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SHORT ANALYTICAL REVIEW

Epidemiology and Estimated Population Burden of Selected Autoimmune Diseases in the United States

Denise L. Jacobson,* Stephen J. Gange,* Noel R. Rose,† and Neil M. H. Graham*

*Department of Epidemiology and †Department of Molecular Microbiology and Immunology, The Johns Hopkins University, School of Hygiene and Public Health, Baltimore, Maryland 21205

Autoimmune diseases cause significant and chronic morbidity and disability. The actual number of persons in the United States that are affected by autoimmune diseases and the resultant magnitude of their impact on the public's health are limited to a few specific diseases. In order to understand the clinical, public health and economic importance of these diseases it is necessary to have estimates of incidence and prevalence rates in the population. In this analysis, we estimate the number of persons affected by 24 autoimmune diseases in the United States by applying mean weighted prevalence and incidence rates obtained from published articles to U.S. Census data. The study was restricted to 24 autoimmune predefined diseases for which there was direct or indirect evidence for autoimmune pathogenesis. Subsequently, we used computerized search software and ancestry searching (bibliographies) to conduct a comprehensive search of articles published from 1965 to the present. Eligible studies included those which adhered to standard disease definitions and which included population-based estimates of incidence or prevalence rates. Mean weighted incidence and prevalence rates were calculated from eligible published studies with greater weight proportionately given to larger studies. The mean rates were then applied to the U.S. Census population figures to estimate the number of persons currently afflicted with each disease and the number of new cases occurring each year in the United States. Only U.S. and European studies were used to estimate prevalence and incidence rates when there were at least six eligible studies available for a disease. When there were fewer than six studies, all available studies were included, regardless of country of origin. The number of eligible incidence and prevalence studies found in the literature varied considerably between the 24 autoimmune diseases selected. The largest number of eligible prevalence studies were conducted on multiple sclerosis (MS), rheumatoid arthritis, and systemic lupus erythematosus (SLE) (≥23), followed by insulin-dependent diabetes (IDDM), myasthenia gravis, primary biliary cirrhosis, and scleroderma (≥7). There were only one to four eligible studies done on 11 other diseases, and no prevalence studies on 6 diseases. Incidence studies were less frequent but the largest number of studies were conducted on IDDM (*n* = 37) and MS (*n* = 28), followed by Graves' disease/hyperthyroidism, glomerulonephritis, primary biliary cirrhosis, rheumatic fever, rheumatoid arthritis, scleroderma, and SLE (≥9). On the other 11 diseases, there were one to six eligible studies, and no studies on 5 diseases. There were no eligible incidence or prevalence studies on Goodpasture's syndrome, idiopathic thrombocytopenia purpura, or relapsing polychondritis. Overall we estimate that 8,511,845 persons in the United States or approximately 1 in 31 Americans are currently afflicted with one of these autoimmune diseases. The diseases with the highest prevalence rates were Graves'/hyperthyroidism, IDDM, pernicious anemia, rheumatoid arthritis, thyroiditis, and vitiligo, comprising an estimated 7,939,280 people or 93% of the total number estimated. Glomerulonephritis, MS, and SLE added an estimated 323,232 people. The prevalence of the other diseases reviewed were rare, less than 5.14/100,000. Most diseases were more common in women. From the incidence data we estimate that 237,203 Americans will develop an autoimmune disease in 1996 and that approximately 1,186,015 new cases of these autoimmune diseases occur in the United States every 5 years. Women were at 2.7 times greater risk than men to acquire an autoimmune disease. After reviewing the medical literature for incidence and prevalence rates of 24 autoimmune diseases, we conclude that many autoimmune diseases are infrequently studied by epidemiologists. As a result the total burden of disease may be an underestimate. The number of studies performed on a disease has not necessarily been related to the public health burden of the conditions reviewed. Individual autoimmune diseases have often been studied as separate entities; however, many share common mechanisms of induction and pathogenesis. Thus, considered as a group of disorders autoimmune diseases are an important cause of morbidity and affect a large number of Americans. Further epidemiologic research is ur-

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gently needed to improve our understanding of the prevalence and incidence of autoimmune disorders, their medical and public health impact, and the cost to the U.S. health system, especially in terms of health service delivery and diagnosis.

INTRODUCTION

Autoimmune diseases are often associated with severe and chronic morbidity (e.g., rheumatoid arthritis, systemic lupus erythematosus, and rheumatic fever) as well as being an important cause of mortality (e.g., scleroderma and myocarditis). Since many diseases occur among young and middle-aged adults, they also are significant contributors to productive years lost in this part of the population. Population-based epidemiologic research on autoimmune diseases has focused on multiple sclerosis, rheumatoid arthritis, and insulin-dependent diabetes, while most other autoimmune diseases appear to have received little or no attention from epidemiologists on a population level. In particular, the prevalence and incidence of autoimmune diseases remains poorly understood, and their collective importance as a public health problem remains largely unknown. For some of the most common diseases, prevalence and incidence rates are readily available (1, 2). However, most of the epidemiologic data available on apparently less common diseases have been obtained from hospital- or clinic-based case series studies. Valid incidence and prevalence rates cannot be estimated from these case series unless all cases are identified within a defined period of time and the population at risk can be accurately enumerated. As a result, there is an urgent need to estimate the number of individuals currently with at least one autoimmune disease in the United States (e.g., prevalent cases) and the number of new cases (incident) per year to determine both the public health impact of these disorders and the significant gaps in our knowledge of the epidemiology of these conditions.

Autoimmune diseases have usually been studied as separate entities, each disease individually, rather than as a group of disorders. From a public health, biologic, and health services standpoint, it is important to consider the prevalence and incidence of these disorders as a group. There is evidence that these diseases cluster so that multiple cases appear in one family; sometimes more than one autoimmune disease occurs in the same patient. Moreover, mechanisms of induction and pathogenesis and methods of treatment may be shared by many autoimmune diseases (3), such as in cancer.

Since the autoimmune etiology of many disorders is in dispute or poorly characterized, we decided to focus on a group of disorders which are generally agreed to fit within accepted definitions of autoimmune disorders. In our attempt to estimate the burden of autoimmune diseases in the United States, we selected 24 diseases which adhere to the criteria of Rose and Bona (4), which are "direct" proof by transfer of antibody to an individual which can reproduce disease or "indirect" evidence by inducing disease in an animal or genetically determined model. Using this list we conducted a comprehensive search of the medical literature since 1965. Data from studies fulfilling our disease definition and study design criteria were used to compute weighted mean incidence and prevalence rates on each disease. We applied these rates to the 1996 population projections from the U.S. Census Bureau (5, 6) to estimate the number of persons currently affected with an autoimmune disease and the number who will develop an autoimmune disease in 1996.

METHODS

Criteria for an Autoimmune Disease

Twenty-four autoimmune diseases were selected for study. Twenty-one were selected using the criteria of Rose and Bona (4), which define an autoimmune disease according to the existence of direct proof or indirect evidence of autoimmune pathogenesis. Direct proof of autoimmune etiology was defined by disease reproducibility through direct transfer of autoantibody or autoantigen-specific T cells to animals or into *in vitro* systems. Indirect evidence of autoimmune etiology was defined by disease reproducibility in animals through experimental immunization with the implicated autoantigen or through cell transfer from animals with genetically determined models of disease. Further, Rose and Bona accepted indirect proof of autoimmunity under conditions where autoantibodies have been isolated or self-reactive T cells can be identified from the major target tissues of those affected with the disease (4). While azoospermia was included on the list of Rose and Bona, we did not include it because studies designed to detect the prevalence of anti-sperm or antitesticular antibodies (which defines azoospermia) in the general population have not been performed. Furthermore, detection of cases of azoospermia is most likely to occur in an infertility clinic, which would be unrepresentative of all cases of azoospermia. Because of their importance and the availability of data, we added three diseases to the list of Rose and Bona: chronic active hepatitis, glomerulonephritis, and rheumatic fever. Addition of these diseases is based on strong circumstantial evidence of an autoimmune etiology together with acceptable epidemiological studies. We have not included Reiter's syndrome because the pathology may be due to a direct effect of infection at the site of the disease rather than an autoimmune pro-

TABLE 1

Autoimmune Disease Definitions Employed for Study Inclusion

Autoimmune disease	Citations	Definition employed
Addison's disease	8, 9	Addison's disease (non-tuberculosis related, non-iatrogenic)
Autoimmune hemolytic anemia	10	Blood test for warm and cold antibodies
Chronic active hepatitis	11, 12	Liver disease, serum LKMI antibody, exclusion of other types of liver disease
Glomerulonephritis	13–21	Immununofluorescence and microscopy of renal biopsy
Goodpasture's syndrome	—	No articles
Graves' disease/hyperthyroidism	22–36	Graves' type thyrotoxicosis with appropriate thyroid function tests, or hyperthyroidism
Idiopathic thrombocytopenia purpura	—	No articles
Insulin dependent diabetes	37–80	Diabetes diagnosis based on insulin dependence
Multiple sclerosis	81–164	Definite or probable multiple sclerosis by clinical criteria
Myasthenia gravis	165–174	Osserman's criteria, or muscle weakness and response to anticholinesterase drug
Myocarditis	175–179	Dallas criteria or autopsy diagnosis
Pemphigus vulgaris	180–183	Direct or indirect immunofluorescence assays or by histology
Pernicious anemia	184	Schilling test positive
Relapsing polychondritis	—	No articles
Polymyositis/dermatomyositis	165, 185–189	Bohan and Peter criteria or equivalent
Primary biliary cirrhosis	190–198	Anti-mitochondrial antibody or liver biopsy
Rheumatic fever and Rheumatic heart disease	19, 199–219	Jones or modified Jones criteria, initial and recurrent attacks included. Chest radiographs for Rheumatic heart disease
Rheumatoid arthritis	220–263	Definite or classical disease determined by ARA,[a] Rome, New York, Bennett and Wood, CIDMS
Scleroderma	185, 264–277	ARA[a] or equivalent criteria for definite disease
Sjogren's	278, 279	Copenhagen or equivalent criteria
Systemic lupus erythematosus	185, 220, 222, 235, 270, 280–303	ARA[a] or equivalent criteria for definite disease
Thyroiditis	24–27, 31, 34, 304	Thyroiditis with appropriate thyroid function tests or hypothyroidism
Uveitis	305–308	Opthamological examination for anterior, posterior, or generalized uveitis
Vitiligo	309–313	Clinical diagnosis

[a] ARA, American Rheumatological Association.

cess following infection (7). Studies conducted solely among children who have Graves' disease/hyperthyroidism, thyroiditis/hypothyroidism, or myocarditis were mentioned separately from those conducted among adults. The number of children affected by a particular disease was added to the total population burden in addition when the adult rate was based on ages greater than the childhood age group (e.g., thyroiditis/hypothyroidism).

Disease Definitions

The specific disease definitions which were utilized to select articles for inclusion into this analysis are listed in Table 1 (8–311). For epidemiologic purposes it is, of course, ideal to have standardized disease definitions in order to compare incidence and prevalence rates across different studies and populations. Where standardized definitions existed and were widely used, these criteria were utilized as inclusion criteria for the following diseases: multiple sclerosis, rheumatic fever, rheumatoid arthritis, scleroderma, and systemic lupus erythematosus (SLE). Within some of these standardized criteria there are gradations of certainty for disease diagnosis. For example, rheumatoid arthritis may be classified as definite, probable, or possible based on the number of clinical characteristics that satisfy the American Rheumatological Association diagnostic criteria. On the diseases where this applies, the level of certainty accepted is specified in Table 1. Otherwise, the diagnosis was assumed to be definite.

The majority of diseases included in our analysis do not have well-standardized published criteria. We have selected criteria for each disease which utilize clinical judgment and appropriate laboratory analyses that best define each disease.

Literature Search

Medline was thoroughly searched for articles between 1965 and 1995 in order to obtain all articles for infrequently studied diseases. All articles within a disease with a key word or subject of epidemiology, prevalence, incidence, disease susceptibility, or risk

factors were reviewed. This combination of words appeared to maximize selection of articles. Articles cited in the bibliography of the articles reviewed were also evaluated for inclusion (ancestry searching). Citations from the book entitled "Epidemiology of Rheumatic Disease" (2) were largely included. Every attempt was made for this list of articles to be inclusive. In some cases an article or book was not accessible. Articles in languages other than English were selected when they were cited in a bibliography and when they were available in a U.S. library.

A thorough search of the literature was performed for rheumatic fever and rheumatic heart disease. Almost all of the studies on rheumatic heart disease were done in developing countries, and many of the studies on rheumatic fever from the United States were performed in populations that were not representative of the U.S. population. Thus, a rate from the Centers for Disease Control 1994 was utilized for rheumatic fever (312). Rheumatic heart disease rates were not estimated because the rates would be derived from studies that are not relevant to the epidemiology of the disease in the United States.

Inclusion/Exclusion Criteria

Most studies that were reviewed and evaluated were selected for inclusion into our analysis. Articles were excluded when there was no incidence or prevalence rate given (e.g., a case series without a population denominator) or where rates could not be calculated from the data available in the article. In order to maintain consistency, however, studies which did not explicitly meet the criteria defined in Table 1 were excluded, as were studies which did not clearly state their disease definition. Papers were also excluded when the authors did not clearly differentiate between definite, probable, or possible cases of disease, as in the case multiple sclerosis and rheumatoid arthritis. In general, inclusion criteria were designed to be conservative such that any bias inadvertently introduced into prevalence and incidence estimates would lead to underestimation of disease rates.

In addition, when prevalence or incidence rates were stratified by demographic subgroup but no overall rate was given, the lowest rate quoted was used. The most recent incidence or prevalence was quoted when rates were presented consecutively over several years of follow-up and no summary rate was given.

Technique for Estimating Pooled (Weighted Mean) Rates

Weighted mean incidence and prevalence rates were calculated for each disease. When there were at least six eligible studies on a specific autoimmune disease, only rates from the United States, Canada, and Europe were pooled to maintain the maximum concurrence in socioeconomic status and ethnicity. When there were fewer than six eligible studies, all available studies, including those from regions other than North America and Europe, were also included in order to calculate the pooled rates. Studies from "other" countries were included so that within the limitations of the available studies, all estimates of disease rates remained based on the largest possible pool of data. The diseases on which the pooled prevalence rate was not solely based on U.S./Canadian or European studies were polymyositis, Sjogren's, thyroiditis/hypothyroidism, uveitis, and vitiligo. For pooled incidence rates, the diseases which were not solely based on U.S./Canadian or European studies were streptococcal glomerulonephritis, myocarditis, myocarditis children, and pemphigus.

The incidence or prevalence rate from each study within a disease category contributed proportionately to the mean incidence or prevalence rate based on the population size of that study. The proportion or weight was determined by dividing the study population denominator by the total of all the study population denominators for each disease. Only studies with a population denominator available were included in the calculation. This weighted method was used on the assumption that larger studies have more precise estimates of rates than smaller studies. Most autoimmune diseases are more prevalent among women. Thus, we estimated the ratio of males to females affected by using a weighted average of the ratios reported in the studies, where the weights were again proportional to the prevalence denominator population. The ratios reported were from prevalent or incident cases depending upon which was reported in each article.

The total population affected by each of the 24 autoimmune diseases was estimated using the May 1996 population projection by the U.S. Census Bureau (5, 6). Different age categories from the Census were applied to different diseases. The age category most frequently cited across studies was utilized. For example, insulin-dependent diabetes (IDDM) is mostly studied in people less than 20 years old, with some variation in the individuals included in the denominator. To estimate the number of persons currently afflicted with IDDM, the average prevalence rate was multiplied by the number of persons less than 20 years old in May 1996. To arrive at the number of men and women affected, the average percentage of men and women afflicted computed above was multiplied by the total number of persons currently afflicted by the disease.

When estimates for individual autoimmune diseases were calculated, differences in trends over time, by ethnic group, and by latitude were not always available or were poorly documented. In some populations, specific ethnic groups (e.g., American Indians) may have a genetic susceptibility that confers higher rates than in

the general U.S. population. However, studies performed exclusively on minority ethnic groups were usually small and contributed less weight to the overall calculation. There are some drawbacks to combining rates across populations even within one country. As medical care evolves, diseases such as rheumatic fever become less prevalent, while rates of other diseases, such as primary biliary cirrhosis, may appear to increase due to improved diagnostic techniques. Given the limitations of the available data and in order to simplify data presentation, these factors were assumed to be consistent in the overall pooled rates (with the exception of the rheumatic fever, which was from the 1994 CDC U.S. surveillance rate).

Presentation of Prevalence Data

Disease rates for diseases with the largest number of prevalence studies were plotted by the year of publication to examine trends over time. All rates are estimated per 100,000 population.

RESULTS

The number of population-based prevalence (Table 2) and incidence (Table 3) studies found by Medline and by ancestry searching from bibliographies are displayed by three areas of the world: the United States/Canada (United States/Canada), Europe, and other countries ("other"). The references for each disease are listed in Table 1.

Number of Prevalence Studies

The highest number of prevalence studies (Table 2) conducted throughout the world were for multiple sclerosis (MS) ($n = 80$), rheumatoid arthritis ($n = 38$), and SLE ($n = 23$). There were 49 eligible studies from Europe on MS, 16 studies on MS from the United States/Canada, and 15 from "other" countries (Table 2). The United States/Canada and Europe each conducted 11 eligible studies on rheumatoid arthritis, while 16 studies were done in "other" regions. SLE was studied with almost equal frequency in all three regions.

A moderate number of eligible prevalence studies were performed on insulin-dependent diabetes ($n = 15$), myasthenia gravis ($n = 9$), primary biliary cirrhosis ($n = 7$), and scleroderma ($n = 9$). Seven of the prevalence studies identified were conducted in Europe and eight in "other" regions on IDDM, while none were initiated in the United States/Canada. All of the prevalence studies on myasthenia gravis and primary biliary cirrhosis were conducted in Europe with the exception of one study on myasthenia gravis from "other" areas. An equal number of prevalence studies were done in the United States/Canada and Europe on scleroderma ($n = 4$), while only one was done in "other" regions.

TABLE 2

Number of Population-Based Prevalence Studies for 24 Autoimmune Diseases Published from 1965 to 1995[a]

Autoimmune Disease	Europe	North America (U.S., Canada)	Other
Addison's	2	0	0
Autoimmune hemolytic anemia	0	0	0
Chronic active hepatitis	1	0	0
Glomerulonephritis			
Primary	1	0	0
IgA	1	0	0
Poststreptococcal	0	0	0
Goodpasture's syndrome	0	0	0
Grave's/hyperthyroidism			
All ages	1	0	0
Children	1	1	0
Idiopathic thrombocytopenia purpura	0	0	0
Insulin-dependent diabetes	7	0	8
Multiple sclerosis	49	16	15
Myasthenia gravis	8	0	1
Myocarditis	0	0	0
Pemphigus	0	0	0
Pernicious anemia	1	0	0
Polymyositis/dermatomyositis	0	1	1
Primary biliary cirrhosis	7	0	0
Relapsing polychondritis	0	0	0
Rheumatic heart disease	0	7	1
Rheumatoid arthritis	11	11	16
Scleroderma	4	4	1
Sjogren's	0	0	2
Systemic lupus erythematosus	8	8	7
Thyroiditis/hypothyroidism			
All ages	1	0	0
Children	1	1	1
Uveitis	1	0	1
Vitiligo	1	0	2

[a] Criteria (Table 1): studies with a male, female, and/or population prevalence rate.

Among the 24 diseases examined, only 8 had at least seven eligible prevalence studies done. There were no eligible prevalence papers on Goodpasture's syndrome, idiopathic thrombocytopenia purpura, or relapsing polychondritis, nor autoimmune hemolytic anemia, myocarditis, or pemphigus. For the other 11 diseases, between one and four prevalence studies were found in the literature on each disease.

Number of Incidence Studies

The highest number of eligible incidence studies (Table 3) were carried out on IDDM ($n = 37$) and MS ($n = 28$), the vast majority of which were from Europe for both diseases, 21 and 20, respectively (Table 3). The remaining incidence studies of MS and IDDM were about equally divided between the United States/Can-

TABLE 3

Number of Population-Based Incidence Studies for 24 Autoimmune Diseases Published from 1965 to 1995[a]

Autoimmune disease	Europe	North America (U.S., Canada)	Other
Addison's disease	1	0	0
Autoimmune hemolytic anemia	1	0	0
Chronic active hepatitis	2	0	0
Glomerulonephritis			
Primary	3	0	0
IgA	5	0	0
Poststreptococcal	1	0	4
Goodpasture's syndrome	0	0	0
Grave's/hyperthyroidism			
All ages	7	2	2
Children	0	0	0
Idiopathic thrombocytopenia purpura	0	0	0
Insulin-dependent diabetes	21	8	8
Multiple sclerosis	20	5	3
Myasthenia gravis	5	0	1
Myocarditis			
All ages	1	2	1
Children	0	0	1
Pemphigus	1	1	2
Pernicious anemia	1	0	0
Polymyositis	0	4	1
Primary biliary cirrhosis	9	0	0
Relapsing polychondritis	0	0	0
Rheumatic fever	2	10	5
Rheumatoid arthritis	4	7	2
Scleroderma	2	5	3
Sjogren's	0	0	0
Systemic lupus erythematosus	7	8	3
Thyroiditis/hypothyroidism			
All ages	2	1	0
Children	0	0	0
Uveitis	3	0	1
Vitiligo	0	0	0

[a] Criteria (Table 1): studies with a male, female, and/or population incidence rate.

ada and the "other" regions. Graves' disease/hyperthyroidism (n = 11), glomerulonephritis (n = 13), rheumatic fever (n = 17), rheumatoid arthritis (n = 13), scleroderma (n = 10), and SLE (n = 18) were the next most frequently studied autoimmune disorders that provided population-based incidence rates. Glomerulonephritis, Graves' disease/hyperthyroidism, and primary biliary cirrhosis were more frequently studied in Europe than the United States. Two studies on Graves' disease/hyperthyroidism were done in both the United States/Canada and "other", and four studies on poststreptococcal glomerulonephritis were done outside of North America and Europe. Although more studies on rheumatic fever, rheumatoid arthritis, scleroderma, and SLE were initiated in the United States/Canada, incidence data were also available from several other countries. We found no studies with appropriate population-based incidence data on Goodpasture's, ITP, or relapsing polychondritis, nor Sjogren's or vitiligo. For the other 11 diseases reviewed there were between one and six eligible studies on each of the reviewed diseases.

Prevalence of Autoimmune Diseases

Using the prevalence data from the 24 reviewed diseases, we estimated the weighted mean prevalence and the number of affected people in the United States for each disease, for men and women separately, and for all 24 autoimmune disorders taken together for which there were rates (Table 4). The autoimmune diseases which are the most prevalent include Graves' disease/hyperthyroidism (1151.5/100,000), IDDM (192/100,000), pernicious anemia (150.9/100,000), rheumatoid arthritis (860/100,000), thyroiditis/hypothyroidism (791.6/100,000), and vitiligo (400.2/100,000) (Table 4). Together, these diseases currently (1996) affect an estimated 7,939,280 persons or 93% of the total number of Americans with one of these autoimmune diseases. Primary glomerulonephritis (40/100,000), multiple sclerosis (58.3/100,000), SLE (23.8/100,000), and Sjogren's (14.4/100,000) were less prevalent diseases. However, based on the 1996 population we estimate that these conditions affect 361,340 people. Each of the other diseases, including Addison's, chronic active hepatitis, myasthenia gravis, polymyositis, primary biliary cirrhosis, scleroderma, and uveitis, have prevalence rates of less than 5.2/100,000. The majority of the autoimmune diseases studied are more prevalent in women than men. IDDM, uveitis, and vitiligo appear to be fairly evenly distributed between men and women. Nonetheless, the rates for other conditions are relatively conservative, and conditions for which there are no data were excluded and did not contribute to the final estimate. Based on these data, we estimated 6,722,573 women and 1,789,273 men with autoimmune diseases in the United States. Overall 8,511,845 or 1 in 31 Americans would be currently affected by an autoimmune disease. This number does not take into account the comorbidity of autoimmune diseases which would lower the total number affected by at least one of these autoimmune diseases.

Incidence of Autoimmune Diseases

Based on eligible studies with population-based estimates of autoimmune disease incidence, we estimated that in 1996 approximately 237,203 Americans will develop an autoimmune disease (Table 5). Women would be at greater risk, in that there will be 2.7 times more women (172,695) than men (64,506) who will develop an autoimmune disease. The diseases with the highest

TABLE 4

Estimated Number of Persons with an Autoimmune Disease in the United States in 1996

Autoimmune disease	Age category	Population in category	Number of studies	Weighted mean prev. rate/100,000	Percentage female[b]	Number of persons with disease		
						Men	Women	Total
Addison's	All	264,755,000	2	5.0	92.5	1000	12,335	13,335
Autoimmune hemolytic anemia	<5	19,454,000	0	—	—	—	—	—
Chronic active hepatitis	All	264,755,000	1	0.4	88.3	136	1,020	1,156
Glomerulonephritis								
Primary[a]	All	264,755,000	1	40.0	31.5	72,494	33,408	105,902
IgA	All	264,755,000	1	23.2	66.7	20,474	40,949	61,423
Strep	<16	62,658,000	0	—	—	—	—	—
Goodpasture's	—	—	—	—	—	—	—	—
Graves'/hyperthyroidism								
All[a]	All	264,755,000	1	1151.5	87.9	370,187	2,678,449	3,048,636
Children	10–19	38,557,000	2	106.9	66.6	13,767	27,439	41,205
Idiopathic thrombocytopenia purpura	—	—	—	—	—	—	—	—
Insulin-dependent diabetes	<20	76,494,000	5	192.0	47.9	76,572	70,320	146,892
Multiple sclerosis	All	264,755,000	64	58.3	64.2	55,156	99,122	154,278
Myasthenia gravis	All	264,755,000	8	5.1	72.7	3,709	9,880	13,589
Myocarditis	All	2,268,553	—	—	—	—	—	—
Pemphigus	>19	188,261,000	0	—	—	—	—	—
Pernicious anemia	All	264,755,000	1	150.9	66.7	133,152	266,303	399,455
Polymyositis/dermatomyositis	All	264,755,000	2	5.1	66.7	4,480	8,983	13,462
Primary biliary cirrhosis	All	264,755,000	7	3.5	88.7	1,043	8,189	9,232
Relapsing polychondritis	—	—	—	—	—	—	—	—
Rheumatic heart disease	<16	62,658,000	0	—	—	—	—	—
Rheumatoid arthritis	>16	202,939,000	21	860.0	74.8	438,120	1,297,978	1,736,099
Schleroderma	>16	202,939,000	6	4.4	92.2	695	8,227	8,922
Sjogren's	All	264,755,000	2	14.4	93.7	2,382	35,726	38,108
Systemic lupus erythematosus	All	264,755,000	16	23.8	88.2	7,467	55,585	63,052
Thyroiditis/Hypothyroidism								
Adult	>19	188,557,000	1	791.65	94.6	79,817	1,410,554	1,490,371
Children	10–19	38,557,000	3	532.1	82.7	35,472	169,687	205,159
Uveitis	All	264,755,000	2	1.7	50.0	2,319	2,319	4,637
Vitiligo	All	264,755,000	2	400.2	52.3	505,072	554,488	1,059,560
Total[a]						1,789,273	6,722,573	8,511,845

[a] Totals may vary due to rounding. Totals include primary glomerulonephritis only and all ages only for Graves'/hyperthyroidism.
[b] The percentage female is derived from new or existing cases, depending on what was reported.

incidence rates from reviewed studies are rheumatoid arthritis (23.7/100,000), thyroiditis/hypothyroidism (21.8/100,000), and uveitis (18.9/100,000), followed by Graves' disease/hyperthyroidism (13.9/100,000) and IDDM (12.2/100,000). These diseases together represent 185,412 people or 78% of the total number of people estimated to develop disease in 1996. Using this same approach, we estimate that approximately 42,137 new cases of primary glomerulonephritis (3.6/100,000), multiple sclerosis (3.2/100,000), polymyositis/dermatomyositis (1.8/100,000), and SLE (7.3/100,000) would occur in 1996. Among the other six diseases reviewed where an incidence study had been performed, the rates were all less than 1.0/100,000, affecting 7,159 people. In addition, the number of people with myocarditis, which was found at autopsy, would contribute 2,495 additional people. This number was determined from the rate times the number of deaths in 1993. Based on these data, we estimate that every 5 years 1,186,015 new cases of autoimmune disease occur in the United States, assuming incidence rates remain constant.

Trends over Time

For the six autoimmune diseases which had the largest number of prevalence estimates available (MS, myasthenia gravis, primary biliary cirrhosis, rheumatoid arthritis, scleroderma, and SLE), we investigated the trend of prevalence values over time. Figure 1 displays the prevalence for each study plotted against the year of publication, which was chosen because of the difficulty in precisely defining the prevalence period for each study. The points indicate those studies based on less than 100,000 individuals (+), 100,000 to 1,000,000 (○), and more than 1,000,000 individuals (●). The

TABLE 5

Estimated Number of Persons Who Will Develop an Autoimmune Disease in the United States in 1996

Autoimmune Disease	Age category	Population in category	Number of studies	Weighted mean incidence rate/100,000	Percentage female[b]	Number of persons with disease		
						Men	Women	Total
Addison's	All	264,755,000	0	—	—	—	—	—
Autoimmune hemolytic anemia	<5	19,454,000	0	—	—	—	—	—
Chronic active hepatitis	All	264,755,000	1	0.7	88.3	218	1,636	1,853
Glomerulonephritis								
Primary[a]	All	264,755,000	3	3.6	31.5	6,481	2,986	9,467
IgA	All	264,755,000	5	2.4	66.7	2,159	4,318	6,476
Strep	<16	62,658,000	5	7.7	41.4	2,840	2,006	4,846
Goodpasture's	—	—	—	—	—	—	—	—
Graves'/hyperthyroidism								
All[a]	All	264,755,000	7	13.9	87.9	4,477	32,394	36,871
Children	10–19	38,557,000	0	—	—	—	—	—
Idiopathic thrombocytopenia purpura	—	—	—	—	—	—	—	—
Insulin-dependent diabetes	<20	76,494,000	20	12.2	47.9	4,880	4,482	9,363
Multiple sclerosis	All	264,755,000	16	3.2	64.2	3,044	5,471	8,515
Myasthenia gravis	All	264,755,000	2	0.4	72.7	277	737	1,014
Myocarditis[c]								
All[a]	All	2,268,553	4	0.1	44.5	1,278	1,217	2,495
Children	<15	49,190	1	4.1	43.5	1,154	862	2,017
Pemphigus	>19	188,261,000	62	0.1	51.5	114	121	235
Pernicious anemia	All	264,755,000	0	—	—	—	—	—
Polymyositis/dermatomyositis	All	264,755,000	3	1.8	66.7	1,625	3,258	4,883
Primary biliary cirrhosis	All	264,755,000	2	0.9	88.7	270	2,120	2,390
Relapsing polychondritis	—	—	—	—	—	—	—	—
Rheumatic fever[d]	<16	62,658,000	1	0.1	48.0	58	54	112
Rheumatoid arthritis	>16	202,939,000	6	23.7	74.8	12,135	35,952	48,088
Scleroderma	>16	202,939,000	3	0.8	92.2	121	1,433	1,555
Sjogren's	All	264,755,000	0	—	—	—	—	—
Systemic lupus erythematosus	All	264,755,000	10	7.3	88.2	2,282	16,989	19,272
Thyroiditis/hypothyroidism								
All	>19	188,557,000	2	21.8	94.6	2,195	38,794	40,989
Children	10–19	38,557,000	0	—			—	—
Uveitis	All	264,755,000	3	18.9	50.0	25,051	25,051	50,101
Vitiligo	All	264,755,000	0	—	—	—	—	—
Total[a]						64,506	172,695	237,203

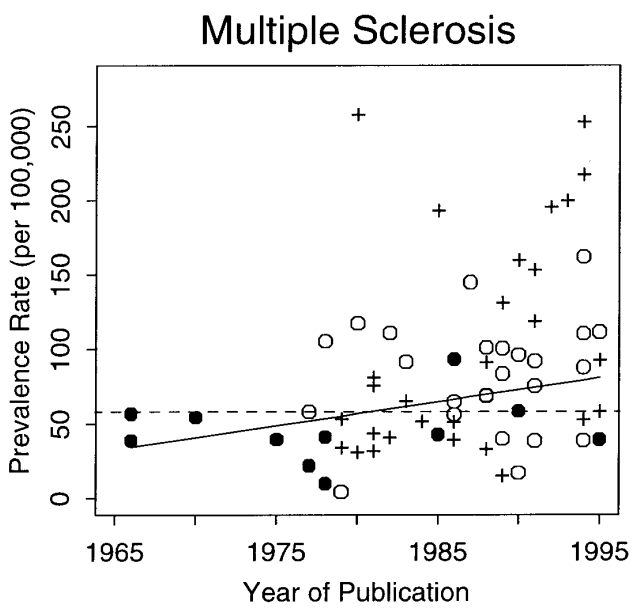
[a] Totals may vary due to rounding. Totals include primary glomerulonephritis only and all ages only for Graves'/hyperthyroidism and myocarditis.
[b] The percentage female is derived from new or existing cases, depending on what was reported.
[c] Population burden for myocarditis is calculated from total number of deaths times rate per 100.
[d] Based on 1994 CDC rate; male female ratio based on previous studies.

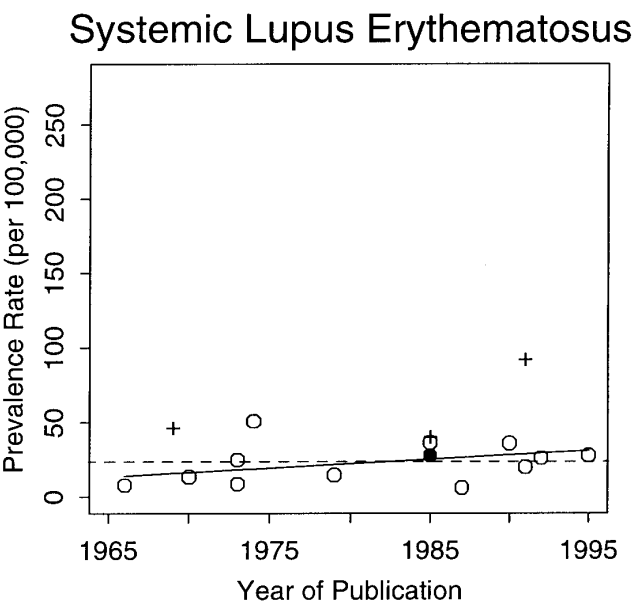
dashed lines indicated the weighted average prevalence estimates, and the solid line indicates a least-squares regression line calculated with points weighted by the study population size. The trends over time were virtually flat for rheumatoid arthritis and SLE and increasing in various magnitudes for the other four diseases, with the most evident increases in MS and primary biliary cirrhosis. The weighted mean rate for scleroderma is lower than that in several of the prevalence studies shown. This is because the study with the lowest rate had the highest population number, which added more weight to the mean estimate.

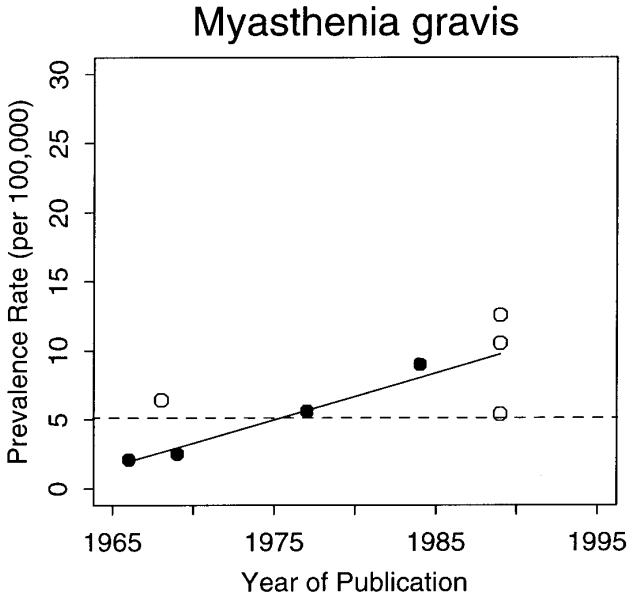
DISCUSSION

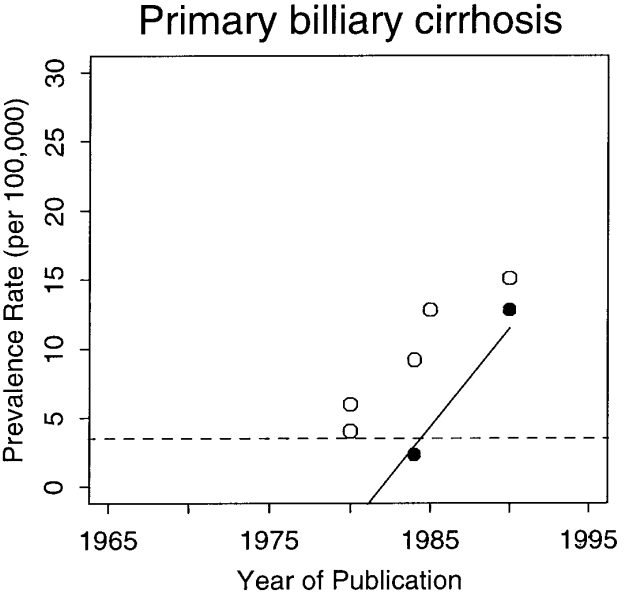
We have conducted a database and bibliography search for articles on the incidence and prevalence

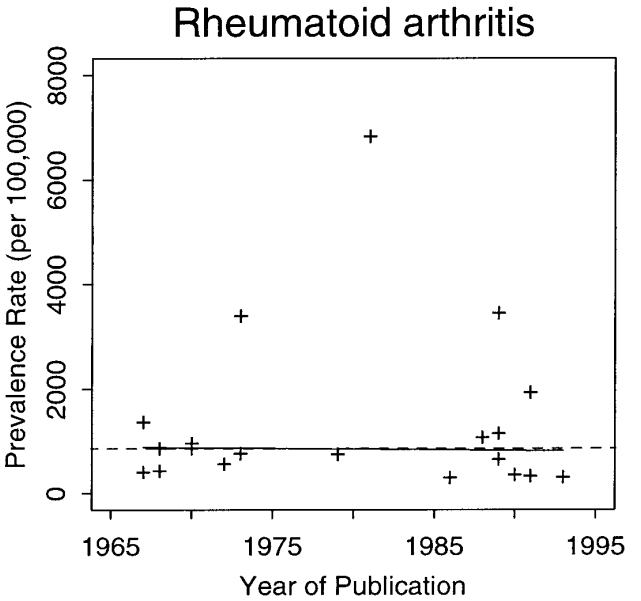
FIG. 1. Prevalence rates of six autoimmune diseases by year of publication. The population size is indicated by the symbols: +, <100,000; ○, 100,000–1,000,000; ●, >1,000,000. The prevalence rates are per 100,000 for all diseases.

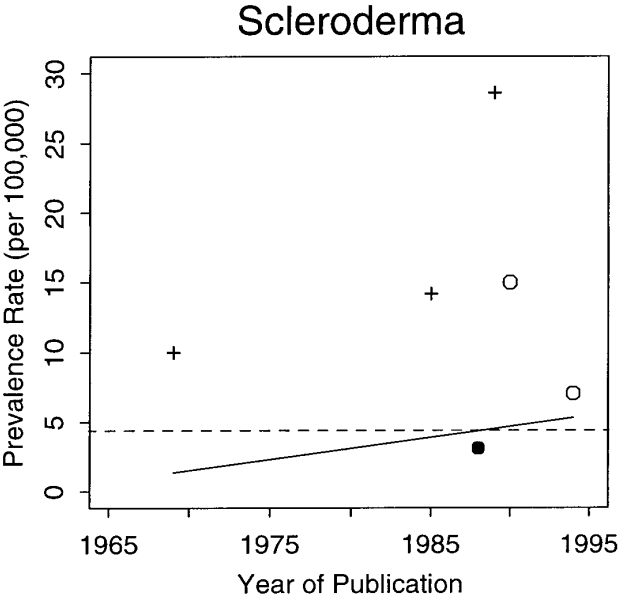

Multiple Sclerosis
Prevalence Rate (per 100,000)
0
50
100
150
200
250
1965
1975
1985
1995
Year of Publication


Systemic Lupus Erythematosus
Prevalence Rate (per 100,000)
0
50
100
150
200
250
1965
1975
1985
1995
Year of Publication


Myasthenia gravis
Prevalence Rate (per 100,000)
0
5
10
15
20
25
30
1965
1975
1985
1995
Year of Publication


Primary billiary cirrhosis
Prevalence Rate (per 100,000)
0
5
10
15
20
25
30
1965
1975
1985
1995
Year of Publication


Rheumatoid arthritis
Prevalence Rate (per 100,000)
0
2000
4000
6000
8000
1965
1975
1985
1995
Year of Publication


Scleroderma
Prevalence Rate (per 100,000)
0
5
10
15
20
25
30
1965
1975
1985
1995
Year of Publication

rates of 24 autoimmune diseases. The greatest number of prevalence studies which fit into our disease criteria were conducted on three well-known autoimmune diseases, multiple sclerosis, rheumatoid arthritis, and systemic lupus erythematosus. The greatest number of eligible incidence studies were conducted on IDDM and multiple sclerosis. Although these diseases have received the most attention from epidemiologists, only rheumatoid arthritis is among the five autoimmune diseases which contribute the highest number of new cases per year. Approximately 176,049 new cases of autoimmune disease per year are due to rheumatoid arthritis, thyroiditis/hypothyroidism, uveitis, and Graves' disease/hyperthyroidism. Rheumatoid arthritis is also among the four most prevalent autoimmune diseases, including Graves' disease/hyperthyroidism, rheumatoid arthritis, thyroiditis/hypothyroidism, and vitiligo; together they currently affect an estimated 7,539,825 people in the United States.

Several diseases with high incidence and/or prevalence rates are very infrequently studied in proportion to the amount of disease attributed to them. Despite the strikingly high incidence and prevalence rates of both Graves' disease/hyperthyroidism and thyroiditis/hypothyroidism we only found 3 and 4 eligible prevalence studies, respectively, conducted on each of these diseases. Incidence studies of Graves' disease/hyperthyroidism were conducted primarily among Europeans, in 7 of 11 eligible studies, while there were only 3 incidence studies on thyroiditis/hypothyroidism. Several other diseases with moderate or high prevalence rates (pernicious anemia and vitiligo) or high incidence rates (uveitis) were infrequently studied on a population basis. The number of incidence or prevalence studies ranged from 0 to 4 for each disease. For example, the estimated prevalence and incidence rates for glomerulonephritis are close to those for multiple sclerosis, each contributing approximately 9500 and 8500 new cases per year, respectively. Nonetheless, there were approximately 40 times as many eligible prevalence studies and 2 times as many incidence studies conducted on multiple sclerosis as on glomerulonephritis. In contrast, while the prevalence rates are relatively low for myasthenia gravis, primary biliary cirrhosis, and scleroderma (1.9–5.1/100,000), a moderate number of prevalence studies were conducted on each of these diseases, ranging between 7 and 9. In addition to the diseases mentioned previously, there were a moderately large number of incidence studies on scleroderma ($n = 10$), SLE ($n = 18$) and rheumatoid arthritis ($n = 13$). Among the remaining diseases reviewed with low incidence and prevalence rates, Addison's disease of the adrenal, chronic active hepatitis, myocarditis, pemphigus, and polymyositis/dermatomyositis were infrequently the focus of incidence or prevalence studies. Finally, we were unable to locate any eligible epidemiologic studies for idiopathic thrombocytopenia purpura, Goodpasture's syndrome, or autoimmune hemolytic anemia.

In summary, the majority of autoimmune diseases we reviewed were significantly understudied. This is in view of the fact that an estimated 8,511,845 people are currently diagnosed with an autoimmune disease in the United States, an estimate which was derived from the eligible published studies which met our criteria using weighted mean prevalence rates. Given that the population of the United States is 264,755,000, this figure translates into one in 31 Americans who are affected. The yearly incidence rate is also significant in that an estimated 237,203 Americans will develop an autoimmune disease in 1996. Because most autoimmune diseases are chronic diseases of long duration, it is not surprising that the number of persons currently affected is almost 36 times the number of persons that will develop an autoimmune disease each year. It was not possible to correct for age due to the absence of age-specific prevalence rates in the literature. While geographical variations do exist for some autoimmune diseases, such as multiple sclerosis, this was not the focus of this paper.

The estimated trends in prevalence rates over time showed some indication of increasing over time. However, inference that this is due to a true increasing prevalence should be done only after other causes for an increase have been eliminated. For example, increases may be explained by better diagnosis or reporting, by improved study design, and/or because populations at higher risk are studied.

Autoimmune diseases are a challenge to study on a population level due to several factors. These include the fact that many conditions are rare or at least uncommon, and that it is difficult to define and ascertain cases. A large number of the diseases we reviewed are rare. Among the 18 diseases with at least one eligible prevalence study, 11 had prevalence rates of less than 100 per 100,000 population and 7 had prevalence rates of less than 6 per 100,000. This poses specific problems for epidemiologic data collection. Researchers must identify a very large population base in order to find enough cases to achieve valid estimates of prevalence. The ease by which cases will be found may depend on whether the disease requires hospitalization at some point. It is easier to identify hospital admissions for rare diseases than it is to locate cases of rare diseases through private physicians' records or at health clinics in the absence of an active surveillance system and/or mandatory disease reporting. Finding an adequate and accurate enumeration of cases requires collaboration within the community. Obtaining records from physicians and clinics in a very large population is time consuming and may not result in high rates of compliance. This is also true for more prevalent diseases. In

addition to case ascertainment, it is also crucial to identify the population base from which the hospital cases or the private physician/clinic cases arose. In some instances, researchers conducted cases series studies whereby they identified all of the cases within a clinic, but they did not enumerate the population from which these cases arose, nor the period of time during which they were collected. These studies could potentially have been important sources of prevalence or incidence data had there been an appropriate denominator population enumerated. Case ascertainment is a formidable constraint to studying rare and less prevalent autoimmune diseases, and it may be one explanation for the limited amount of data on the majority of these diseases.

Another constraint to doing research on autoimmune diseases is the lack of standardized definitions on most of the diseases we reviewed. With standardized criteria developed through consensus panels, researchers can be more certain that they are accurately identifying cases, and that the cases are correctly categorized according to the level of certainty of the diagnosis. Some studies were excluded from our analysis because the authors did not state the criteria they used to define a case, or they did not indicate the certainty of diagnosis for diseases such as rheumatoid arthritis or multiple sclerosis where the level of certainty is included in the standardized criteria. Standardized definitions also allow researchers to compare incidence and prevalence rates across studies, knowing that the differences in rates are unlikely to be due to a difference in disease criteria. There is clearly a need for more consensus panels to be formed to address these issues.

Many autoimmune diseases are difficult to diagnose because autoantibodies, for example, are often found in normal, healthy individuals. This is the case for thyroiditis and SLE. Under these circumstances, cases may be overdiagnosed or undiagnosed due to lack of a clear "cut point" in serological tests.

Bearing in mind the constraints mentioned that make epidemiologic research on autoimmune diseases a challenge, we discovered that many autoimmune diseases are understudied and that many of the studies we reviewed were incomplete from an epidemiologic perspective. Frequently, the number of cases, the population number, and/or the disease criteria were missing from papers, making it difficult to estimate mean population weighted incidence or prevalence rates. For some diseases there were no incidence or no prevalence rates. As a result, when the overall burden of disease was calculated some diseases had to be excluded from the calculation, giving an underestimate of the true total burden. In addition, the actual burden of disease on the U.S. population must be estimated using rates derived outside North America, which in some cases might not be directly applicable. Twice as many studies were conducted in Europe as in the United States/Canada or in "other" regions.

In our attempt to estimate the mean incidence and prevalence rates for 24 diseases, we selected diseases which are broadly accepted as having an autoimmune origin, and then included papers which fit a strict set of disease criteria. Our estimates might be conservative for a number of reasons. First, we have only selected diseases which are commonly considered to be autoimmune, based on laboratory evidence (4). Other researchers may add to this list of diseases based on different criteria. This would lead to a greater overall estimate of the number of persons affected by an autoimmune disease, compared to our estimate. Second, current rates for some diseases might be higher than the mean rates we have estimated if there is an increasing trend over time in disease rates. We computed mean rates from data collected over a maximum of 30 years. Current rates might be higher due to implementation of improved diagnostic tools over time, allowing for improved detection of cases. If there is an increase in rates over time due to improved diagnostic capabilities, these mean rates would tend to be an underestimate of current rates, and, thus, an underestimate of the number of people affected today. Additionally, if most of the rates that went into the calculation of the mean rate were from studies done in countries without improved diagnostic tools, the mean rates might be underestimates of current U.S. rates as well. Thyroiditis may be an underestimate if one chooses to use histological evidence of lymphoid cell infiltrates in the thyroid as the "gold standard" rather than biochemical or immunological evidence (31). IDDM might also be an underestimate if some persons with Type 1 diabetes have been classified with Type 2 diabetes.

Although we believe our weighted mean rates for the vast majority of conditions *and* for the overall population burden were conservative, there were four instances where our estimates of disease rates might be overestimates of current actual rates. The incidence of rheumatic fever declined in this country until the 1980s when it began to reappear (219). It began to decline presumably through the use of antibiotic treatment for Group A streptococcal infection, improved hygiene, and decreased crowding. Speculation about its reappearance leads to theories of renewed crowding, less compulsive treatment of streptococcal infections, and reemergence of rheumatogenic strains. Most of the recent studies in the United States were conducted in Hawaii. The ethnic mix of the Hawaiian population is different to the mainland United States and it is likely these estimates may slightly overestimate rheumatic fever incidence in the rest of the United States. The rates ranged from 0.2 to 61 per 100,000 from 1973 to 1992. Thus, we decided to use the reported disease rates in 1993 from the Centers for Disease Control to estimate

the current rate. In addition, the rates for poststreptococcal glomerulonephritis might be overestimates because four of five of the studies were from countries outside the United States. However, the rates for streptococcal glomerulonephritis alone were not used to estimate the total burden of disease. The rates for primary glomerulonephritis as a whole were. These studies were primarily from Europe. Seven of eight studies on rheumatic heart disease are from outside the United States and the other is among American Indians. These rates are extremely high, are not likely to be indicative of U.S. rates, and were not included. No substitute rate was given. Finally, there were only two eligible studies on Sjogren's syndrome, one from China and one from Japan. The prevalence rate is high in the Chinese study, 774/100,000, and much lower in Japan, 13.9/100,000. Our estimates of the total burden of autoimmune disease in the United States may also be high because it is not clear how many persons with one autoimmune disorder will develop other disorders. Several studies have shown that 5–8% of persons with insulin-dependent diabetes have clinical hypo/hyperthyroidism (313). Due to a lack of data on the rate of comorbidity, the number of persons in the population affected by one or more conditions is difficult to estimate accurately. Adding rates from each disease separately may overestimate the overall prevalence rate of persons with at least one autoimmune disease. With these caveats in mind, to our knowledge, we have compiled the most comprehensive collection of and analysis of incidence and prevalence rates to date. Our estimates of the number of persons affected by an autoimmune disease in the U.S. population is the most data-driven estimate currently available and did not include contributions from conditions where no eligible data were available. In these circumstances, the overall estimate is likely to be relatively conservative.

This review of the published literature on the epidemiology of autoimmune disease rates has shown that there is a preeminent need for further population-based epidemiologic studies on the majority of these diseases. To begin with if rates are to be determined for the U.S. population, more studies in the United States must be performed, because rates from non-U.S., non European countries might not be applicable to the U.S. population given genetic differences. Second, specialists in autoimmune diseases need to form consensus panels to develop standardized case definitions that can be applied to epidemiologic research. Researchers must be able to identify cases using commonly available clinical and laboratory data. Third, to obtain estimates that are generalizable to the U.S. population, the denominators need to be clearly defined. Random samples of the U.S. population are one method to obtain representative estimates of the rate of autoimmune diseases and verification of physician and hospital records would be necessary to confirm disease diagnoses. If a sample is to include a large geographic area, cooperation between health care providers in the region is crucial to obtain all cases, including hospital cases and community cases. This can be accomplished through intensive surveys of health care facilities and patient advocacy groups, for example. Comorbidity of disease must be included in these surveys. With these types of comprehensive efforts, we can get a better understanding of the true rates of disease in the United States and in other regions of the world.

As a result of this analysis we found that autoimmune diseases as a group are a significant source of morbidity in the world. Our estimate of over 8,500,000 people with disease in the United States is certainly an underestimate because we restricted our analysis to well-characterized disorders for which there is substantial evidence of an autoimmune etiology and well-documented epidemiological data. Autoimmune diseases represent a population burden and public health problem of considerable importance. Because many of these diseases are chronic and require intensive medical intervention, their impact on health service delivery appears to be underestimated. Although the actual impact on costs and health service needs are unknown, it is clear that autoimmune diseases as a group have an impact on many aspects of modern life, including years of productive life lost, a decrease in quality of life, and economic hardship. The time may have come to start to implicitly consider autoimmune diseases as a group of related disorders rather than as a single independent entity. By considering these diseases as a group, not only will it help to facilitate research efforts but it may improve diagnosis and health services to those in need.

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