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

Emily C. Somers, Sara L. Thomas, Liam Smeeth, and Andrew J. Hall

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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...
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-cell biology in human disease is undergoing revision given recent advances such as the identification of the unique T-helper 1 (Th1) cell predominance (14), although understanding of T-cell biology in human disease is undergoing further study to understand the role of cytokines in disease pathways. 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 morbidity 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

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 regression 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 considered 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 rheumatoid 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 deviation, 17.3) for autoimmune thyroiditis, 42.9 years (standard deviation, 12.9) for multiple sclerosis, and 19.7 years (standard 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 between rheumatoid arthritis and autoimmune thyroiditis; in both the autoimmune thyroiditis and rheumatoid arthritis index 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 sclerosis 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 expected incidence rates. No material difference was found in the standardized incidence ratios thus calculated, although comorbid autoimmune thyroiditis in the inception cohort of female rheumatoid arthritis patients reached significance (data not shown).

Similar associations were found when analyses were restricted to inception cohorts, although estimates were more...
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 underascertained 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

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**Figure 2.** Sex-specific standardized incidence ratios and 95% confidence intervals for the existence of comorbid autoimmune diseases within each index disease category (a standardized incidence ratio of 100 indicates unity). Estimates correspond to the primary and secondary modeling approaches, as described in the Materials and Methods section of the text. For disease combinations for which no comorbid cases were observed and the standardized incidence ratio was consequently zero, the point estimate is graphed with the value of 1 to conform to the log scale, and a 1-tail, 97.5% confidence interval is presented. Solid symbols (▲): females; hollow symbols (△): males. Comorbid autoimmune diseases: ▲/△, rheumatoid arthritis (RA); ■/●, autoimmune thyroiditis (AIT); ♦/♦, multiple sclerosis (MS). IDDM, insulin-dependent diabetes mellitus.
bias warrants consideration since patients with chronic condi-
tions are seen more frequently by general practitioners. We
found a suggestion of increased rates of comorbid diagnoses
among patients in the highest quartile for consulting rate ($\geq 13
average annual general practitioner visits). However, qualitative
rather than statistical assessment of the potential for de-
tection bias for each disease combination is more appropriate,
because consulting behavior is an imperfect proxy and may
also be related to index disease severity. Consideration of the
interrelations between all 4 diseases informs interpretation of
the paired findings, and the putative inverse relation between
multiple sclerosis and rheumatoid arthritis—albeit failing to
reach statistical significance—argues against pervasive detect-
tion bias. Likewise, similarities in direction and magnitude of
associations regardless of diagnostic sequences support the
existence of true associations between the diseases under study.

Another consideration is whether treatment of an index au-
toimmune disease affects risk of developing a comorbid disease.
Although nonspecific immunosuppressives could in theory de-
crease risk of a comorbid autoimmune disease, targeted thera-
pies could have differential effects. For example, an intriguing
finding based on a rodent model of chronic demyelination in-
dicates 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 hypothryroidism 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).

### 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 MS</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.

The GPRD facilitates investigation of diseases with varying referral patterns without the selection biases inherent to clinic-based studies, and it captures disorders such as thyroid disease that may not reach tertiary care settings. However, detection bias warrants consideration since patients with chronic conditions were 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 pharmacoeconomicologic implications, because it undermines the assertion that cases of multiple sclerosis among patients treated with tumor necrosis factor inhibitors are simply coincidental given an underlying autoimmune diagnosis. Since our study period predated availability of tumor necrosis factor inhibitors in the United Kingdom, our results were not confounded by this treatment parameter, providing a unique opportunity to characterize baseline rates of coexistence in a population of rheumatoid arthritis and multiple sclerosis patients naive to this type of biologic therapy. Although mechanisms underlying the inverse relation between rheumatoid arthritis and multiple sclerosis will need to be elucidated, our results indicate that these 2 diseases do not entirely share the same risk factor profiles and that certain factors in the causal pathways may confer susceptibility for one of these diseases yet protection against the other. Our data further support the concept that the Th1/Th2 classification of diseases is overly simplistic.

The GPRD facilitates investigation of diseases with varying referral patterns without the selection biases inherent to clinic-based studies, and it captures disorders such as thyroid disease that may not reach tertiary care settings. However, detection bias warrants consideration since patients with chronic conditions are seen more frequently by general practitioners. We found a suggestion of increased rates of comorbid diagnoses among patients in the highest quartile for consulting rate ($\geq 13$ average annual general practitioner visits). However, qualitative rather than statistical assessment of the potential for detection bias for each disease combination is more appropriate, because consulting behavior is an imperfect proxy and may also be related to index disease severity. Consideration of the interrelations between all 4 diseases informs interpretation of the paired findings, and the putative inverse relation between multiple sclerosis and rheumatoid arthritis—albeit failing to reach statistical significance—argues against pervasive detection bias. Likewise, similarities in direction and magnitude of associations regardless of diagnostic sequences support 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 diabetics. 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 particular interest to comorbidity research 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 significant 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>RA index (n = 18,408)</strong></td>
<td><strong>RA index (n = 18,408)</strong></td>
<td><strong>RA index (n = 18,408)</strong></td>
</tr>
<tr>
<td>Total</td>
<td>Obs</td>
<td>105</td>
</tr>
<tr>
<td>Female</td>
<td>Obs</td>
<td>99</td>
</tr>
<tr>
<td>Male</td>
<td>Obs</td>
<td>6</td>
</tr>
<tr>
<td><strong>AIT index (n = 19,136)</strong></td>
<td><strong>AIT index (n = 19,136)</strong></td>
<td><strong>AIT index (n = 19,136)</strong></td>
</tr>
<tr>
<td>Total</td>
<td>Obs</td>
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</tr>
<tr>
<td>Female</td>
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<tr>
<td>Male</td>
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<tr>
<td><strong>MS index (n = 3,136)</strong></td>
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<td><strong>MS index (n = 3,136)</strong></td>
</tr>
<tr>
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<td>Female</td>
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<tr>
<td>Male</td>
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<tr>
<td><strong>IDDM index (n = 3,084)</strong></td>
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</tr>
<tr>
<td>Total</td>
<td>Obs</td>
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</tr>
<tr>
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</tr>
<tr>
<td>Male</td>
<td>Obs</td>
<td>3</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.

a Adjusted for age and calendar period.

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