CLINICAL RESEARCH STUDY

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Prevalence and Relative Risk of Other Autoimmune Diseases in Subjects with Autoimmune Thyroid Disease

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ABSTRACT

BACKGROUND: Common autoimmune disorders tend to coexist in the same subjects and to cluster in families.

METHODS: We performed a cross-sectional multicenter study of 3286 Caucasian subjects (2791 with Graves' disease; 495 with Hashimoto's thyroiditis) attending UK hospital thyroid clinics to quantify the prevalence of coexisting autoimmune disorders. All subjects completed a structured questionnaire seeking a personal and parental history of common autoimmune disorders, as well as a history of hyperthyroidism or hypothyroidism among parents.

RESULTS: The frequency of another autoimmune disorder was 9.67% in Graves' disease and 14.3% in Hashimoto's thyroiditis index cases ($P = .005$). Rheumatoid arthritis was the most common coexisting autoimmune disorder (found in 3.15% of Graves' disease and 4.24% of Hashimoto's thyroiditis cases). Relative risks of almost all other autoimmune diseases in Graves' disease or Hashimoto's thyroiditis were significantly increased (>10 for pernicious anemia, systemic lupus erythematosus, Addison's disease, celiac disease, and vitiligo). There was relative "clustering" of Graves' disease in the index case with parental hyperthyroidism and of Hashimoto's thyroiditis in the index case with parental hypothyroidism. Relative risks for most other coexisting autoimmune disorders were markedly increased among parents of index cases.

CONCLUSION: This is one of the largest studies to date to quantify the risk of diagnosis of coexisting autoimmune diseases in more than 3000 index cases with well-characterized Graves' disease or Hashimoto's thyroiditis. These risks highlight the importance of screening for other autoimmune diagnoses if subjects with autoimmune thyroid disease present with new or nonspecific symptoms.

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KEYWORDS: Autoimmune diseases; Autoimmune thyroid disease; Prevalence; Relative risk

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The autoimmune thyroid diseases, Graves' disease and Hashimoto's thyroiditis, are common, affecting up to 2% of the UK population.[1] There is an accepted notion that autoimmune diseases coexist in the same person and in families, although this has been studied only in small groups of subjects with autoimmune thyroid disease (the most common autoimmune disease). Autoimmune diseases associated with increased prevalences of thyroid autoimmunity include type 1 diabetes,[2,3] vitiligo,[4] Addison's disease,[5] and multiple sclerosis.[6,7] In general, studies have been hampered by small sample sizes and by the use of control populations not matched for age, gender, or geographic location.[8]

CLINICAL SIGNIFICANCE

- Patients with a primary diagnosis of autoimmune thyroid disease are at significantly increased risk of additional autoimmune diseases, and these risks can be quantified.
- There is clear evidence for parental and index case clustering of Graves' disease and Hashimoto's thyroiditis.
- Screening for other autoimmune diagnoses might be indicated if subjects with autoimmune thyroid disease present with new or nonspecific symptoms.

It is well established that there is significant clustering of autoimmune thyroid disease within families, with 40% to 50% of patients reporting another family member with a thyroid disorder.[9] Furthermore, there are marked differences in autoimmune thyroid disease prevalence between genders with 5-to 10-fold excesses in women for both Graves' disease and Hashimoto's thyroiditis.[10] Although the precise pathogenetic mechanisms are unknown, autoimmune thyroid disease is believed to reflect a multifactorial mode of inheritance, resulting from an interaction between the products of multiple genes conferring susceptibility (or protection) and various environmental triggers.[11] Clear evidence of the genetic component arises from twin studies for Graves' disease[9,12] and Hashimoto's thyroiditis[13] with concordance rates of 30% to 40% in monozygotic twins and 0% to 7% in dizygotic twins.

We set out to quantify the risk of coexisting autoimmune diseases in an extensive cohort of more than 3000 UK subjects with well-characterized autoimmune thyroid disease, as well as in their parents, and to compare findings for Graves' disease and Hashimoto's thyroiditis and also for women and men.

MATERIALS AND METHODS

We designed the protocol for our national UK collection of DNA for studies of genetic susceptibility to autoimmune thyroid diseases[14-16] to include prospective and systematic collection of clinical data, including information regarding the coexistence of other common autoimmune disorders in index cases and their parents. Patients were recruited between February 2002 and July 2007.

The study cohort (n = 3286) comprised 2791 Caucasian subjects with Graves' disease (2317 female/474 male) and 495 Caucasian subjects with Hashimoto's thyroiditis (427 female/68 male) who were recruited from specialist referral center thyroid clinics in Birmingham, Bournemouth, Cambridge, Cardiff, Exeter, Leeds, Sheffield, and Newcastle, United Kingdom.[14] Individuals included in the study were self-identified as white and of European ancestry and came from mainland United Kingdom. The participation rate among eligible patients was high (~90%). The cohort was almost identical to that used in our genetics studies with the exception of exclusion (because of selection bias) of 13 subjects with Addison's disease and coexistent autoimmune thyroid disease recruited from an Addison's cohort in a single center. All patients fulfilling standard criteria for the diagnosis of autoimmune thyroid disease were eligible for the study.[15,16] Graves' disease was defined by the presence of biochemical hyperthyroidism with (i) diffuse uptake on radionuclide scan/diffuse goiter on ultrasound scan or (ii) Graves' ophthalmopathy (NOSPECS score ≥ 2[17]); (iii) positive autoantibodies to the thyroid-stimulating hormone receptor; (iv) diffuse goiter on physical examination and positive antibodies to thyroglobulin or thyroid peroxidase; or (v) confirmation of a lymphocytic infiltrate in thyroid histology. Hashimoto's thyroiditis was defined by the presence of biochemical hypothyroidism and (i) positive antibodies to thyroglobulin or thyroid peroxidase; (ii) the presence of lymphocytic infiltrate in a fine-needle aspirate; or (iii) the presence of a diffuse goiter on physical examination.

All subjects gave informed written consent to participate. The study was approved by a Multi Center Research Ethics Committee and corresponding Local Ethics Research Committees. Patients were interviewed by a trained research nurse or specialist physician at enrollment into the study. A structured questionnaire was completed seeking a parental history of thyroid diseases and other common autoimmune diseases, as well as a history of these disorders in the index case. The age at diagnosis of Graves' disease and Hashimoto's thyroiditis in the index case was recorded, as was the age at recruitment. A parental history of thyroid dysfunction was recorded on the basis of index case recall as being positive for hyperthyroidism or hypothyroidism. If index cases were unsure of the diagnosis in their parents, or if the diagnosis was not clear from recall of administered therapies (eg, antithyroid drugs or radioiodine), the records were considered negative. Diagnoses of other autoimmune disorders also were based on patient recall, with verification in the index case through cross-checking with current records and medications by the recruiting physicians. Only records

Table 1 Population Prevalences of Autoimmune Diseases in the United Kingdom Adult Female and Male Population

Autoimmune Disease	UK Population Prevalence (%)	UK Female Population Prevalence (%)	UK Male Population Prevalence (%)	References
Hashimoto's/hypothyroidism	0.80	1.65	0.2	(1,7,8,10)
Graves'/hyperthyroidism	0.65	2.3	0.145	(1,7,8,10)
Type 1 diabetes	0.34	0.34	0.34	(7,8,18,19)
Rheumatoid arthritis	0.55	1.07	0.47	(3,7,8)
Pernicious anemia	0.13	0.13	0.12	(3,7,8)
Systemic lupus erythematosus	0.027	0.048	0.005	(7,8,21,22)
Addison's disease	0.009	0.009	0.009	(7,8)
Celiac disease	0.05	0.054	0.047	(3)
Vitiligo	0.1	0.11	0.093	(3)
Multiple sclerosis	0.13	0.25	0.1	(20,35)
Myasthenia gravis	0.015	0.02	0.01	(7,8,23)
Inflammatory bowel disease	0.26	0.26	0.26	(24)

confirming evidence of coexisting autoimmune diseases were considered positive. Cross-checking of reported diseases with parents' records was not performed because this fell outside the remit of the study approval. The study is therefore one of confirmed disease history for index cases and one of reported disease history for the parents of index cases.

The relative risk for each of the different autoimmune diseases was calculated by dividing the observed prevalence by the best estimate of UK population prevalence based on the current literature (Table 1). Where appropriate, gender-specific prevalence rates were used.[1,3,7,8,10,18-24]

Statistical analyses were performed using SigmaStat software version 3.2 (SPSS Science Software UK Ltd, Birmingham, UK) and Minitab version 15 (Minitab Inc, Coventry, UK). Two proportion tests and the Fisher exact test were used to compare binomial proportions, and Mann–Whitney *U* tests were used for comparisons of mean ages. The single exact binomial proportion test was used to determine the significance of the relative risk of each autoimmune disease compared with the relevant UK population risk. Relative risks in parents were calculated combining prevalence rates for mothers and fathers, using UK population prevalence rates.

RESULTS

Some 9.67% of the 2791 subjects with Graves' disease and 14.3% of the 495 patients with Hashimoto's thyroiditis had another autoimmune disorder ($P = .005$). Among index cases with Graves' disease and Hashimoto's thyroiditis, rheumatoid arthritis was most common (Table 2A,B). There were higher prevalences of Addison's disease (10-fold higher, $P < .001$) and pernicious anemia (3-fold higher, $P = .004$) in those with Hashimoto's thyroiditis, when compared with subjects with Graves' disease. There were no significant differences in autoimmune disorder prevalences among Graves' disease or Hashimoto's thyroiditis when those recruited from different centers were compared (data not shown).

Comparing female and male index cases with Graves' disease (Table 2A), type 1 diabetes ($P = .011$) and myasthenia gravis ($P = .001$) were more prevalent in men. Addison's disease, celiac disease, and multiple sclerosis were reported exclusively among female index cases with Graves' disease. For Hashimoto's thyroiditis, there were no significant differences in the prevalence of other autoimmune disorders between men and women.

The mean age at diagnosis of Graves' disease was 43 years and 42.5 years for patients with Hashimoto's thyroiditis (P = NS). The mean age at recruitment was not different comparing Graves' disease (47.3 years) with Hashimoto's thyroiditis subjects (47.5 years, P = NS). For patients with no coexisting autoimmune disease and for those with an additional autoimmune disorder, there were no significant differences in age at recruitment to the study, or age at diagnosis, between Graves' disease and Hashimoto's thyroiditis (Table 2A, B). Similarly, when comparing male and female patients, there were no significant differences in either age at diagnosis or at recruitment. When comparing age at diagnosis of Graves' disease between index cases with different autoimmune diseases (Table 3), those with coexisting rheumatoid arthritis were significantly older compared with patients with no coexisting autoimmune diseases ($P < .001$), as well as those reporting type 1 diabetes ($P < .001$), vitiligo ($P < .001$), or inflammatory bowel disease ($P = .003$). Similarly, subjects reporting coexisting pernicious anemia were older compared with index cases without any associated autoimmune disease ($P = .04$) and those with coexisting type 1 diabetes ($P = .03$).

Almost all autoimmune diseases examined were reported more frequently in the autoimmune thyroid disease index cases than the described background prevalence rates in the UK population (Table 4). These relative risks were greater than 10 for pernicious anemia, systemic lupus erythemato-

Table 2 Prevalence of Coexisting Autoimmune Diseases in Index Cases with Graves' Disease **(A)** and Hashimoto's Thyroiditis **(B)**

A

Associated Autoimmune Disease	Graves' Disease							
	Women N = 2317	Mean Age[a] (y)	Mean Age[b] (y)	Men N = 474	Mean Age[a] (y)	Mean Age[b] (y)	Total N = 2791	*P* Value Men vs Women
Type 1 diabetes	18 (0.78%)	34.0	39.0	13 (2.74%)	35.0	37.0	31 (1.11%)	.011
Rheumatoid arthritis	76 (3.28%)	50.0	56.5	12 (2.53%)	55.0	60.0	88 (3.15%)	.356
Pernicious anemia	34 (1.47%)	44.5	51.0	5 (1.05%)	57.0	71.0	39 (1.40%)	.438
Systemic lupus erythematosus	13 (0.56%)	50.0	52.0	2 (0.42%)	43.0	38.5	15 (0.54%)	.679
Addison's disease	3 (0.13%)	37.0	46.0	0 (0%)			3 (0.11%)	.083
Celiac disease	25 (1.08%)	39.0	43.0	0 (0%)			25 (0.90%)	.015
Vitiligo	30 (1.29%)	41.0	46.5	10 (2.11%)	43.5	45.5	40 (1.43%)	.245
Multiple sclerosis	8 (0.35%)	50.5	51.0	0 (0%)			8 (0.29%)	.366
Myasthenia gravis	1 (0.04%)	56.0	56.0	5 (1.05%)	44.0	52.0	6 (0.21%)	.001
Inflammatory bowel disease	25 (1.08%)	43.0	49.0	2 (0.42%)	47.5	52.5	27 (0.97%)	.299
None	2088 (90.12%)	41.5	45.5	429 (90.51%)	45.0	48.0	2517 (90.2%)	.866

B

Associated Autoimmune Disease	Hashimoto's Thyroiditis								*P* Value Graves' Disease vs Hashimoto's Thyroiditis
	Women N = 427	Mean Age[a] (y)	Mean Age[b] (y)	Men N = 68	Mean Age[a] (y)	Mean Age[b] (y)	Total N = 495	*P* Value Men vs Women	
Type 1 diabetes	5 (1.17%)	34.0	53.0	0 (0%)			5 (1.01%)	1.000	.838
Rheumatoid arthritis	20 (4.68%)	46.0	54.0	1 (1.47%)	64.0	64.0	21 (4.24%)	.336	.259
Pernicious anemia	19 (4.45%)	39.0	51.0	0 (0%)			20 (4.04%)	.091	.004
Systemic lupus erythematosus	3 (0.70%)	52.0	53.0	0 (0%)			3 (0.61%)	1.000	.745
Addison's disease	5 (1.17%)	42.0	55.0	2 (2.94%)	62.5	68.0	7 (1.41%)	.248	<.001
Celiac disease	5 (1.17%)	50.0	70.0	0 (0%)			5 (1.01%)	1.000	.813
Vitiligo	12 (2.81%)	37.5	49.5	1 (1.47%)	29.0	29.0	13 (2.63%)	1.000	.113
Multiple sclerosis	3 (0.70%)	44.0	45.0	1 (1.47%)	57.0	57.0	4 (0.81%)	.447	.093
Myasthenia gravis	1 (0.23%)	29.0	34.0	0 (0%)			1 (0.20%)	1.000	1.000
Inflammatory bowel disease	3 (0.70%)	55.0	62.0	1 (1.47%)	50.0	50.0	4 (0.81%)	.447	1.000
None	362 (84.78%)	41.5	46.0	62 (91.18%)	46.5	49.5	424 (85.66%)	.194	.005

Age at diagnosis of Graves' disease or Hashimoto's thyroiditis (age[a]) and age at recruitment to the study (age[b]) are noted. *P* values comparing prevalences in men versus women and in Graves' disease versus Hashimoto's thyroiditis subjects are displayed.

sus, Addison's disease, celiac disease, and vitiligo. Male patients with Graves' disease were at high risk of myasthenia gravis ($P < .001$). The relative risks were similar among index cases with Graves' disease and Hashimoto's thyroiditis, with the exception of Addison's disease.

The mothers of index cases with either Graves' disease or Hashimoto's thyroiditis were reported to have a history of thyroid dysfunction in 17.5% and 23.6%, respectively (Table 5A). The mothers of index cases with Graves' disease were reported to have hyper- and hypothyroidism with similar frequency (P = NS), but in contrast, the mothers of index cases with Hashimoto's thyroiditis had a higher frequency of hypothyroidism than hyperthyroidism ($P < .001$). Furthermore, mothers of index cases with Graves' disease were more likely to report hyperthyroidism compared with the mothers of those with Hashimoto's thyroiditis ($P < .001$), and hypothyroidism was more common in mothers of patients with Hashimoto's thyroiditis than mothers of those with Graves' disease ($P < .001$).

The fathers of index cases with either Graves' disease or Hashimoto's thyroiditis had thyroid dysfunction in 3.1% and 5.7%, respectively (Table 5B). Fathers of index cases with Graves' disease were more likely to have hyperthyroidism than hypothyroidism ($P = .017$), whereas fathers of

Table 3 Median Age and Interquartile Range at Diagnosis of Graves' Disease in Patients According to the Type of Coexisting Autoimmune Disease

Coexisting Autoimmune Disease	No. of Patients	Median Age at Diagnosis of Graves' Disease (y)	Interquartile Range (y)
Type 1 diabetes	31	35	26.8-42.3
Rheumatoid arthritis	88	51[a,b,c,d (Note 1)]	40.0-60.25
Pernicious anemia	39	45.5[e,f (Note 2)]	34.0-57.0
Celiac disease	25	39	31.5-46.5
Vitiligo	40	43	30.0-47.0
Inflammatory bowel Disease	25	43	29.8-49.5
None	2517	41	31.0-52.0

Data for patients with no other autoimmune diseases also are displayed. Note 1: Comparing rheumatoid arthritis with [a]type 1 diabetes ($P < .001$), [b]vitiligo ($P < .001$), [c]inflammatory bowel disease ($P = .003$), and [d]patients without coexisting autoimmune diseases ($P < .001$). Note 2: Comparing pernicious anemia with [e]type 1 diabetes ($P = .03$) and [f]patients without coexisting autoimmune diseases ($P = .04$).

index cases with Hashimoto's thyroiditis more frequently had hypothyroidism than hyperthyroidism ($P = .007$). Similar to the findings in mothers, fathers of patients with Hashimoto's thyroiditis were more likely to have hypothyroidism when compared with fathers of Graves' disease index cases ($P < .001$), whereas rates of hyperthyroidism

Table 4 Relative Risk of Diagnosis of Other Autoimmune Diseases in Female **(A)** and Male Index **(B)** Cases with Graves' Disease or Hashimoto's Thyroiditis Calculated Using United Kingdom Prevalence Data (Table 1)

A

	Diagnosis of Graves' Disease in Female Index Case			Diagnosis of Hashimoto's Thyroiditis in Female Index Case		
Associated Autoimmune Disease	Relative Risk	95% CI	*P* Value	Relative Risk	95% CI	*P* Value
Type 1 diabetes	2.29	1.36-3.60	.005	3.44	1.12-7.97	.016
Rheumatoid arthritis	3.07	2.42-3.82	<.001	4.38	2.70-6.67	<.001
Pernicious anemia	11.29	7.83-15.72	<.001	34.22	20.77-52.78	<.001
Systemic lupus erythematosus	11.69	6.23-20.0	<.001	14.64	3.02-47.5	<.001
Addison's disease	14.39	2.97-41.99	.001	130.11	42.37-301.26	<.001
Celiac disease	19.98	12.95-29.42	<.001	21.69	7.06-50.21	<.001
Vitiligo	11.77	7.96-16.76	<.001	25.55	13.28-44.16	<.001
Multiple sclerosis	1.38	0.60-2.72	.398	2.81	0.58-8.16	.093
Myasthenia gravis	2.15	0.06-12.01	1.00	11.71	0.30-64.90	.082
Inflammatory bowel disease	4.14	2.69-6.11	<.001	2.70	0.56-7.84	.430

B

	Diagnosis of Graves' Disease in Male Index Case			Diagnosis of Hashimoto's Thyroiditis in Male Index Case		
Associated Autoimmune Disease	Relative Risk	95% CI	*P* Value	Relative Risk	95% CI	*P* Value
Type 1 diabetes	8.07	4.32-13.66	<.001			
Rheumatoid arthritis	5.39	2.80-9.32	<.001	3.13	0.26-54.64	.094
Pernicious anemia	8.79	2.86-20.37	<.001			
Systemic lupus erythematosus	84.39	10.22-303.16	<.001			
Addison's disease				326.80	39.8-1136.01	<.001
Celiac disease						
Vitiligo	22.69	10.93-41.35	<.001	15.81	0.40-85.20	.061
Multiple sclerosis				14.71	0.37-79.2	.066
Myasthenia gravis	105.49	34.34-244.44	<.001			
Inflammatory bowel disease	1.62	0.20-5.83	.640	5.66	0.14-30.48	.162

CI = confidence interval.
P values were calculated using the single exact binomial proportion test.

Table 5 Prevalence of Coexisting Autoimmune Diseases in Mothers **(A)** and Fathers **(B)** of Patients with Graves' Disease and Hashimoto's Thyroiditis

A

Associated Autoimmune Disease	Graves' Disease in Index Cases Mothers			Hashimoto's Thyroiditis in Index Cases Mothers			*P* Value Graves' Disease vs Hashimoto's Thyroiditis
	Affected Mothers of Female Index Cases N = 2317	Affected Mothers of Male Index Cases N = 474	Total Affected Mothers of All Index Cases N = 2791	Affected Mothers of Female Index Cases N = 427	Affected Mothers of Male Index Cases N = 68	Total Affected Mothers of All Index Cases N = 495	
Hyperthyroidism	201 (8.68%)	47 (9.92%)	248 (8.89%)	19 (4.45%)	3 (4.41%)	22 (4.44%)	<.001
Hypothyroidism	202 (8.72%)	38 (8.02%)	240 (8.60%)	82 (19.2%)	13 (19.12%)	95 (19.19%)	<.001
Type 1 diabetes	28 (1.21%)	9 (1.9%)	37 (1.32%)	14 (3.28%)	1 (1.47%)	15 (3.03%)	.033
Rheumatoid arthritis	253 (1.09%)	65 (13.71%)	318 (11.39%)	52 (12.18%)	8 (11.76%)	60 (12.12%)	.646
Pernicious anemia	72 (3.11%)	10 (2.11%)	82 (2.94%)	12 (2.81%)	1 (1.47%)	13 (2.63%)	.692
Systemic lupus erythematosus	5 (0.22%)	2 (0.42%)	7 (0.25%)	2 (0.47%)	0 (0%)	2 (0.40%)	.632
Addison's disease	1 (0.04%)	0 (0%)	1 (0.04%)	0 (0%)	0 (0%)	0 (0%)	1.000
Celiac disease	11 (0.47%)	1 (0.21%)	12 (0.43%)	1 (0.23%)	1 (1.47%)	2 (0.40%)	1.000
Vitiligo	15 (0.65%)	3 (0.63%)	18 (0.65%)	5 (1.17%)	1 (1.47%)	6 (1.21%)	.270
Multiple sclerosis	13 (0.56%)	2 (0.42%)	15 (0.54%)	2 (0.47%)	0 (0%)	2 (0.40%)	1.000
Myasthenia gravis	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	
Inflammatory bowel disease	14 (0.60%)	7 (1.48%)	21 (0.75%)	1 (0.23%)	1 (1.47%)	2 (0.40%)	.562

B

Associated Autoimmune Disease	Graves' Disease in Index Cases Fathers			Hashimoto's Thyroiditis in Index Cases Fathers			*P* Value Graves' disease vs Hashimoto's Thyroiditis
	Affected Fathers of Female Index Cases N = 2317	Affected Fathers of Male Index Cases N = 474	Total Affected Fathers of All Index Cases N = 2791	Affected Fathers of Female Index Cases N = 427	Affected Fathers of Female Index Cases N = 68	Total Affected Fathers of all Index Cases N = 495	
Hyperthyroidism	46 (1.99%)	8 (1.69%)	54 (1.93%)	7 (1.64%)	0 (0%)	7 (1.41%)	.379
Hypothyroidism	27 (1.17%)	5 (1.05%)	32 (1.15%)	16 (3.75%)	5 (7.35%)	21 (4.24%)	.001
Type 1 diabetes	25 (1.08%)	7 (1.48%)	32 (1.15%)	10 (2.34%)	0 (0%)	10 (2.02%)	.188
Rheumatoid arthritis	79 (3.41%)	19 (4.01%)	98 (3.51%)	10 (2.34%)	1 (1.47%)	11 (2.22%)	.085
Pernicious anemia	15 (0.65%)	5 (1.05%)	20 (0.72%)	7 (1.64%)	0 (0%)	7 (1.41%)	.208
Systemic lupus erythematosus	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	
Addison's disease	2 (0.09%)	0 (0%)	2 (0.07%)	0 (0%)	0 (0%)	0 (0%)	1.000
Celiac disease	3 (0.13%)	1 (0.21%)	4 (0.14%)	1 (0.23%)	0 (0%)	1 (0.20%)	.558
Vitiligo	14 (0.60%)	2 (0.42%)	16 (0.57%)	2 (0.47%)	0 (0%)	2 (0.40%)	1.000
Multiple sclerosis	8 (0.35%)	2 (0.42)	10 (0.36%)	2 (0.47%)	0 (0%)	2 (0.40%)	.700
Myasthenia gravis	2 (0.09%)	0 (0%)	2 (0.07%)	1 (0.23%)	0 (0%)	1 (0.20%)	.387
Inflammatory bowel disease	11 (0.47%)	2 (0.42%)	13 (0.47%)	2 (0.47%)	0 (0%)	1 (0.20%)	.708

P values comparing Graves' disease and Hashimoto's thyroiditis are displayed.

Table 6 Relative Risk of Diagnosis of Other Autoimmune Diseases in Parents of Index Cases with Graves' Disease or Hashimoto's Thyroiditis Calculated Using United Kingdom Prevalence Data (Table 1)

	Diagnosis of Graves' Disease in Index Case			Diagnosis of Hashimoto's Thyroiditis in Index Case		
Associated Autoimmune Disease	Relative Risk	95% CI	*P* Value	Relative Risk	95% CI	*P* Value
Hyperthyroidism	8.32	7.43-9.29	<.001	4.51	3.03-6.43	<.001
Hypothyroidism	6.09	5.40-6.84	<.001	14.65	12.22-17.36	<.001
Type 1 diabetes	3.64	2.83-4.59	<.001	7.43	4.83-10.90	<.001
Rheumatoid arthritis	13.55	12.32-14.86	<.001	13.04	10.26-16.29	<.001
Pernicious anemia	14.10	11.48-17.03	<.001	15.54	9.53-23.87	<.001
Systemic lupus erythematosus	4.65	1.87-9.56	.001	7.48	1.97-26.96	.030
Addison's disease	5.97	1.23-17.44	.015			
Celiac disease	5.73	3.28-9.30	<.001	6.10	1.25-17.66	.014
Vitiligo	6.09	4.22-8.50	<.001	8.08	3.50-15.86	<.001
Multiple sclerosis	3.45	2.23-5.08	<.001	3.11	1.17-7.93	.042
Myasthenia gravis	2.39	0.29-8.63	.638	6.73	0.17-37.43	.138
Inflammatory bowel disease	2.34	1.62-3.27	<.001	1.17	0.24-3.40	1.000

CI = confidence interval.
P values were calculated through the single exact binomial proportion test.

were similar in fathers of patients with Hashimoto's thyroiditis and Graves' disease (P = NS).

When the prevalence of other autoimmune diseases among the parents of index cases was examined (Tables 5A, B), a similar pattern was observed to that described for the index cases; the most commonly reported disorders were type 1 diabetes, rheumatoid arthritis, and pernicious anemia for both mothers and fathers, and for both Graves' disease and Hashimoto's thyroiditis index case parents. The prevalence of rheumatoid arthritis was especially high in the mothers of index cases with either Graves' disease or Hashimoto's thyroiditis, with a lower prevalence among fathers (P = NS).

Similar to the findings in index cases, all the autoimmune diseases investigated except myasthenia gravis (in Graves' disease and Hashimoto's thyroiditis) and inflammatory bowel disease (in Hashimoto's thyroiditis) were reported more commonly in parents of patients with autoimmune thyroid disease than in the background UK population. Relative risks were greater than 10 for rheumatoid arthritis and pernicious anemia in parents of index cases (Table 6). The relative risks of diagnosis of hyperthyroidism and hypothyroidism also were significantly increased among the parents of index cases, especially for parental hyperthyroidism in Graves' disease cases ($P < .001$) and parental hypothyroidism in Hashimoto's thyroiditis cases ($P < .001$).

DISCUSSION

We have quantified the risk of coexisting autoimmune diseases in more than 3000 index cases with well-characterized Graves' disease or Hashimoto's thyroiditis. Rheumatoid arthritis was the most prevalent coexisting autoimmune disease in subjects with autoimmune thyroid disease and in their parents. We demonstrated high relative risks for the diagnosis of several organ-specific autoimmune disorders, including pernicious anemia, Addison's disease, and celiac disease. There were quantitative differences in reported frequencies of autoimmune disorders when comparing Graves' disease and Hashimoto's thyroiditis index cases, findings not accounted for by differences in age at diagnosis of the thyroid disorder or age at recruitment to the study. In addition, we demonstrated index case and parental clustering of hyper- and hypothyroidism.

The higher prevalences and relative risks of rheumatoid arthritis in parents compared with index cases suggest a strong disease association. This may, in part, reflect the age difference between index cases and their parents, given the increasing prevalence of rheumatoid arthritis with age, although similar prevalences of other autoimmune disorders reported for index cases and parents argue against this being a major factor. Index cases with coexisting rheumatoid arthritis were older at diagnosis of Graves' disease, and it is plausible that the same age-related autoimmune mechanisms contribute to the pathogenesis of both these autoimmune diseases. Several studies of subjects with rheumatoid arthritis have provided evidence of association with either thyroid disease or the presence of thyroid antibodies.[8,25] The present study reports the reciprocal association, these findings together providing strong evidence for true disease association.

The association between autoimmune thyroid disease and Addison's disease was especially striking. This apparent association may have been exaggerated by the influence of Addison's disease on thyroid function, because of the well-described increase in serum thyroid stimulating hormone found in untreated glucocorticoid deficiency, leading to a sometimes incorrect diagnosis of permanent hypothyroidism. This is unlikely to be a major contributory factor because other phenotypic features were required to confirm

a diagnosis of Hashimoto's thyroiditis in addition to biochemical hypothyroidism. It is possible that subjects with coincident Hashimoto's thyroiditis and Addison's disease remained under hospital follow-up longer than subjects without coincident Addison's disease, leading to recruitment bias, so that the described relative risks can only be applied to a hospital-based Hashimoto's thyroiditis population. Because subjects with Graves' disease, as those with Hashimoto's thyroiditis, are typically discharged from specialist follow-up once treatment has been stabilized, it is unlikely that duration of follow-up accounts for the marked difference between risks observed in index cases with Graves' disease and Hashimoto's thyroiditis.

Type 1 diabetes was especially common among male index cases with Graves' disease. Few studies have examined the association between autoimmune thyroid disease and type 1 diabetes, although a high prevalence of undiagnosed autoimmune thyroid disease has been reported in screened diabetes clinic populations.[26] Strong support for a true association between autoimmune thyroid disease and type 1 diabetes also is provided by genetic studies,[2] including recent genome-wide association studies indicating shared susceptibility loci for these 2 diseases.[27]

Our data, showing strikingly high relative risks for other autoimmune diagnoses in subjects with Graves' disease and Hashimoto's thyroiditis, support the existence of common pathogenetic mechanisms between autoimmune thyroid disease and celiac disease,[8] pernicious anemia,[28] multiple sclerosis,[7,8] vitiligo,[4] and systemic lupus erythematosus.[29] For each autoimmune disease investigated, the present data provide novel information about disease clustering, strongly supporting the presence of true disease associations. Although some disease associations were common to both Graves' disease and Hashimoto's thyroiditis, there also were significant differences in the prevalences and relative risks for these 2 groups. This may indicate the existence of different susceptibility genes, as highlighted by recent description of Graves' disease-specific gene associations,[30] or may reflect specific and differing environmental triggers.

Our data confirm previous findings of index case and parental clustering of Graves' disease and Hashimoto's thyroiditis,[15] and indicate significantly increased relative risks of hyperthyroidism and hypothyroidism in parents of patients with autoimmune thyroid disease. We demonstrated a predominant association of Graves' disease with parental hyperthyroidism and Hashimoto's thyroiditis with parental hypothyroidism.

The strengths of this study are the size of the patient cohort and the careful assessment of the underlying autoimmune thyroid disease, allowing comparison between Graves' disease and Hashimoto's thyroiditis. There are some limitations. The calculation of relative risks was limited by a relative paucity of contemporary population prevalence data for the United Kingdom, determining that age-matched comparisons could not be performed. Because the mean ages at diagnosis of thyroid dysfunction and of recruitment into the study were not significantly different, it is unlikely that the differences between Graves' disease and Hashimoto's thyroiditis are attributable to age. Moreover, the calculation of relative risks provided strong supporting evidence for differences between Graves' disease and Hashimoto's thyroiditis, and between genders, which were evident from our cross-sectional comparisons. Although relative risk results reported here could reflect referral bias to large centers, it is unlikely that referral bias has influenced the observed differences between genders and between Graves' disease and Hashimoto's thyroiditis. Our data are derived from a UK Caucasian iodine-replete population. Caution should therefore be exercised in extrapolating our findings. The diagnosis of other autoimmune disorders among index cases was self-reported, although verified by cross-checking of records. Diagnoses described in parents by their index case children were not confirmed. Self-reporting of thyroid dysfunction has been shown to have a relatively high sensitivity,[31] although specificity of self-reporting is lower. It might be expected that index cases would under-report, rather than over-report, other autoimmune disorders in their parents. Because we had limited information regarding the diagnosis of thyroid dysfunction in parents, we did not attempt to distinguish autoimmune thyroid dysfunction from other causes of thyroid dysfunction among parents; in the United Kingdom, autoimmune thyroid disease is the predominant cause of thyroid dysfunction.[1,10] The number of participants with Graves' disease was higher than those with Hashimoto's thyroiditis because most patients with hypothyroidism are followed in primary care. The data relating to patients with Hashimoto's thyroiditis should therefore only be applied to a hospital population.

CONCLUSIONS

Overall, our data provide strong evidence of significantly increased risks of coexisting autoimmune diseases in subjects with autoimmune thyroid disease. Given the strikingly increased relative risks for other autoimmune diseases compared with the general UK population, as well as the nonspecific symptoms and thus well-documented frequent delay in diagnosis of these disorders,[32,33] we propose that a low threshold for screening for these diagnoses should be used. This applies especially to patients with autoimmune thyroid disease who remain nonspecifically unwell or who develop new symptoms despite adequate treatment. In addition, we propose that further investigation of susceptibility genes common to more than one autoimmune disorder, such as human leukocyte antigen, *CTLA4, CD25,* and *PTPN22*,[34] as well as investigation of disease-specific genetic variations, will ultimately allow elucidation of the relative contributions of a host of genetic and environmental factors to the causation of these common disorders that frequently coexist.

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