

Asthma and Risk of Selective IgA Deficiency or Common Variable Immunodeficiency: A Population-Based Case-Control Study

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Abstract

Objective: To determine the association between a history of asthma and a diagnosis of selective IgA deficiency (sIgAD)/common variable immunodeficiency (CVID).

Patients and Methods: This population-based case-control study included residents of Olmsted County, Minnesota, who met the Pan-American Group for Immunodeficiency/European Society for Immunodeficiencies diagnostic criteria for sIgAD/CVID between January 1, 1964, through December 31, 2008. Each case had 4 age- and sex-matched controls (2 from the community and 2 from a list of individuals who had undergone an immune work-up). We ascertained asthma status by applying predetermined criteria for asthma.

Results: We identified 39 cases: 26 (66.7%) had sIgAD and 13 (33.3%) had CVID. Of the 39 cases, 51.3% were men ($n=20$) and 97.1% were white (33 of 34 patients). The mean age at the index date (the time when criteria were met) of sIgAD/CVID was 34.2 years. Of the 39 cases, 9 (23.1%) had a history of asthma before the index date of sIgAD/CVID; of the 156 controls, 16 (10.3%) had a history of asthma before the index date (odds ratio, 2.77; 95% CI, 1.09-7.06; $P=.03$). A history of asthma (before or after the index date of sIgAD/CVID) was more prevalent in sIgAD/CVID cases (30.8%; $n=12$) than in matched controls (11.5%; $n=18$) (odds ratio, 3.57; 95% CI, 1.50-8.51; $P=.01$).

Conclusion: Asthmatic patients are more likely to have a diagnosis of sIgAD/CVID than nonasthmatic individuals. This association may potentially account for the increased risks of bacterial infections in some individuals with asthma.

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Asthma is the most common chronic illness in childhood and a major cause of morbidity in adults, affecting 9.6% to 13% of US children,^{1,2} 7.7% to 10.1% of US adults,^{2,3} and 300 million people globally.⁴ Individuals with asthma have an increased risk of serious pneumococcal disease,^{5,6} and this association has also been found with *Streptococcus pyogenes*,⁷ otitis media,⁸ and *Bordetella pertussis* infections.⁹ The Advisory Committee on Immunization Practices of the United States now recommends that all adult asthmatic patients (19-64 years old) receive a single dose of 23-valent pneumococcal vaccine to prevent serious pneumococcal disease.¹⁰ The mechanisms underlying the increased risk of microbial infections in asthmatic patients are unknown. Previous studies have found that individuals

with asthma or other atopic conditions have impaired innate¹¹⁻¹⁵ and adaptive¹⁶⁻²⁰ immunity, which may result in an increased risk of microbial infections.

Another potential hypothesis, other than global immune incompetence, for the increased risk of microbial infections in asthmatic patients is that the presence of an underlying primary immunodeficiency (PID), such as selective IgA deficiency (sIgAD) or common variable immunodeficiency (CVID), the latter being frequently associated with sinopulmonary infections, may be disproportionately overrepresented in patients with asthma due to unrecognized yet shared immunogenetic mechanisms. The etio-pathogenesis of sIgAD and CVID, which are the two most common PIDs, is multifactorial. The exact causal mechanism underlying sIgAD

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is an area of ongoing investigation. With a reported 20% of patients with sIgAD having detectable autoantibodies, most of whom have not previously received exogenous immunoglobulin, recent evidence has suggested that probable causes include autoimmune mechanisms along with probable defects in the maturation of B cells into IgA-producing plasma cells (eg, isotype-switching defect or post-switch defect).²¹⁻²³ There may be other causes for sIgAD that have not been fully elucidated.²¹ Common variable immunodeficiency is probably an oligogenic PID in most patients, with a monogenic etiology in a few.^{24,25} Some investigators have regarded these two conditions as part of a spectrum of immunodeficiency, with severity ranging from IgA deficiency to panhypogammaglobulinemia²⁶⁻³⁰ and a common molecular etiology, at least in some cases. Examples include the reported sequence variations in the *TNFRSF13B* gene encoding the TACI protein (TACI gene transmembrane activator and calcium modulator and cyclophilin ligand interactor), which is involved in isotype class switching to IgA, or the major histocompatibility complex genes.³⁰⁻³²

Indeed, many cross-sectional studies have reported a higher prevalence of asthma or other atopic conditions in patients with sIgAD³³⁻⁴¹ or CVID, suggesting a potential association.⁴²⁻⁴⁴ However, little is known about whether patients with asthma or other atopic conditions are predisposed to (ie, asthma as a preceding factor) development of sIgAD or CVID over time or whether asthma or atopy could be a phenotypic marker for a subgroup of patients with sIgAD/CVID. To date, to our knowledge, no population-based study has evaluated whether asthma represents a predisposing risk factor for the diagnosis of sIgAD or CVID. Given the potential delay in diagnosis of sIgAD (mean duration of 10.5 years)⁴⁵ and CVID (median duration of 5.8 years)⁴⁶ and the increased risk of microbial infections in asthmatic patients, this information may be useful for early identification of a subgroup of asthmatic patients with sIgAD or CVID to better manage risk of infections and other conditions. We hypothesized that a history of asthma is more prevalent in individuals with a diagnosis of sIgAD or CVID than in matched controls without sIgAD or CVID.

PATIENTS AND METHODS

This study was approved by the Mayo Clinic Institutional Review Board and the institutional review board at Olmsted Medical Center, Rochester, Minnesota.

Study Population and Setting

The characteristics of the Olmsted County population are similar to those of the US white population except for a higher proportion of the working population being employed in the health care industry.⁴⁷ Under the auspices of the Rochester Epidemiology Project (REP),^{48,49} patients who grant authorization for use of their medical records for research (95% acceptance rate) are each assigned a unique identifier. All clinical diagnoses are electronically indexed, and information from every episode of care is contained in detailed patient-based medical records. Essentially, all medical care settings and providers are linked. Using REP resources, a previous study reported that incidence rates of asthma for this community are similar to those for other communities.⁵⁰ The incidence rate of asthma in Rochester, Minnesota, was 238 cases per 100,000 persons, which is comparable with those in other communities, such as Tecumseh, Michigan (250 per 100,000 persons), during the study period.⁵⁰

Study Design

This study was designed as a population-based, cumulative-incidence, case-control study in which cases occurring during the study period (January 1, 1964, through December 31, 2008) were included but controls were selected from among individuals who had not been diagnosed as having sIgAD or CVID at the end of the study period. In this study, we included patients with sIgAD or CVID owing to the relative frequency of these PIDs compared with others.²⁶⁻³⁰ Controls were matched to cases by birthday (within 1 year), sex, clinic registration year (within 1 year), and clinic visit date within 1 year of the index date of the case. Thus, cases and controls had a similar follow-up duration. We then compared the frequency of a history of asthma before the index date of sIgAD/CVID and a history of ever having had asthma (regardless of the index date of sIgAD/CVID) between cases and controls. Data abstraction from medical record review was conducted by a physician (H.D.Y.) who

was blinded throughout the entire study regarding the study hypothesis and participant status (case or control).

Participant Selection

Case Ascertainment. To identify all potential sIgAD/CVID cases in adults and children, we used 3 different data sources: (1) the REP database listing all Olmsted County residents with a unique identifier (*International Classification of Diseases* 9 codes used: 279.01, 279.06, 279.03, and 279.0), (2) a clinical immunology laboratory database listing all individuals who had undergone an immunology work-up between 1984 and 2008, and (3) a previous study database for PID.⁵¹ Merging all these data sources, we identified 228 potential sIgAD/CVID cases.

Subsequently, we applied the Pan-American Group for Immunodeficiency (PAGID)/European Society for Immunodeficiencies (ESID) criteria for sIgAD/CVID.⁵² Briefly, the criteria for complete sIgAD include (1) IgA level less than 7 mg/dL (to convert to mg/L, multiply by 10) and normal IgG and IgM levels, (2) age older than 4 years, and (3) other causes of hypogammaglobulinemia ruled out. The criteria for probable sIgAD included (1) IgA level at least less than 2 SD below normal for age with normal IgG and IgM levels, (2) age older than 4 years, and (3) other causes of hypogammaglobulinemia ruled out. We included definite and probable sIgAD cases in this study. The criteria for probable CVID included (1) low IgG or low IgA/low IgM levels, (2) absence of functional antibody responses to protein or polysaccharide antigens (diphtheria toxoid, tetanus toxoid, *H influenzae* B, pneumococcal vaccines, and isohemagglutinins) or IgG levels less than 400 mg/dL (to convert to g/L, multiply by 0.001),⁵³ (3) age older than 2 years, and (4) recurrent sinopulmonary infections. The criteria for possible CVID included (1) low IgG, IgA, or IgM levels; (2) absence of antibody response to peptide or polysaccharide antigens (diphtheria, tetanus toxoid, *H influenzae* B, or pneumococcal vaccine polyvalent) or absence of isohemagglutinin or IgG level less than 400 mg/dL; (3) age older than 2 years; and (4) recurrent sinopulmonary infections.⁵⁴ In this study, we included probable and possible CVID cases. The criteria for recurrent infection were based on the Jeffrey Modell Foundation Medical Advisory Board's 10 warning signs for PID.⁵⁴

We excluded (1) individuals who did not meet the PAGID/ESID criteria for sIgAD/CVID (eg, <2 years of age for CVID and <4 years of age for sIgAD), (2) people without research authorization for using medical records for research, (3) non-Olmsted County residents (to exclude referral patients from elsewhere), and (4) individuals with documented hypogammaglobulinemia due to primary or secondary immunodeficiency suggested by the PAGID/ESID criteria: drug-induced conditions (eg, immunosuppressants and high-dose systemic corticosteroids), genetic disorders (eg, ataxia telangiectasia), infectious diseases (eg, human immunodeficiency virus infection), malignancy (eg, chronic lymphocytic leukemia), other systemic diseases (eg, protein-losing enteropathy), chromosomal anomalies (eg, chromosome 18q syndrome), reported PIDs other than sIgAD/CVID,⁵⁵ and the conditions listed in Table 1, which made ascertainment of asthma difficult.

Identification of Controls. After eligible cases were identified, to address detection bias (ie, asthma status may influence a likelihood of sIgAD/CVID), we identified two sets of controls. Controls were matched to cases by birthday (within 1 year), sex, clinic registration date, and clinic visit date within 1 year of the index date of sIgAD/CVID. One set of controls was 2 controls per case (ie, 1:2 matching) randomly selected from the REP database (ie, Olmsted County residents without sIgAD/CVID) who met the matching criteria. Another set of controls included 2 controls selected from an immunology database listing all Olmsted County residents who had normal results of an immunologic work-up and who met the matching criteria. Therefore, 1 case had 4 controls (2 controls from the community and 2 controls from the immunology laboratory database). The exclusion criteria for controls were the same as those for cases.

Exposure Ascertainment (Asthma Status).

For ascertaining the asthma status of all the cases and controls, we conducted comprehensive medical record reviews to apply predetermined criteria for asthma. These criteria, delineated in Table 1, have been extensively used in research for asthma epidemiology and were found to have high reliability.^{47,56-65} We included both definite and probable asthma because most probable asthma cases become

TABLE 1. Definition of Asthma

Patients were considered to have definite asthma if a physician had made a diagnosis of asthma or if each of the following 3 conditions were present, and they were considered to have probable asthma if only the first 2 conditions were present:

1. History of cough, dyspnea, or wheezing OR history of cough or dyspnea plus wheezing on examination
2. Substantial variability in symptoms from time to time or periods of weeks or more when symptoms were absent
3. Two or more of the following:
 - Sleep disturbance by nocturnal cough and wheeze
 - Nonsmoker (aged ≥ 14 y)
 - Nasal polyps
 - Blood eosinophilia $>300/\mu\text{L}$
 - Positive wheal-and-flare skin test results OR elevated serum IgE level
 - History of hay fever or infantile eczema OR cough, dyspnea, and wheezing regularly on exposure to an antigen
 - Pulmonary function tests showing 1 FEV₁ or FVC value $<70\%$ of predicted and another with $\geq 20\%$ improvement to an FEV₁ $>70\%$ of predicted OR a methacholine challenge test showing a $\geq 20\%$ decrease in FEV₁
 - Favorable clinical response to bronchodilator therapy

Patients were excluded from the study if any of the following conditions were present:

- Pulmonary function tests that found FEV₁ to be consistently $<50\%$ of predicted or diminished diffusion capacity
- Tracheobronchial foreign body at or about the incidence date
- Wheezing occurring only in response to anesthesia or medications
- Bullous emphysema or pulmonary fibrosis on chest radiography
- PIZZ α_1 -antitrypsin
- Cystic fibrosis
- Other major chest disease, such as juvenile kyphoscoliosis or bronchiectasis

FEV₁ = forced expiratory volume in 1 second; FVC = forced vital capacity.

definite over time.^{47,65} Given the difficulty in determining the accurate time of development of sIgAD/CVID, we determined whether asthma status by predetermined criteria might precede the diagnosis of sIgAD/CVID instead of the actual development of sIgAD/CVID.

Data Analyses

The primary analysis was to compare the frequency of a history of asthma before the index date (diagnosis date) of sIgAD/CVID between sIgAD/CVID cases and their matched controls. The secondary analysis was to compare the frequency of a history of ever having asthma between sIgAD/CVID cases and their matched controls. In the analysis, we combined sIgAD and CVID cases because each category had a small sample size and could be considered part of a spectrum of humoral immunodeficiency conditions. Matched analysis was performed using a conditional logistic regression model to calculate odds ratios (ORs) and their corresponding 95% CIs. First, we calculated the OR for the association between asthma and sIgAD/CVID using cases and all controls combined (1:4 matching). Subsequently, we performed analysis using cases and their

matched controls from the community and the immunology laboratory database separately (ie, 1:2 matched analysis for cases and their community controls and 1:2 matched analysis for cases and their immunology laboratory controls). All the analyses were performed using a commercially available software program (SAS version 9.1; SAS Institute Inc).

RESULTS

Study Participants

Initially, we identified 228 potential sIgAD/CVID cases from 3 different data sources, and 189 were excluded on the basis of the exclusion criteria. The reasons for exclusion were (1) failure to meet the PGID/ESID criteria ($n=86$), (2) no research authorization ($n=12$), (3) non-Olmsted County residency ($n=22$), and (4) secondary immunodeficiency ($n=69$ [39 for leukemia or malignant lymphoma, 16 for immunosuppressive drugs, and 14 for renal failure]). Thus, 39 cases were enrolled in this study: 26 with sIgAD (66.7%) and 13 with CVID (33.3%). Of these 39 cases, 51.3% were men ($n=20$) and 97.1% were white (33 of 34

patients). The mean age at the index date of sIgAD/CVID was 34.2 years. Characteristics of the study participants are summarized in Table 2.

Association Between Asthma and sIgAD/CVID

Overall, of the 39 cases, 9 (23.1%) had a history of asthma before the index date (diagnosis) of sIgAD/CVID; of the 156 controls, 16 (10.3%) had a history of asthma before the index date (diagnosis) (OR, 2.77; 95% CI, 1.09-7.06; $P=.03$). A history of ever having asthma was more prevalent in sIgAD/CVID cases (30.8%; $n=12$) than in matched controls (11.5%; $n=18$) (OR, 3.57; 95% CI, 1.50-8.51; $P=.01$) (Tables 2 and 3).

In a separate analysis using the control group from the community alone, the association between a history of asthma before the index date and the incidence of sIgAD/CVID remained significant (OR, 3.52; 95% CI, 1.05-11.75; $P=.04$), and this was true for the association between a history of ever having asthma and the diagnosis of sIgAD/CVID (OR, 4.98; 95% CI, 1.58-15.71; $P=.01$) (Table 3). If we limit the analysis to cases and laboratory controls, the association between a history of asthma before the index date and the diagnosis of sIgAD/CVID was not significant (OR, 2.46; 95% CI, 0.84-7.17; $P=.10$), but the association between a history of ever having asthma and the diagnosis of sIgAD/CVID was significant (OR, 3.02; 95% CI, 1.09-8.35; $P=.03$). Asthma

developed in 9 of the 39 patients before the index date of sIgAD/CVID. Of these 9 asthmatic patients, only 1 was taking a systemic corticosteroid within 3 months of the index date of sIgAD/CVID, and 3 were taking an inhaled corticosteroid or a nasal topical corticosteroid.

DISCUSSION

The results of this study indicate that a history of asthma and a history of ever having had asthma are associated with an increased diagnosis of sIgAD/CVID compared with those without such histories (OR, 2.46-4.98). Unlike previous studies, because this study is a population-based study, it is less susceptible to selection (or susceptibility) bias. However, detection bias is a major concern in investigating the association because exposure status (asthma) might potentially affect a likelihood of detection of outcomes (sIgAD/CVID). Because of this concern, we enrolled two sets of control groups (ie, community controls and laboratory controls). We limited the analysis to cases vs laboratory controls (who had normal immunology work-up findings) because the laboratory control group is likely to share a similar clinical history (eg, frequent infections) and access to medical care for evaluation. The results indicated that the association was still significant and consistent except for the association between a history of asthma and sIgAD/CVID, which approached statistical significance due to limited statistical power. Because we matched

TABLE 2. Characteristics of sIgAD/CVID Cases and Their Matched Controls^a

Variable	Cases (n=39)	All controls (n=156)	P value	Community controls (n=78)	P value	Laboratory controls (n=78)	P value
Male sex, No. (%)	20 (51.3)	80 (51.3)	>.99	40 (51.3)	>.99	40 (51.3)	>.99
Age at disease occurrence (y), mean $\pm$ SD (median)	34.2 $\pm$ 24.2 (32.0)	34.2 $\pm$ 23.9 (32.5)	.99	34.2 $\pm$ 24.0 (32.0)	>.99	34.2 $\pm$ 23.9 (33.0)	.99
White race, No. (%) ^b	33 (97.1)	133 (91.7)	.28	65 (91.6)	.29	68 (91.9)	.31
Educational level, No. (%) ^c			.33		.08		.61
High school degree or less	24 (61.5)	109 (69.9)		63 (80.8)		46 (59.0)	
Some college	4 (10.3)	22 (14.1)		7 (9.0)		15 (19.2)	
College degree	7 (18.0)	14 (9.0)		4 (5.1)		10 (12.8)	
Graduate school degree	4 (10.3)	11 (7.1)		4 (5.1)		7 (9.0)	
Asthma before the index date, No. (%)	9 (23.1)	16 (10.3)	.03	7 (9.0)	.04	9 (11.5)	.10
Asthma ever, No. (%)	12 (30.8)	18 (11.5)	.01	7 (9.0)	.01	11 (14.1)	.03
Comorbid conditions, No. (%)	9 (23.1)	18 (11.5)	.06	10 (12.8)	.16	8 (10.3)	.06

^aCVID = common variable immunodeficiency; sIgAD = selective IgA deficiency.

^bFor race, data was unavailable for 16 participants (5 cases, 7 community controls, and 4 laboratory controls).

^c χ^2 Test for trend.

TABLE 3. Association Between Asthma and sIgAD/CVID Stratified by Different Control Groups Based on Matched Analysis

	All controls		Community controls		Laboratory controls	
	OR matched (95% CI)	P value	OR matched (95% CI)	P value	OR matched (95% CI)	P value
Asthma before the index date	2.77 (1.09-7.06)	.03	3.52 (1.05-11.75)	.04	2.46 (0.84-7.17)	.10
Asthma ever	3.57 (1.50-8.51)	.01	4.98 (1.58-15.71)	.01	3.02 (1.09-8.35)	.03

CVID = common variable immunodeficiency; OR = odds ratio; sIgAD = selective IgA deficiency.

the clinic registration year and the index date between cases and controls, ensuring a similar follow-up duration, a differential follow-up duration between asthmatic and nonasthmatic individuals in case-control pairs is unlikely to explain the association. Also, both exposure status (asthma) and outcomes (sIgAD/CVID) were ascertained by predetermined criteria, and the data abstractor was blinded to the hypothesis and the status of cases and controls. Thus, performance bias is unlikely. Of 39 patients with sIgAD/CVID, only 1 asthmatic person was taking a low-dose systemic corticosteroid (a 13-mg prednisone-equivalent dose) at the index date of sIgAD/CVID. Hence, exposure to corticosteroid (susceptibility bias) is also unlikely to account for the association. We also conducted a subgroup analysis for definite vs probable sIgAD/CVID. The association of asthma with definite CVID (OR, 15.4; 95% CI, 1.76-135.00; $P=.01$) and probable CVID (OR, 13.5; 95% CI, 1.51-125; $P=.02$) seems to be consistent, although the CI is large due to a small sample size. Also, asthma was consistently associated with the development of definite sIgAD (OR, 2.24; 95% CI, 0.79-6.31; $P=.13$) and probable sIgAD (OR, 5.04; 95% CI, 0.82-30.00; $P=.08$), but they only approached statistical significance due to the limited sample size. Therefore, asthmatic patients are more likely to represent patients with the sIgAD/CVID diagnosis compared with nonasthmatic individuals over time. Given the potential delay in diagnosis of sIgAD (mean duration of 10.5 years)⁴⁵ and CVID (median duration of 5.8 years)⁴⁶ and the increased risk of microbial infections in asthmatic patients, asthmatic patients with recurrent infections may be an important target population in which screening for sIgAD/CVID may be considered.

Most previous studies assessed the prevalence of asthma or other atopic conditions in patients with sIgAD (15%-83%).^{33,34,36,41}

However, there are a few longitudinal studies that have assessed whether asthmatic patients are at higher risk for sIgAD or CVID over time. A few cross-sectional studies reported that IgA levels tend to be lower or deficient in asthmatic patients compared with nonasthmatic individuals.^{66,67} At present, the role of asthma or atopy in the diagnosis and prognosis of sIgAD or CVID is unknown. To our knowledge, this is the first population-based study investigating the epidemiologic relationship between asthma and sIgAD/CVID by predetermined criteria for asthma and sIgAD/CVID.

However, given the difficulty in determining the accurate time of the incidence of sIgAD/CVID due to the asymptomatic nature of the disease, it is plausible that sIgAD or CVID might precede asthma. If this is true, these study findings still provide an important insight into the potential role of sIgAD/CVID in the development of asthma. For example, it could be hypothesized that patients with sIgAD/CVID would lose part of the capacity to block the entry of allergens through the mucosa, which could induce sensitization predisposing to the development of asthma.

The mechanisms for the association between asthma and sIgAD/CVID are unknown, and, therefore, we can only speculate on the basis of previously published data. *TNFRSF13B* variants have been suggested as a potential molecular defect associated with sIgAD and CVID,^{30,31} although they account for only 6.25% of sIgAD and 8% to 21% of CVID,^{30,68} suggesting a role for other genetic defects in the etiopathogenesis of sIgAD/CVID. Although little is known about the role of *TNFRSF13B* gene sequence variations in the development of asthma or atopy, a recent study found that Swedish children with *TNFRSF13B* sequence variations had a 2-fold increased risk of wheezing at 2 and 4 years of age and a

2.5-fold increased risk of asthma at 4 years of age independent of IgE levels.⁶⁹ Further studies on the mechanisms underlying this association are needed.

This study has limitations inherent of a retrospective study, including possible selection or detection bias. A prospective longitudinal study is needed to replicate these study findings. However, a population-based study approach may minimize this concern. Also, the study approach with the laboratory control reduced detection bias. The low prevalence of sIgAD/CVID (a small number of cases) resulted in limited statistical power. However, we could detect the association between asthma and sIgAD/CVID. The present study participants were predominantly white, which may limit the broad application or generalization of the study findings.

CONCLUSION

Asthma is associated with sIgAD/CVID in certain individuals. Because asthma is heterogeneous, it would be important to examine the phenotype of asthma associated with the immune conditions and to assess whether the association can be further specified in a way to identify a subgroup of asthmatic patients with the immune conditions. Further studies are needed to replicate these study findings.

ACKNOWLEDGMENT

We are grateful for administrative support from Elizabeth Krusemark and Denise Chase and for research support from the staff of the Pediatric Asthma Epidemiology Research Unit at Mayo Clinic. We thank Elizabeth Mellon and Drs Avni Joshi and Brian Brennan for their support.

Abbreviations and Acronyms: CVID = common variable immunodeficiency; ESID = European Society for Immunodeficiencies; OR = odds ratio; PAGID = Pan-American Group for Immunodeficiency; PID = primary immunodeficiency; sIgAD = selective IgA deficiency

Grant Support: This work was supported by a grant from the T. Denny Sanford Collaborative Research Fund, a partnership between Sanford Health and Mayo Clinic. This study was made possible by the Rochester Epidemiology Project (grant number R01-AG034676; Principal Investigators: Walter A. Rocca, MD, and Barbara P. Yawn, MD, MSc).

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