9)	1.4 (0.5–4.2)	11 (10.9)	1.2 (0.6–2.4)
Pneumonia (viral or bacterial)	91 (14.1)	6 (20.0)	6 (20.0)	1.6 (0.6–4.2)	18 (17.8)	1.3 (0.8–2.3)
Cataract	32 (4.9)	4 (12.9)	4 (12.9)	3.3 (1.0–10.8)	5 (4.9)	0.9 (0.3–2.4)
Other thyroid disease	36 (5.6)	2 (6.5)	2 (6.5)	1.3 (0.3–5.7)	4 (4.0)	0.7 (0.2–2.0)
Chronic kidney infections or pyelonephritis	18 (2.8)	0	0	—	3 (3.0)	1.1 (0.3–3.8)
Kidney stones	28 (4.4)	2 (6.5)	2 (6.5)	1.3 (0.3–5.8)	5 (5.1)	1.1 (0.4–2.9)
Herpes zoster	34 (5.3)	2 (6.5)	2 (6.5)	1.3 (0.3–5.6)	12 (12.1)	2.4 (1.2–4.8)
Eczema	34 (5.3)	2 (6.5)	2 (6.5)	1.3 (0.3–5.5)	8 (8.1)	1.6 (0.7–3.6)
Mononucleosis	30 (4.7)	2 (6.5)	2 (6.5)	1.3 (0.3–5.7)	3 (3.0)	0.6 (0.2–2.1)
Depression requiring medication or shock therapy	44 (6.8)	2 (6.5)	2 (6.5)	0.9 (0.2–4.0)	6 (6.0)	0.8 (0.4–2.0)

OR = odds ratio; CI = confidence interval.

^{*} Incident cases are physician-confirmed cases with a diagnosis date between the baseline and Phase 2 interviews.[†] Prevalent cases are physician-confirmed cases with a diagnosis date before the baseline interview.[‡] Frequencies of characteristics do not always add up to the total number of cases and controls because of missing data.[§] All estimates are adjusted for birth date (matching factor) and state.

TABLE 3

Associations between family medical history and rheumatoid arthritis

	Controls (<i>n</i> = 675)		Incident cases (<i>n</i> = 33) [*]		Prevalent cases (<i>n</i> = 102) [†]	
	No. (%)	No. (%) [‡]	OR (95% CI) [§]	No. (%) [‡]	OR (95% CI) [§]	
Lung cancer	43 (6.7)	3 (9.1)	1.4 (0.4–4.7)	12 (11.9)	1.8 (0.9–3.6)	
Breast cancer	75 (11.6)	3 (9.1)	0.8 (0.2–2.7)	16 (16.2)	1.5 (0.8–2.6)	
Melanoma	62 (9.7)	5 (15.2)	1.6 (0.6–4.5)	5 (5.1)	0.5 (0.2–1.3)	
Nonmelanoma skin cancer	65 (10.1)	7 (21.2)	2.4 (1.0–5.9)	8 (8.1)	0.7 (0.3–1.6)	
Lymphoma	21 (3.3)	0	—	4 (4.0)	1.3 (0.4–3.8)	
Prostate cancer	66 (10.2)	3 (9.4)	0.9 (0.3–3.1)	7 (7.1)	0.7 (0.3–1.5)	
Other cancer	113 (17.6)	3 (9.1)	0.5 (0.1–1.6)	17 (17.2)	1.0 (0.6–1.7)	
Myocardial infarction before age 50	65 (10.2)	4 (12.1)	1.2 (0.4–3.4)	8 (8.2)	0.8 (0.4–1.7)	
Diabetes mellitus	160 (25.0)	13 (39.4)	1.9 (0.9–4.0)	28 (28.0)	1.2 (0.7–1.8)	
Kidney failure	28 (4.4)	2 (6.3)	1.2 (0.3–5.6)	8 (8.0)	1.7 (0.8–4.0)	

OR = odds ratio; CI = confidence interval.

^{*} Incident cases are physician-confirmed cases with a diagnosis date between the baseline and Phase 2 interviews.

[†] Prevalent cases are physician-confirmed cases with a diagnosis date before the baseline interview.

[‡] Frequencies of characteristics do not always add up to the total number of cases and controls because of missing data.

[§] All estimates are adjusted for birth date (matching factor) and state.