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Antigenic Challenge in the Etiology of Autoimmune Disease in Women

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Abstract

Infection has long been implicated as a trigger for autoimmune disease. Other antigenic challenges include receipt of allogeneic tissue or blood resulting in immunomodulation. We investigated antigenic challenges as possible risk factors for autoimmune disease in women using the Health and Retirement Study, a nationally representative longitudinal study, linked to Medicare files, years 1991–2007. The prevalence of autoimmune disease (rheumatoid arthritis, Hashimoto's disease, Graves' disease, systemic lupus erythematosus, celiac disease, systemic sclerosis, Sjögren syndrome and multiple sclerosis) was 1.4% in older women (95% CI: 1.3%, 1.5%) with significant variation across regions of the United States. The risk of autoimmune disease increased by 41% (95% CI of incidence rate ratio (IRR): 1.10, 1.81) with a prior infection-related medical visit. The risk of autoimmune disease increased by 90% (95% CI of IRR: 1.36, 2.66) with a prior transfusion without infection. Parity was not associated with autoimmune disease. Women less than 65 years of age and Jewish women had significantly elevated risk of developing autoimmune disease, as did individuals with a history of heart disease or end-stage renal disease. Antigenic challenges, such as infection and allogeneic blood transfusion, are significant risk factors for the development of autoimmune disease in older women.

Keywords

autoimmune disease; gender; infection; transfusion; parity

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1. Introduction

Female predominance in many autoimmune diseases is remarkable [1,2]. Jacobson and colleagues reported that 95% of patients with thyroiditis, 92% of adults with systemic sclerosis, 88% of patients with systemic lupus erythematosus, and 88% of patients with Graves' disease are women [3]. While gender is a known predictor of many autoimmune diseases, the reasons why women are at greater risk of autoimmune diseases remain speculative [4].

Infectious agents have been hypothesized as triggers of autoimmune disease through molecular mimicry, alterations in self-antigens, immune cell activation or infection-mediated inflammation [4–6]. Conversely, some investigators have argued for the "hygiene hypothesis" which suggests that increases in autoimmune diseases over time are correlated with decreases in the incidence of infection, particularly during childhood [7–9]. Unfortunately, there have been few population-based studies to substantiate or refute these hypotheses.

Other antigenic challenges include exposure to allogeneic tissue – that is, from genetically dissimilar individuals – either through a blood transfusion or tissue/organ transplantation. Such exposures have been shown to induce an inflammatory response, often with the production of proinflammatory cytokines and changes in chemokine expression [10–12]. Interrupters of selected chemokine pathways have been shown to suppress inflammation in mouse models of rheumatoid arthritis and systemic lupus [13,14].

Pregnancy is another instance in which genetically dissimilar cells may be transferred, in this case, between mother and fetus [15,16]. Microchimerism, the presence of genetically dissimilar cells within an individual, has been shown to persist in women for up to 38 years after delivery [17]. Preliminary studies have suggested a possible relationship between fetal microchimerism (fetal cells in parous women) and systemic sclerosis, Sjögren syndrome, Hashimoto's thyroiditis and Graves' disease [18–20]. Moreover, iatrogenic microchimerism has been shown to occur in patients after blood transfusions; in trauma patients, 3–4% of peripheral blood leukocytes were found to be of donor origin [21].

With access to a nationally representative sample of older Americans who have been studied longitudinally over an extended period of time, we sought to evaluate the underlying hypothesis that antigenic challenge may affect the risk of autoimmune disease in women.

2. Materials and Methods

A retrospective cohort study was conducted. Women in the Health and Retirement Study (HRS), an ongoing longitudinal study of the older American population, formed the cohort [22]. Information regarding diagnoses of autoimmune disease was available from Medicare files from the Centers for Medicare and Medicaid Services (CMS) which were linked to data from participants in the HRS, a national area probability sample of US households [22]. CMS inpatient standard analytical files (SAFs), outpatient SAFs, skilled nursing facility SAFs, home health SAFs, carrier/Part B files and denominator files were used from years 1991 through 2007. The autoimmune diseases studied were rheumatoid arthritis (ICD-9 codes 714.0–714.8), Hashimoto's disease or autoimmune hypothyroidism (ICD-9 code 245.2), Graves' disease (ICD-9 code 242.0), systemic lupus erythematosus (ICD-9 code 710.0), celiac disease (ICD-9 code 579.0), systemic sclerosis (ICD-9 code 710.1), Sjögren syndrome (ICD-9 code 710.2) and multiple sclerosis (ICD-9 code 340).

Exposures to antigenic challenges (infection, allogeneic blood, transplantation) were extracted from information within the CMS files. We determined the number of infection-

related visits for hospital stays, emergency department visits, outpatient facility/clinic visits, skilled nursing facility stays and at home health visits by using ICD-9 codes that explicitly stated infection or provided evidence of infection (purulent, suppurative, septic, pyogenic or abscess). Allogeneic blood transfusion information was obtained for hospital stays, emergency department visits, outpatient facility visits, skilled nursing facility stays and home health visits, using transfusion-related procedure codes (ICD-9-CM 99.0x), revenue center codes (38x, 39x), blood value codes, current procedural terminology codes (36430, 36455) and Healthcare Common Procedure Coding System codes (P90xx). Information regarding transplantation of kidney, liver, lung, heart, spleen, intestine, pancreas, or bone marrow was also extracted from procedure and diagnosis codes. We also determined hospital stays in which no infection or transfusion occurred. Dates of visits or stays with infection, transfusion and transplantation were extracted as well.

Other variables from the HRS included number of children, age at first interview, race (Caucasian, African-American, other), ethnicity (Mexican-American, other Hispanic, non-Hispanic), religion, body mass index (BMI; kg/m^2), smoking (current) at the time of the first interview, and region of the country of the participant's residence. A history of heart disease, end-stage renal disease, stroke, diabetes mellitus, and cancer were also available as self-reported by the participants during each biennial interview (e.g., individuals reporting a doctor's diagnosis of heart disease at any time during the study period were classified as having a history of heart disease).

Initially, prevalence rates of the individual and combined autoimmune diseases were calculated (per 100,000 person-years) with survey weighting to the reference population, American women with fee-for-service Medicare (n=9429 in the sample). Second, we examined risk factors prior to disease onset using incident cases of autoimmune disease within the cohort. A diagnosis was considered an incident event if the woman did not have any medical record of the disease for at least 5 years prior to the (new) diagnosis. To allow for ascertainment of antigenic exposures prior to the development of autoimmune disease, we included only those infection-related stays/visits, transfusion-related stays/visits and other hospital stays in the first five years from the date of the first interview. Women who were in the study for 10 years or more were included. Survey-weighted Poisson regression was conducted to assess predictors of autoimmune diseases, offset by (log) person-years of follow-up. Antigenic challenges were initially modeled as binary (yes/no) and then modeled as continuous (number of visits with infection, number of visits with a blood transfusion, number of children). In the final models, transfusion-related visits were evaluated in persons with no infection-related visits. This was done to separate possible causal pathways. Randomized controlled trials have shown that transfusion with allogeneic red blood cells increases the risk of infection [23]. Therefore, we wished to evaluate the possible effects of transfusion separately from those of infection. In addition, we assessed whether a hospital stay (without infection or transfusion) was a risk factor for autoimmune disease.

There were a small percentage of missing values for body mass index (0.17%), religion (0.13%) and number of children (2.94%); missing values were imputed prior to regression analyses. All reported estimates of effect were weighted to account for the sample design of the HRS [24]. The estimated reduction in the number of cases was calculated using the underlying population size (weighted cell count) and differences in absolute risk [25]. Analyses were conducted in Stata/MP 11.0. Alpha was set at 0.05, 2-tailed.

3. Results

The prevalence of the autoimmune disease in older American women (median age at first interview, 70 years) was 1.4% and varied throughout the United States (Table 1). The lowest

prevalence was in the western states, with higher prevalence in the South and Northeast (*P*=0.009). There were significant regional differences in prevalence of rheumatoid arthritis (*P*=0.014) and systemic sclerosis (*P*=0.038).

For the investigation of risk factors of autoimmune disease, there were 4721 women without autoimmune disease at study onset who were followed for a mean of 14.4 years (SD 2.4) and median of 14.9 years (interquartile range, 12.2 to 17.0 years). The mean age of the participants was 70.9 years at the time of the first interview (95% CI: 70.5, 71.3) and their mean BMI was 26.3 kg/m^2 (95% CI: 26.1, 26.5). There were 418 incident cases of autoimmune disease which occurred at a mean age of 78.2 years (95% CI: 77.2, 79.2).

Risk factors were initially examined individually, in unadjusted models (Table 2). The incidence of autoimmune disease was greater in women younger than 65 years of age than those 65 or older. There were no significant differences in the incidence of autoimmune disease by race or ethnicity. Jewish women more frequently developed autoimmune disease than non-Jewish women; this was evident for rheumatoid arthritis as well. When categorized into 4 groups, BMI was not significantly associated with autoimmune disease (Table 2). However, when modeled as a continuous variable, BMI was significantly associated with autoimmune disease in the unadjusted model; each unit increase in BMI yielded a 2% increase in autoimmune disease (95% CI: 1.01, 1.04) and 3% increase in the rate of rheumatoid arthritis (95% CI: 1.01, 1.05). Smoking and parity (number of children) were not associated with the development of autoimmune disease in this cohort. The incidence of autoimmune disease was significantly elevated in women who had a previous visit in which an infection was recorded, as well as a visit in which a transfusion occurred. There was only one person who received an organ transplant in the first five years of the study (who also received a transfusion), so the effects of transplantation could not be assessed in this study. In unadjusted models, a history of end-stage renal disease and heart disease were each associated with autoimmune disease in women.

Predictors of autoimmune disease in women adjusted for all study-related risk factors are given in Table 3, with antigenic exposure coded as binary (yes/no) for infection, blood transfusion, and parity. The risk of autoimmune disease increased by 41% for women who had a previous medical visit in which an infection occurred. For every infection-related visit, the risk of autoimmune disease increased by 3% (Table 4). A similar pattern was evident for women who developed rheumatoid arthritis. In addition, the risk of autoimmune disease increased by 90% for women who experienced a transfusion, as shown in Table 3. For every visit in which a transfusion occurred (without infection), the risk of autoimmune disease increased by 43% and the risk of rheumatoid arthritis increased by 44% (Table 4). During the 5 years after study entry, 11.5% of women had at least one transfusion-related visit and 32.6% had at least one infection, as recorded in the medical records. However, the absolute risk difference for transfusion was twice as great as that for infection. If these exposures were causal in nature, a 10% reduction in transfusion-related visits would have yielded 487 fewer incident cases of autoimmune disease over the study period and a 10% reduction in infection-related visits (without transfusion) would have yielded 229 fewer incident cases of autoimmune disease in older American women.

There was no relationship between parity and the risk of autoimmune disease, or rheumatoid arthritis specifically, in this cohort. Younger age remained significant in the final adjusted models, although BMI and smoking did not. Women of Jewish religion were at greater risk of autoimmune disease and of rheumatoid arthritis. Histories of heart disease and end-stage renal disease were also associated with autoimmune disease in the final models.

4. Discussion

In this investigation, the theory of antigenic challenge in the development of autoimmune disease was supported for both infection and transfusion. The results suggest that chronic exposure to infectious agents and allogeneic blood components promotes immunomodulation. The nexus between inflammation, infection and immunomodulation (both reactivity and suppression) has been well documented [4,26,27]. This is consistent with previous investigations implicating infection and inflammation as contributors to autoimmune disease [8,28,29]. The significance of both transfusion and infection in the final models suggests that each of these factors may be important contributors to the onset of autoimmune disease in women. While red blood cell transfusion has been shown to increase the incidence of infection in randomized controlled trials [23], our results suggest that transfusion may also affect the immune system via non-infectious mechanisms. CMS records do not capture every infection that may have occurred in the participants but our results may indicate that an infection serious enough to warrant medical attention is necessary for triggering autoimmune disease. It is also possible that an infection requiring medical services is a marker for more frequent infections in general. The results show that hospital stays *per se*, or other factors associated with hospitalization, were not associated with the development of autoimmune disease; the significant predictors were specifically medical visits/stays in which an infection or a transfusion was recorded.

Previous studies of blood transfusion and rheumatoid arthritis reported contradictory results [30,31]. In these studies, the ascertainment of blood transfusion was via recall of information. Such methods may be inadequate, since blood is often transfused during surgery when the patient is under anesthesia or during the post-surgical period when the patient is medicated and therefore, may be unaware of whether or not a transfusion occurred. In the United States, it is not required that hospitalized patients be specifically informed if they received a transfusion (and >80% of transfusions occur in the hospital [32]). In our study, blood transfusion was documented in the medical record at the time when the subject was hospitalized, seen in the emergency department, visited an outpatient facility/clinic, in a skilled nursing facility or received home health care. Since transfusion is only administered by clinicians, dates of occurrence of the stay or visit were known.

Parity was not associated with autoimmune disease in older women. Guthrie and colleagues conducted a population-based study of parity and gravidity on the risk of rheumatoid arthritis [33]. They found that parous women exhibited a reduction in the risk of rheumatoid arthritis within 1–15 years after delivery but there was no association between parity and rheumatoid arthritis more than 15 years post-partum. The underlying hypothesis was that fetal microchimerism may affect later risk in the mother [33]. In our study, there was no association between parity and autoimmune disease in general, or rheumatoid arthritis. Since the mean age of onset of the autoimmune disease was 78 years, parous women in our cohort were more than 15 years post-partum and therefore, our results concur with the previous findings. A limitation was our inability to assess number of pregnancies in addition to parity. Fetal microchimerism is possible with each pregnancy and therefore, our assessment using parity alone could be less sensitive than a true measure of gravidity.

We found that younger women were at greater risk of developing autoimmune disease than older women. There are changes to the immune system with age, including reports of increased regulatory T cell levels with older age [34]. Animal studies indicate both an increased number of regulatory T cells and an increased level of suppression per cell as age rises [35]. Regulatory T cells function as suppressors of the immune response and their deficiency or defects in their function have been associated with several autoimmune diseases in humans [36,37]. Therefore, the inverse association between age and autoimmune

disease in our study could be partially explained by the age-related increase in regulatory T cells.

The prevalence of rheumatoid arthritis has been reported as 1.37% in women from Minnesota [38] which is similar to our finding of 1.09% in a representative sample of older American women nationally. Worldwide, the prevalence of rheumatoid arthritis has varied from 0.3% to 2.0% in different populations of women [39]. Data from the Third National Health and Nutrition Examination Study indicated that the prevalence of systemic lupus erythematosus was 100 per 100,000 women in year 2000 [40]; results from our study indicate the prevalence to be 135 per 100,000 older women. In total, our investigation showed that 1.42% of older women in the United States had one of the eight autoimmune diseases under investigation. We chose not to include type 1 diabetes mellitus in this cohort because of the lower incidence in older women and the inability to adequately distinguish insulin-dependent type 2 diabetes mellitus from type 1 diabetes in the records. In addition, some autoimmune diseases, such as hemolytic anemia and immune thrombocytopenic purpura, were too rare to investigate in this cohort. Therefore, the 1.4% prevalence figure is likely to be less than the overall prevalence of autoimmune disease in older women. Of note, Cooper and colleagues summarized the evidence regarding prevalence of all autoimmune diseases (combined) with a correction for under-ascertainment and reported the prevalence as 7.6 to 9.4% for all age and gender groups combined [41].

Unfortunately, we did not have genetic information on the subjects. Many autoimmune diseases have demonstrated a genetic component [42,43], although some studies of concordance in twins indicate that the genetic factors do not completely explain the incidence of several autoimmune diseases [44,45]. It is possible that the increased risk of autoimmune disease in Jewish women was due to genetic differences although undefined environmental exposures cannot be ruled out. However, this finding was incidental to the main hypotheses of interest and therefore, would benefit from replication in another study.

The association between heart disease and autoimmune diseases is consistent with evidence implicating an underlying inflammatory response [46,47]. Prospective studies have shown an association between atherosclerosis and both inflammation and chronic infection [48,49]. Moreover, this association appears general, in that infections of the respiratory tract, urinary tract and other types of infection have been associated with atherogenesis, with heterogeneity among organisms [48]. Immune dysfunction has also been demonstrated in patients with end-stage renal disease [50]. The degree of alteration in immune function in end-stage renal disease is quite extensive, resulting in increased rates of infection with chronic immunosuppression and increased chronic inflammation due to immunoactivation [50]. We modeled end-stage renal disease and heart disease such that any history of these diseases was captured; the intent was to recognize the pro-inflammatory states that may be evident for many years prior to a physician’s diagnosis. Therefore, in our investigation, heart disease and end-stage renal disease were associated with autoimmune diseases, but without directionality; the extent to which one precedes the other was not known. It is notable, however, that our findings regarding infection and transfusion remained significant after adjustment for heart disease and end-stage renal disease. We did not have the statistical power necessary to assess interactions among these factors but this may be of interest in future studies.

While the underlying mechanisms for the elevated risk of autoimmune disease from infection and transfusion could not be fully explored in this investigation, it is important to note that both of these risk factors are modifiable and thus, to some extent, preventable. While the numbers of possible cases prevented with a 10% reduction in exposure were modest, the long-term disability and healthcare costs associated with autoimmune diseases

can be extensive [51]. There has been greater emphasis on reducing healthcare-associated infections in hospitals nationwide [52]. Moreover, conservative approaches to the use of red blood cell transfusion (i.e., lower hemoglobin triggers) have been found to provide similar clinical benefit or less harm than traditional approaches [23], prompting initiatives in blood management [53]. Whether these efforts succeed in lowering the prevalence of such antigenic challenges and whether this translates into lower rates of autoimmune disease is yet to be demonstrated.

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Table 1

Prevalence of Autoimmune Diseases in Female Medicare Beneficiaries in the United States by Region, Health and Retirement Study, 1991–2007

Disease	Northeast		Midwest		South		West		All	
	Prevalence[a]	95% CI	Prevalence[a]	95% CI	Prevalence[a]	95% CI	Prevalence[a]	95% CI	Prevalence[a]	95% CI
Rheumatoid arthritis	1164	924, 1403	970	841, 1099	1220	1084, 1357	881	759, 1003	1087	1001, 1174
Graves' disease	173	89, 257	148	99, 197	114	83, 146	76	28, 124	127	103, 151
Systemic lupus erythematosus	166	69, 263	150	85, 215	134	109, 159	80	33, 127	135	108, 161
Hashimoto's disease	94	38, 150	74	47, 101	77	24, 129	61	14, 108	76	51, 101
Sjören syndrome	56	15, 98	91	60, 123	104	76, 133	57	24, 91	85	67, 102
Multiple sclerosis	53	28, 77	57	35, 79	36	16, 56	61	19, 103	49	36, 61
Celiac disease	26	0, 57	25	9, 41	34	15, 54	11	0, 29	27	16, 37
Systemic sclerosis	15	0, 34	57	27, 86	28	11, 45	15	0, 35	31	19, 43
Autoimmune diseases (combined)	1525	1240, 1810	1359	1217, 1502	1558	1417, 1699	1113	992, 1235	1425	1331, 1519

Abbreviations: CI, confidence interval.

[a] per 100,000 person-years.

TABLE 2

Characteristics of Participants and Unadjusted Incidence Rate Ratios for Rheumatoid Arthritis and Autoimmune Disease in Female Medicare Beneficiaries, Health and Retirement Study, 1991–2007

		Rheumatoid arthritis		Autoimmune disease[a]	
	n, sample	IRR	95%CI	IRR	95%CI
Age at first interview:					
<65 years	977	1.00	(reference)	1.00	(reference)
65–69 years	720	0.48	0.31, 0.73	0.53	0.37, 0.76
70–74 years	1664	0.49	0.34, 0.70	0.45	0.34, 0.61
≥75 years	1360	0.64	0.46, 0.87	0.53	0.39, 0.71
Race:					
Caucasian	3989	1.00	(reference)	1.00	(reference)
African-American	617	1.33	0.91, 1.94	1.14	0.85, 1.52
Other	115	1.60	0.77, 3.34	1.25	0.64, 2.43
Hispanic:					
Not Hispanic	4439	1.00	(reference)	1.00	(reference)
Mexican-American	151	1.27	0.88, 1.85	1.11	0.73, 1.70
Other Hispanic	131	1.30	0.54, 3.11	1.13	0.53, 2.40
Religion:					
Jewish	139	1.89	1.14, 3.13	1.87	1.27, 2.76
Non-Jewish	4582	1.00	(reference)	1.00	(reference)
Body mass index at first interview:					
Underweight (<18.5 kg/m^2)	127	1.00	(reference)	1.00	(reference)
Normal (18.5–24.9 kg/m^2)	1937	1.30	0.51, 3.29	1.73	0.72, 4.19
Overweight (25.0–29.9 kg/m^2)	1726	1.47	0.58, 3.71	1.81	0.77, 4.28
Obese (≥30.0 kg/m^2)	931	1.83	0.72, 4.66	2.27	0.92, 5.55
Smoked at first interview:					
No	4148	1.00	(reference)	1.00	(reference)
Yes	573	0.99	0.67, 1.46	1.08	0.79, 1.48
Number of children:					
0	1480	1.00	(reference)	1.00	(reference)

		Rheumatoid arthritis		Autoimmune disease[a]	
	n, sample	IRR	95%CI	IRR	95%CI
1	2169	1.30	0.79, 2.14	1.35	0.94, 1.95
2	4198	0.84	0.53, 1.32	0.91	0.66, 1.28
≥3	8934	1.09	0.68, 1.75	1.02	0.72, 1.45
Transfusion-related visit:					
No	4182	1.00	(reference)	1.00	(reference)
Yes	539	1.69	1.25, 2.30	1.60	1.23, 2.07
Infection-related visit:					
No	3222	1.00	(reference)	1.00	(reference)
Yes	1499	1.42	1.13, 1.80	1.31	1.04, 1.66
End-stage renal disease:					
No	4667	1.00	(reference)	1.00	(reference)
Yes	54	3.68	1.88, 7.19	2.86	1.53, 5.32
Heart disease:					
No	2945	1.00	(reference)	1.00	(reference)
Yes	1776	1.52	1.16, 2.01	1.41	1.13, 1.76
Stroke:					
No	3872	1.00	(reference)	1.00	(reference)
Yes	849	1.01	0.75, 1.37	1.02	0.79, 1.30
Diabetes mellitus:					
No	3784	1.00	(reference)	1.00	(reference)
Yes	937	1.07	0.80, 1.43	1.13	0.87, 1.46
Cancer:					
No	3829	1.00	(reference)	1.00	(reference)
Yes	892	1.10	0.86, 1.42	1.23	0.97, 1.56
Region of residence:					
Northeast	838	1.09	0.63, 1.87	1.41	0.88, 2.25
Midwest	1228	0.86	0.55, 1.34	0.99	0.71, 1.39
South	1860	1.41	0.91, 2.17	1.42	1.00, 2.04
West	795	1.00	(reference)	1.00	(reference)

Abbreviations: IRR, incidence rate ratio; CI, confidence interval.

[a] Includes rheumatoid arthiritis, Graves' disease, systemic lupus erythematosus, Hashimoto's disease, Sjoren syndrome, celiac disease, systemic sclerosis, multiple sclerosis.

TABLE 3

Adjusted Incidence Rate Ratios of Rheumatoid Arthritis and Autoimmune Disease in Female Medicare Beneficiaries, Health and Retirement Study, 1991–2007

	Rheumatoid arthritis			Autoimmune disease[a]		
	IRR	**95% CI**	***P* value**	**IRR**	**95% CI**	***P* value**
Infection-related visit	1.44	1.11, 1.86	0.007	1.41	1.10, 1.81	0.007
Transfusion-related visit[b]	1.74	1.22, 2.48	0.003	1.90	1.36, 2.66	<0.001
Other hospital stay[c]	1.05	0.81, 1.36	0.692	0.99	0.80, 1.22	0.930
Parous (yes/no)	1.01	0.65, 1.55	0.975	0.96	0.70, 1.32	0.815
Age (years)	0.98	0.96, 1.00	0.029	0.97	0.95, 0.98	0.001
Body mass index (kg/m^2)	1.02	0.99, 1.05	0.128	1.01	0.99, 1.03	0.393
Race:						
Caucasian	1.00	reference)		1.00	(reference)	
African-American	1.11	0.72, 1.71	0.638	0.95	0.69, 1.32	0.775
Other	1.45	0.68, 3.10	0.334	1.13	0.60, 2.15	0.697
Ethnicity:						
Mexican-American	1.17	0.74, 1.84	0.489	1.13	0.71, 1.81	0.606
Other Hispanic	1.19	0.45, 3.18	0.719	1.07	0.48, 2.40	0.863
Not Hispanic	1.00	reference)		1.00	(reference)	
Jewish religion	2.03	1.17, 3.52	0.012	1.90	1.24, 2.93	0.004
Smoked at first interview	0.91	0.60, 1.37	0.631	0.92	0.63, 1.32	0.634
History of end-stage renal disease	2.79	1.33, 5.86	0.008	2.22	1.11, 4.45	0.025
History of heart disease	1.43	1.08, 1.90	0.013	1.35	1.08, 1.69	0.010
History of stroke	0.95	0.71, 1.27	0.742	1.01	0.78, 1.30	0.955
History of diabetes mellitus	0.81	0.59, 1.11	0.188	0.92	0.70, 1.20	0.532
History of cancer	1.07	0.82, 1.39	0.632	1.20	0.94, 1.55	0.148
Region of residence:						
Northeast	1.03	0.60, 1.77	0.902	1.38	0.88, 2.18	0.161
Midwest	0.83	0.53, 1.30	0.408	0.98	0.69, 1.38	0.888
South	1.29	0.83, 2.00	0.248	1.35	0.94, 1.93	0.099

	Rheumatoid arthritis			Autoimmune disease[a]		
	IRR	**95% CI**	***P* value**	**IRR**	**95% CI**	***P* value**
West	1.00	reference)		1.00	(reference)	

Abbreviations: IRR, incidence rate ratio; CI, confidence interval.

[a] Includes rheumatoid arthiritis, Graves' disease, systemic lupus erythematosus, Hashimoto's disease, Sjoren syndrome, celiac disease, systemic sclerosis, multiple sclerosis.

[b] In persons without an infection-related visit.

[c] Hospital stay without infection or transfusion.

TABLE 4

Adjusted Incidence Rate Ratios of Rheumatoid Arthritis and Autoimmune Disease in Female Medicare Beneficiaries, Health and Retirement Study, 1991–2007

	Rheumatoid arthritis			Autoimmune disease[a]		
	IRR[b]	95% CI	*P* value	IRR[b]	95% CI	*P* value
Number of infection-related visits	1.03	1.02, 1.04	<0.001	1.03	1.02, 1.04	<0.001
Number of transfusion-related visits[c]	1.44	1.15, 1.82	0.002	1.43	1.18, 1.74	<0.001
Number of other hospital stays[d]	1.03	0.91, 1.15	0.663	1.03	0.94, 1.13	0.535
Number of children	1.01	0.96, 1.06	0.734	0.98	0.93, 1.03	0.382
Age (years)	0.98	0.96, 1.00	0.039	0.97	0.95, 0.99	0.001
Body mass index (kg/m^2)	1.02	1.00, 1.05	0.101	1.01	0.99, 1.03	0.289
Jewish religion	2.00	1.16, 3.45	0.014	1.85	1.19, 2.88	0.007

Abbreviations: IRR, incidence rate ratio; CI, confidence interval.

[a] Includes rheumatoid arthritis, Graves' disease, systemic lupus erythematosus, Hashimoto's disease, Sjoren syndrome, celiac disease, systemic sclerosis, multiple sclerosis.

[b] Adjusted for race, ethnicity, smoking, region of residence, and history of end-stage renal disease, heart disease, stroke, diabetes mellitus and cancer.

[c] In persons without an infection-related visit.

[d] Hospital stay without infection or transfusion.