Autoimmune Diseases Co-occurring Within Individuals and Within Families

A Systematic Review

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

Background: Autoimmune diseases have been observed to coexist both within individuals and within families. It is unclear whether clinical reports of comorbid autoimmune diseases represent chance findings or true associations. This systematic review evaluates the current level of evidence on the coexistence of selected autoimmune diseases within individuals and families. We reviewed the associations among 4 T_H1-associated autoimmune diseases: insulin-dependent diabetes mellitus, autoimmune (Hashimoto) thyroiditis, rheumatoid arthritis, and multiple sclerosis.

Methods: Studies quantifying the coexistence between the selected diseases, published through March 2004, were identified from Medline and Embase searches. Study eligibility was determined on the basis of preestablished criteria, and relevant data were extracted according to a fixed protocol. We determined the prevalence of comorbid autoimmune disease according to index disease and then compiled summary statistics. Heterogeneity among studies was assessed by exact likelihood ratio tests and Monte Carlo inference.

Results: We found 54 studies that met the eligibility criteria. Of these, 52 studies examined the coexistence of disease within individuals and 9 studies examined within-family associations. The majority of studies were uncontrolled and did not account for confounding factors. There was substantial evidence for heterogeneity among studies. Although inconclusive, the data appear to support an increased prevalence of autoimmune thyroiditis among patients with rheumatoid arthritis and those with insulin-dependent diabetes mellitus, and an inverse association between rheumatoid arthritis and multiple sclerosis.

Conclusion: Although the available evidence does not permit firm conclusions regarding comorbidities among the selected autoimmune diseases, results are sufficiently suggestive to warrant further study.

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From the Departments of *Infectious and Tropical Diseases and ‡Epidemiology and Population Health, London School of Hygiene & Tropical Medicine, London, U.K.; and the †Division of Rheumatology, University of Michigan, Ann Arbor, MI.

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Correspondence: Emily C. Somers, University of Michigan Health System, Division of Rheumatology, 1150 W. Medical Center Dr., 5520 MSRB 1, Ann Arbor, MI 48109-0680. E-mail: emsomers@umich.edu.

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Autoimmune diseases include a diverse group of chronic disorders associated with substantial public health impact.[1] Anecdotal evidence suggests that autoimmune diseases tend to coexist both within individuals and within families, and the concept of an autoimmune diathesis is widely accepted. However, the patterns of association among autoimmune diseases have not been evaluated in a systematic fashion, and it is unclear whether clinical reports of comorbid autoimmune diseases represent chance findings or true associations.

Animal models demonstrate a clear association between different types of autoimmune disorders. For example, nonobese diabetic mice frequently develop thyroiditis and sialoadenitis in addition to autoimmune insulin-dependent diabetes.[2] These mice crossed with KRN mice (a T-cell receptor transgenic line) develop a disease, closely resembling human rheumatoid arthritis.[3] SJL mice (a model of experimental autoimmune encephalomyelitis) are highly susceptible to a number of experimentally induced autoimmune diseases.[4] Although genetic background is important, exogenous factors (such as level of microbial exposure or xenobiotics) can modulate the development of disease in autoimmune-prone animal models.[5–7]

Common features in the immunoepidemiology of various autoimmune diseases are recognized, and reports of shared risk factors are emerging.[8–10] However, the etiologies of most autoimmune diseases remain poorly understood. Because autoimmune diseases are conventionally treated by separate medical specialties according to type of organ involvement, there are missed opportunities to study these diseases as a group. We are interested in the premise that interaction between genetic background and early life programming due to environmental exposures may result in general susceptibility to autoimmune disease. Characterization of the extent to which particular combinations of autoimmune diseases occur in excess of that expected by chance may offer insight into shared pathophysiological mechanisms.

We undertook a systematic literature review to quantify the coexistence of selected autoimmune diseases within individuals and families. We reviewed the associations among 4 autoimmune diseases: insulin-dependent diabetes mellitus (IDDM), autoimmune (Hashimoto) thyroiditis (AIT), rheumatoid arthritis (RA), and multiple sclerosis (MS). We chose to focus on these diseases for several reasons. Evidence of associations between these diseases in animal models imparts plausibility for their coexistence in humans. Moreover, these

diseases are sufficiently common, in contrast to many other autoimmune diseases, to provide a reasonable expectation of detecting them in combination.

A further consideration is that these disorders are widely considered to be T_H1-associated. Mosmann et al[11] described 2 functional subsets of T-helper cells in mice, T_H1 and T_H2, characterized by different patterns of cytokine secretion. T_H1 and T_H2 cells are also distinguishable on the basis of chemokine receptors.[12] Immune-mediated disorders in mouse models can be classified as T_H1- or T_H2-associated according to the predominant cytokine profile. Although this is an oversimplified approach for the classification of disease in humans, and additional subsets of T cells have been more recently identified (Th3 and Tr1),[13] the 4 diseases that we included in this review have nonetheless been described as having characteristics of T_H1 predominance.[14,15] One can speculate that mutual genetic or environmental factors influencing cytokine regulation or T-cell polarization are relevant to T_H1-associated disorders, and that these conditions would tend to coexist within individuals and possibly within families.

METHODS

Identification of Studies and Data Extraction

We identified studies quantifying the coexistence of selected autoimmune diseases, published through March 2004, from Medline (Ovid) and Embase electronic databases. These databases cover literature from 1966 and from 1980, respectively. Identification of articles was performed by searching the databases on a combination of thesaurus terms. No language restrictions were applied. In Medline, thesaurus terms for the 4 prespecified autoimmune diseases were exploded for "diabetes mellitus, type 1," "multiple sclerosis," "arthritis, rheumatoid," and "thyroiditis, autoimmune" or "thyroiditis, subacute" or "thyroid diseases." For all diseases, the search was restricted to the subheadings of complications, epidemiology, etiology, genetics, and physiopathology. The results from each search were crosstabulated with all the other searches to identify publications with any combination of at least 2 of the specified diseases. A similar search strategy was used in Embase (list of terms available on request). Review articles published within the last 5 years on the epidemiology of each of the autoimmune diseases were also identified. Reference lists from all relevant articles were examined for studies that were not captured by the computerized searches. A textbook on rheumatic disease epidemiology[16] was also reviewed.

Studies were eligible for inclusion in the review if the coexistence of 2 or more prespecified autoimmune diseases, either within individuals or among first-degree relatives (parents, siblings, children), was reported. Uncontrolled case series were eligible if a denominator was documented. For studies of individuals, the denominator was the total number of index disease cases. For family studies, the denominator was considered to be the number of relatives rather than the number of families. Studies were excluded if: (1) they were clinical/laboratory studies that selected patients based on prespecified proportions of comorbid autoimmune conditions (eg, a case–control study of patients with RA with IDDM versus patients with RA without IDDM); (2) they were restricted to seroprevalence of autoantibodies rather than clinical disease (because autoantibodies can occur in healthy individuals); (3) there was insufficient distinction between diagnostic categories (eg, type 1 vs type 2 diabetes, rheumatoid arthritis vs osteoarthritis, autoimmune vs nonautoimmune thyroid disease); (4) they were restricted to families having multiple members with autoimmune diseases; (5) they were restricted to women during pregnancy or the postpartum period; or (6) their results were not sufficiently clear to determine prevalence. Furthermore, articles were excluded if autoimmune disease coexistence was reported in the context of a known genetic syndrome, eg, autoimmune polyglandular syndrome.[17] For studies with index disease case groups meeting eligibility criteria, but control groups failing to meet criteria (eg, cross-sectional studies that recruited "healthy controls"), only data regarding the index disease case groups were included in this review. For the purposes of this review, we did not consider patients with only "subclinical" hypothyroidism (elevated thyroid-stimulating hormone [TSH] but normal thyroid function, ie, normal circulating concentrations of free T_3 and T_4) to have autoimmune thyroiditis.[18]

A primary reviewer screened all titles and abstracts of publications identified by the literature search for eligibility. Articles were rejected if they clearly did not meet eligibility criteria. The full text of all articles possibly meeting inclusion criteria was obtained and screened. A secondary reviewer was consulted in cases in which eligibility of the article was unclear.

We categorized each study according to index and comorbid disease. For example, if a series of patients with RA was evaluated for the presence of another disease, we considered RA to be the index disease and any secondary condition as comorbid. Controls (when applicable) were persons who did not have the index disease but may have been positive for the comorbid disease. For the family studies, we use the term "case proband" to represent individuals with the index disease and the term "control proband" for nonindex disease controls. Similarly, "case relatives" are relatives of the case probands, and "control relatives" are relatives of the control probands. We included any results regarding the prevalence of comorbid disease among probands in the section on intraindividual disease.

We used a standardized data collection form to extract data, including study design and population, number of index disease cases and controls, incidence/prevalence of coexistent autoimmune diseases, diagnostic criteria used for index and comorbid diseases, potential confounding factors (eg, sex, age), and crude and adjusted relative risk estimates (odds ratios [OR] or standardized prevalence ratios, as appropriate) with 95% confidence intervals (CIs). The effect estimates refer to comorbid autoimmune diseases within index disease cases compared with controls. For family studies, data collection was modified to include the number of index disease and control probands, and the number and proportion of relatives of probands with coexistent autoimmune diseases.

Analysis

We computed comorbid autoimmune disease prevalence and corresponding exact binomial 95% CIs separately for index disease cases and controls. For studies that included raw data from control or reference groups without presentation of risk estimates relative to the index group, we calculated measures of relative risk (RR) and 95% CIs. We used ORs and exact 95% CIs for case–control studies. For studies including population-based reference data, we calculated standardized prevalence ratios (SPRs) and CIs based on the Poisson distribution for comparison of the observed number of comorbid cases with that expected based on the population reference values. We assessed heterogeneity among studies (within each combination of diseases) by exact likelihood ratio tests and Monte Carlo inference to determine whether it was appropriate to obtain pooled estimates of prevalence or relative risk. We conducted statistical analyses using Stata version 8 (Stata Corp., College Station, TX) and StatXact version 6 (Cytel Software Corp., Cambridge, MA).

RESULTS

Studies Identified

We identified 1187 publications from the Medline and Embase searches, of which we judged 86 to be potentially eligible based on initial screening. Of these, 39 met inclusion criteria. We identified a further 67 articles from reference lists for screening, of which 15 fit inclusion criteria. Thus, in total, we included 54 articles in this review. Studies are summarized in Tables 1 and 2.

Comorbidity of Autoimmune Diseases Within Individuals

Fifty-two studies examined the coexistence within individuals of at least 2 of the selected autoimmune diseases. Only 16 of these studies had control groups or presented expected values based on population data. For each of the within-individual studies, the prevalence estimates and 95% CI for comorbid autoimmune diseases within index disease cases are displayed in a forest plot (Fig. 1). For context, background prevalence estimates based on data from a systematic review of epidemiologic data from the United States by Jacobson et al[19] are as follows: RA 0.86%, IDDM 0.19%, AIT 0.79% adults/0.53% children (10–19 years), and MS 0.06%. However, these estimates provide only a crude comparison for the studies summarized in this review, because the populations varied considerably in terms of demographic structures, geographic locations, and time periods.

With the exception of comorbid RA among MS index cases, there was strong evidence of heterogeneity for all disease combinations (P for heterogeneity all <0.0001). Given such heterogeneity, we did not focus on pooled estimates or perform an overall meta-analysis. Study findings are reviewed here according to each index disease category.

Rheumatoid Arthritis

Eleven intraindividual studies included RA as the index disease; one additional study included juvenile rheumatoid arthritis (JRA) index cases. Five studies examined the coexistence of IDDM[20–24] with IDDM prevalence among RA index cases ranging from 0.32% to 5.95%. Of the 2 studies with controls,[21,22] ORs were undefined, because neither study found any coexistent IDDM in the control groups. Neither study adjusted for confounders such as sex or age. The only population-based study, which arguably followed the most rigorous methodology, found no association between IDDM and RA when standardized to the source population.

Eight studies[20,22,25–30] examined the prevalence of comorbid AIT (autoimmune thyroiditis) among RA index cases, with estimates ranging from 0.5% to 9.8%. A ninth study of JRA index cases found 4.5% prevalence for comorbid AIT.[31] Of the 4 controlled studies,[22,25,27,28] all found increased odds ratios for AIT among the RA cases versus controls, although CIs were wide and overlapped one in 2 cases. One of the studies was from a postmortem setting, limiting its comparability to the other studies.[25] The only population-based study found no association based on expected values from the source population.[20]

Insulin-Dependent Diabetes Mellitus

Twenty-seven studies[32–58] with IDDM as the index disease were identified. All studies assessed coexistent AIT and one also examined coexistent JRA.[47] Comorbid AIT prevalence among the IDDM cases ranged from 0% to 24%. The study with the second highest prevalence[40] was a long-term follow-up assessment of adults who had been diagnosed with IDDM as children or adolescents; the other studies were conducted in pediatric to young adult populations. None of the studies was population-based, and the only controlled study[45] found no cases of AIT in the control group of "healthy" children, although it is unclear whether the latter category excluded children with prevalent clinical thyroid disease.

Multiple Sclerosis

Seven studies were included,[59–65] some of which explored more than one comorbid disease. The coexistence of RA was assessed in 5 studies,[59–62,64] with prevalence estimates ranging from 0.35% to 2.4%; a sixth study[65] that assessed comorbid JRA found 0.28% prevalence. Comorbid RA among patients with MS was the only disease combination for which there was no evidence of heterogeneity among studies ($P = 0.17$). The weighted mean prevalence of RA in patients with MS was 0.63% (excluding the JRA study). Two studies[61,64] had control groups; one found no cases of comorbid RA among hospital-based controls, and the other found an OR of less than 1.0 for comorbid RA among MS cases versus spouse or friend controls, although the CIs were wide and overlapped one. A third study[62] documented an SPR of 0.60 (95% CI = 0.2–1.41), but the reference values were derived from geographic regions outside of the MS study area.

IDDM coexistence was assessed in 6 studies,[59,61–65] with prevalence estimates ranging from 0% to 2.6%. There was no evidence for an association between IDDM and MS in the 2 controlled studies.[61,64] However, the study that included referent data from its source population found an increased association between IDDM and MS.[63]

TABLE 1. Summary of Studies Examining Coexistence of Autoimmune Diseases Within Individuals, Grouped by Index Disease

Author Study Period or Publication Date Location	Study Population Sex/Age—Index Cases Duration of Index Disease	Control or External Population Sex/Age—Controls	Comorbid Disease	Diagnostic Criteria		No. of Cases/ No. of Controls	Comorbidity		OR or SPR (95% CI)*
				Index Disease	Comorbid Disease		Among Cases No. (%)	Among Controls No. (%)	
Rheumatoid arthritis									
Linos[20]	Population-based	Rochester, MN population	IDDM	ARA[79]	IDDM—Palumbo[80]		31 (6)	—	SPR 0.93 (0.6–1.3)[†‡]
1950–1974	F 74.1%/age NR		AIT		AIT—Furszyfer[81]	521/NA	11 (2)		SPR1.39 (0.7–2.5)[†‡]
Rochester, MN	Duration NR								
Panczel[21§]	Case–control, hospital-based	Arthrosis	IDDM	ARA[82]	IDDM-NDDG[83]	310/310	1 (<1)	0 (0)	OR = undefined[‡]
1980–1983		F 92.3%/56.6 ± 13 y							
Hungary	F 92.3%/56.2 ± 11 y								
	Duration NR								
Thomas[22]	Case–control, clinic-based	OA	IDDM	ARA[79]	IDDM—age and insulin	295/307	2 (1)	0 (0)	OR = undefined[‡‖]
1983 (pub)	Sex NR/52 y (21–83)	NR/53 y (21–91 y)							
London, U.K.	Duration NR		AIT		AIT-NR		8 (3)	6 (2)	1.4 (0.4–4.9)[‡]
Hakala[23]	Hospital series	—	IDDM	ARA[82]	NR	1460/NA	9 (1)	—	—
1992 (pub)	Sex NR/age NR								
Finland	Duration NR								
Vaidya[24]	Clinic-based series	—	IDDM	ARA[84]	NR	123/NA	4 (3)	—	—
2002 (pub)	F 65%/53.7 y								
Newcastle-upon-Tyne, U.K.	<2 y								
Becker[25]	Necropsy-based case–control	Postmortem, non-RA	AIT	ARA[85]	AIT—histology/ anatomy	51/15,672	5 (10)	139 (1)	12.1 (3.7–31.1)
1941–1961		Sex/age—NR							
MN	Sex NR/age NR								
	Duration NR								
Herrmann[26§]	Clinic-based series	—	AIT	NR	AIT—clinical/lab/ ultrasound	201/NA	3 (1)	—	—
1990 (pub)	F 86%/49.2 y								
Leipzig, Germany	Duration NR								
Benamour[29§]	Clinic-based	—	AIT	ARA[84]	AIT—NR	404/NA	2 (<1)	—	—
1981–1991	F 87.4%/34.4 (15–74 y)								
Casablanca, Morocco	>3 y for 45% of patients								
Shiroky[27]	Case–control, clinic-based	OA or fibromyalgia	AIT	ARA[84]	AIT—biopsy-proven	119/108	6 (5)	1 (1)	5.7 (0.67–263.68)[‡]
1993 (pub)	F 76.5%/58.7 y (21–84)	F 86.1%/58.8 y (29–86)							
Montreal, Canada	Duration NR								

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TABLE 1. Continued

Author Study Period or Publication Date Location	Study Population Sex/Age—Index Cases Duration of Index Disease	Control or External Population Sex/Age—Controls	Comorbid Disease	Diagnostic Criteria		No. of Cases/ No. of Controls	Comorbidity		OR or SPR (95% CI)*
				Index Disease	Comorbid Disease		Among Cases No. (%)	Among Controls No. (%)	
Pongratz[28§] 1998–1999 Graz, Austria	Case-control, clinic-based F 88.3%/63 ± 14 y Duration NR	OA F 82.6%/70 ± 12.3 y	AIT	ARA[84]	OA—ACR[86–88]	383/409	35 (9)	15 (4)	2.6 (1.4–5.3)
Alpigiani[31] 1998–2000 Genoa, Italy	Clinic-based JRA study F 63.6%/12 (1.9–25y) 6.8 (0.3–22.5 y)	—	AIT	EULAR[89]	Lab/ultrasound	66/NA	3 (5)	—	—
Chan[30] 2001(pub) Liverpool, U.K.	Clinic-based F 90.6%/age NR Duration NR	—	AIT	ARA[84]	AIT—lab	64/NA	2 (3)	—	—
Insulin-dependent diabetes mellitus									
Gilani[32] 1984 (pub) NY/FL	Cross-sectional, clinic-based F 39.7%/8.8 y Newly diagnosed	—	AIT	NR	AIT—clinical/lab	58/NA	2 (3)	—	—
Betterle[33] 1984 (pub) Padua, Italy	Cross-sectional F 45.6%/19 y (2–67 y) 28 wk (1 wk–12 y)	—	AIT	NR	AIT—NR	239/NA	2 (1)	—	—
Sanchez-Lugo[48] 1988 Puerto Rico	Clinic-based F 55%/1–20 y 4.2 y	—	AIT	NR	AIT—lab	65/NA	1 (2)	—	—
Pavia Sesma[34§] 1989 (pub) Barcelona, Spain	Cross-sectional, clinic-based F 46.7%/4–18 y 0–8 y	—	AIT	Physician diagnosis	AIT—Fisher[90]	225/NA	16 (7)	—	—
McKenna[35] 1990 (pub) Boston, MA	Cross-sectional, hospital-based F 57.1%/13.9 ± 3.7 y 4.6 ± 4.2 y (0–17)	—	AIT	NR	AIT—clinical/lab	371/NA	9 (2)	—	—
Burek[36] 1990 (pub) U.S.	Cross-sectional, clinic-based F 59.7%/pediatric–adolescent Duration NR	—	AIT	Age <15 and insulin	AIT—clinical/lab	159/NA	14 (9)	—	—

Kontiainen[37] 1990 (pub) Helsinki, Finland	Cross-sectional, clinic-based Sex NR/21.1 ± 4.5 y 12.4 ± 7.1 y	—	AIT	NR	AIT—lab	141/NA	10 (7)	—	—
Gruneiro De Papendieck[38§] 1988–1991 Buenos Aires, Argentina	Cross-sectional, clinic-based F 62%/13.5 y (4.6–20) 4.6 ± 4.4 y	—	AIT	NR	AIT—lab	107/NA	9 (8)	—	—
Gamba[39§] 1991–1993 Turin, Italy	Clinic-based series F 41.9%/30 ± 9.3 y 13.5 ± 8.1 y (2–34 y)	—	AIT	NR	AIT—clinical/lab	167/NA	7 (4)	—	—
McCanlies[40] 1993 Pittsburgh, PA	Cross-sectional, hospital-based F ~50%/~42.2 y 35 y	—	AIT	Age <17 and insulin	AIT—clinical/lab	259/NA	40 (15)	—	—
Wong[50] 1993 (pub) Hong Kong	Clinic-based F 61.5%/7.9 (1.7–13.5 y) at IDDM onset 4.0 ± 1.6 y	—	AIT	NDDG[83]	AIT—lab	26/NA	0 (0)	—	—
Tsai[49] 1993 (pub) Taiwan	Clinic-based F 68%/7.2 (0.3–15 y) at IDDM onset 4.2 (0.1–14.3 y)	—	AIT	NDDG[83]	AIT—lab	65/NA	0 (0)	—	—
Prina Cerai[51] 1994 (pub) Italy	Hospital-based F 41.2%/13.5 ± 2.2 7.9 ± 2.8	—	AIT	NR	AIT—lab	144/NA	2 (1)	—	—
Darendeliler[41] 1994 (pub) Marmara, Turkey	Cross-sectional, clinic-based F 53%/11 (2.3–22 y) Median 2.3 y (0.1–15.3 y)	—	AIT	NR	AIT—clinical/lab/ultrasound	83/NA	2 (2)	—	—
Radetti[42] 1995 (pub) Italy/Croatia/Slovenia/Austria	Multicenter, clinic-based Sex NR /9.6 y at IDDM onset 3.7 ± 3 y	—	AIT	Clinical/treatment	AIT—lab/ultrasound	1419/NA	55 (4)	—	—

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TABLE 1. Continued

Author Study Period or Publication Date Location	Study Population Sex/Age—Index Cases Duration of Index Disease	Control or External Population Sex/Age—Controls	Comorbid Disease	Diagnostic Criteria		No. of Cases/ No. of Controls	Comorbidity		OR or SPR (95% CI)*
				Index Disease	Comorbid Disease		Among Cases No. (%)	Among Controls No. (%)	
Chuang[43] 1996 (pub) Taipei, Taiwan (Han Chinese)	Cross-sectional, clinic-based F 59%/18 y at IDDM onset 7.8 y	—	AIT	NDDG[83]	AIT—clinical/lab	83/NA	0 (0)	—	—
Lorini[44] 1996 (pub) Pavia, Italy	Cross-sectional, clinic-based F 48%/1.2–21 y at IDDM diagnosis 3–10 y	—	AIT	NR	AIT—biopsy confirmed	90/NA	9 (10)	—	—
Molina Lacasa[52§] 1993–1996 Barcelona, Spain	Clinic-based F 59%/27.4 y 10.4 wk	—	AIT	NDDG[83]	AIT—lab	100/NA	5 (5)	—	—
Fernandez-Castaner[53] 1993–1997 Barcelona, Spain	Cross-sectional, clinic-based F 43%/27 ± 11 (all ≥14 y) 10.2 ± 10.7 wk	—	AIT	Insulin-dependence[91]	AIT—lab	111/NA	7 (6)	—	—
Hansen[45] 1997 Funen County, Denmark	Case–control F 47.6%/13 y (2–18) 4.8 y (0.2–13.3 y)	Healthy children Age-/sex-matched; F 47.6%/13 y (1–18)	AIT	NR	AIT—clinical/lab/ultrasound	105/105	1 (1)	0 (0)	OR = undefined‖
Roldan[46] 1999 (pub) Madrid, Spain	Cross-sectional, clinic-based F 47.5%/15.6 (2.2–20 y) 7.1 y (0–18.5)	—	AIT	NR	AIT—lab	204/NA	1 (<1)	—	—
Menon[55] 1996–1999 New Delhi, India	Clinic-based F 54%/6.4 ± 1.5 y at IDDM onset 17.4 ± 4.8 mo	—	AIT	ADA[92]	AIT—clinical/lab/biopsy	35/NA	1 (3)	—	—
Hanukoglu[47] 1997–2000 Israel	Clinic series, multicenter F 43.1%/13 y ± 4.9 Duration NR	—	AIT JRA	Age <18 y	AIT—clinical/lab JRA—NR	109/NA	7 (6) 1 (1)	—	—

Umpierrez[57] 1983–2001 TN	Clinic-based, longitudinal (18-y follow up) F 55%/19 ± 2 at IDDM onset Duration NR	NHANES III data[93]	AIT	Insulin dependence and age ≤39 y	AIT—lab (all subclinical patients started thyroid replacement)[#]	58/NA	0 (0)[#]	—	SPR=undefined[‖]
Park[54] 2000 (pub) Seoul, Korea	Random sample from Korean Seoul Registry F 50.4%/12 (3–22 y) 4.6 ± 3 y	—	AIT	ADA[94]	—	115/NA	27 (23)	—	—
Radaideh[56] 2000–2001 Amman, Jordan	Clinic-based F 52%/19.6 ± 9 y 6 ± 6.6 y	—	AIT	Thyroid hormone treatment		79/NA	3 (4)	—	—
Kordonouri[58] 2004 Berlin, Germany	Clinic-based F 43.5%/9.2 (0.3–17.7 y) at IDDM onset 4.4 (0.2–12.4 y)	—	AIT	NR	AIT—lab/ultrasound	147/NA	8 (5)	—	—
Multiple sclerosis									
Wynn[59] 1905–1984 Olmsted Country, MN	Population-based F 72.3%/33 at diagnosis Duration NR	—	RA IDDM AIT	Poser[95]	NR	206/NA	5 (2) 3 (1) 8 (4)	— — —	—
Baker[60] 1955–1970 Melbourne, Australia	Chart review, hospital-based Sex NR/age NR Duration NR	—	RA AIT	NR	NR	326/NA	2 (1) 2 (1)	— —	—
De Keyser[62] 1979–1984 London, U.K.	Chart review, clinic-based F 64.9%/NR Duration NR	Published data from other populations[96–98]	RA IDDM AIT	Poser[95]	NR	828/NA	5 (1) 4 (<1) 4 (<1)	— — —	SPR = 0.60 (0.20–1.41) SPR = 0.97 (0.26–2.47) SPR = 0.60 (0.16–1.55)
Midgard[61] 1986–1987 Norway	Population-based cases F 59%/median 35–39 y Duration NR	Non-MS inpatients Age-/sex-matched; F 58%/median 35–39 y	RA IDDM	Bauer[99]	NR	155/200	3 (2) 0 (0)	0 (0) 0 (0)	OR = undefined [‖] OR = undefined [‖]
Marrosu[63] 1989–2000 Sardinia, Italy	Cross-sectional, clinic-based F 68.8%/34.5 y (10–67 y) Duration NR	Oristano population	IDDM	Poser[95]	IDDM—ADA[94]	1090/NA	28 (3)	—	SPR = 4.8 (3.2–6.9)[‡]

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TABLE 1. Continued

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				Index Disease	Comorbid Disease		Among Cases No. (%)	Among Controls No. (%)	
Broadley[64] 2000 (pub) U.K.	Case–control F 75.5%/40.6 y (19–60 y) Duration NR	Spouse or friend NR/42.8 y (19–68 y)	RA IDDM AIT	Poser[95]	NR	571/375	2 (<1)[#] 4 (1) 3 (1)[#]	5 (1)[#] 1 (<1) 4 (1)[#]	OR = 0.26 (0–1.6)[‡¶] OR = 2.6 (0.3–130)[‡¶] OR = 0.9 (0.2–6)[‡¶]
Heinzlef[65] 2000 (pub) Paris, France	Clinic-based series F 67%/45.6 y ± 11.3 15.4 y	—	JRA IDDM AIT	Poser[95]	NR	357/NA	1 (<1) 0 (0) 3 (1)	—	—
Autoimmune thyroiditis									
Becker[66]** 1926–1960 Rochester, MN	Necropsy series F 69%/52.9 y (8–85 y) Duration NR	—	RA	Histologic (necropsy)	NR	153/NA	8 (5)	—	—
Furszyfer[67] 1935–1967 Rochester, MN	Population-based F 97.6%/~35 y Duration NR	—	RA	Histologic in 69%; else clinical/lab	NR	246/NA	7 (3)	—	—
Mulhern[68] 1948–1963 Baltimore, MD	Case–control; hospital-based F 100%/47 y Duration NR	Colloid goiter or cystic breast disease Age-, sex-, race-matched	RA IDDM	Histologic	RA—ARA[79] IDDM—NR	170/340	5 (3) 5 (3)	2 (1) 17 (5)	OR = 5 (0.8–54)[‡¶] OR = 0.6 (0.16–1.7)[‡¶]
Becker[69]** 1955–1960 MN	Case–control, clinic-based Sex NR/age NR Duration NR	Acute granulomatous thyroiditis Sex/age—NR	RA	Histologic in 64%; else clinical/lab	RA—ARA[85]	506/243	20 (4)	1 (<1)	9.96 (1.6–414.4)[‡]
Buchanan[70] 1961 (pub) Glasgow, U.K.	Case–control, clinic-based F 91.2%/50 y (39–68 y) Duration NR	Clinic-based F 100%/55 y	RA	Clinical/lab or histologic	RA—Kellgren and Lawrence100 (including hand x-rays)	34/179	6 (18)	2 (1)	19 (3–196)
Masi[71] 1965(pub) Baltimore, MD	Case–control, necropsy-based Sex NR/age NR Duration NR	Postmortem, non-AIT Age-, sex-, race-matched	RA IDDM	Histologic (necropsy)	Histologic/ clinical	74/74	1 (1) 11 (15)	2 (3) 8 (11)	0.5 (0.01–9.7)[‡¶] 1.4 (0.5–4.4)[‡¶]

*Crude OR/SPR presented unless otherwise specified; the majority of studies did not adjust for confounders.
[†]Accounted for age, calendar period, sex.
[‡]Calculated in Stata.
[§]Article translated from original language of publication.
[‖]OR undefined due to zero cases of comorbid AID in the control group or SPR undefined due to zero expected cases.
[¶]OR unmatched (paired data not reported).
[#]Data provided by authors on request.
**Population potentially overlaps slightly with Becker.[69]

ACR indicates American College of Rheumatology; ADA, American Diabetes Association; AID, autoimmune disease; ARA, American Rheumatism Association; clinical, clinical features of disease observed by examination; EULAR, European League Against Rheumatism; lab, laboratory assessment of thyroid function (eg, thyroid hormones or antithyroid antibodies); NA, not applicable; NDDG, National Diabetes Data Group; NHANES, National Health and Nutrition Examination Survey; NR, not reported; OA, osteoarthritis; (pub), year of publication (reported if study period not cited).

TABLE 2. Main Findings From Studies Examining Coexistence of Autoimmune Diseases Within Families

Author Study Period or Publication Date Location	Study Population	Comorbid Disease	Diagnostic Criteria	Proband No. of Cases/ No. of Controls	Relatives of Probands*			Comments
					No.	Comorbid No. (%)	OR or SPR† (95% CI)	
Rheumatoid arthritis/juvenile rheumatoid arthritis								
Panczel[21]‡ 1980–83 Hungary	Sex/age NR	IDDM	RA—ARA[82] IDDM—NDDG[83]	310/310	1777 1973	15 (1) 0 (0)	OR undefined	Probands and relatives interviewed and examined
Thomas[22] 1983 (pub) London, U.K.	Sex/age NR	IDDM	RA—ARA[79] IDDM—clinical	295/307	2081 2299	19 (1) 8 (<1)	2.6 (1.1–7.0)§	
Lin[72] 1998 (pub) U.S.	Case relatives: F 50%, 0–60+ y Control relatives: F 52%, 0–60+ y	IDDM	RA—ARA[84] IDDM—medical record	29/14	218 98	6 (3) 2 (2)	1.36 (0.24–14.0)§	Case–control; control probands were friends of RA probands Structured interview + physician/medical record confirmation
Prahalad[73] 2002 (pub) Cincinnati, OH	Case relatives: F 52.3%, 48 y ± 19 Control relatives: F 50.6%, 47 y ± 19	IDDM AIT MS	JRA—ACR[101] Other-self-report JRA—ACR[101] Other-self-report	110/45	1228 496	5 (<1) 0 (0) 66 (5) 8 (2) 5 (<1) 0 (0)	OR undefined 3.5 (1.6–7.9) OR undefined	1° and 2° relatives included (1° comprised 36%) JRA cases were hospital/clinic-based Controls = healthy volunteers, frequency matched by age ≥10 y
Insulin-dependent diabetes mellitus								
Hanukoglu[47] 1997–2000 Israel	Case relatives: F 51.2%, 29.0 y ± 16.2	JRA AIT	IDDM—age <18 y Other—clinical/lab	109/NA	412	4 (1) 11 (3)	—	Serologic screening for thyroid disease performed and medical history reviewed
Multiple sclerosis								
Marrosu[63] 1989–2000 Sardinia, Italy	Sex/age NR	IDDM	MS—Poser[95] IDDM—ADA[94]	1090/NA	5480	53 (1) 19 (3)	SPR = 1.79 (1.34–2.34)§	Standardized to Oristano population
Midgard[61] 1996 Norway	Sex/age NR	RA IDDM	MS—Bauer[99] Other—NR	155/200	717 991	32 (3) 25 (4) 21 (2)	0.82 (0.43–1.5) 1.67 (0.89–3.16)	Neurologist interview
Heinzlef[65] 2000 (pub) Paris, France	Sex/age NR	RA IDDM AIT	MS—Poser[95] Other—NR	357/NA	1971	5 (<1) 7 (<1) 2 (<1)	—	

Continued on next page

TABLE 2. Continued

Author Study Period or Publication Date Location	Study Population	Comorbid Disease	Diagnostic Criteria	Proband No. of Cases/ No. of Controls	Relatives of Probands* No.	Comorbid No. (%)	OR or SPR† (95% CI)	Comments
Broadley[64] 2000 (pub) Paris, France	Case relatives: Sex NR, 55.7 y (1–93)	RA	MS-Poser[95]	571/375	2124	14 (1)‖	0.96 (0.39–2.5)§¶	Self-report data verified by physician
		IDDM	Other—NR			7 (<1)		
		AIT				2 (<1)		
Broadley[64] 2000 (pub) U.K.	Case relatives: Sex NR, 55.7 y (1–93)	RA	MS-Poser[95] Other—NR	571/375	2124 1315	14 (1)‖ 9 (1)‖	0.96 (0.39–2.5)§¶	Self-report data verified by physician
	Control relatives: sex NR, 55.7 y (1–95)	IDDM	MS-Poser[95] Other—NR			11 (1)‖ 5 (<1)‖	1.36 (0.4–5.0)§¶	
		AIT	MS-Poser[95] Other—NR			49 (2)‖ 16 (1)‖	1.92 (1.1–3.6)§¶	

*1° relatives unless otherwise noted.
†Adjusted OR/SPR were not available for any of the studies.
‡Article translated from original language of publication.
§Calculated in Stata.
‖Data provided by authors on request.
¶OR unmatched (paired data not reported).
JRA indicates juvenile RA; 1°, first-degree relative (parents, siblings); 2°, second-degree relative (grandparents, aunts, uncles, first cousins).

Five studies examining the prevalence of coexistent AIT among MS cases documented estimates ranging from 0.48% to 3.9%.[59,60,62,64,65] Neither study with referents or controls found evidence of association between AIT and MS.[62,64]

Autoimmune Thyroiditis

Six studies included AIT as the index disease.[66–71] All assessed comorbid RA, with prevalence estimates ranging from 1.4% to 17.6%. There was no consistent trend for association between RA and AIT in the 4 controlled studies.[68–71]

Comorbidity of Autoimmune Diseases Within Families

Nine studies examined coexistent disease among family members of index disease cases, only 2 of which did not report proband data.[72,73]

Rheumatoid Arthritis

Three controlled studies assessed IDDM prevalence among family members of RA cases[21,22,72]; a fourth study was conducted among family members of JRA cases.[73] The data suggest an increased prevalence of IDDM among family members of patients with RA or those with JRA versus relatives of controls. Findings from the JRA study indicate an increased odds of AIT in the case versus control relatives, but no association for MS.

Insulin-Dependent Diabetes Mellitus

A single study[47] examined the coexistence of the selected autoimmune diseases among family members of patients with IDDM. The prevalences of comorbid JRA and AIT among first-degree family members were 0.97% and 2.7%, respectively.

Multiple Sclerosis

Four studies assessed IDDM in relatives of probands,[61,63–65] with a suggestion of increased prevalence of IDDM among relatives of MS probands, based on 2 controlled studies[61,64] and a third with referent population data.[63]

Three of the studies also assessed RA; there was lack of association for RA among relatives of MS probands in the 2 controlled studies.[61,64] Two studies assessed AIT; the only controlled study found increased odds of AIT among relatives of MS probands versus control relatives.[64]

Autoimmune (Hashimoto) Thyroiditis

We found no family studies with AIT as the index disease meeting eligibility criteria for this review.

DISCUSSION

This review focuses on 4 T_H1-associated autoimmune disorders. The concept that autoimmune diseases tend to coexist is fairly well established in the clinical community, although based largely on anecdotal evidence. Further conjecture that T_H1-predominant conditions in particular might be expected to correlate with one another adds impetus to the need to quantify relationships among such diseases. To our knowledge, this review represents the first systematic attempt

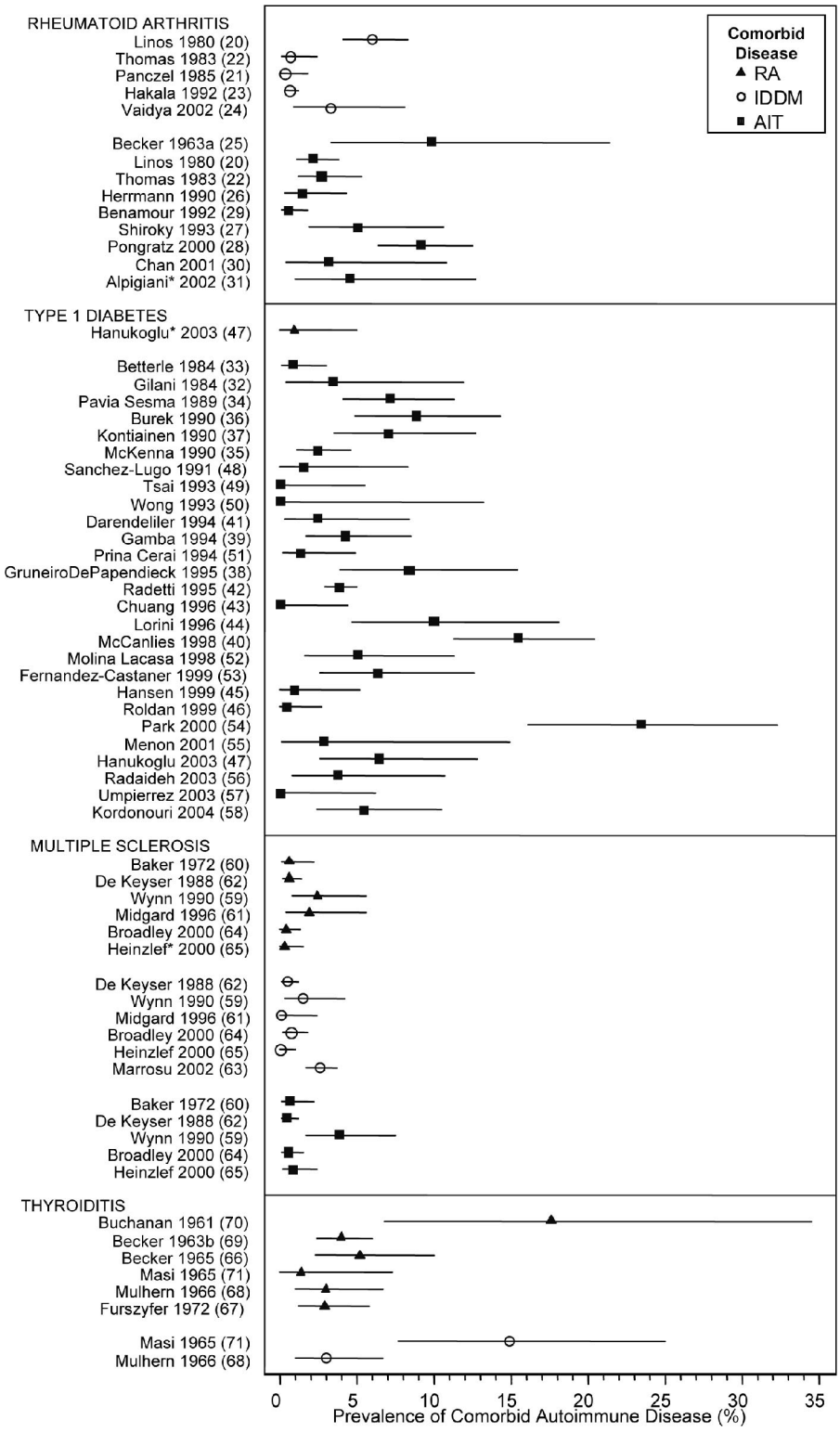

FIGURE 1. Forest plot displaying prevalence estimates for comorbid autoimmune diseases within index disease populations. Due to substantial heterogeneity between studies, pooled prevalence estimates are not presented. The majority of studies were uncontrolled so measures of association are not displayed. The studies with asterisks are those that involved juvenile patients with rheumatoid arthritis.

to evaluate the evidence from observational studies linking a group of T_H1-associated autoimmune diseases.

We chose to focus on studies of clinical autoimmune disease. We excluded studies in which the index or comorbid conditions were based on autoantibody seropositivity in the absence of clinical disease. It is important to draw a distinction between "autoimmunity" and "autoimmune disease." Autoimmunity such as the presence of autoreactive T and B

lymphocytes (eg, autoantibodies) is not necessarily associated with pathology or adverse clinical manifestations. In fact, the concept of autoreactivity has evolved to include the premise that low levels are physiological and may be involved in lymphocyte selection.[74] Furthermore, transient elevations in autoantibody levels may occur as a byproduct of nonautoimmune phenomena such as infections.[75,76] The biochemical milieu (eg, cytokine profile) and environmental factors are thought to be important determinants of whether autoimmunity progresses to clinical disease.

Our decision to restrict this review to data on clinical disease was particularly relevant to the issue of thyroid autoimmunity, because studies examining the presence of comorbid thyroid autoantibodies accounted for a large number of exclusions. Although autoantibodies are useful as diagnostic tools, they have low sensitivity and specificity when screening for or classifying autoimmune diseases. For example, the prevalence of thyroid microsomal (peroxidase) antibodies in the general population may range up to 12% and even higher among the elderly.[77] Furthermore, in a longitudinal, population-based study, Hawkins et al[77] determined that of 135 people with positive thyroid microsomal antibodies at baseline, 53 (39%) were negative at 6 years follow up. It should be noted that interpretation of autoantibody studies would need to account for factors such as assay methodology and sensitivity, and the autoantibody titers used as cutoffs to indicate positive versus negative results.

Of the 54 studies that met criteria for inclusion in this review, the majority were reports of uncontrolled series. Due to substantial heterogeneity among studies, it was inappropriate to derive pooled estimates to summarize the data, except for the prevalence of RA among patients with MS. Although far from conclusive, the literature suggests some positive associations between diseases. Data appear to support an increased prevalence of AIT in both patients with RA and those with IDDM—a finding that corresponds with common clinical opinion. The IDDM studies predominantly included children and adolescents. Although only one within-individual IDDM study was controlled, the high prevalence estimates for comorbid AIT are remarkable given that AIT is generally found in older individuals. Conversely, one would expect RA and IDDM to be increased among patients with AIT if etiologic factors are shared between these diseases. Overall, the evidence points to an increased prevalence of RA among patients with AIT, but there are insufficient data to evaluate comorbid IDDM. An intriguing finding is the suggestion of a modest inverse association between RA and MS based on studies within patients with MS and relatives of MS probands. Likewise, the weighted mean prevalence of RA among patients with MS is lower than conventional estimates for RA in the general population, although caution should be applied for this type of comparison. It is even more difficult to draw inference for the other combinations of diseases studied. However, it is interesting to note the pattern of investigations that have been undertaken. Reports related to patients with IDDM focused almost exclusively on comorbid AIT, whereas for MS, each of the other autoimmune diseases was studied. RA and AIT investigations were limited to each other and IDDM. None of the intraindividual studies looked at comorbid MS. Furthermore, only 9 family studies were included.

Numerous factors are likely to have contributed to the broad spectrum of results. The studies varied considerably in terms of their underlying populations and structure. Characteristics of the patient populations undoubtedly affect prevalence estimates. Sex, age, and, to a lesser extent, race are known to be strongly associated with autoimmune diseases, making it critical to account for these factors. Although most studies provided summary statistics for age and sex, the analyses did not adjust for their confounding effects. Information on race was reported in only a few instances. Duration of index disease may also be a key issue, although many of the reports did not include such data. Study designs also differed; few of the studies were population-based, and several of the hospital- or clinic-based series did not describe their selection procedures. The extent to which the data are generalizable from the tertiary care setting must be considered, because a substantial proportion of the studies was based on such populations. Conditions such as autoimmune thyroid disorders may also fail to reach hospital attention. Alternatively, the possibility of surveillance bias must be entertained in that the rate of detection of comorbid conditions may increase during the diagnosis or clinical management of chronic conditions such as those included in this review.

Interestingly, studies involving MS index cases tended to have larger sample sizes, and more often included population-based data, in comparison with studies for other diseases. Correspondingly, as depicted in Figure 1, the ranges of prevalence estimates for comorbid diseases among MS index patients were considerably narrower than for other disease combinations, and there was lack of evidence for heterogeneity between studies of RA among MS index cases.

Varying diagnostic criteria were used for the classification of cases, and, over time, the characteristics of diagnostic tests evolved (eg, autoantibody assays). Because in general, the sensitivity of tests improves over time, prevalence rates could spuriously increase. These changes are likely to have had particular influence on the diagnosis of autoimmune thyroiditis. For instance, there has been a shift in practice from histologic diagnosis to diagnosis based on clinical and laboratory evidence. Because the studies spanned approximately 75 years, however, genuine changes in prevalence and incidence rates are also plausible. For serologic studies relying on laboratory testing as the basis for AIT diagnosis, it is often unclear whether treatments affecting thyroid function (including thyroid replacement therapy) were accounted for. Also, nomenclature and classification schemes for thyroid diseases have not been standardized to the same extent as for other diseases considered in this review. In fact, not one of the studies included here referred to published guidelines for the diagnosis of thyroid disease. This seriously affects the comparability among epidemiologic studies, which use various terminology and case definitions. Moreover, it is important not to group overt and subclinical hypothyroidism, because the latter indicates a mild state of

thyroid hypofunction rather than a disease entity.[18] In addition, some studies define the term "subclinical hypothyroidism" as elevated serum TSH, whereas others consider it to mean elevated serum TSH in conjunction with thyroid autoantibodies.[78]

Given the low prevalence of many autoimmune diseases, individual studies tend to have inadequate sample sizes and power to demonstrate whether an association exists between various autoimmune diseases. Unfortunately, we could not perform meta-analyses given the variability between studies. Publication bias is another issue in that studies with positive results may be more likely to be published. For the present topic, this problem may have been mitigated by the fact that in many studies, the association between autoimmune diseases was not intended as a primary outcome but rather as supplemental information. Case ascertainment may also differ in studies designed to look at "any autoimmune disease" versus those with a predesignated list of diseases.

These issues make it difficult to draw firm conclusions about the extent of coexistence of the selected autoimmune diseases within individuals and families. Further research in this area can be useful, because it is clear that the co-occurrence of autoimmune diseases is likely to be as much due to common environmental factors as genetic susceptibility.

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