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The epidemiology of Graves' disease: Evidence of a genetic and an environmental contribution

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A B S T R A C T

Previous family and twin studies have indicated that Graves' disease has a heritable component. Family studies have also shown that some autoimmune disease cluster in families and genetic studies have been able to show shared susceptibility genes. In the present nation-wide study we describe familial risk for Graves' disease among parents and offspring, singleton siblings, twins and spouses with regard to age of onset, gender and number and type of affected family members. Additionally familial association of Graves' disease with any of 33 other autoimmune and related conditions was analyzed. The Swedish Multigeneration Register on 0–75-year-old subjects was linked to the Hospital Discharge Register from years 1987–2007. Standardized incidence ratios (SIRs) were calculated for individuals whose relatives were hospitalized for Graves' disease compared to those whose relatives were unaffected. The total number of hospitalized Graves' patients was 15,743. Offspring with an affected family member constituted 3.6% of all patients among offspring. The familial SIR was 5.04 for individuals whose sibling was affected but it increased to 310 when two or more siblings were affected; the SIR in twins was 16.45. Familial risks were higher for males than for females. The SIR was increased to 6.22 or 30.20 when parental age was limited to 50 or 20 years, respectively. Graves' disease associated with 19 other autoimmune and related conditions, including Addison's disease, type 1 diabetes mellitus, Hashimoto/hypothyroidism, pernicious anemia, polymyositis/dermatomyositis, myasthenia gravis, discoid lupus erythematosus and localized scleroderma. Remarkably, there was a high disease concordance of 2.75 between spouses. The clustering between spouses suggests environmental effects on Graves' disease which may contribute to the observed gender effects. The demonstrated high risks should be considered in clinical counseling and in prevention plans.

1. Introduction

Thyroid hormones stimulate the basal metabolic rate through regulation of carbohydrate and lipid metabolism. The thyroid gland synthesizes thyroid hormones in response to thyroid stimulating hormone (TSH or thyrotropin) which binds to its receptor TSHR on thyroid follicular cells. Thyroid hormones stimulate the basal metabolic rate through regulation of carbohydrate and lipid metabolism. Graves' disease is an autoimmune disorder in which antibodies towards TSHR cause a hyperfunction of the tissue [1]. Graves' disease is a common cause of hyperthyroidism or thyrotoxicosis with an annual incidence of 30/100,000 according to Swedish studies [2,3]. The prevalence of Graves disease is related to iodine intake, rather small changes of which may influence the prevalence [4]. Graves disease is more common in women than in men with a peak incidence at 30–60 years [2,3].

Graves' disease is thought to be caused by environmental triggers, such as psychosocial stress, smoking and immune modulators, in genetically susceptible individuals, as shown by a higher disease concordance in monozygotic than dizygotic twins [5–8]. The high risk in women at the reproductive age suggests some risk factors related to female sex hormone but no clear explanations have been found. Familial risks between siblings have been estimated to range from 5 to 12 but the studies are either old or small [5,9]. Graves' and Hashimoto's diseases are often associated with other autoimmune diseases such as systemic lupus erythematosus, Addison's disease and autoimmune polyendocrine syndrome [7,8,10,11]. Several disease susceptibility loci have been identified for Graves' disease,

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including the HLA locus, CTLA-4, CD40, PTPN22, TSH and TSHR [7,8,12,13]. Some of these are shared with other autoimmune diseases.

The availability of a Multigeneration Register in Sweden provides a reliable access to families throughout the last century. This Register has been extensively used to study hospitalized diseases through linkage to the Hospital Discharge Register, including familial autoimmune diseases [14–19]. In the present article we study familial risks for Graves' disease among parents and offspring, singleton siblings, twins and spouses. Both concordant and discordant associations are studied with any of the other 33 autoimmune and related diseases. These 33 diseases were autoimmune, inflammatory and related conditions, selected because of etiological hypothesis or previous association studies. Because many autoimmune diseases show marked gender preferences in prevalence, sex-specific familial risks were also analyzed [20]. With a total patient population of 431,763, of whom 15,743 were diagnosed with Graves' disease, this is the largest family study published on these diseases; the associations of Graves' disease and many of the discordant diseases have never been reported before. The advantage of the present study is that all the results emanate from a single population of medically confirmed cases in a country of high medical standard and reasonably uniform diagnostics.

2. Methods

A thyroid research database was constructed by linking several national Swedish registers, based on the MigMed 2 datasets at Center for Primary Health Care Research, Malmö, Lund University. Statistics Sweden provided the Multigeneration Register where persons born in Sweden in 1932 and later (second generation) were linked to their parents (first generation), registered shortly after birth. Families could be defined by linking all the children to their parents. Sibships can only be defined for the second generation. Linkages were carried out to national census data, in order to obtain individual socioeconomic status. The final links were made by adding individual data from the Swedish Hospital Discharge Register that records data on all discharges after a minimal stay of one night with dates of hospitalization and diagnoses since the 1964 with a complete nation-wide coverage since 1986. A flowchart of the linkages has been published elsewhere [21]. All linkages were performed by the use of the individual national identification number that is assigned to each person in Sweden for their lifetime. This number was replaced by a serial number for each person in order to provide anonymity. The serial number was used to check that each individual was only entered once, for his or her first appearance with a defined diagnosis. Over 11.8 million individuals in 3.9 million families were included in this database; 8.9 million individuals belonged to the second generation which had reached age 75 years at the end of the follow-up, which spanned from 1987 to 2007 [22].

SIRs were calculated for concordant (same) or discordant (different) autoimmune disease, compared with men and women whose relatives were not affected by these conditions. Patients diagnosed with Graves' disease were retrieved from hospital discharges reported according to different versions of the International Classification of Diseases (ICD). Graves' disease was selected by code 242.0 'thyrotoxicosis with toxic diffuse goiter' in the 9th (1987–1996) and by code E05.0 'thyrotoxicosis with diffuse goiter' in the 10th (1997–2007) version. The individual variables controlled for in the analysis include gender (when not specifically analyzed), age at diagnosis (categorized in 5 year intervals), socioeconomic status (six groups: farmers, unskilled/skilled workers, white collar workers, professionals, self-employed and all others) and region (three groups: large cities, Stockholm, Gothenburg and Malmo, Southern Sweden and Northern Sweden), the latter allowing adjustment for regional differences in hospitalization. Person-years were calculated from start of follow-up on January 1, 1987 until hospitalization/diagnosis of disease, death, emigration, or closing date, December 31, 2007. Standardized incidence ratios (SIRs) and 95% confidence intervals (CIs) were calculated for familial risks as the ratio of observed (O) to expected (E) number of cases. The expected number of cases was calculated for age, sex, period, region and socioeconomic status-specific standard incidence rates for those whose relatives were not hospitalized for Graves' disease or other defined autoimmune desease [23]. By this procedure all siblings in families of two or more affected sibling contribute cases and they are compared to single case families using the described person-year calculation. In rare families where more than two siblings were affected, each was counted as an individual patient. Separate familial risks were calculated for offspring whose parents were affected (sibling not affected), for siblings (parents not affected) and for offspring whose parents and at least another sibling were affected. Genetic modes of inheritance were search by using these three types of probands.

In the present results an estimate of the degree of environmental contribution to the familial risk is given by risks between spouses. Spouses were defined for the population older than 25

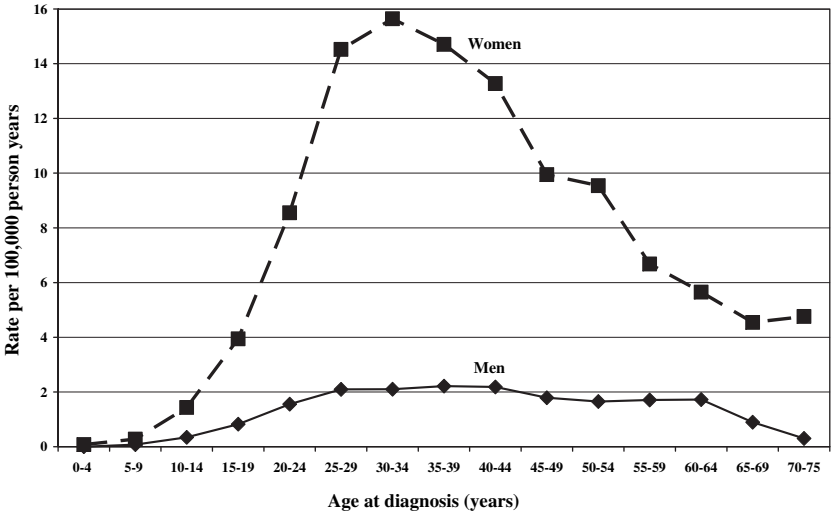

Fig. 1. Age-specific hospitalizations of Graves' disease in men and women.

Table 1
Familial risks for Graves' disease.

Proband	O	SIR	95% CI	
Parent only	161	**4.49**	**3.82**	**5.24**
Parents <50 years	110	**6.22**	**5.11**	**7.50**
Parents <30 years	24	**7.99**	**5.11**	**11.90**
Parents <20 years	6	**30.20**	**10.87**	**66.16**
Singleton sibling only	159	**5.04**	**3.03**	**8.33**
Two or more singleton siblings	9	**310.34**	**99.49**	**836.75**
Both parent and singleton sibling	2	4.51	0.43	16.60
Twins	22	**16.45**	**7.28**	**35.28**
Spouses	36	**2.75**	**1.93**	**3.82**

O = observed number of cases; SIR = standardized incidence ratio; CI = confidence interval.
Bold type: 95% CI does not include 1.00.

years through common children. When this is lower than the risk between blood relatives, a genetic contribution is likely and the risk between twins would be expected to exceed that of singleton siblings.

The study was approved by the regional ethical review board in Lund.

3. Results

The total number of hospitalized Graves' disease patients was 15,743 of whom 9626 belonged to the offspring generation. The highest hospitalization rates for Graves' disease were in age group 30–34 years for women but for men the maximal rate was in ages 25–49 years (Fig. 1). These gender differences in age of hospitalization influence gender-specific familial risk in the subsequent analysis.

3.1. Familial risks for Graves' disease

Familial risks for Graves' disease in offspring are shown in Table 1 according to mutually exclusive proband categories: parent only, singleton sibling only, parent & sibling (multiplex), twin and spouse. The total number of familial Graves' disease cases in offspring was 342 (excluding spouses), which constituted 3.6% of all Graves disease patients. The SIR for offspring was 4.49 when a parent was diagnosed with Graves' disease. The SIR was increased to 4.84 ($N = 166$, 95% CIs 4.13–5.64) when the parental age was limited to 75 years, which was the maximal age for the offspring population. The SIR was increased to 6.22 or 30.20 when the parental age was limited to 50 or 20 years, respectively. The SIR for Graves' disease in singleton siblings was 5.04 ($N = 159$) and it increased to 310 ($N = 9$) when two siblings were affected probands; in twins the SIR was 16.45 ($N = 22$). Remarkably, there was a high disease concordance of 2.75 between spouses. The spouses were not preferentially hospitalized close in time: the SIR was 2.70 ($N = 18$, 95% CI 1.60–4.27) when the spouses were hospitalized less than five years apart compared to the SIR of 2.81 ($N = 18$, 95% CIs 1.66–4.46).

Table 3
Sex-specific familial risks for Graves' disease.

Proband	Men				Women			
	O	SIR	95% CI		O	SIR	95% CI	
By parent								
Father	4	4.15	1.08	10.73	30	5.65	3.81	8.08
Mother	26	5.39	3.51	7.90	108	4.00	3.28	4.82
By singleton sibling								
Men	19	27.81	11.82	61.53	11	3.36	1.18	8.53
Women	13	3.30	1.24	8.00	116	4.90	2.87	8.32
By twins								
Men	4	83.86	15.42	306.65	0			
Women	0				18	18.22	7.62	40.80

O = observed number of cases; SIR = standardized incidence ratio; CI = confidence interval.

Age-specific familial risks for singleton siblings are shown in Table 2. Male risks were higher than female risks in each age group, being overall 6.92 and 4.72, respectively. The SIRs showed marked age dependence. The SIR was 13.85 for both genders when the first hospitalization took place before age 20 years compared to an SIR of 3.42 for those first hospitalized after age 49 years. When both the case and the sibling proband were diagnosed before age 20 years the SIR was 47.28.

Table 3 shows gender-specific familial risks for Graves' disease. There were no significant gender-specific effects among male and female offspring of affected father or mother. However, among singleton siblings, there was a high risk of 27.82 among brothers compared to the SIR of 4.90 for sisters. The risks were lowest for opposite sex siblings. A similar pattern was observed for twins, with high risk of 83.86 for brothers, compared to an SIR of 18.22 for sisters; no opposite sex twins were found.

3.2. Familial risks for Graves' disease and other autoimmune diseases

The total numbers of patients diagnosed with any of the 34 autoimmune diseases was 431,763, of whom 238,252 were offspring (Table 4). The largest diagnostic groups among offspring were asthma (92,544 patients), type 1 diabetes mellitus (21,168), ulcerative colitis (20,572), followed by Graves' disease, Crohn's disease and rheumatoid arthritis, each over 16,000 patients. The numbers of patients in offspring is shown in parenthesis after the disease name in Table 4. The SIR for Graves' disease in offspring was increased also when a parent was diagnosed with 11 of the 33 diseases studied, including Addison's disease (2.52), asthma (1.18), Hashimoto/hypothyroidism (2.04), myasthenia gravis (2.04), pernicious anemia (1.82), polymyalgia rheumatica (1.26),

Table 2
SIR for Graves' disease in singleton siblings by age at hospitalization.

Age at hospitalization (years)	Men				Women				All			
	O	SIR	95% CI		O	SIR	95% CI		O	SIR	95% CI	
<20	4	**17.35**	**3.19**	**63.43**	15	**13.15**	**5.19**	**30.74**	19	**13.85**	**5.89**	**30.65**
20–29	10	**8.92**	**3.00**	**23.29**	50	**7.04**	**3.69**	**13.13**	60	**7.29**	**3.94**	**13.28**
30–39	9	**6.05**	**1.94**	**16.32**	37	**3.92**	**1.95**	**7.65**	46	**4.21**	**2.18**	**7.95**
40–49	4	3.83	0.71	14.02	16	**2.72**	**1.10**	**6.26**	20	**2.89**	**1.24**	**6.31**
≥50	5	**6.73**	**1.50**	**22.38**	9	2.69	0.86	7.24	14	**3.42**	**1.32**	**8.14**
All	32	**6.92**	**3.34**	**13.83**	127	**4.72**	**2.78**	**7.94**	159	**5.04**	**3.03**	**8.33**
Both singleton siblings <20	2	**56.98**	**3.80**	**296.35**	6	**44.74**	**11.39**	**138.64**	8	**47.28**	**14.28**	**132.40**
Both singleton siblings <30	13	**22.09**	**8.28**	**53.57**	40	**12.45**	**6.28**	**23.99**	53	**13.94**	**7.38**	**25.80**

O = observed number of cases; SIR = standardized incidence ratio; CI = confidence interval.
Bold type: 95% CI does not include 1.00.

Table 4
Familial SIR for Grave's disease and autoimmune disorders according to the proband.

Autoimmune condition (case in offspring)	Parent only				Singleton sibling only				Both parent and sibling				Twins				Spouses			
	O	SIR	95% CI		O	SIR	95% CI		O	SIR	95% CI		O	SIR	95% CI		O	SIR	95% CI	
Addison disease (1005)	9	**2.52**	**1.14**	**4.81**	9	3.06	0.98	8.24	1	769.23	0.31	4409.43	0				1	0.53	0.00	3.04
Amyotrophic lateral sclerosis (1521)	29	1.41	0.94	2.03	6	1.19	0.30	3.70	0				0				8	0.71	0.30	1.41
Ankylosing spondylitis (3566)	15	1.16	0.65	1.91	13	0.99	0.37	2.39	0				0				15	1.29	0.72	2.13
Asthma (92544)	331	**1.18**	**1.06**	**1.32**	148	1.10	0.66	1.83	13	1.03	0.55	1.77	1	0.29	0.00	2.34	141	1.15	0.97	1.35
Autoimmune hemolytic anemia (258)	5	1.76	0.56	4.14	0				0				0				0	0.00	0.79	3.21
Behcet disease (1514)	10	1.37	0.65	2.52	5	0.95	0.21	3.14	0				0				7	1.47	0.58	3.05
Celiac disease (9304)	8	1.10	0.47	2.17	16	1.30	0.53	3.00	1	7.60	0.00	43.56	0				4	1.14	0.30	2.94
Chorea minor (23)	0				0				0				0				0			
Chronic rheumatic heart disease (1752)	67	1.14	0.88	1.45	6	0.97	0.25	3.01	0				0				32	1.22	0.83	1.72
Crohn disease (16164)	32	0.95	0.65	1.34	54	1.14	0.61	2.11	0				0				29	1.21	0.81	1.74
Diabetes mellitus type I (21168)	5	**3.37**	**1.06**	**7.92**	62	**2.14**	**1.16**	**3.87**	1	20.08	0.01	115.11	1	1.56	0.00	12.64	0			
Discoid lupus erythematosus (226)	4	2.62	0.68	6.76	5	**6.03**	**1.35**	**20.07**	0				0				1	1.62	0.00	9.30
Hashimoto/hypothroidism (2824)	57	**2.04**	**1.54**	**2.64**	15	1.81	0.71	4.23	3	**37.41**	**7.05**	**110.73**	2	9.78	0.65	50.86	4	0.51	0.13	1.31
Immune thrombocytopenic purpura (2748)	7	1.18	0.47	2.44	9	1.83	0.59	4.93	0				0				2	0.61	0.06	2.25
Localized scleroderma (224)	3	1.19	0.22	3.52	5	**6.62**	**1.48**	**22.02**	0				0				1	1.45	0.00	8.30
Lupoid hepatitis (250)	0				1	1.28	0.00	10.34	0				0				0			
Multiple sclerosis (7709)	34	1.22	0.84	1.70	30	1.21	0.58	2.46	2	5.40	0.51	19.87	0				10	0.63	0.30	1.17
Myasthenia gravis (1164)	14	**2.04**	**1.11**	**3.43**	6	1.59	0.40	4.93	0				0				4	1.07	0.28	2.78
Pernicious anemia (488)	43	**1.82**	**1.32**	**2.46**	1	0.59	0.00	4.75	0				0				19	**1.95**	**1.17**	**3.06**
Polyarteritis nodosa (336)	6	1.60	0.58	3.50	1	0.91	0.00	7.38	0				0				2	1.02	0.10	3.77
Polymyalgia rheumatica (4241)	104	**1.26**	**1.03**	**1.53**	16	0.98	0.40	2.26	0				0				26	0.85	0.55	1.25
Polymyositis/dermatomyositis (679)	9	**2.48**	**1.12**	**4.73**	6	2.82	0.72	8.75	0				0				3	1.57	0.30	4.64
Primary biliary cirrhosis (351)	4	0.93	0.24	2.40	1	0.75	0.00	6.11	0				0				1	0.57	0.00	3.27
Psoriasis (7626)	49	1.09	0.81	1.44	31	1.07	0.52	2.16	2	2.68	0.25	9.87	0				39	**1.62**	**1.15**	**2.21**
Reiter disease (226)	1	2.40	0.00	13.75	0				0				0				1	1.89	0.00	10.85
Rheumatic fever (1782)	10	1.06	0.51	1.96	4	0.60	0.11	2.21	0				0				3	0.45	0.08	1.33
Rheumatoid arthritis (16012)	270	**1.48**	**1.31**	**1.67**	70	1.38	0.76	2.47	6	1.73	0.62	3.78	1	0.58	0.00	4.68	91	**1.35**	**1.09**	**1.66**
Sarcoidosis (5643)	44	**1.53**	**1.11**	**2.05**	32	1.53	0.74	3.06	0				1	1.52	0.00	12.32	18	1.09	0.64	1.72
Sjören syndrome (596)	5	1.23	0.39	2.90	2	1.01	0.07	5.24	0				0				0			
Systemic lupus erythematosus (2800)	19	1.40	0.84	2.20	16	1.84	0.74	4.23	2	**14.33**	**1.35**	**52.69**	1	4.19	0.00	33.99	7	1.43	0.57	2.96
Systemic sclerosis (2381)	18	1.34	0.79	2.12	10	1.37	0.46	3.57	0				0				3	0.44	0.08	1.30
Ulcerative colitis (20572)	68	**1.30**	**1.01**	**1.65**	89	1.39	0.79	2.42	1	0.86	0.00	4.92	0				47	1.19	0.87	1.58
Wegener granulomatosis (929)	46	1.25	0.91	1.66	4	1.31	0.24	4.79	0				0				13	1.00	0.53	1.71
All (238252)	1485	**1.43**	**1.35**	**1.50**	830	**1.52**	**1.00**	**2.30**	34	**1.62**	**1.12**	**2.26**	29	1.79	0.85	3.65	568	**1.19**	**1.09**	**1.29**

O = observed number of cases; SIR = standardized incidence ratio; CI = confidence interval.
Bold type: 95% CI does not include 1.00. SIR with underlining, 99% CI does not include 1.00.

polymyosistis/dermatomyositis (2.48), rheumatoid arthritis (1.48), sarcoidosis (1.53) and ulcerative colitis (1.30). The risk was 1.43 when a parent presented with any autoimmune and related conditions. Because a lot of comparisons are done, we have calculated also 99% CIs and show the 1% significance by the underlined SIRs; 4 of the above 11 associations reached this significance level.

For discordant disease among singleton siblings (Table 4), the SIR for Graves' disease was only increased for type 1 diabetes mellitus (2.14), discoid lupus erythematosus (high risk of 6.03) and localized scleroderma (high risk 6.62). SIRs for Graves' disease were increased when a parent and a sibling were diagnosed with Hashimoto/hypothyroidism (37.41) and systemic lupus (14.33). In one multiplex family a high SIR of 14.33 was found with systemic lupus. Spouse correlation for Graves' disease was increased with pernicious anemia (1.95), psoriasis (1.62) and rheumatoid arthritis (1.35).

Many autoimmune diseases show gender preferences (the numbers of hospitalized women for each disease are reported elsewhere [19]) and in Table 5 we carried out analyses specifically for men and women as in Table 4 (two first sets of columns). Additionally, an analysis in a reverse order was carried out, i.e., SIRs were calculated for autoimmune disease in offspring when parents were diagnosed with Graves' disease (third and fourth set of columns). These are completely independent analyses and identical results would add to the weight of evidence. Significant associations at least for one gender were found for asthma, type 1 diabetes, rheumatoid arthritis and ulcerative colitis. As new findings, female SIR for ankylosing spondylitis was 2.21, female SIR for sarcoidosis was 1.61 and male and female SIRs for celiac disease were 1.56 and 1.68, respectively.

In Table 5, only the gender of the offspring was controlled for; however, we have carried out an analysis by also controlling the parental gender (data not shown). Case numbers were small and confidence intervals wide. The only associations showing evidence on true gender-specificity were for Graves' disease in daughters when mothers were diagnosed with Addison's disease ($N = 6$, SIR 2.78, 95% CI 1.00–6.09) or polymyositis/dermatomyositis ($N = 8$, SIR 3.97, 95% CI 1.69–7.85). For neither condition were male-specific pairs found. In the gender-specific analysis, two new associations were found, chronic rheumatic heart disease in daughters ($N = 7$, SIR 3.37, 95% CI 1.33–6.98) or multiple sclerosis in daughters ($N = 28$, SIR 1.68, 95% CI 1.11–2.42) both with maternal Graves' disease.

4. Discussion

There is a well known genetic basis and familial clustering of Graves' disease [1,8,24–27]. The novel aspects of the present study are the nation-wide data on familial risks in Graves disease', with remarkable effects of the number of affected probands, age of onset and gender, and a high disease concordance between spouses. Additionally, we defined familial risks for Graves' disease across 33 other disease diseases in a systematic way in a single population which has never been done before. Limitations of the study include unavailability of laboratory data to verify the used discharge diagnoses and lack of information on risk factors, such as psychosocial life events and smoking. On the other hand, the diagnostics of Graves' disease has been in place in the Swedish hospitals throughout the study period. Furthermore, as Graves' disease is the

Table 5
SIR for Grave's disease in offspring whose parents were diagnosed with autoimmune disorders and SIR for autoimmune disorders in offspring whose parents were diagnosed with Grave's disease.

Autoimmune disorders in parents	Grave's disease in men				Grave's disease in women				Autoimmune disorders in men				Autoimmune disorders in women			
	O	SIR	95% CI		O	SIR	95% CI		O	SIR	95% CI		O	SIR	95% CI	
Addison disease	2	4.00	0.38	14.70	7	2.28	0.90	4.73	3	1.58	0.30	4.67	2	0.92	0.09	3.39
Amyotrophic lateral sclerosis	6	1.98	0.71	4.33	23	1.31	0.83	1.97	1	0.29	0.00	1.66	1	0.44	0.00	2.55
Ankylosing spondylitis	0				15	1.35	0.75	2.22	12	1.22	0.63	2.14	9	**2.21**	**1.00**	**4.21**
Asthma	55	**1.36**	**1.03**	**1.78**	276	**1.15**	**1.02**	**1.30**	225	1.08	0.94	1.23	178	**1.17**	**1.00**	**1.35**
Autoimmune hemolytic anemia	0				5	2.05	0.65	4.83	0				0			
Behcet disease	2	1.93	0.18	7.09	8	1.27	0.54	2.52	7	1.66	0.66	3.44	0			
Celiac disease	1	0.94	0.00	5.39	7	1.12	0.44	2.32	25	**1.56**	**1.01**	**2.30**	40	**1.68**	**1.20**	**2.29**
Chorea minor	0				0				0				0			
Chronic rheumatic heart disease	10	1.18	0.56	2.18	57	1.13	0.86	1.47	2	0.52	0.05	1.92	8	**3.23**	**1.38**	**6.40**
Crohn disease	8	1.65	0.71	3.27	24	0.83	0.53	1.24	31	0.96	0.65	1.36	37	1.07	0.75	1.47
Diabetes mellitus type I	1	3.78	0.00	21.64	4	3.28	0.85	8.48	105	**2.17**	**1.78**	**2.63**	87	**2.08**	**1.66**	**2.56**
Discoid lupus erythematosus	1	3.92	0.00	22.47	3	2.35	0.44	6.97	0				0			
Hashimoto thyroiditis	6	1.44	0.52	3.16	51	**2.14**	**1.59**	**2.82**	3	1.11	0.21	3.28	13	1.57	0.83	2.69
Immune thrombocytopenic purpura	0				7	1.37	0.54	2.84	6	1.12	0.40	2.45	6	1.10	0.40	2.41
Localized scleroderma	0				3	1.40	0.26	4.15	0				2	3.18	0.30	11.69
Lupoid hepatitis	0				0				1	2.77	0.00	15.88	0			
Multiple sclerosis	4	0.98	0.26	2.54	30	1.26	0.85	1.80	10	1.01	0.48	1.87	28	1.39	0.93	2.02
Myasthenia gravis	4	**4.04**	**1.05**	**10.44**	10	1.70	0.81	3.14	2	1.25	0.12	4.59	2	0.67	0.06	2.47
Pernicious anemia	6	1.63	0.59	3.57	37	**1.86**	**1.31**	**2.56**	1	1.06	0.00	6.09	2	2.37	0.22	8.72
Polyarteritis nodosa	1	1.76	0.00	10.08	5	1.57	0.50	3.69	1	1.54	0.00	8.83	0			
Polymyalgia rheumatica	18	1.50	0.89	2.37	86	1.22	0.98	1.51	6	0.89	0.32	1.95	15	1.71	0.95	2.82
Polymyositis/dermatomyositis	1	1.79	0.00	10.26	8	**2.60**	**1.11**	**5.16**	1	0.96	0.00	5.51	3	1.94	0.37	5.74
Primary biliary cirrhosis	0				4	1.08	0.28	2.78	0				0			
Psoriasis	3	0.47	0.09	1.39	46	1.19	0.87	1.59	19	1.28	0.77	2.01	19	1.28	0.77	2.01
Reiter disease	0				1	2.74	0.00	15.72	1	1.29	0.00	7.41	0			
Rheumatic fever	2	1.45	0.14	5.34	8	1.00	0.43	1.97	4	0.73	0.19	1.89	3	1.93	0.36	5.70
Rheumatoid arthritis	38	**1.46**	**1.03**	**2.00**	232	**1.49**	**1.30**	**1.69**	24	1.37	0.87	2.03	64	**1.53**	**1.18**	**1.96**
Sarcoidosis	4	1.00	0.26	2.58	40	**1.61**	**1.15**	**2.20**	11	0.83	0.41	1.49	9	1.07	0.48	2.04
Sjören syndrome	0				5	1.44	0.45	3.39	0				3	1.57	0.30	4.65
Systemic lupus erythematosus	3	1.54	0.29	4.57	16	1.38	0.79	2.25	3	1.69	0.32	5.01	16	1.72	0.98	2.80
Systemic sclerosis	2	1.01	0.10	3.71	16	1.40	0.80	2.28	6	1.13	0.41	2.47	3	0.65	0.12	1.94
Ulcerative colitis	6	0.79	0.28	1.73	62	**1.39**	**1.06**	**1.78**	64	**1.36**	**1.05**	**1.74**	51	**1.35**	**1.01**	**1.78**
Wegener granulomatosis	7	1.25	0.50	2.60	39	1.25	0.89	1.70	0				1	0.65	0.00	3.71
All	220	**1.46**	**1.27**	**1.66**	1265	**1.42**	**1.34**	**1.50**	604	**1.27**	**1.18**	**1.38**	746	**1.58**	**1.47**	**1.70**

O = observed number of cases; SIR = standardized incidence ratio; CI = confidence interval.
Bold type: 95% CI does not include 1.00. SIR with underlining, 99% CI does not include 1.00.

most common form of hyperthyroidism, accounting for 75% of all [2], any diagnostic inaccuracies are most likely to be small. Earlier Swedish studies also show that hospitalization for hyperthyroidism is practically complete for all diagnosed patients [2,3]. Abraham-Nordling and coworkers contacted all health care centers in Stockholm and reported that these had treated no other hyperthyroidism patients but those 1431 patients that were found in hospital records from 2003 to 2005 [2]; a similar study from southern Sweden on 336 by Lantz and coworkers found no patients who would have not been hospitalized [3].

A high degree of hospitalization has been reported for, e.g., type 1 diabetes mellitus, Crohn's disease, ulcerative colitis, rheumatoid arthritis and celiac disease, as discussed elsewhere together with diagnostic accuracy [28]. For many diseases no data however are available and it can be assumed that patients with severe disease are preferentially hospitalizes. Hashimoto's disease/hypothyroidism appears to be an example of diseases with a low degree of hospitalization [6,29]; for these diseases a preferential hospitalization of family members may be possible. However, the effects should be strongest for cohabiting spouses which were increased only for three discordant associations but not for Hashimoto's disease/hypothyroidism (SIR 0.51).

In early 1900s it was recognized that Sweden had areas of endemic goiter whereby table salt iodization was introduced in 1936 with 10 mg/kg and the dose was increased to 50 mg/kg in 1966 [2]. Surveys of intake of iodine in the population have concluded that the intake is sufficient [2,30]. Even though a proportion of the present study population was born before the second iodine fortification, it is not obvious how iodine intake differences would influence the results, particularly in relation to autoimmune diseases with no relation to iodine intake.

4.1. Spouse correlation: environmental effects

The high spouse correlation of 2.75 suggests the operation of some form of environmental sharing. In our previous family studies of autoimmune disorders, spouse correlations were marginally increased, such as 1.17 for rheumatoid arthritis [19]. For diseases for which smoking is a strong risk factor, much higher than for Graves disease [31–33], a correlation of 1.57 was found for obstructive chronic bronchitis and 1.55 for emphysema [34]. An unexplained high spouse correlation of 2.35 was, however, recently observed for amyotrophic lateral sclerosis [21]. The mechanisms behind the spouse correlation may be shared smoking habits, psychosocial risk factors, stress and infections, all of which may precipitate many autoimmune conditions [35,36]. In a Japanese study, the highest stress score was associated with a relative risk of 7.7 but the effects of stress and smoking were only observed in women [37]. The present study showed no tendency for spouses to be preferentially hospitalized close in time ruling out the possibility that concurrent hospitalizations or life events would explain the findings.

Shared psychosocial risk factors, stress and infections may also precipitate many other autoimmune conditions which may explain the discordant associations between spouses [35,36]. Interestingly,

smoking is a risk factor for all the conditions for which significant spouse correlation was observed, including Graves' disease, psoriasis and rheumatoid arthritis, although it is also a risk factor for multiple sclerosis for which no spouse correlation was found [31–33].

4.2. Familial Graves' disease

Familial patients accounted for 3.6% of all offspring Graves disease patients. The risk was almost equal in offspring of affected parents (4.84 when parental age was adjusted to the age of the offspring generation, maximally 75 years) and in singleton siblings (5.09), suggesting that recessive inheritance was of minor importance because this would have increased preferentially sibling risks. However, both of these risks were clearly higher than the risks among spouses, providing evidence, together with the twin data, on a heritable etiology, possibly modified by gene–environment interactions. The present familial risks are lower than those between 5 and 12 reported in previous literature for Graves' disease; however, they were based on small samples [5,9]. The present data showed strong modification of risk by age and the high risks reported in the literature may point to a relatively young population under study. The Danish study on thyrotoxicosis, also based on hospitalized cases, gave odds ratios of 2.9 for parents and 5.2 for siblings, not very different of our results of 4.49 and 5.04, respectively [26].

The highest familial risk of 310 was observed for individuals who had at least two affected siblings and these patients accounted for 0.1% of all Graves' disease patients in the offspring generation. If a sibling proband was hospitalized before age 20 (0.2% of all patients), the risk was close to 14; if the parental proband was hospitalized before age 20, the risk was 30 (0.05% of all patients). The number of early onset cases was relatively small but the related high risks are likely to point to the effects of high penetrance genes. The SIR for twins was 16.45. We had no zygosity data on twins but because their risk was over three times higher than that for singleton siblings and because all affected twin pares were of same sex it is likely that they were mainly monozygotic.

4.3. Graves' disease and other autoimmune diseases

The novel results on discordant familial associations of Graves' disease/hyperthyroidism with other autoimmune and related conditions found 11 significant associations among a total of 33 diseases and four of these were significant at the 1% level. Addison's disease showed a high association of 2.52, which could suggest an etiological contribution by autoimmune polyendocrine syndrome, as also type 1 diabetes mellitus (3.37 from parent, 2.14 from sibling), Hashimoto/hypothyroidism and pernicious anemia were associated [7,11,38]. Other disease with strong association with Graves' disease were discoid lupus erythematosus (sibling risk 6.03, higher than for concordant Graves' disease), localized scleroderma (sibling risk 6.62), polymyositis/dermatomyositis (2.46) and myasthenia gravis (2.04). Even common diseases, such as asthma and rheumatoid arthritis, showed associations but environmental factors could contribute to these as discussed above in the context of spouse correlation. The association with asthma was weak (1.18) but similar weak associations have been found in our studies on type 1 diabetes, multiple sclerosis and rheumatoid arthritis [19,28,39]. Notably, the associations with discoid lupus erythematosus and localized scleroderma were only observed among siblings which may suggest involvement of recessive inheritance.

In addition to the 11 associations from parental probands and two from sibling probands, discussed above, systemic lupus erythematosus, ankylosing spodylitis, celiac disease, sarcoidosis, chronic rheumatic heart disease and multiple sclerosis (total 19) showed positive associations in separate analyses. As many autoimmune diseases show female predilection, gender-specific analyses were carried out but leading to small case numbers at the end. The only associations showing evidence on true gender-specificity were for Graves' disease in daughters when mothers were diagnosed with Addison's disease and polymyositis/dermatomyositis.

The study included many comparisons (about 200, not including spouses) and obviously some of the Graves' diseases associations with 19 other diseases were chance findings. Curiously, however, no protective associations were found. In order to guard against chance findings, 99%CI were used, and seven of the associations in Tables 4 and 5 reached at least this significance level. Another guard against false positives was to assess how many associations were replicated in the independent analysis (i.e., different probands or reversed analysis). These were only four diseases, asthma, type 1 diabetes, Hashimoto/hypothyroidism, rheumatoid arthritis and ulcerative colitis; all but ulcerative colitis were significant at 1% level in some analyses.

5. Conclusions

This population-level study showed familial risks between different kinds of family members for Graves' diseases. The clustering between spouses suggests environmental effects on the disease which may also contribute the observed gender effects. Familial risks were particularly high for twins, for individual with two or more affected singleton siblings and for individuals whose parents or siblings were affected at an early age. The demonstrated high risks should be considered in clinical counseling and in prevention plans. The identification of the suggested environmental factors is a challenge and inability to control for such factors will be a serious limitation to studies searching for susceptibility genes of Graves' diseases.

Many [19] associations of Graves' disease with other autoimmune diseases were found. Although some the associations may be chance findings, it is likely that most will remain as true findings. For example, the component diseases of autoimmune polyendocrine syndrome, Addison's disease, type 1 diabetes mellitus, Hashimoto/hypothyroidism and pernicious anemia all showed strong associations with Graves' disease. Interestingly, the associations with discoid lupus erythematosus and localized scleroderma were only observed among siblings, suggesting involvement of recessive inheritance. Putative female-specific effects for Graves' disease were found between Addison's disease and polymyositis/dermatomyositis. Most of the clustering cannot be explained by the known genetic basis of these diseases, suggesting promising prospects for gene finding studies.

Conflict of interest

None declared.

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