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Recent Insights in the Epidemiology of Autoimmune Diseases: Improved Prevalence Estimates and Understanding of Clustering of Diseases

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Abstract

Previous studies have estimated a prevalence of a broad grouping of autoimmune diseases of 3.2%, based on literature review of studies published between 1965 and 1995, and 5.3%, based on national hospitalization registry data in Denmark. We examine more recent studies pertaining to the prevalence of 29 autoimmune diseases, and use these data to correct for the underascertainment of some diseases in the hospitalization registry data. This analysis results in an estimated prevalence of 7.6–9.4%, depending on the size of the correction factor used. The rates for most diseases for which data are available from many geographic regions span overlapping ranges. We also review studies of the co-occurrence of diseases within individuals and within families, focusing on specific pairs of diseases to better distinguish patterns that may result in insights pertaining to shared etiological pathways. Overall, data support a tendency for autoimmune diseases to co-occur at greater than expected rates within proband patients and their families, but this does not appear to be a uniform phenomenon across all diseases. Multiple sclerosis and rheumatoid arthritis is one disease pair that appears to have a decreased chance of coexistence.

Keywords

Autoimmune disease; Comorbidity; Disease burden; Epidemiology; Prevalence

1. Introduction

A seminal paper in the epidemiology of autoimmune diseases, published in 1997, gathered and synthesized 30 years of studies on 24 autoimmune diseases [1]. This compilation was a comprehensive analysis of the incidence, prevalence, and temporal changes in disease patterns. It was also the first comprehensive analysis of the totality of the burden represented by this collection of diseases. Applying the individual disease rates to the United States population,

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Jacobson et al. estimated that the prevalence of these 24 autoimmune diseases was 3.2%. A different approach was taken by Eaton et al. [2], who used national hospitalization registry data in Denmark from 1977 to 2001 to estimate the prevalence of 31 autoimmune diseases, and the co-occurrence of diseases within individuals and within families. The estimated prevalence of these autoimmune diseases was 5.3%. Walsh and Rau extended the analysis of the burden of autoimmune diseases by analyzing its relative ranking in terms of mortality risk among women under the ages of 65 [3]. Within each age group, the collection of 24 autoimmune diseases specified by Jacobsen et al. [1] ranked within the top 10 causes of death. These studies have been instrumental in promoting funding for autoimmune disease research, and in promoting connections between researchers and advocacy groups focusing on specific diseases.

A limitation of the Jacobsen et al. study [1] is that for some diseases, the data used were from studies conducted more than 30 years ago. In addition, data were aggregated across all geographic areas, although incidence and prevalence rates may vary by more than an order of magnitude. In this paper, we examine recent studies pertaining to the prevalence of a broad array of autoimmune diseases, separating out data from different areas. We also review studies of the co-occurrence of diseases within individuals and within families, focusing on specific pairs of diseases to better distinguish patterns that may result in insights pertaining to shared etiological pathways. Specific recommendations regarding the design of future epidemiologic studies that could address limitations identified in the current literature are also discussed.

2. Autoimmune Disease Prevalence Data

The prevalence studies included in this analysis were limited to studies in which the date used to define prevalence was within the last 20 years (1989–2008). For diseases and areas in which numerous studies were available, however, we used a more restrictive time period (1995 – 2008 for myasthenia gravis and rheumatoid arthritis; 2000 – 2008 for celiac disease, Crohn disease, ulcerative colitis, type 1 diabetes, multiple sclerosis, and systemic lupus erythematosus). We did not find any prevalence studies meeting this time restriction for Guillain Barre syndrome, pemphigoid, pemphigus, dermatomyositis, polymyositis, or hematologic conditions (autoimmune hemolytic anemia, idiopathic thrombocytopenic purpura, or pernicious anemia), so these diseases are not included in the summary table (Table 1). In addition, we excluded two of the diseases included in Eaton et al.'s study [2], interstitial cystitis and endometriosis, because there is less certainty regarding their classification as autoimmune conditions. Thus, this analysis of prevalence data is based on 29 diseases [4–145].

As noted by Eaton et al. [2], the prevalence estimates from the Danish hospitalization registry data are significantly underestimated for diseases with low hospitalization rates. This underestimation is most evident for alopecia, celiac disease, hyperthyroidism, hypothyroidism, psoriasis and vitiligo, for which the rates are 5 to 10 times higher in studies from Europe or the United States using a broader ascertainment method. Although polymyalgia rheumatica and some of the Sjögren disease rates are also lower in the Eaton et al. data, the Eaton et al. estimates are not directly comparable to the estimates from the studies limited to older populations (e.g., ages ≥ 50 years). The celiac disease studies are primarily screening studies which include asymptomatic disease detected through antibody testing in conjunction with follow-up biopsies. In a study of 50,700 adults in the Netherlands, the prevalence of clinically diagnosed celiac disease (defined on the basis of adherence to a gluten free diet in conjunction with diagnosis confirmation) was 16 per 100,000, and the prevalence of undiagnosed disease was 350 per 100,000 [9].

How much would the total prevalence of autoimmune diseases estimated from Eaton et al. increase if corrected for this underascertainment? Multiplying Eaton et al.'s number of cases

of alopecia, hyperthyroidism, hypothyroidism, psoriasis and vitiligo by 5, as a conservative adjustment factor, and excluding interstitial cystitis and endometriosis from the calculations, results in a total of 459,422 cases of autoimmune disease. This total needs to be adjusted for duplicate counting of comorbidities among individuals. In Eaton et al.'s analysis, there were 289,228 people with one or more diseases compared with a total number of diseases of 320,358. Applying the ratio of the number of affected people to the number of diseases ($289,228 \div 320,358$, or 0.90) to the new total of 459,422 diseases results in a figure of 414,719 affected individuals, which would be 7.6% of the total population of 5,472,032. Using a higher adjustment rate for four of these diseases (alopecia, hypothyroidism, psoriasis and vitiligo, each multiplied by 10), results in an estimated total prevalence of 9.0% Including a 10-fold correction for the underrepresentation of undiagnosed celiac disease increases the estimated total prevalence to 9.4%

There is a lack of current prevalence data from areas other than Europe and North America for many of the autoimmune diseases (Table 1). The rates for most diseases are similar (or span overlapping ranges) across geographic areas. For uveitis, however, the prevalence reported from one study in India [144] is much higher than the data from studies in the United States and Finland [142,143]. In contrast, multiple sclerosis rates are, in general, higher in the United States and Europe compared with estimates from other countries (Table 1).

3. Co-Occurrence of Autoimmune Diseases

Autoimmune diseases have conventionally been considered as distinct disorders, likely as a consequence of their being treated by separate medical specialties based on organ system of involvement. Characterization of the extent to which particular combinations of autoimmune diseases occur in excess to that expected by chance may offer insight into shared pathophysiologic mechanisms and aid in the targeting of therapeutic strategies.

Clinical data on the associations among autoimmune diseases have predominantly been derived from anecdotal evidence or small studies from tertiary care settings. Despite the need for more large-scale, population-based epidemiologic research in this area, common clinical perception is that autoimmune diseases tend to co-exist both within individuals and families, and the concept of an autoimmune diathesis is widely accepted. Delineation of clinical patterns of aggregation, in concert with recognition of shared genetic features, will provide etiologic clues to this set of diseases. Since most autoimmune diseases are individually uncommon, often convenience samples from tertiary care settings are used, and achieving adequate statistical power to detect rare disease combinations is difficult. Thus, rather than providing an exhaustive account of all studies of autoimmune comorbidities, this overview is intended to highlight key studies with large or population-based samples, with adequate control or reference population data, if available for given disease combinations. Findings from major intra-individual and intra-family studies examining autoimmune disease associations within individuals are summarized in Tables 2 and 3, and studies within families are summarized in Table 4.

Disease Co-occurrence Within Individuals

Studies examining the coexistence among autoimmune diseases typically begin with patients with an index disease, and assess the occurrence of other comorbid conditions within the index population. As outlined in Table 2, the key studies on coexistence have focused in particular on the following diseases as index conditions: multiple sclerosis, rheumatoid arthritis, autoimmune thyroiditis (hypothyroidism), type 1 diabetes, inflammatory bowel disease, and vitiligo. The most comprehensive of such studies was based on the United Kingdom (UK) General Practice Research Database (GPRD) [146]. This population-based study included four index conditions, and was unique in that it incorporated the sequence of diagnoses in its design so that diagnosis of the index condition preceded diagnosis of the comorbid condition. In

contrast, classification of the index condition in other studies was based on special interest or availability of a particular patient population, and did not imply that the index condition occurred before the comorbid conditions. After controlling for age and calendar year in the UK GPRD study, Somers et al. found increased coexistence of rheumatoid arthritis, thyroiditis, and type 1 diabetes versus that expected based on population-based incidence rates during the same time period. The most striking association was for thyroiditis among type 1 diabetes patients, where there was a greater than fourfold excess risk of thyroiditis than expected. However, this study documented an inverse association between rheumatoid arthritis and multiple sclerosis, regardless of diagnostic sequence. Sex-specific results were similar to those for both sexes combined.

Multiple sclerosis as an index disease was also examined in other population-based studies. In two Danish record linkage studies by Nielsen et al., increased incidence of type 1 diabetes [147], ulcerative colitis, pemphigoid and pemphigus foliaceus, but decreased incidence of rheumatoid arthritis and temporal arteritis [148], were found compared to the general Danish population. Ramagopalan et al. found increased occurrence of pernicious anemia and autoimmune thyroid disease (hypo- or hyper-) in a Canadian case-control study using spousal controls, but did not detect an overall increase in autoimmune disease based on ten diseases studied [149].

Three studies examined index inflammatory bowel disease and comorbid autoimmune conditions. In an index population of ulcerative colitis patients in Crete, Koulentaki et al found an 30 fold increase of primary biliary cirrhosis [150]. Weng et al. [151] studied a number of comorbid autoimmune diseases among inflammatory bowel disease patients and matched controls in the Kaiser Permanente Medical Care Plan (USA), and found significantly increased occurrence of psoriasis, rheumatoid arthritis, multiple sclerosis and combined category of 6 other diseases (Addison disease, hemolytic anemia, primary biliary cirrhosis, immune thrombocytopenia purpura, Sjögren disease and systemic sclerosis). They did not detect an association for the following comorbid conditions: type 1 diabetes, systemic lupus erythematosus, vitiligo, autoimmune thyroid disease (Grave's & Hashimoto's combined), or chronic glomerulonephritis. Cohen et al. [152] analyzed data from two medical claims databases from the United States, and likewise found significantly increased occurrence of rheumatoid arthritis, multiple sclerosis and psoriasis. Further, they detected a positive association with ankylosing spondylitis.

Eaton et al. examined the associations between 31 autoimmune diseases based on Danish hospital data [2]. Since this enabled the estimation of 465 pairwise comorbidities, these data are not summarized in Table 2. However, as synthesized by the authors, a few patterns emerged, including a tendency for positive associations between pairs (only 12 negative associations were found, i.e., ORs < 1.0), and the connective tissue diseases in general had higher comorbidities than other types of autoimmune diseases. A simplified tabulation of the intra-individual associations observed Eaton et al. [2] and the other studies described above is presented in Table 3.

Disease Co-occurrence Within Families

Studies of autoimmune diseases within families have often been restricted to assessing the occurrence of a proband disease in pedigrees, but a growing number have examined the aggregation of various autoimmune diseases within families of case and control probands. As summarized elsewhere, such research tends to indicate familial predilection for both proband and additional autoimmune diseases [153]. However, many studies have relied on self-reported family history, and reliability of such data may be questionable. For instance, in a study of relatives of systemic lupus erythematosus patients and population controls, the total confirmation rate of self-reported family history of autoimmune diagnoses excluding cases

with unavailable medical records was 76%; the rate was 44% when all reported cases were included [154]. Another study of familial autoimmunity found that females tend to be more aware of family medical history versus males; moreover, males reported significantly higher rates of autoimmune disease in the presence of their spouse versus when their spouse was absent [149]. Given these considerations, we have restricted our summary of family studies to those with physician or medical record verification of autoimmune disease diagnoses in relatives of proband cases and controls (Table 4). However, aside from studies based on record linkage (e.g., the Danish studies utilizing national registers), most family studies were only able to confirm positive reports of autoimmune disease. Thus underascertainment of familial cases remains a concern, particularly if recognition of family history of autoimmune disease is differential between case and control probands.

In the Danish study by Eaton et al. examining 31 autoimmune diseases, the authors observed high familial autoimmunity for individual diseases, i.e., the occurrence of the proband (index) disease within family members, with a tendency for a higher magnitude of association within siblings versus parent-offspring pairs [2]. However, they found little evidence to support the aggregation of other (non-index) autoimmune diseases within families. The authors interpret these observations to suggest that the genetic origins for autoimmune diseases are more specific than general, and that the finding of stronger associations within sib versus parent-offspring pairs further emphasizes the role of the environment.

In contrast, other family studies have documented significant increases in various autoimmune diseases among first degree relatives of case versus control probands. In a Danish study of multiple sclerosis probands by Nielsen et al. which assessed rates of 42 autoimmune diseases, increased rates were found for polyarteritis nodosa, Addison's, and Crohn's, as well as autoimmune disease in general (based on the composite category for the 42 diseases) [148]. In a separate study, Nielsen et al. found increased type 1 diabetes in families of multiple sclerosis probands [147]. A case control study using spousal controls by Broadley et al. found increases in autoimmune disease based on a composite of 9 diseases, as well as increases in Hashimoto's and Graves disease [155].

A study of systemic lupus erythematosus probands by Cooper et al. found increased Hashimoto's and autoimmune disease in general (based on 11 diseases) in the relatives of lupus patients versus control relatives [154]. Anaya et al. found an increase in autoimmune thyroid disease (hypo- or hyper-) in type 1 diabetes patients [156], and in another study by Anaya et al. found evidence for increases in systemic lupus erythematosus and general autoimmune disease (based on 9 diseases) in the relatives of probands with primary Sjögren disease [157]. Finally, a study of idiopathic inflammatory myopathy patients found increases in general autoimmune disease (based on 25 diseases) and autoimmune thyroid disease (hypo- or hyper-) [158]. It may be more feasible to detect statistically significant associations with thyroid diseases than with less common autoimmune diseases.

4. Discussion

Jacobsen et al.'s review of studies published from 1965 to 1995 resulted in an estimated prevalence of a broad group of 24 autoimmune diseases of 3.2% [1]. However, this estimated was limited in terms of the number of diseases included and the lack of recent data for many diseases. This approach also does not taken into account the co-occurrence of diseases within an individual, and thus is an estimate of the number of individual diseases diagnosed within a population rather than the number of people affected by any of group of autoimmune diseases. The approach based on hospitalization registry data in Denmark from 1977 to 2001 presented by Eaton et al. allows for the direct estimation of the prevalence of a group of disease in a population, without double-counting of individuals. The estimated prevalence of 31 diseases

in this study was 5.3% [2]. Applying a correction to Eaton et al.'s estimates for 6 diseases for which reliance on hospitalization data produced significant underascertainment (alopecia, celiac disease, hyperthyroidism, hypothyroidism, psoriasis and vitiligo), we calculated a corrected prevalence of 7.6 – 9.4% (depending on the size of the correction factor). Although considerable variation in the rates for some diseases has been seen (e.g., multiple sclerosis), the rates for most diseases for which data are available from many geographic regions span overlapping ranges. Thus although this estimate is primarily based on a population-based study from Denmark, it may apply to countries in other parts of the world.

Estimates of the prevalence of individual diseases and of individuals with any of a group of diseases provide data needed for health policy discussions and in setting research priorities, and can aid in health services planning. Expansion and enhancement of the database of disease incidence and prevalence studies within and across specific geographic areas would also allow for the assessment of temporal trends in disease rates. There are many challenges, however, to conducting population-based epidemiologic studies of the prevalence or incidence of specific autoimmune diseases. Many of these diseases are relatively rare and are characterized by heterogeneous clinical presentations and complex case definitions. Few are routinely diagnosed based on a biopsy. For some diseases, the International Classification of Diseases (ICD) system does not provide a specific code. For example, we have found at least four ICD-9-CM codes used for antiphospholipid antibody syndrome, including: other and unspecified nonspecific immunological findings (795.79), primary hypercoagulable state, (289.81), hemorrhagic disorder due to circulating anticoagulants (286.5), and other and unspecified coagulation defects (286.9). Another example of the limitation of ICD coding is diabetes. The most recent revision of the ICD classification system, ICD-10, was the first to distinguish between type 1 and type 2 diabetes, and it will take some time to determine the accuracy of this new coding scheme. Improving the specificity of disease codes, and facilitating their adaptation across medical specialties, would enable better estimates of these diseases.

Hospitalization data registries, where available for a population, can provide a valuable resource for epidemiologic studies. Because of the underascertainment that is inherent in a registry that only includes hospitalized patients, however, the usefulness of these registries would be greatly enhanced by an evidence-based answer to specific questions regarding the sensitivity and specificity of the hospitalization data used for disease classification. For example, a clinical study that is based on an inception cohort of patients with a specific disease could be analyzed to determine the proportion of patients who are hospitalized within a period of the diagnosis, and for these patients, the proportion who would have been correctly identified as having the disease based on the hospitalization coding data. For some diseases, additional sources of case ascertainment, such as laboratory or biopsy records and pharmacy records may be needed to accurately estimate disease incidence or prevalence. Inclusion of multiple sources allows for capture-recapture analytic methods, which may further improve the accuracy of the resulting estimates [159]

Death certificate data have also been used to estimate the relative ranking of autoimmune diseases among causes of death [3]. Studies of several autoimmune diseases have reported considerable under-reporting of these diseases on death certificates, however, even when contributing causes of death are included in the analysis. For example, in studies of multiple sclerosis patients in the United Kingdom [160] and type 1 diabetes patients in Germany [161], 27% and 29%, respectively of the death certificates did not include any mention of these respective diseases. Underascertainment rates were higher (40% and 42%, respectively) in studies of systemic lupus erythematosus [162] and rheumatoid arthritis [163]

Aggregate findings from the literature pertaining to co-occurrence of diseases indicate that certain autoimmune diseases co-occur at greater than expected rates within patients and their

families, though a small number of disease pairs (e.g., multiple sclerosis and rheumatoid arthritis) appear to have a decreased chance of coexistence. Disease associations are more evident within individuals, and in families stronger associations have been found among sibling versus parent-offspring pairs. The precise measurement of the frequency of multiply affected individuals and how this varies by disease, time, and place is likely to reflect gene-environment interaction.

Rapid expansion of knowledge related to the genetics of autoimmune disease is currently underway. Data from twin, linkage and association studies point to a complex mode of inheritance, and indicate that genes involved in autoimmune disorders are pleiotropic rather than disease specific. Becker describes the “common variant/multiple disease” hypothesis stating that common alleles manifesting in a given disorder under particular genetic/environmental conditions may have the potential to give rise to alternate clinical phenotypes when combined with a different set of genetic and environmental factors [164]. Accumulating data support the premise that clinically distinct autoimmune diseases may have common susceptibility genes. For instance, a major United Kingdom-based genome-wide association study published in 2007 identified several loci with associations to more than one autoimmune disease [1, 2007 #432]. As summarized by Lettre and Rioux, at least 68 genetic risk variants have now been associated with various autoimmune diseases, in contrast to only 15 that were recognized prior to 2006 [166].

Both genetic and epidemiologic data indicate that predisposition likely exists for particular combinations of autoimmune diseases, but not in a uniform fashion across all autoimmune diseases. For instance, the PTPN22 risk allele has been strongly associated with type 1 diabetes, rheumatoid arthritis and thyroiditis, but not multiple sclerosis [167]. This finding is compatible with clinical results Somers et al.'s population-based UK study encompassing 33.5 million person-years of data, which documented intra-individual coexistence of type 1 diabetes, rheumatoid arthritis and thyroiditis beyond that expected, but suggestion of reduced risk between multiple sclerosis and rheumatoid arthritis for either diagnostic sequence (standardized incidence ratios 79.8 and 73.2 and for index diagnosis of multiple sclerosis and rheumatoid arthritis, respectively) [146]. An inverse association between multiple sclerosis and rheumatoid arthritis was likewise found in two population-based Danish studies by Eaton et al. [2] and Nielsen et al. [148] (odds ratios 0.8 and 0.5, respectively), and a systematic review of the literature published in 2006 [168]. Coupling results from such studies will aid in the understanding of the clinical relevance of proposed autoimmune susceptibility genes. Further characterization of the concordance between genetic and epidemiologic evidence will enhance our understanding of autoimmune disease pathways.

Improved delineation of the prevalence, incidence and coexistence of autoimmune diseases is also important for the interpretation of pharmacoepidemiologic data. For example, post-marketing surveillance of TNF inhibitors signaled the possible development of multiple sclerosis, though without prior availability of data on the coexistence of rheumatoid arthritis and multiple sclerosis, it could be argued that rheumatoid arthritis patients have an inherent predilection for the development of multiple sclerosis. As discussed by Somers et al., in light of recent data indicating an inverse association between rheumatoid arthritis and multiple sclerosis, the development of multiple sclerosis in patients treated with TNF inhibitors can reasonably be ascribed as a risk of treatment [146].

Continued and improved surveillance of autoimmune diseases around the world will improve our understanding of disease burden and temporal trends. Since autoimmune diseases are conventionally treated by separate medical specialties according to type of organ involvement, there have been missed opportunities to study these diseases as a group. Further studies of the relationships among autoimmune diseases are indicated in order to enhance our understanding

of the etiology of this set of diseases. We are pleased to contribute to this special issue of the Journal of Autoimmunity in dedication of Dr. Noel Rose's outstanding contributions to autoimmunology, including the epidemiology of autoimmune disease [170–176], the establishment of the American Autoimmune Related Disease Association (AARDA) [177] and we note that this issue is part of the Journal of Autoimmunity's recognition of outstanding figures in immunology [178–180].

References

- [1]. Jacobson DL, Gange SJ, Rose NR, Graham NM. Epidemiology and estimated population burden of selected autoimmune diseases in the United States. *Clin Immunol Immunopathol* 1997;84:223–43. [PubMed: 9281381]
- [2]. Eaton WW, Rose NR, Kalaydjian A, Pedersen MG, Mortensen PB. Epidemiology of autoimmune diseases in Denmark. *J Autoimmun* 2007;29:1–9. [PubMed: 17582741]
- [3]. Walsh SJ, Rau LM. Autoimmune diseases: a leading cause of death among young and middle-aged women in the United States. *Am J Public Health* 2000;90:1463–6. [PubMed: 10983209]
- [4]. Kong MF, Jeffcoate W. Eighty-six cases of Addison's disease. *Clin Endocrinol (Oxf)* 1994;41:757–61. [PubMed: 7889611]
- [5]. Lovas K, Husebye ES. High prevalence and increasing incidence of Addison's disease in western Norway. *Clin Endocrinol (Oxf)* 2002;56:787–91. [PubMed: 12072049]
- [6]. Laureti S. Is the Prevalence of Addison's Disease Underestimated? *J Clin Endocrinol Metab* 1999;84:1762. [PubMed: 10323417]
- [7]. Safavi KH, Muller SA, Suman VJ, Moshell AN, Melton LJ 3rd. Incidence of alopecia areata in Olmsted County, Minnesota, 1975 through 1989. *Mayo Clin Proc* 1995;70:628–33. [PubMed: 7791384]
- [8]. Roka V, Potamianos SP, Kapsoritakis AN, Yiannaki EE, Koukoulis GN, Stefanidis I, et al. Prevalence of coeliac disease in the adult population of central Greece. *Eur J Gastroenterol Hepatol* 2007;19:982–7. [PubMed: 18049168]
- [9]. Schweizer JJ, von Blomberg BM, Bueno-de Mesquita HB, Mearin ML. Coeliac disease in The Netherlands. *Scand J Gastroenterol* 2004;39:359–64. [PubMed: 15125468]
- [10]. Johannsson GF, Kristjansson G, Cariglia N, Thorsteinsson V. The prevalence of celiac disease in blood donors in Iceland. *Dig Dis Sci* 2009;54:348–50. [PubMed: 18600451]
- [11]. Menardo G, Brizzolara R, Bonassi S, Marchetti A, Dante GL, Pistone C, et al. Population screening for coeliac disease in a low prevalence area in Italy. *Scand J Gastroenterol* 2006;41:1414–20. [PubMed: 17101572]
- [12]. Lohi S, Mustalahti K, Kaukinen K, Laurila K, Collin P, Rissanen H, et al. Increasing prevalence of coeliac disease over time. *Aliment Pharmacol Ther* 2007;26:1217–25. [PubMed: 17944736]
- [13]. Akbari MR, Mohammadkhani A, Fakheri H, Javad Zahedi M, Shahbakhani B, Nouraie M, et al. Screening of the adult population in Iran for coeliac disease: comparison of the tissue-transglutaminase antibody and anti-endomysial antibody tests. *Eur J Gastroenterol Hepatol* 2006;18:1181–6. [PubMed: 17033439]
- [14]. Bdioui F, Sakly N, Hassine M, Saffar H. Prevalence of celiac disease in Tunisian blood donors. *Gastroenterol Clin Biol* 2006;30:33–6. [PubMed: 16514380]
- [15]. Mankai A, Landolsi H, Chahed A, Gueddah L, Limem M, Ben Abdesslem M, et al. Celiac disease in Tunisia: serological screening in healthy blood donors. *Pathol Biol (Paris)* 2006;54:10–3. [PubMed: 16376174]
- [16]. Gomez JC, Selvaggio GS, Viola M, Pizarro B, la Motta G, de Barrio S, et al. Prevalence of celiac disease in Argentina: screening of an adult population in the La Plata area. *Am J Gastroenterol* 2001;96:2700–4. [PubMed: 11569698]
- [17]. Oliveira RP, Sdepanian VL, Barreto JA, Cortez AJ, Carvalho FO, Bordin JO, et al. High prevalence of celiac disease in Brazilian blood donor volunteers based on screening by IgA antitissue transglutaminase antibody. *Eur J Gastroenterol Hepatol* 2007;19:43–9. [PubMed: 17206076]
- [18]. Gursay S, Guven K, Simsek T, Yurci A, Torun E, Koc N, et al. The prevalence of unrecognized adult celiac disease in Central Anatolia. *J Clin Gastroenterol* 2005;39:508–11. [PubMed: 15942437]

- [19]. Lakatos L, Mester G, Erdelyi Z, Balogh M, Szipocs I, Kamaras G, et al. [Epidemiology of inflammatory bowel diseases in Veszprem county of Western Hungary between 1977 and 2001]. *Orv Hetil* 2003;144:1819–27. [PubMed: 14596020]
- [20]. Pavlovic-Calic N, Salkic NN, Gegic A, Smajic M, Alibegovic E. Crohn's disease in Tuzla region of Bosnia and Herzegovina: a 12-year study (1995–2006). *Int J Colorectal Dis* 2008;23:957–64. [PubMed: 18548259]
- [21]. Herrinton LJ, Liu L, Lewis JD, Griffin PM, Allison J. Incidence and prevalence of inflammatory bowel disease in a Northern California managed care organization, 1996–2002. *Am J Gastroenterol* 2008;103:1998–2006. [PubMed: 18796097]
- [22]. Kappelman MD, Rifas-Shiman SL, Kleinman K, Ollendorf D, Bousvaros A, Grand RJ, et al. The prevalence and geographic distribution of Crohn's disease and ulcerative colitis in the United States. *Clin Gastroenterol Hepatol* 2007;5:1424–9. [PubMed: 17904915]
- [23]. Loftus CG, Loftus EV Jr, Harmsen WS, Zinsmeister AR, Tremaine WJ, Melton LJ 3rd, et al. Update on the incidence and prevalence of Crohn's disease and ulcerative colitis in Olmsted County, Minnesota, 1940–2000. *Inflamm Bowel Dis* 2007;13:254–61. [PubMed: 17206702]
- [24]. Costas Armada P, Garcia-Mayor RV, Larranaga A, Seguin P. [Prevalence and incidence of Crohn's disease in Galicia, Spain]. *Med Clin (Barc)* 2008;130:715. [PubMed: 18501145]
- [25]. Jacobsen BA, Fallingborg J, Rasmussen HH, Nielsen KR, Drewes AM, Puho E, et al. Increase in incidence and prevalence of inflammatory bowel disease in northern Denmark: a population-based study, 1978–2002. *Eur J Gastroenterol Hepatol* 2006;18:601–6. [PubMed: 16702848]
- [26]. Gearry RB, Richardson A, Frampton CM, Collett JA, Burt MJ, Chapman BA, et al. High incidence of Crohn's disease in Canterbury, New Zealand: results of an epidemiologic study. *Inflamm Bowel Dis* 2006;12:936–43. [PubMed: 17012964]
- [27]. Appleyard CB, Hernandez G, Rios-Bedoya CF. Basic epidemiology of inflammatory bowel disease in Puerto Rico. *Inflamm Bowel Dis* 2004;10:106–11. [PubMed: 15168809]
- [28]. Hilmi I, Tan YM, Goh KL. Crohn's disease in adults: observations in a multiracial Asian population. *World J Gastroenterol* 2006;12:1435–8. [PubMed: 16552816]
- [29]. Abdul-Baki H, ElHajj I, El-Zahabi LM, Azar C, Aoun E, Zantout H, et al. Clinical epidemiology of inflammatory bowel disease in Lebanon. *Inflamm Bowel Dis* 2007;13:475–80. [PubMed: 17206720]
- [30]. Zvidi I, Hazazi R, Birkenfeld S, Niv Y. The prevalence of Crohn's disease in Israel: a 20-year survey. *Dig Dis Sci* 2009;54:848–52. [PubMed: 18649132]
- [31]. Ostrauskas R. The prevalence of type 1 diabetes mellitus among adolescents and adults in Lithuania during 1991–2004. *Medicina (Kaunas)* 2007;43:242–50. [PubMed: 17413254]
- [32]. Forouhi NG, Merrick D, Goyder E, Ferguson BA, Abbas J, Lachowycz K, et al. Diabetes prevalence in England, 2001--estimates from an epidemiological model. *Diabet Med* 2006;23:189–97. [PubMed: 16433718]
- [33]. Jansson SP, Andersson DK, Svardsudd K. Prevalence and incidence rate of diabetes mellitus in a Swedish community during 30 years of follow-up. *Diabetologia* 2007;50:703–10. [PubMed: 17268796]
- [34]. Knox SA, Harrison CM, Britt HC, Henderson JV. Estimating prevalence of common chronic morbidities in Australia. *Med J Aust* 2008;189:66–70. [PubMed: 18637769]
- [35]. Bahillo MP, Hermoso F, Ochoa C, Garcia-Fernandez JA, Rodrigo J, Marugan JM, et al. Incidence and prevalence of type 1 diabetes in children aged <15 yr in Castilla-Leon (Spain). *Pediatr Diabetes* 2007;8:369–73. [PubMed: 18036062]
- [36]. Rosenbauer J, Icks A, Giani G. Incidence and prevalence of childhood type 1 diabetes mellitus in Germany--model-based national estimates. *J Pediatr Endocrinol Metab* 2002;15:1497–504. [PubMed: 12503857]
- [37]. Duncan GE. Prevalence of diabetes and impaired fasting glucose levels among US adolescents: National Health and Nutrition Examination Survey, 1999–2002. *Arch Pediatr Adolesc Med* 2006;160:523–8. [PubMed: 16651496]
- [38]. Wu D, Kendall D, Lunt H, Willis J, Darlow B, Frampton C. Prevalence of Type 1 diabetes in New Zealanders aged 0–24 years. *N Z Med J* 2005;118:U1557. [PubMed: 16027748]

- [39]. Moore KR, Harwell TS, McDowall JM, Helgersson SD, Gohdes D. Three-year prevalence and incidence of diabetes among American Indian youth in Montana and Wyoming, 1999 to 2001. *J Pediatr* 2003;143:368–71. [PubMed: 14517522]
- [40]. Peter SA, Johnson R, Taylor C, Hanna A, Roberts P, McNeil P, et al. The incidence and prevalence of type-1 diabetes mellitus. *J Natl Med Assoc* 2005;97:250–2. [PubMed: 15712788]
- [41]. Al-Herbish AS, El-Mouzan MI, Al-Salloum AA, Al-Qurachi MM, Al-Omar AA. Prevalence of type 1 diabetes mellitus in Saudi Arabian children and adolescents. *Saudi Med J* 2008;29:1285–8. [PubMed: 18813413]
- [42]. Moussa MA, Alsaied M, Abdella N, Refai TM, Al-Sheikh N, Gomez JE. Prevalence of type 1 diabetes among 6- to 18-year-old Kuwaiti children. *Med Princ Pract* 2005;14:87–91. [PubMed: 15785099]
- [43]. Primo J, Merino C, Fernandez J, Moles JR, Llorca P, Hinojosa J. Incidence and prevalence of autoimmune hepatitis in the area of the Hospital de Sagunto (Spain). *Gastroenterol Hepatol* 2004;27:239–43. [PubMed: 15056409]
- [44]. Werner M, Prytz H, Ohlsson B, Almer S, Bjornsson E, Bergquist A, et al. Epidemiology and the initial presentation of autoimmune hepatitis in Sweden: a nationwide study. *Scand J Gastroenterol* 2008;43:1232–40. [PubMed: 18609163]
- [45]. Boberg KM, Aadland E, Jahnsen J, Raknerud N, Stiris M, Bell H. Incidence and prevalence of primary biliary cirrhosis, primary sclerosing cholangitis, and autoimmune hepatitis in a Norwegian population. *Scand J Gastroenterol* 1998;33:99–103. [PubMed: 9489916]
- [46]. Hurlburt KJ, McMahon BJ, Deubner H, Hsu-Trawinski B, Williams JL, Kowdley KV. Prevalence of autoimmune liver disease in Alaska Natives. *Am J Gastroenterol* 2002;97:2402–7. [PubMed: 12358264]
- [47]. Lee YM, Teo EK, Ng TM, Khor C, Fock KM. Autoimmune hepatitis in Singapore: a rare syndrome affecting middle-aged women. *J Gastroenterol Hepatol* 2001;16:1384–9. [PubMed: 11851837]
- [48]. Rautiainen H, Salomaa V, Niemela S, Karvonen AL, Nurmi H, Isoniemi H, et al. Prevalence and incidence of primary biliary cirrhosis are increasing in Finland. *Scand J Gastroenterol* 2007;42:1347–53. [PubMed: 17918011]
- [49]. Pla X, Vergara M, Gil M, Dalmau B, Cistero B, Bella RM, et al. Incidence, prevalence and clinical course of primary biliary cirrhosis in a Spanish community. *Eur J Gastroenterol Hepatol* 2007;19:859–64. [PubMed: 17873609]
- [50]. James OF, Bhopal R, Howel D, Gray J, Burt AD, Metcalf JV. Primary biliary cirrhosis once rare, now common in the United Kingdom? *Hepatology* 1999;30:390–4. [PubMed: 10421645]
- [51]. Kim WR, Lindor KD, Locke GR 3rd, Therneau TM, Homburger HA, Batts KP, et al. Epidemiology and natural history of primary biliary cirrhosis in a US community. *Gastroenterology* 2000;119:1631–6. [PubMed: 11113084]
- [52]. Sood S, Gow PJ, Christie JM, Angus PW. Epidemiology of primary biliary cirrhosis in Victoria, Australia: high prevalence in migrant populations. *Gastroenterology* 2004;127:470–5. [PubMed: 15300579]
- [53]. Delgado J, Sperber AD, Novack V, Delgado B, Edelman L, Gaspar N, et al. The epidemiology of primary biliary cirrhosis in southern Israel. *Isr Med Assoc J* 2005;7:717–21. [PubMed: 16308995]
- [54]. Hollowell JG, Staehling NW, Flanders WD, Hannon WH, Gunter EW, Spencer CA, et al. Serum TSH, T(4), and thyroid antibodies in the United States population (1988 to 1994): National Health and Nutrition Examination Survey (NHANES III). *J Clin Endocrinol Metab* 2002;87:489–99. [PubMed: 11836274]
- [55]. Flynn RW, MacDonald TM, Morris AD, Jung RT, Leese GP. The thyroid epidemiology, audit, and research study: thyroid dysfunction in the general population. *J Clin Endocrinol Metab* 2004;89:3879–84. [PubMed: 15292321]
- [56]. Heydari P, Ordookhani A, Azizi F. Goiter rate, serum thyrotropin, thyroid autoantibodies and urinary iodine concentration in Tehranian adults before and after national salt iodization. *J Endocrinol Invest* 2007;30:404–10. [PubMed: 17598973]
- [57]. Mayr WT, Pittock SJ, McClelland RL, Jorgensen NW, Noseworthy JH, Rodriguez M. Incidence and prevalence of multiple sclerosis in Olmsted County, Minnesota, 1985–2000. *Neurology* 2003;61:1373–7. [PubMed: 14638958]

- [58]. Hader WJ, Yee IM. Incidence and prevalence of multiple sclerosis in Saskatoon, Saskatchewan. *Neurology* 2007;69:1224–9. [PubMed: 17875910]
- [59]. Warren SA, Svenson LW, Warren KG. Contribution of incidence to increasing prevalence of multiple sclerosis in Alberta, Canada. *Mult Scler* 2008;14:872–9. [PubMed: 18573834]
- [60]. Svenson LW, Warren S, Warren KG, Metz LM, Patten SB, Schopflocher DP. Prevalence of multiple sclerosis in First Nations people of Alberta. *Can J Neurol Sci* 2007;34:175–80. [PubMed: 17598594]
- [61]. Granieri E, Economou NT, De Gennaro R, Tola MR, Caniatti L, Govoni V, et al. Multiple sclerosis in the province of Ferrara: evidence for an increasing trend. *J Neurol* 2007;254:1642–8. [PubMed: 18008026]
- [62]. Granieri E, Monaldini C, De Gennaro R, Guttmann S, Volpini M, Stumpo M, et al. Multiple sclerosis in the Republic of San Marino: a prevalence and incidence study. *Mult Scler* 2008;14:325–9. [PubMed: 18208882]
- [63]. Grimaldi LM, Palmeri B, Salemi G, Giglia G, D'Amelio M, Grimaldi R, et al. High prevalence and fast rising incidence of multiple sclerosis in Caltanissetta, Sicily, southern Italy. *Neuroepidemiology* 2007;28:28–32. [PubMed: 17164567]
- [64]. Iuliano G, Napoletano R. Prevalence and incidence of multiple sclerosis in Salerno (southern Italy) and its province. *Eur J Neurol* 2008;15:73–6. [PubMed: 18042236]
- [65]. Papathanasopoulos P, Gourzoulidou E, Messinis L, Georgiou V, Leotsinidis M. Prevalence and incidence of multiple sclerosis in western Greece: a 23-year survey. *Neuroepidemiology* 2008;30:167–73. [PubMed: 18382116]
- [66]. Debouverie M, Pittion-Vouyovitch S, Louis S, Roederer T, Guillemin F. Increasing incidence of multiple sclerosis among women in Lorraine, Eastern France. *Mult Scler* 2007;13:962–7. [PubMed: 17623734]
- [67]. Gray OM, McDonnell GV, Hawkins SA. Factors in the rising prevalence of multiple sclerosis in the north-east of Ireland. *Mult Scler* 2008;14:880–6. [PubMed: 18573832]
- [68]. McGuigan C, McCarthy A, Quigley C, Bannan L, Hawkins SA, Hutchinson M. Latitudinal variation in the prevalence of multiple sclerosis in Ireland, an effect of genetic diversity. *J Neurol Neurosurg Psychiatry* 2004;75:572–6. [PubMed: 15026499]
- [69]. Dahl OP, Aarseth JH, Myhr KM, Nyland H, Midgard R. Multiple sclerosis in Nord-Trøndelag County, Norway: a prevalence and incidence study. *Acta Neurol Scand* 2004;109:378–84. [PubMed: 15147459]
- [70]. De Sa J, Paulos A, Mendes H, Becho J, Marques J, Roxo J. The prevalence of multiple sclerosis in the District of Santarem, Portugal. *J Neurol* 2006;253:914–8. [PubMed: 16502218]
- [71]. Chancellor AM, Addidle M, Dawson K. Multiple sclerosis is more prevalent in northern New Zealand than previously reported. *Intern Med J* 2003;33:79–83. [PubMed: 12603579]
- [72]. Toro J, Sarmiento OL, Diaz del Castillo A, Satizabal CL, Ramirez JD, Montenegro AC, et al. Prevalence of multiple sclerosis in Bogota, Colombia. *Neuroepidemiology* 2007;28:33–8. [PubMed: 17164568]
- [73]. Callegaro D, Goldbaum M, Morais L, Tilbery CP, Moreira MA, Gabbai AA, et al. The prevalence of multiple sclerosis in the city of Sao Paulo, Brazil, 1997. *Acta Neurol Scand* 2001;104:208–13. [PubMed: 11589649]
- [74]. Cristiano E, Patrucco L, Rojas JI, Caceres F, Carra A, Correale J, et al. Prevalence of multiple sclerosis in Buenos Aires, Argentina using the capture-recapture method. *Eur J Neurol* 2009;16:183–7. [PubMed: 19138341]
- [75]. Houzen H, Niino M, Hata D, Nakano F, Kikuchi S, Fukazawa T, et al. Increasing prevalence and incidence of multiple sclerosis in northern Japan. *Mult Scler* 2008;14:887–92. [PubMed: 18573833]
- [76]. Alter M, Kahana E, Zilber N, Miller A. Multiple sclerosis frequency in Israel's diverse populations. *Neurology* 2006;66:1061–6. [PubMed: 16606919]
- [77]. Alshubaili AF, Alramzy K, Ayyad YM, Gerish Y. Epidemiology of multiple sclerosis in Kuwait: new trends in incidence and prevalence. *Eur Neurol* 2005;53:125–31. [PubMed: 15860917]
- [78]. El-Salem K, Al-Shimmery E, Horany K, Al-Refai A, Al-Hayk K, Khader Y. Multiple sclerosis in Jordan: A clinical and epidemiological study. *J Neurol* 2006;253:1210–6. [PubMed: 16649096]
- [79]. Etemadifar M, Janghorbani M, Shaygannejad V, Ashtari F. Prevalence of multiple sclerosis in Isfahan, Iran. *Neuroepidemiology* 2006;27:39–44. [PubMed: 16804333]

- [80]. Turk Boru U, Alp R, Sur H, Gul L. Prevalence of multiple sclerosis door-to-door survey in Maltepe, Istanbul, Turkey. *Neuroepidemiology* 2006;27:17–21. [PubMed: 16770082]
- [81]. Oopik M, Kaasik AE, Jakobsen J. A population based epidemiological study on myasthenia gravis in Estonia. *J Neurol Neurosurg Psychiatry* 2003;74:1638–43. [PubMed: 14638881]
- [82]. Poulas K, Tsibri E, Kokla A, Papanastasiou D, Tsouloufis T, Marinou M, et al. Epidemiology of seropositive myasthenia gravis in Greece. *J Neurol Neurosurg Psychiatry* 2001;71:352–6. [PubMed: 11511710]
- [83]. Zivadinov R, Jurjevic A, Willheim K, Cazzato G, Zorzon M. Incidence and prevalence of myasthenia gravis in the county of the coast and Gorski kotar, Croatia, 1976 through 1996. *Neuroepidemiology* 1998;17:265–72. [PubMed: 9705586]
- [84]. Kalb B, Matell G, Pirskanen R, Lambe M. Epidemiology of myasthenia gravis: a population-based study in Stockholm, Sweden. *Neuroepidemiology* 2002;21:221–5. [PubMed: 12207149]
- [85]. Robertson NP, Deans J, Compston DA. Myasthenia gravis: a population based epidemiological study in Cambridgeshire, England. *J Neurol Neurosurg Psychiatry* 1998;65:492–6. [PubMed: 9771771]
- [86]. Wirtz PW, Nijhuis MG, Sotodeh M, Willems LN, Brahim JJ, Putter H, et al. The epidemiology of myasthenia gravis, Lambert-Eaton myasthenic syndrome and their associated tumours in the northern part of the province of South Holland. *J Neurol* 2003;250:698–701. [PubMed: 12796832]
- [87]. Sanchez JL, Uribe CS, Franco AF, Jimenez ME, Arcos-Burgos OM, Palacio LG. Prevalence of myasthenia gravis in Antioquia, Colombia. *Rev Neurol* 2002;34:1010–2. [PubMed: 12134295]
- [88]. Holtsema H, Mourik J, Rico RE, Falconi JR, Kuks JB, Oosterhuis HJ. Myasthenia gravis on the Dutch antilles: an epidemiological study. *Clin Neurol Neurosurg* 2000;102:195–8. [PubMed: 11154803]
- [89]. Doran MF, Crowson CS, O'Fallon WM, Hunder GG, Gabriel SE. Trends in the incidence of polymyalgia rheumatica over a 30 year period in Olmsted County, Minnesota, USA. *J Rheumatol* 2002;29:1694–7. [PubMed: 12180732]
- [90]. Salvarani C, Gabriel SE, O'Fallon WM, Hunder GG. Epidemiology of polymyalgia rheumatica in Olmsted County, Minnesota, 1970–1991. *Arthritis Rheum* 1995;38:369–73. [PubMed: 7880191]
- [91]. Andrianakos A, Trontzas P, Christoyannis F, Dantis P, Voudouris C, Georgountzos A, et al. Prevalence of rheumatic diseases in Greece: a cross-sectional population based epidemiological study. The ESORDIG Study. *J Rheumatol* 2003;30:1589–601. [PubMed: 12858464]
- [92]. Gelfand JM, Weinstein R, Porter SB, Neimann AL, Berlin JA, Margolis DJ. Prevalence and treatment of psoriasis in the United Kingdom: a population-based study. *Arch Dermatol* 2005;141:1537–41. [PubMed: 16365254]
- [93]. Shbeeb M, Uramoto KM, Gibson LE, O'Fallon WM, Gabriel SE. The epidemiology of psoriatic arthritis in Olmsted County, Minnesota, USA, 1982–1991. *J Rheumatol* 2000;27:1247–50. [PubMed: 10813295]
- [94]. Alamanos Y, Papadopoulos NG, Voulgari PV, Siozos C, Psychos DN, Tympanidou M, et al. Epidemiology of psoriatic arthritis in northwest Greece, 1982–2001. *J Rheumatol* 2003;30:2641–4. [PubMed: 14719208]
- [95]. Love TJ, Gudbjornsson B, Gudjonsson JE, Valdimarsson H. Psoriatic arthritis in Reykjavik, Iceland: prevalence, demographics, and disease course. *J Rheumatol* 2007;34:2082–8. [PubMed: 17696270]
- [96]. Madland TM, Apalset EM, Johannessen AE, Rossebo B, Brun JG. Prevalence, disease manifestations, and treatment of psoriatic arthritis in Western Norway. *J Rheumatol* 2005;32:1918–22. [PubMed: 16206347]
- [97]. Pedersen OB, Svendsen AJ, Ejstrup L, Skytthe A, Junker P. The occurrence of psoriatic arthritis in Denmark. *Ann Rheum Dis* 2008;67:1422–6. [PubMed: 18208866]
- [98]. Wilson FC, Icen M, Crowson CS, McEvoy MT, Gabriel SE, Kremers HM. Time trends in epidemiology and characteristics of psoriatic arthritis over 3 decades: a population-based study. *J Rheumatol* 2009;36:361–7. [PubMed: 19208565]
- [99]. Minaur N, Sawyers S, Parker J, Darmawan J. Rheumatic disease in an Australian Aboriginal community in North Queensland, Australia. A WHO-ILAR COPCORD survey. *J Rheumatol* 2004;31:965–72. [PubMed: 15124258]

- [100]. Guillemain F, Saraux A, Guggenbuhl P, Roux CH, Fardellone P, Le Bihan E, et al. Prevalence of rheumatoid arthritis in France: 2001. *Ann Rheum Dis* 2005;64:1427–30. [PubMed: 15800010]
- [101]. Kiss CG, Lovei C, Suto G, Varju C, Nagy Z, Fuzesi Z, et al. Prevalence of rheumatoid arthritis in the South-Transdanubian region of Hungary based on a representative survey of 10,000 inhabitants. *J Rheumatol* 2005;32:1688–90. [PubMed: 16142861]
- [102]. Carmona L, Villaverde V, Hernandez-Garcia C, Ballina J, Gabriel R, Laffon A. The prevalence of rheumatoid arthritis in the general population of Spain. *Rheumatology (Oxford)* 2002;41:88–95. [PubMed: 11792885]
- [103]. Akar S, Birlik M, Gurler O, Sari I, Onen F, Manisali M, et al. The prevalence of rheumatoid arthritis in an urban population of Izmir-Turkey. *Clin Exp Rheumatol* 2004;22:416–20. [PubMed: 15301237]
- [104]. Kacar C, Gilgil E, Tuncer T, Butun B, Urhan S, Arikan V, et al. Prevalence of rheumatoid arthritis in Antalya, Turkey. *Clin Rheumatol* 2005;24:212–4. [PubMed: 15940553]
- [105]. Symmons D, Turner G, Webb R, Asten P, Barrett E, Lunt M, et al. The prevalence of rheumatoid arthritis in the United Kingdom: new estimates for a new century. *Rheumatology (Oxford)* 2002;41:793–800. [PubMed: 12096230]
- [106]. Chaiamnuay P, Darmawan J, Muiriden KD, Assawatanabodee P. Epidemiology of rheumatic disease in rural Thailand: a WHO-ILAR COPCORD study. *Community Oriented Programme for the Control of Rheumatic Disease. J Rheumatol* 1998;25:1382–7. [PubMed: 9676773]
- [107]. Dans LF, Tankeh-Torres S, Amante CM, Penserga EG. The prevalence of rheumatic diseases in a Filipino urban population: a WHO-ILAR COPCORD Study. *World Health Organization. International League of Associations for Rheumatology. Community Oriented Programme for the Control of the Rheumatic Diseases. J Rheumatol* 1997;24:1814–9. [PubMed: 9292809]
- [108]. Minh Hoa TT, Darmawan J, Chen SL, Van Hung N, Thi Nhi C, Ngoc An T. Prevalence of the rheumatic diseases in urban Vietnam: a WHO-ILAR COPCORD study. *J Rheumatol* 2003;30:2252–6. [PubMed: 14528525]
- [109]. Dai SM, Han XH, Zhao DB, Shi YQ, Liu Y, Meng JM. Prevalence of rheumatic symptoms, rheumatoid arthritis, ankylosing spondylitis, and gout in Shanghai, China: a COPCORD study. *J Rheumatol* 2003;30:2245–51. [PubMed: 14528524]
- [110]. Chopra A, Patil J, Billempelly V, Relwani J, Tandle HS. Prevalence of rheumatic diseases in a rural population in western India: a WHO-ILAR COPCORD Study. *J Assoc Physicians India* 2001;49:240–6. [PubMed: 11225138]
- [111]. Spindler A, Bellomio V, Berman A, Lucero E, Baigorria M, Paz S, et al. Prevalence of rheumatoid arthritis in Tucuman, Argentina. *J Rheumatol* 2002;29:1166–70. [PubMed: 12064829]
- [112]. Thomas E, Hay EM, Hajeer A, Silman AJ. Sjogren's syndrome: a community-based study of prevalence and impact. *Br J Rheumatol* 1998;37:1069–76. [PubMed: 9825745]
- [113]. Bjerrum KB. Keratoconjunctivitis sicca and primary Sjogren's syndrome in a Danish population aged 30–60 years. *Acta Ophthalmol Scand* 1997;75:281–6. [PubMed: 9253975]
- [114]. Alamanos Y, Tsifetaki N, Voulgari PV, Venetsanopoulou AI, Siozos C, Drosos AA. Epidemiology of primary Sjogren's syndrome in north-west Greece, 1982–2003. *Rheumatology (Oxford)* 2006;45:187–91. [PubMed: 16332955]
- [115]. Trontzas PI, Andrianakos AA. Sjogren's syndrome: a population based study of prevalence in Greece. The ESORDIG study. *Ann Rheum Dis* 2005;64:1240–1. [PubMed: 16014690]
- [116]. Dafni UG, Tzioufas AG, Staikos P, Skopouli FN, Moutsopoulos HM. Prevalence of Sjogren's syndrome in a closed rural community. *Ann Rheum Dis* 1997;56:521–5. [PubMed: 9370875]
- [117]. Tomsic M, Logar D, Grmek M, Perkovic T, Kveder T. Prevalence of Sjogren's syndrome in Slovenia. *Rheumatology (Oxford)* 1999;38:164–70. [PubMed: 10342631]
- [118]. Zhang NZ, Shi CS, Yao QP, Pan GX, Wang LL, Wen ZX, et al. Prevalence of primary Sjogren's syndrome in China. *J Rheumatol* 1995;22:659–61. [PubMed: 7791159]
- [119]. Kabasakal Y, Kitapcioglu G, Turk T, Oder G, Durusoy R, Mete N, et al. The prevalence of Sjogren's syndrome in adult women. *Scand J Rheumatol* 2006;35:379–83. [PubMed: 17062438]
- [120]. Le Guern V, Mahr A, Mouthon L, Jeanneret D, Carzon M, Guillemin L. Prevalence of systemic sclerosis in a French multi-ethnic county. *Rheumatology (Oxford)* 2004;43:1129–37. [PubMed: 15213329]

- [121]. Alamanos Y, Tsifetaki N, Voulgari PV, Siozos C, Tsamandouraki K, Alexiou GA, et al. Epidemiology of systemic sclerosis in northwest Greece 1981 to 2002. *Semin Arthritis Rheum* 2005;34:714–20. [PubMed: 15846586]
- [122]. Arias-Nunez MC, Llorca J, Vazquez-Rodriguez TR, Gomez-Acebo I, Miranda-Fillooy JA, Martin J, et al. Systemic sclerosis in northwestern Spain: a 19-year epidemiologic study. *Medicine (Baltimore)* 2008;87:272–80. [PubMed: 18794710]
- [123]. Airo P, Tabaglio E, Frassi M, Scarsi M, Danieli E, Rossi M. Prevalence of systemic sclerosis in Valtrompia in northern Italy. A collaborative study of rheumatologists and general practitioners. *Clin Exp Rheumatol* 2007;25:878–80. [PubMed: 18173923]
- [124]. Mayes MD, Lacey JV Jr, Beebe-Dimmer J, Gillespie BW, Cooper B, Laing TJ, et al. Prevalence, incidence, survival, and disease characteristics of systemic sclerosis in a large US population. *Arthritis Rheum* 2003;48:2246–55. [PubMed: 12905479]
- [125]. Robinson D Jr, Eisenberg D, Nietert PJ, Doyle M, Bala M, Paramore C, et al. Systemic sclerosis prevalence and comorbidities in the US, 2001–2002. *Curr Med Res Opin* 2008;24:1157–66. [PubMed: 18430269]
- [126]. Arnett FC, Howard RF, Tan F, Moulds JM, Bias WB, Durban E, et al. Increased prevalence of systemic sclerosis in a Native American tribe in Oklahoma. Association with an Amerindian HLA haplotype. *Arthritis Rheum* 1996;39:1362–70. [PubMed: 8702445]
- [127]. Roberts-Thomson PJ, Jones M, Hakendorf P, Kencana Dharmapatni AA, Walker JG, MacFarlane JG, et al. Scleroderma in South Australia: epidemiological observations of possible pathogenic significance. *Intern Med J* 2001;31:220–9. [PubMed: 11456035]
- [128]. Chakravarty EF, Bush TM, Manzi S, Clarke AE, Ward MM. Prevalence of adult systemic lupus erythematosus in California and Pennsylvania in 2000: estimates obtained using hospitalization data. *Arthritis Rheum* 2007;56:2092–4. [PubMed: 17530651]
- [129]. Naleway AL, Davis ME, Greenlee RT, Wilson DA, McCarty DJ. Epidemiology of systemic lupus erythematosus in rural Wisconsin. *Lupus* 2005;14:862–6. [PubMed: 16302684]
- [130]. Lopez P, Mozo L, Gutierrez C, Suarez A. Epidemiology of systemic lupus erythematosus in a northern Spanish population: gender and age influence on immunological features. *Lupus* 2003;12:860–5. [PubMed: 14667105]
- [131]. Alamanos Y, Voulgari PV, Siozos C, Katsimpri P, Tsintzos S, Dimou G, et al. Epidemiology of systemic lupus erythematosus in northwest Greece 1982–2001. *J Rheumatol* 2003;30:731–5. [PubMed: 12672191]
- [132]. Peschken CA, Esdaile JM. Systemic lupus erythematosus in North American Indians: a population based study. *J Rheumatol* 2000;27:1884–91. [PubMed: 10955328]
- [133]. Al-Arfaj AS, Al-Balla SR, Al-Dalaan AN, Al-Saleh SS, Bahabri SA, Mousa MM, et al. Prevalence of systemic lupus erythematosus in central Saudi Arabia. *Saudi Med J* 2002;23:87–9. [PubMed: 11938371]
- [134]. Bossingham D. Systemic lupus erythematosus in the far north of Queensland. *Lupus* 2003;12:327–31. [PubMed: 12729060]
- [135]. Mahr A, Guillemin L, Poissonnet M, Ayme S. Prevalences of polyarteritis nodosa, microscopic polyangiitis, Wegener's granulomatosis, and Churg-Strauss syndrome in a French urban multiethnic population in 2000: a capture-recapture estimate. *Arthritis Rheum* 2004;51:92–9. [PubMed: 14872461]
- [136]. Watts RA, Lane SE, Bentham G, Scott DG. Epidemiology of systemic vasculitis: a ten-year study in the United Kingdom. *Arthritis Rheum* 2000;43:414–9. [PubMed: 10693883]
- [137]. Ormerod AS, Cook MC. Epidemiology of primary systemic vasculitis in the Australian Capital Territory and south-eastern New South Wales. *Intern Med J* 2008;38:816–23. [PubMed: 18771432]
- [138]. Haugeberg G, Bie R, Bendvold A, Larsen AS, Johnsen V. Primary vasculitis in a Norwegian community hospital: a retrospective study. *Clin Rheumatol* 1998;17:364–8. [PubMed: 9805179]
- [139]. Koldingsnes W, Nossent H. Epidemiology of Wegener's granulomatosis in northern Norway. *Arthritis Rheum* 2000;43:2481–7. [PubMed: 11083271]
- [140]. Gibson A, Stamp LK, Chapman PT, O'Donnell JL. The epidemiology of Wegener's granulomatosis and microscopic polyangiitis in a Southern Hemisphere region. *Rheumatology (Oxford)* 2006;45:624–8. [PubMed: 16368729]

- [141]. Gritz DC, Wong IG. Incidence and prevalence of uveitis in Northern California; the Northern California Epidemiology of Uveitis Study. *Ophthalmology* 2004;111:491–500. [PubMed: 15019324]discussion
- [142]. Suhler EB, Lloyd MJ, Choi D, Rosenbaum JT, Austin DF. Incidence and prevalence of uveitis in Veterans Affairs Medical Centers of the Pacific Northwest. *Am J Ophthalmol* 2008;146:890–6. e8. [PubMed: 19027424]
- [143]. Paivonsalo-Hietanen T, Tuominen J, Saari KM. Uveitis in children: population-based study in Finland. *Acta Ophthalmol Scand* 2000;78:84–8. [PubMed: 10726797]
- [144]. Dandona L, Dandona R, John RK, McCarty CA, Rao GN. Population based assessment of uveitis in an urban population in southern India. *Br J Ophthalmol* 2000;84:706–9. [PubMed: 10873978]
- [145]. Lu T, Gao T, Wang A, Jin Y, Li Q, Li C. Vitiligo prevalence study in Shaanxi Province, China. *Int J Dermatol* 2007;46:47–51. [PubMed: 17214719]
- [146]. Somers EC, Thomas SL, Smeeth L, Hall AJ. Are individuals with an autoimmune disease at higher risk of a second autoimmune disorder? *Am J Epidemiol* 2009;169:749–55. [PubMed: 19224981]
- [147]. Nielsen NM, Westergaard T, Frisch M, Rostgaard K, Wohlfahrt J, Koch-Henriksen N, et al. Type 1 diabetes and multiple sclerosis: A Danish population-based cohort study. *Arch Neurol* 2006;63:1001–4. [PubMed: 16831970]
- [148]. Nielsen NM, Frisch M, Rostgaard K, Wohlfahrt J, Hjalgrim H, Koch-Henriksen N, et al. Autoimmune diseases in patients with multiple sclerosis and their first-degree relatives: a nationwide cohort study in Denmark. *Mult Scler* 2008;14:823–9. [PubMed: 18573841]
- [149]. Ramagopalan SV, Dymant DA, Valdar W, Herrera BM, Criscuoli M, Yee IM, et al. Autoimmune disease in families with multiple sclerosis: a population-based study. *Lancet Neurol* 2007;6:604–10. [PubMed: 17560172]
- [150]. Koulentaki M, Koutroubakis IE, Petinaki E, Tzardi M, Oekonomaki H, Mouzas I, et al. Ulcerative colitis associated with primary biliary cirrhosis. *Dig Dis Sci* 1999;44:1953–6. [PubMed: 10548342]
- [151]. Weng X, Liu L, Barcellos LF, Allison JE, Herrinton LJ. Clustering of inflammatory bowel disease with immune mediated diseases among members of a northern california-managed care organization. *Am J Gastroenterol* 2007;102:1429–35. [PubMed: 17437504]
- [152]. Cohen R, Robinson D Jr, Paramore C, Fraeman K, Renahan K, Bala M. Autoimmune disease concomitance among inflammatory bowel disease patients in the United States, 2001–2002. *Inflammatory Bowel Diseases* 2008;14
- [153]. Anaya JM, Gomez L, Castiblanco J. Is there a common genetic basis for autoimmune diseases? *Clin Dev Immunol* 2006;13:185–95. [PubMed: 17162361]
- [154]. Cooper GS, Wither J, McKenzie T, Claudio JO, Bernatsky S, Fortin PR. The prevalence and accuracy of self-reported history of 11 autoimmune diseases. *J Rheumatol* 2008;35:2001–4. [PubMed: 18785310]
- [155]. Broadley SA, Deans J, Sawcer SJ, Clayton D, Compston DA. Autoimmune disease in first-degree relatives of patients with multiple sclerosis. A UK survey. *Brain* 2000;123(Pt 6):1102–11. [PubMed: 10825350]
- [156]. Anaya JM, Castiblanco J, Tobon GJ, Garcia J, Abad V, Cuervo H, et al. Familial clustering of autoimmune diseases in patients with type 1 diabetes mellitus. *J Autoimmun* 2006;26:208–14. [PubMed: 16503115]
- [157]. Anaya JM, Tobon GJ, Vega P, Castiblanco J. Autoimmune disease aggregation in families with primary Sjogren's syndrome. *J Rheumatol* 2006;33:2227–34. [PubMed: 17086607]
- [158]. Ginn LR, Lin JP, Plotz PH, Bale SJ, Wilder RL, Mbauya A, et al. Familial autoimmunity in pedigrees of idiopathic inflammatory myopathy patients suggests common genetic risk factors for many autoimmune diseases. *Arthritis Rheum* 1998;41:400–5. [PubMed: 9506566]
- [159]. Stephen C. Capture-recapture methods in epidemiological studies. *Infect Control Hosp Epidemiol* 1996;17:262–6. [PubMed: 8935735]
- [160]. Hirst C, Swingle R, Compston DA, Ben-Shlomo Y, Robertson NP. Survival and cause of death in multiple sclerosis: a prospective population-based study. *J Neurol Neurosurg Psychiatry* 2008;79:1016–21. [PubMed: 18303108]
- [161]. Muhlhauser I, Sawicki PT, Blank M, Overmann H, Richter B, Berger M. Reliability of causes of death in persons with Type I diabetes. *Diabetologia* 2002;45:1490–7. [PubMed: 12436331]

- [162]. Calvo-Alen J, Alarcon GS, Campbell R Jr, Fernandez M, Reveille JD, Cooper GS. Lack of recording of systemic lupus erythematosus in the death certificates of lupus patients. *Rheumatology (Oxford)* 2005;44:1186–9. [PubMed: 15956088]
- [163]. Laakso M, Isomaki H, Mutru O, Koota K. Death certificate and mortality in rheumatoid arthritis. *Scand J Rheumatol* 1986;15:129–33. [PubMed: 3749825]
- [164]. Becker KG. The common variants/multiple disease hypothesis of common complex genetic disorders. *Med Hypotheses* 2004;62:309–17. [PubMed: 14962646]
- [165]. Genome-wide association study of 14,000 cases of seven common diseases and 3,000 shared controls. *Nature* 2007;447:661–78. [PubMed: 17554300]
- [166]. Lettre G, Rioux JD. Autoimmune diseases: insights from genome-wide association studies. *Hum Mol Genet* 2008;17:R116–21. [PubMed: 18852199]
- [167]. Criswell LA, Pfeiffer KA, Lum RF, Gonzales B, Novitzke J, Kern M, et al. Analysis of families in the multiple autoimmune disease genetics consortium (MADGC) collection: the PTPN22 620W allele associates with multiple autoimmune phenotypes. *Am J Hum Genet* 2005;76:561–71. [PubMed: 15719322]
- [168]. Somers EC, Thomas SL, Smeeth L, Hall AJ. Autoimmune diseases co-occurring within individuals and within families: a systematic review. *Epidemiology* 2006;17:202–17. [PubMed: 16477262]
- [169]. Alkhateeb A, Fain PR, Thody A, Bennett DC, Spritz RA. Epidemiology of vitiligo and associated autoimmune diseases in Caucasian probands and their families. *Pigment Cell Res* 2003;16:208–14. [PubMed: 12753387]
- [170]. Shoenfeld Y, Selmi C, Zimlichman E, Gershwin ME. The autoimmunologist: geoepidemiology, a new center of gravity, and prime time for autoimmunity. *J Autoimmun* 2008;31:325–330.
- [171]. Eaton WW, Rose NR, Kalaydjian A, Pedersen MG, Mortensen PB. Epidemiology of autoimmune diseases in Denmark. *J Autoimmun* 2007;29:1–9. [PubMed: 17582741]
- [172]. Rose NR. Autoimmunity in coxsackievirus infection. *Curr Top Microbiol Immunol* 2008;323:293–314. [PubMed: 18357776]
- [173]. Lieberman EB, Hutchins GM, Herskowitz A, Rose NR, Baughman KL. Clinicopathologic description of myocarditis. *J Am Coll Cardiol* 1991;18:1617–1626. [PubMed: 1960305]
- [174]. Rose NR, Neumann DA, Herskowitz A. Autoimmune myocarditis: concepts and questions. *Immunol Today* 1991;12(8):253–255. [PubMed: 1680335]
- [175]. Rose NR, Hill SL. The pathogenesis of postinfectious myocarditis. *Clin Immunol Immunopathol* 1996;80(3 Pt 2):S92–S99. [PubMed: 8811068]
- [176]. Rasooly L, Burek CL, Rose NR. Iodine-induced autoimmune thyroiditis in NOD-H-2h4 mice. *Clin Immunol Immunopathol* 1996;81(3):287–292. [PubMed: 8938107]
- [177]. Mackay IR, Leskovsek NV, Rose NR. Cell damage and autoimmunity: a critical appraisal. *J Autoimmun* 2008;30:5–11. [PubMed: 18194728]
- [178]. Whittingham S, Rowley MJ, Gershwin ME. A tribute to an outstanding immunologist - Ian Reay Mackay. *J Autoimmun* 2008;31:197–200. [PubMed: 18502096]
- [179]. Gershwin ME. Bone marrow transplantation, refractory autoimmunity and the contributions of Susumu Ikehara. *J Autoimmun* 2008;30:105–107. [PubMed: 18243658]
- [180]. Blank M, Gershwin ME. Autoimmunity: from the mosaic to the kaleidoscope. *J Autoimmun* 2008;30:1–4. [PubMed: 18191539]

Table 1

Recent Prevalence Data for Autoimmune Diseases, by Geographic Area

Disease ^a	Hospital-based Data, Denmark ^b			Hospital and non-Hospital- based Data		
	Rate per 100,000	Rate per 100,000	Study Area	Reference	Rate per 100,000	Study Area
Addison	18	11-14	UK, Italy, Norway	[4-6]		
Alopecia	21	1700	US	[7]		
Celiac disease	50	180-350	Greece, Netherlands	[8,9]	140-280	Iran, Tunisia
		740-1000	Iceland, Italy	[10,11]	470-600	Brazil, Argentina
		1900	Finland	[12]	900	Turkey
Crohn disease	225	28-53	Bosnia-Herzegovina, Hungary	[19,20]	6-53	Puerto Rico, Malaysia, Lebanon
		96-201	US, Spain, Denmark, New Zealand	[21-26]	113	Israel
Ulcerative colitis	378	143-294	US, Hungary, Denmark, New Zealand	[19,21-23,25,26]	6	Lebanon
					102	Puerto Rico
Diabetes	946	118	Lithuania	[31]		
All ages		340-570	UK, Sweden, Australia	[32-34]		
Ages < 20		87-120	Spain, Germany	[35,36]		
Ages < 20		227-355	US, New Zealand	[37,38]	31	Bahamas
Ages < 20		70	US- American Indian	[39]	110-270	Kuwait, Saudi Arabia
Liver - Chronic active hepatitis	45	11-17	Spain, Sweden, Norway	[43-45]	3-8	Singapore
		36	US-Alaska Natives	[46]		
Liver - Primary biliary cirrhosis	12	15-40	Norway, Finland, Spain, UK, US Australia	[45,48-51]	4-18	Israel
		4-20		[52]		
Thyroid - Hyper	629	500	US	[54]	20	Iran
		626	UK	[55]		
Thyroid - Hypo	62	300	US	[54]	350	Iran
		2980	UK	[55]		
Multiple sclerosis	182	177-358	US, Canada	[57-60]	4-20	Colombia, Brazil, Argentina
		100	Canada-First Nations	[60]	13	Japan
		121-200	Italy, Greece, France, Ireland, Norway	[61-69]	11-62	Israel, Kuwait, Jordan, Iran
		46		[70]	101	Turkey
Myasthenia gravis	18	50	Portugal New Zealand	[71]	3	Colombia
		8-15	Greece, Estonia, Croatia	[81-83]	7	Curacao and Aruba
			Netherlands, Sweden, UK	[84-86]		
Polymyalgia rheumatica	112	739 ^b	US	[89,90]		
		150-370 ^b	Greece	[91]		
Psoriasis	197	696-1527	US, UK	[92,93]		
Psoriatic arthritis		57	Greece	[94]		
		140-190	Iceland, Norway, Denmark, US	[95-98]		
Rheumatoid arthritis	381	500	Australia-Aborigine	[99]		
		310-810	France, Hungary, Spain, Turkey, Greece, UK	[91,100-105]	120-280	Thailand, Philippines, Vietnam, China
					510-550	India, Pakistan, Argentina
Sjögren disease	48	3500	UK	[112]	197	
		110	Denmark (ages 30-60)	[113]	330-770	China
		93-150	Greece	[91,114,115]	720-1560	Turkey (women)
		600	Greece - (women)	[116]		
		600	Slovenia	[117]		
Systemic sclerosis	23	5-34	France, Greece, Spain, Italy, US	[120-125]	20-24	Australia

Disease ^a	Hospital-based Data, Denmark ^b						Hospital and non-Hospital- based Data			
	Studies from Europe, North America, Australia, New Zealand			Studies from Asia, Middle East, Caribbean, South America						
	Rate per 100,000	Rate per 100,000	Study Area	Reference	Rate per 100,000	Study Area	Reference	Rate per 100,000	Study Area	Reference
Systemic lupus erythematosus	32	10–66 34–150 42	US-Native Americans US, Spain, Greece Canada-1 st Nations	[126] [128–131] [132]	30 19 45	Philippines Saudi Arabia Australia	[107] [133] [134]			
Systemic vasculitis		9–14	France, UK	[135,136]	93	Australia-aboriginal	[134]			
Wegener granulo-matosis	10	2–10	France, Norway, Australia, New Zealand	[135,137–140]	10	Australia	[137]			
Uveitis (iridocyclitis)	149	69–115	US, Finland	[141–143]	730	India	[144]			
Vitiligo	29				93	China	[145]			

^a Addison = primary adrenal insufficiency; diabetes = type 1 diabetes, systemic vasculitis based on the total of polyarteritis nodosa, microscopic polyangiitis, Wegener's granulomatosis, and Churg-Strauss syndrome.

^b based on data from Eaton et al., 2007; population-based study in Denmark using hospitalization records from 2001

^c rates per population ages >= 50 years

Table 2

Intra-person coexistence of autoimmune diseases

Reference Location Data source; Measure of Association ^a	Index disease cases; Control or reference population	Comorbid autoimmune disease(s)	Probands/Controls n (%) or n observed / n expected	Measure of Association (95% Confidence Interval)
Somers [146] United Kingdom, General Practice Research Database (pop-based); SIR	RA (n=22,888) RA AIT (n=26,198) AIT MS (n=4,332) MS T1DM (n=6,170) T1DM T1DM; UK general population	AIT MS RA MS RA AIT RA AIT MS	337 / 208.6 13 / 17.8 296 / 224.7 23 / 20.7 30 / 37.6 61 / 42.2 72 / 44.9 175 / 39.0 15 / 12.5	161.5 (145, 180) 73.2 (39, 125) 131.8 (117, 148) 111.0 (70, 167) 79.8 (54, 114) 144.4 (110, 185) 160.3 (125, 202) 449.0 (385, 521) 120.2 (67, 198)
Nielsen [148] Denmark Danish MS & Hospital Discharge Registers; SIR	MS (n=10,596); Danish general population	42 diseases ^b Ulcerative colitis Pemphigoid Pemphigus RA Temporal arteritis	133 / 153.1 29 / 14.9 12 / 0.8 2 / 0.03 28 / 53.0 11 / 20.6	0.9 (0.7, 1.0) 2.0 (1.4, 2.8) 15.4 (8.7, 27.1) 53.6 (13.4, 214.3) 0.5 (0.4, 0.8) 0.5 (0.3, 0.97)
Nielsen [147] Denmark Danish MS & Hospital Discharge Registers; SIR	MS (n=6078); Danish general population	T1DM	11 / 3.38	3.3 (1.8, 5.9)
Ramagopalan [149] Canada Longitudinal, pop-based MS study (19 centers); OR	MS (n=5031); Spousal controls (n=2707)	T1DM RA Ulcerative colitis Crohn disease Psoriasis Pernicious anemia SLE Vitiligo AITD MG ≥1 of above	19 (0.4); 24 (0.5) 153 (3.0); 66 (2.4) 9 (0.2); 4 (0.2) 11 (0.2); 4 (0.2) 293 (5.8); 146 (5.4) 123 (2.4); 25 (0.9) 28 (0.6); 7 (0.3) 35 (0.7); 12 (0.4) 395 (7.9); 116 (4.3) 7 (0.1); 3 (0.1) Not reported	0.7 (0.3, 1.6) ^c 1.3 (0.9, 1.7) ^c 1.2 (0.3, 5.4) ^c 1.5 (0.4, 6.4) ^c 1.1 (0.9, 1.3) ^c 2.7 (1.7, 4.3) ^c 2.2 (0.9, 5.9) ^c 1.6 (0.8, 3.3) ^c 1.9 (1.5, 2.4) ^c 1.3 (0.3, 7.5) ^c 1.1 (95% CI 0.86–1.2) ^c
Weng [151] California, US Kaiser Permanente Medical Care Plan; OR	IBD (n=12,601); Matched controls from database (n=50,404)	Psoriasis T1DM RA MS SLE Vitiligo AITD Chron glomer 6 other diseases ≥1 of above	242 (1.9); 495 (1.0) 122 (1.0); 346 (0.7) 165 (1.3); 307 (0.6) 49 (0.4); 74 (0.2) 27 (0.2); 72 (0.1) 23 (0.2); 53 (0.1) 32 (0.2); 104 (0.1) 14 (0.1); 29 (0.1) 46 (0.4); 77 (0.2) 2139 (17.0); 5131 (10.2)	1.7 (1.5, 2.0) 1.2 (0.9, 1.4) 1.9 (1.5, 2.3) 2.3 (1.6, 3.3) 1.3 (0.8, 2.1) 1.4 (0.8, 2.4) 1.1 (0.7, 1.6) 1.8 (0.9, 3.5) 2.1 (1.4, 3.0) 1.5 (1.4, 1.6)
Cohen [152] United States IMS Health & MarketScan (MKT) Claims databases; OR	IBD cases; matched controls from database MKT: IBD cases (n=6,139); controls (n=64,556) IMS: IBD cases (n=18,603); controls (n=66,969)	AS (MKT) AS (IMS) MS (MKT) MS (IMS) Psoriasis (MKT) Psoriasis (IMS) RA (MKT) RA (IMS)	not reported not reported not reported not reported not reported not reported not reported not reported	5.83 (3.93, 8.64) 7.79 (5.81, 10.83) 1.56 (1.18, 2.05) 1.53 (1.23, 1.91) 1.4 (1.27, 1.68) 1.51 (1.32, 1.73) 2.05 (1.84, 2.29) 2.72 (2.43, 3.04)
Alkhateeb [169] United States/Canada & United Kingdom Vitiligo Foundation/Society members; SPR	Vitiligo n=2078; Published population rates	Addison IBD Pernicious anemia SLE AITD 7 other diseases ^b	8 (0.38) / 0.1 ^c 14 (0.67) / 7.69 ^c 37 (1.78) / 3.12 ^c 4 (0.19) / 0.5 ^c 354 (17.0) / 39.5 ^c see footnote ^b	†8000 (3454, 15763) ^c †184.2 (101, 309) ^c †1185.9 (835, 1635) ^c †800.0 (218, 2048) ^c †896.2 (805, 995) ^c no association
Koulentaki [150] Crete Clinical series; SPR Eaton [2] Denmark Danish Hospital Discharge Register	Ulcerative colitis (n=412); Crete general population 31 autoimmune diseases	Primary biliary cirrhosis 465 pairwise comorbidities	2 / 0.06 see text for summary	‡3258.0 (395, 11769) see text for summary

Disease abbreviations used in table: AIT, autoimmune thyroiditis (hypo-); AITD, autoimmune thyroid disease (includes hypo- and hyper-); AS, ankylosing spondylitis; Chron glomer, chronic glomerulonephritis; IBD, inflammatory bowel disease; MG, myasthenia gravis; MS, multiple sclerosis; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus; T1DM, type 1 (insulin-dependent) diabetes mellitus.

^aOR, odds ratio; SIR, standardized incidence ratio (100 represents unity) and SPR, standardized prevalence ratio (100 represents unity)

^bData not shown for other pairs with no association detected

^ccalculation not published by study authors, therefore calculated by authors of review

Potential autoimmune disease associations within individuals described in the literature

Autoimmune hemolytic anemia		Hem
Autoimmune thrombocytopenic purpura		↑ AITP
Primary adrenal insufficiency (Addison's)		Add
Alopecia		Alop
Celiac disease		Cel
Inflammatory bowel disease		↑ IBD
Diabetes (type 1)		T1DM
Liver - Chronic active hepatitis		Hep
Liver - Primary biliary cirrhosis		↑ PBC
Thyroid - Hyperthyroidism (Grave's)		Grav
Thyroid - Hypothyroidism (Hashimoto's)		↑ Hash
Multiple sclerosis		↑ MS
Myasthenia gravis		MG
Polymyalgia rheumatica		PmR
Psoriasis		↑ Psor
Psoriatic arthritis		PsA
Rheumatoid arthritis		↑ RA
Ankylosing spondylitis		↑ AS
Idiopathic inflammatory myopathy		↑ IIM
Sjögren's syndrome		↑ Sjog
Systemic sclerosis (scleroderma)		↑ SSc
Systemic lupus erythematosus		SLE
Systemic vasculitis		↑ Vasc
Uveitis (iridocyclitis)		Uvei
Pemphigoid		↑ PemD
Pemphigus		↑ PemS

Vit
↓
NIH-PA Author Manuscript
↓
NIH-PA Author Manuscript
↓
NIH-PA Author Manuscript
Vitiligo

↑ positive association
↓ negative association

Table 4

Autoimmune co-occurrence in first degree relatives of index disease probands and controls (with disease verification by physician or chart review)

Reference Location, Data source, Measure of Association	Index disease; Control probands or reference population	Comorbid autoimmune disease(s)	First degree relative of probands / controls n (%); n (%) or n observed / n expected	Measure of Association (95% Confidence Interval)
Ginn [158] Maryland, USA Consecutive IIM patients referred to National Institutes of Health, OR	IIM probands (n=21); proband relatives (n=151); Control probands (n=21), Control relatives (n=143)	≥1 of 25 diseases ^b AITD	33 (21.9) / 7 (4.9) 13 (8.6) / 1 (0.7)	5.5 (2.3, 12.9) 13.4 (1.9, 572.3) ^d
Nielsen [147] Denmark Danish MS & Hospital Discharge Registers, SIR	MS probands (n=11,862), proband relatives (n= 14,771); Danish general population	T1DM	56 / 34.3	1.6 (1.3, 2.1)
Nielsen [148] Denmark Danish MS & Hospital Discharge Registers, SIR	MS probands (n=10,596), proband relatives (n=20,800); Danish general population	≥1 of 42 diseases ^b polyarteritis nodosa Addison disease Crohn disease UC	288; 235.9 4; 1.1 4; 1.2 44; 31.3 51; 39.1	1.2 (1.1, 1.4) 3.7 (1.4, 10.0) 3.4 (1.3, 9.0) 1.4 (1.04, 1.9) 1.3 (0.99, 1.7)
Broadley[155] United Kingdom MS referrals from throughout United Kingdom; spousal controls, OR	MS proband families (n=571); control families (n=375) ^c	≥1 of 11 diseases	96 (16.8) / 44 (11.7)	1.7 (1.1, 2.6)
Cooper [154] Canada SLE probands from 11 rheumatology clinics; population matched controls, OR	SLE proband relatives (n=626); Control relatives (n=267)	AIT Grave RA SLE SSc Sjögren's PM/DM APS Hemolytic anemia MS Vitiligo	37 (5.9) / 6 (2.2) 14 (2.2) / 0 (0) 15 (2.4) / 0 (0) 15 (2.4) / 0 (0) 3 (0.5) / 0 (0) 6 (1.0) / 0 (0) 0 (0.0) / 0 (0) 1 (0.2) / 0 (0) 1 (0.2) / 0 (0) 2 (0.3) / 0 (0) 0 (0) / 0 (0)	2.7 (1.1, 8.0) ^d ^e ^e ^e ^e ^e ^e ^e ^e ^e ^e
Anaya [156] Colombia, Multicenter cohort of consecutive T1DM patients; matched healthy controls	T1DM probands (n=98), proband relatives (n=312); Control probands (n=113), Control relatives (n=362)	≥1 of above ≥1 of 18 diseases SLE Vitiligo AITD	73 (11.7) / 6 (2.2) 26 (8.3) / 9 (2.4) 1 (0.3) / 0 (0) 1 (0.3) / 3 (0.8) 15 (4.8) / 6 (1.7)	5.7 (2.5, 16.3) ^d 3.56 (1.64, 7.73) ^e 0.4 (0.0, 4.8) ^d 3 (1.15, 7.82)
Anaya [157] Colombia Sjogren's clinical cohort (females); matched cases without autoimmune disease from same clinic, OR	Sjögren's probands (n=101), proband relatives (n=876) Control (n=124), control relatives (n=857)	SLE RA SSc PBC Vitiligo MS T1DM Grave AIT ≥1 of above	8 (7.9) / 1 (0.8) 15 (14.9) / 10 (8.1) 2 (2.0) / 0 (0) 1 (1.0) / 0 (0) 4 (4.0) / 3 (2.4) 1 (1.0) / 0 (0) 3 (3.0) / 1 (0.8) 1 (1.0) / 1 (0.8) 25 (2.9) / 17 (2.0) 56 (6.4) / 33 (3.9)	7.9 (1.1, 350.4) ^d 1.5 (0.6, 3.7) ^d ^e ^e 1.3 (0.2, 8.9) ^d ^e 2.9 (0.2, 154.6) ^d 1.0 (0.0, 76.9) ^d 1.5 (0.7, 2.9) ^d 1.7 (1.1, 2.7)

Disease abbreviations used in table : AIT, autoimmune thyroiditis (hypo-); AITD, autoimmune thyroid disease (includes hypo- and hyper-); APS, antiphospholipid antibody syndrome; IIM, idiopathic inflammatory myopathy; MS, multiple sclerosis; PBC, primary biliary cirrhosis; PM/DM, polymyositis/dermatomyositis; RA, rheumatoid arthritis; SSc, systemic sclerosis (scleroderma); SLE, systemic lupus erythematosus; T1DM, type 1 (insulin-dependent) diabetes mellitus ; UC, ulcerative colitis

^aOR, odds ratio; SIR, standardized incidence ratio (100 represents unity)

^bData not shown for other pairs with no association detected

^canalysis based on number of families, not number of relatives

^d calculation not published by study authors, therefore calculated by authors of review

^e OR and 95% CIs not calculated due to zero cell count