Are Individuals With an Autoimmune Disease at Higher Risk of a Second Autoimmune Disorder?

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Limited evidence suggests that autoimmune diseases tend to co-occur, although data are needed to determine whether individuals with an existing autoimmune disorder are at increased risk of a second disorder. The authors conducted a series of population-based cohort studies, utilizing the United Kingdom General Practice Research Database, to assess intraindividual risks of coexistence of rheumatoid arthritis (RA), autoimmune thyroiditis (AIT), multiple sclerosis (MS), and insulin-dependent diabetes mellitus (IDDM) during 1990–1999. Sex-specific age- and calendar-period standardized incidence ratios (SIRs) were calculated for development of a second autoimmune disease among index populations including 22,888 RA, 26,198 AIT, 4,332 MS, and 6,170 IDDM patients compared with the general population. Among those with IDDM, adjusted AIT rates were higher than expected for both males (SIR = 646.0, 95% confidence interval (CI): 466, 873) and females (SIR = 409.6, 95% CI: 343, 485), as were RA rates for females (SIR = 181.6, 95% CI: 136, 238). Coexistence of AIT and RA was also shown for either disease sequence (sex-specific SIRs = 130.4–162.0). However, point estimates suggested an inverse relation between RA and MS, irrespective of diagnostic sequence. This study demonstrates coexistence of RA, AIT, and IDDM at higher than expected rates but reduced comorbidity between RA and MS.

Autoimmune diseases cause substantial chronic morbidity; have a major impact on quality of life, health care utilization, and economic costs; and are associated with increased mortality. Although many autoimmune diseases are individually rare, collectively they have been estimated to afflict 1 in 31 Americans (1) and are a leading cause of death among young and middle-aged women (2). However, unlike other diseases with a common underlying pathogenesis (e.g., cancers or cardiovascular diseases), autoimmune disorders have traditionally been considered separate entities, and their etiologies are largely unknown (3). As a result, international organizations have emphasized the need for population-based epidemiologic research on autoimmune disorders (4).

The concept of shared autoimmunity within individuals and families, sometimes referred to as the “kaleidoscope of autoimmunity,” has gained acceptance (5–8), but it remains unclear whether there are predisposing factors to autoimmunity in general or to specific combinations of autoimmune diseases. Recent progress includes the identification of several loci with associations to more than one autoimmune disease in a large, United Kingdom–based genome-wide association study (9). However, clinical data related to the co-occurrence of autoimmune diseases are predominantly based on uncontrolled case series or small case-control studies from tertiary care settings, with few studies accounting for confounders such as age and sex (10). Defining the rates of coexistence of specific autoimmune diseases would provide clues about the shared pathogenesis of these autoimmune disorders and inform health planning and preventative strategies, and doing so would also aid interpretation of pharmacoepidemiologic research. For instance, a temporal association has been demonstrated between biologic

Abbreviations: GPRD, General Practice Research Database; IDDM, insulin-dependent diabetes mellitus.
treatments for autoimmune disorders (e.g., tumor necrosis factor inhibitors) and onset of central nervous system demyelination or multiple sclerosis (11–13). Without knowing the rate of coexistence of autoimmune disorders in the population, it is difficult to establish whether this occurrence is an adverse effect of biologics or simply the expected development of multiple autoimmune diseases within the same person.

We tested the hypothesis that autoimmune diseases coexist at a rate greater than expected by chance by performing a series of cohort studies in the population-based United Kingdom General Practice Research Database (GPRD). We focused on 4 diseases—rheumatoid arthritis, autoimmune thyroiditis, multiple sclerosis, and insulin-dependent (type 1) diabetes mellitus (IDDM). These diseases have been considered to share cytokine profiles indicative of T-helper 1 (Th1) cell predominance (14), although understanding of T-cell biology in human disease is undergoing revision given recent advances such as the identification of the unique T-helper 17 (Th17) subset (15). In addition, animal models have linked IDDM, autoimmune thyroiditis, and rheumatoid arthritis (16–18).

MATERIALS AND METHODS

Database and study population

The GPRD is described in detail elsewhere (19). It is the largest source of continuous data on morbidity and prescribing practice in the United Kingdom, comprising anonymized clinical records of patients registered with contributing general practices. Data include all morbid events, hospitalizations and specialist referrals/outcomes, prescriptions, significant test results, and dates of onset for chronic or recurrent conditions. The GPRD practices are representative of those in the United Kingdom in terms of geographic distribution, size, and the age and sex distributions of registered patients (20).

The period for this study was January 1, 1990, to December 31, 1999, encompassing approximately 33.5 million person-years at risk. We obtained ethics approval for this research from the Scientific and Ethical Advisory Group of the GPRD.

Identification of cases

Medical codes for the 4 autoimmune diseases of interest were identified from a GPRD coding dictionary by 4 investigators. For all 4 diseases, eligible cases needed to have at least one diagnostic code for the disease. General practitioners are not required to reenter diagnostic codes for chronic conditions once a diagnosis has been recorded (21). Additional eligibility criteria for autoimmune thyroiditis comprised a history of treatment for hypothyroidism and no history of thyroidectomy or radio-iodine therapy prior to a patient’s first autoimmune thyroiditis medical code. In iodine-replete areas, more than 90% of noniatrogenic hypothyroidism is autoimmune (22). For IDDM, eligible patients required a record of insulin treatment and an age at diagnosis of less than 35 years. For each disease, the date corresponding to the first relevant autoimmune disease record represented the date of diagnosis.

Statistical analysis

We performed a series of cohort studies to determine whether the rate of comorbid autoimmune disease(s) among index autoimmune disease patients was greater than expected by chance. In each cohort, all members were “exposed” to a first (index) autoimmune disease, and the outcome of interest was a subsequent (comorbid) autoimmune disease. We performed separate analyses for each pair and sequence of autoimmune diseases except for IDDM, which was considered only as an index disease because of its substantially younger age distribution compared with the other 3 diseases. Sex-specific age- and calendar-period standardized incidence ratios were calculated, comparing the incidence rate of the second autoimmune disease in index autoimmune disease patients with that in the general population registered with the GPRD as a whole (the reference population). For example, the rheumatoid arthritis index cohort comprised all patients diagnosed with rheumatoid arthritis as an index disease. The incidence for each of the other (comorbid) autoimmune diseases in the rheumatoid arthritis cohort was compared with the respective GPRD incidence rates for these diseases.

Calculating GPRD reference incidence rates. Cases were potentially incident if the date of diagnosis occurred during the study period, while the patient was registered with a practice contributing data to the GPRD. Because of retrospective recording of past diagnoses, incidence rates have been shown to be overestimated during the initial months after patients first register with a contributing general practice. The relevant time period during which overestimation occurs varies by disease, as demonstrated by Lewis et al. (23). We therefore undertook a series of analyses to determine the appropriate time periods for estimating incident cases, using a hazard function–based modification of the Lewis method that we developed previously, as described elsewhere (24). We determined that, for patients registering with a practice after it began contributing data to the GPRD, the minimum length of follow-up prior to diagnosis required to include patients as incident was 10 months for rheumatoid arthritis, 7 months for autoimmune thyroiditis, 5 months for multiple sclerosis, and 6 months for IDDM.

Crude and stratum-specific reference incidence rates were calculated by dividing the number of incident cases by age-, sex-, and calendar-year-specific GPRD population denominators. We also smoothed incidence rates by fitting fractional polynomials to the raw incidence rates to reduce random error from adjacent rate estimates (25, 26).

Conducting comorbidity analyses. Our primary analysis included all cases in the exposed cohorts, that is, patients with diagnoses of the index and comorbid autoimmune diseases occurring either before or during follow-up in the GPRD (Figure 1). For each cohort analysis, we used Lexis expansion to stratify person-time by age (in 5-year bands) and calendar period (single years). Chronologic age was used as the time scale for this analysis to directly account for age effects without parametric assumptions with respect to age (27–29). Patient follow-up continued until the earliest of the development of the comorbid autoimmune disease, death, the patient ceasing registration with the general population, or a minimum length of follow-up of 6 months for multiple sclerosis, 5 months for autoimmune thyroiditis, 7 months for rheumatoid arthritis, and 10 months for IDDM
practice contributing data to the GPRD, or the end of the
study on December 31, 1999 (Figure 1).
Secondary analyses were restricted to patients with both
index and comorbid diagnoses occurring during follow-up
in the GPRD (inception cohorts; Figure 1A) since these
diagnoses have been subject to quality control. Poisson re-
gression was used within these cohorts to investigate the
effects of consulting behavior and smoking (consultation
and smoking data were not available for pre-GPRD
follow-up). Consulting behavior was calculated as the
average annual number of visits from the time of the index
diagnosis until the end of the follow-up period and was
categorized into quartiles (0–4, 5–8, 9–12, ≥13) or consid-
ered missing for patients with less than 3 months of follow-
up after the index diagnosis. Smoking status was classified
as never, former, or current smoker, with missing data fitted
as a separate category in the analysis.
Data management and analysis were performed by using
SAS version 8 (SAS Institute, Inc., Cary, North Carolina)
and Stata version 8 (Stata Corporation, College Station,
Texas) software.

RESULTS
The index populations included 22,888 people with rheu-
atoid arthritis (70.2% female), 26,198 with autoimmune
thyroiditis (85.2% female), 4,332 with multiple sclerosis
(68.9% female), and 6,170 with IDDM (46.4% female).
Mean ages at diagnosis were 55.3 years (standard deviation,
17.5) for rheumatoid arthritis, 58.2 years (standard devia-
tion, 17.3) for autoimmune thyroiditis, 42.9 years (standard
deviation, 12.9) for multiple sclerosis, and 19.7 years (stan-
dard deviation, 9.8) for IDDM. Age distributions were
similar for patients diagnosed before or during follow-up
in the GPRD (data not shown).
The main results of the comorbidity analyses for all disease
combinations are summarized in Figure 2 and Table 1. Among
those with IDDM as the index autoimmune disease, age- and
calendar-period-adjusted rates of autoimmune thyroiditis
were more than 6 times higher than expected for males and
4 times higher for females. There was also an almost 2-fold
increase in adjusted rates of rheumatoid arthritis among
females. Other analyses demonstrated an interrelation be-
tween rheumatoid arthritis and autoimmune thyroiditis; in
both the autoimmune thyroiditis and rheumatoid arthritis in-
dex cohorts, we found evidence that subsequent occurrence of
the comorbid condition (rheumatoid arthritis or autoimmune
thyroiditis) was raised. In contrast was less evidence of an
association between multiple sclerosis and either autoimmune
thyroiditis or IDDM, except for a small increase in the risk of
autoimmune thyroiditis for females with index multiple scle-
rosis in one model. However, an inverse relation between
multiple sclerosis and rheumatoid arthritis was demonstrated,
irrespective of which disease was the index. Although the
confidence intervals overlapped 100, point estimates indicated
a substantial risk reduction for both males and females in each
of the models, with the negative association consistently of
stronger magnitude among males.
All modeling was repeated by utilizing smoothed ex-
pected incidence rates. No material difference was found
in the standardized incidence ratios thus calculated, al-
though comorbid autoimmune thyroiditis in the inception
cohort of female rheumatoid arthritis patients reached sig-
nificance (data not shown).
Similar associations were found when analyses were re-
stricted to inception cohorts, although estimates were more

Figure 1. Schematic for handling person-time that displays the various scenarios for accrual of person-time using, as an example, rheumatoid
arthritis (RA) as the index disease and autoimmune thyroiditis (AIT) as the comorbid disease. The inverted triangles labeled RA and AIT indicate
relative times of diagnosis of these diseases. The solid black lines indicate the period of person-time included in the comorbidity analyses. Primary
analyses encompassed scenarios A and B. Secondary analyses were restricted to the inception cohort (A). As illustrated in scenario C, when the
index disease of interest is diagnosed after the comorbid disease of interest, person-time is not included in the index analysis; in this example, RA is
actually the comorbid disease, so the patient would instead be eligible for inclusion in the AIT index analyses. GPRD, General Practice Research
Database; 1°C176, secondary; 2°C176, primary.

imprecise because of smaller numbers (Appendix Table 1). Sex-specific Poisson regression models for each disease pair and diagnostic sequence revealed no relation between smoking and secondary autoimmune disease (data not shown). For consulting behavior, increased rates of comorbid autoimmune diseases were found in the highest levels of consulting for some disease pairs; however, sample sizes in each stratum were small, and the incidence rate ratio estimates were statistically unstable.

**DISCUSSION**

This population-based study demonstrated positive associations between autoimmune thyroiditis, rheumatoid arthritis, and IDDM and suggests an inverse association between rheumatoid arthritis and multiple sclerosis, regardless of diagnostic sequence and after accounting for sex, age, and calendar period. To our knowledge, this research is the most comprehensive to date related to the coexistence of autoimmune disease within individuals.

Associations between autoimmune diseases may be understated by clinicians since, conventionally, they are treated in different clinical specialties (30). The coexistence of 2 autoimmune endocrinopathies, autoimmune thyroiditis and IDDM, has arguably been the best recognized. This study provides robust evidence for an increased incidence of autoimmune thyroiditis among IDDM patients. A moderate, bidirectional association within individuals was also found between rheumatoid arthritis and autoimmune thyroiditis. Since autoimmune thyroiditis and rheumatoid arthritis are among the most common of all autoimmune diseases, there was statistical power to detect smaller risk magnitudes for this pair of diseases compared with other combinations. Our research further documented that rheumatoid arthritis occurs at a higher rate than expected among IDDM patients, with the association most clearly detected for females.

Interrelations between multiple sclerosis and the other 3 diseases are more complex. This study does not support an association between multiple sclerosis and IDDM, although, because of the small number of comorbid cases, statistical

Coexistence of Autoimmune Diseases in Individuals

Table 1. Observed and Expected Number of Comorbid Autoimmune Disease Cases and Standardized Incidence Ratios Among Female and Male Index Autoimmune Patients in the United Kingdom General Practice Research Database, 1990–1999

<table>
<thead>
<tr>
<th></th>
<th>Comorbid AIT</th>
<th>Comorbid MS</th>
<th>Comorbid RA</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Obs</td>
<td>Exp</td>
<td>SIR*</td>
</tr>
<tr>
<td>RA index (n = 22,888)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>337</td>
<td>208.61</td>
<td>161.5***</td>
</tr>
<tr>
<td>Female</td>
<td>310</td>
<td>191.32</td>
<td>162.0***</td>
</tr>
<tr>
<td>Male</td>
<td>27</td>
<td>17.28</td>
<td>156.2*</td>
</tr>
<tr>
<td>AIT index (n = 26,198)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>23</td>
<td>20.72</td>
<td>111.0</td>
</tr>
<tr>
<td>Female</td>
<td>23</td>
<td>19.34</td>
<td>118.9</td>
</tr>
<tr>
<td>Male</td>
<td>0</td>
<td>1.38</td>
<td>0.0</td>
</tr>
<tr>
<td>MS index (n = 4,332)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>61</td>
<td>42.24</td>
<td>144.4**</td>
</tr>
<tr>
<td>Female</td>
<td>58</td>
<td>39.24</td>
<td>147.8**</td>
</tr>
<tr>
<td>Male</td>
<td>3</td>
<td>3.00</td>
<td>99.9</td>
</tr>
<tr>
<td>IDDM index (n = 6,170)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>175</td>
<td>38.97</td>
<td>449.0***</td>
</tr>
<tr>
<td>Female</td>
<td>133</td>
<td>32.47</td>
<td>409.6***</td>
</tr>
<tr>
<td>Male</td>
<td>42</td>
<td>6.50</td>
<td>646.0***</td>
</tr>
</tbody>
</table>

Abbreviations: AIT, autoimmune thyroiditis; CI, confidence interval; Exp, expected; IDDM, insulin-dependent diabetes mellitus; MS, multiple sclerosis; Obs, observed; RA, rheumatoid arthritis; SIR, standardized incidence ratio.

* P < 0.05; **P < 0.01; ***P < 0.001.

Both incident and prevalent index cases were included (primary analysis).

Adjusted for age and calendar period.

A 1-tail, 97.5% CI was calculated because there were zero expected cases.

precision was particularly low for this pair of diseases. Taken as a whole, the data also failed to support an association between multiple sclerosis and autoimmune thyroiditis. However, contrary to our hypothesis, the data suggested reduced comorbidity between multiple sclerosis and rheumatoid arthritis, although confidence intervals overlapped 100. This novel finding has important pharmacoepidemiologic implications, because it undermines the assertion that cases of multiple sclerosis among patients treated with tumor necrosis factor inhibitors are simply coincidental given an absence of true associations between the diseases under study. Therefore, the existence of true associations between the diseases under study.

Another consideration is whether treatment of an index autoimmune disease affects risk of developing a comorbid disease. Although nonspecific immunosuppressives could in theory decrease risk of a comorbid autoimmune disease, targeted therapies could have differential effects. For example, an intriguing finding based on a rodent model of chronic demyelination indicates that administration of thyroid hormone can enhance remyelination under certain conditions (31, 32). Relevance of this finding to multiple sclerosis in humans is unknown, but, hypothetically, routine treatment of hypothyroidism could diminish the risk of multiple sclerosis. Conversely, there have been reports that interferon-beta treatment for multiple sclerosis can induce antithyroid antibodies and thyroiditis (33–35), although this finding has been refuted by others (36–38).

Unlike previous studies, we used a statistically powerful data source (>30 million person-years) to investigate uncommon autoimmune disorders as exposures and outcomes. Our analytic approach, including use of Lexis expansion to classify person-time according to multiple time scales simultaneously, is a novel adaptation of methods more traditionally used in the context of occupational epidemiology. Autoimmune disease incidence is strongly influenced by age, sex, and calendar period. We were able to generate sex-specific expected rates from the underlying source population, using the same case definitions and categorization of age and calendar period in narrow bands, rather than relying on population data derived from differing methodology, time periods, or geographic regions.

However, this study highlights that, even when using the largest available population-based source of longitudinal data, power was limited to investigate some rare disease combinations or to perform meaningful subset analyses. Another limitation is that, since the GPRD is a broad-spectrum database not customized for particular research questions, classification of disease status relied upon diagnoses recorded by general practitioners in the course of routine clinical practice and did not follow standardized, disease-specific protocols. For example, differentiation of type 1 versus type 2 diabetes may have been imperfect because some diagnostic codes were nonspecific for the type of diabetes, although the additional requirements in our case definition of age less than 35 years at diagnosis and insulin treatment would be expected to eliminate the vast majority of type 2 diabetes. It was not possible during the course of this study to access original medical records to directly validate diagnoses and their dates of occurrence, although independent studies have documented the high quality and completeness of GPRD morbidity data (19).

Overall, this research confirms that some autoimmune diseases co-occur with one another at a rate greater than expected by chance, but it reveals that this phenomenon is not generalized across all autoimmune diseases. Our results may be of value for targeting screening for comorbid autoimmune diseases among individuals with specific autoimmune index disorders to limit subsequent ill health. Assessment of the utility and cost-effectiveness of thyroid screening warrants consideration for IDDM and rheumatoid arthritis patients, and at significantly younger ages than in the general population. Also, vigilance for early signs of rheumatoid arthritis is indicated in autoimmune thyroiditis and IDDM populations, since early treatment is critical to minimizing irreversible damage. Establishing patterns of coexistence between autoimmune diseases may inform better classification of this set of diseases, and it may provide important clues as to their pathogenesis. Future research should be aimed at identifying the factors underlying the clinical associations between autoimmune diseases.

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Conflict of interest: none declared.

REFERENCES


Appendix Table 1. Data From Secondary Analyses, Restricted to Inception Cohorts, Regarding Observed and Expected Number of Comorbid Autoimmune Disease Cases and Standardized Incidence Ratios Among Female and Male Index Autoimmune Patients in the United Kingdom General Practice Research Database, 1990–1999

<table>
<thead>
<tr>
<th>Comorbid AIT</th>
<th>Comorbid MS</th>
<th>Comorbid RA</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Observations</strong></td>
<td><strong>Expected</strong></td>
<td><strong>SIR</strong></td>
</tr>
<tr>
<td><strong>RA index (n = 18,408)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>105</td>
<td>91.48</td>
</tr>
<tr>
<td>Female</td>
<td>99</td>
<td>83.01</td>
</tr>
<tr>
<td>Male</td>
<td>6</td>
<td>8.47</td>
</tr>
<tr>
<td><strong>AIT index (n = 19,136)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>8</td>
<td>6.96</td>
</tr>
<tr>
<td>Female</td>
<td>8</td>
<td>6.49</td>
</tr>
<tr>
<td>Male</td>
<td>0</td>
<td>0.47</td>
</tr>
<tr>
<td><strong>MS index (n = 3,136)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>12</td>
<td>11.83</td>
</tr>
<tr>
<td>Female</td>
<td>11</td>
<td>10.92</td>
</tr>
<tr>
<td>Male</td>
<td>1</td>
<td>0.92</td>
</tr>
<tr>
<td><strong>IDDM index (n = 3,084)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>16</td>
<td>2.43</td>
</tr>
<tr>
<td>Female</td>
<td>13</td>
<td>2.12</td>
</tr>
</tbody>
</table>

Abbreviations: AIT, autoimmune thyroiditis; CI, confidence interval; Exp, expected; IDDM, insulin-dependent diabetes mellitus; MS, multiple sclerosis; Obs, observed; RA, rheumatoid arthritis; SIR, standardized incidence ratio.

* P < 0.01; **P < 0.001.

* Adjusted for age and calendar period.

b A 1-tail 97.5% CI was calculated since there were zero expected cases.
