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Family history of cancer and non-malignant diseases and risk of childhood acute lymphoblastic leukemia: A Children's Oncology Group Study

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Abstract

Background—Studies of family history of cancer and non-malignant diseases in childhood acute lymphoblastic leukemia (ALL) show inconsistent findings. Most studies show no increased risk with family history of cancer. Non-malignant diseases such as allergic diseases, autoimmune diseases, birth defects and thyroid diseases have been reported to be associated with ALL.

Methods—We conducted a case-control study of family history of cancer and selected non-malignant conditions (allergic diseases, autoimmune diseases, birth defects, and thyroid diseases). ALL cases were obtained from Children's Cancer Group institutions from January 1989 to June 1993. Controls were recruited via random digit dialing. Family history for first degree relatives and grandparents of ALL cases and controls was collected by structured telephone questionnaires. Conditional logistical regression was used to calculate odds ratios adjusting for potential confounders.

Results—We found a borderline association of ALL and having a family member with a history of cancer in cases (n = 1842) compared to controls (n = 1986) (OR = 0.98, 95%CI = 0.93, 1.00) and an inverse association for esophageal cancer based on small numbers. Family history of food and drug allergies demonstrated a modestly reduced risk (OR = 0.83, 95%CI = 0.73, 0.95) as did family history of rheumatoid arthritis (OR = 0.79, 95%CI = 0.65, 0.96). There were no associations with family history of any autoimmune diseases, immunodeficiencies, birth defects, thyroid diseases and risk of childhood ALL.

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Conclusions—These results show no association of overall family history of cancer with childhood ALL, while providing additional evidence for an inverse association with family history of allergic disease. Two potentially new associations of ALL with family history of esophageal cancer and rheumatoid arthritis require confirmation in other studies and validation with medical records.

Keywords

Pediatric; Cancer; Acute lymphoblastic leukemia; Case–control study; Autoimmune; Allergies; Family history

1. Introduction

Acute lymphoblastic leukemia (ALL) is the most common childhood malignancy, affecting 3.9 per 100,000 children at ages 0–14 each year in the United States [1,2]. Causal factors contributing to the risk of ALL include several congenital diseases as well as exposure to ionizing radiation, but the causes of a large proportion of the cases remain unknown [3–5]. The identification of other risk factors leading to ALL is thus an important objective for future research.

Family history of cancer and other diseases can provide insight into the genetic (and/or shared environmental) basis of an illness. Several studies of ALL have examined family history of disease, but have not provided consistent conclusions [6–15]. Most studies show no increased risk with a family history of cancer, but associations with specific cancer sites including brain, breast, colon/rectum, genital, lip/oral, kidney cancer, and testicular teratomas have been reported [16–20]. We investigated the association of family history of specific cancers and non-malignant diseases in one of the largest case–control studies of childhood ALL conducted to date.

2. Materials and methods

2.1. Study population

A detailed description of the methods used for this case–control study has been published elsewhere [21]. Case eligibility included being newly diagnosed with ALL prior to age 15 years at a former Children's Cancer Group (CCG) institution from January 1, 1989 to June 15, 1993. The CCG was a National Cancer Institute-funded cooperative clinical trials group composed of institutions in the United States, Canada, and Australia now encompassed by the Children's Oncology Group [22]. Of the 120 CCG institutes, 108 from the US and Canada participated in this study. Approximately 50% of childhood leukemia cases in the US were cared for by CCG institutes during the time of the study period [23]. Cases were eligible if the patient's biological mother had a telephone in the home and spoke English. Controls were identified using a random digit dialing methodology [24]. Controls were individually matched to the cases on age (no more than a 25% difference in age at diagnosis of the case, with a maximum difference of ±2 years), sex, race (white, black, or other), and telephone area code and exchange of the case's residence at diagnosis.

2.2. Data collection

Separate telephone interviews with mothers and fathers were conducted using structured questionnaires. Of the 2081 eligible cases, 1914 mothers of cases (92.1%) completed a telephone interview and 1842 were matched (88.6%). There were 167 (7.9%) non-participants among the eligible cases including 70 (3.4%) due to parental refusals, 41 (2.0%) due to physician refusals, 18 (0.9%) who were lost to follow-up, and 38 (1.8%) who did not

participate for other reasons. Of the 2597 identified controls, 1987 mothers of controls (76.5%) completed interviews. One control was not matched to a case leading to a total of 1986 (76.5%) controls. There were 610 (23.5%) non-participants among the eligible controls including, 457 (17.6%) due to parental refusals, 17 (0.7%) who were lost to follow-up, and 136 (5.2%) who did not participate for other reasons. Seventy-two cases were not able to be matched on age and race to controls resulting in a total of 1842 matched case–control pairs (1:1 match = 1704 sets, 1:2 match = 132 sets, 1:3 = 6 sets). Paternal interviews were completed for 86.5% of eligible cases (1801/2081) and 69.8% of controls (1813/2597).

Family history information was collected for full and half siblings by maternal interview. When available each biological parent completed questions on their family history. For cases where a direct paternal interview was not obtainable, mothers were asked to provide surrogate data. Specifically, the interview collected all cancer diagnoses (classified according to International Classification of Diseases, Ninth Edition (ICD-9) codes) and age at diagnosis. Data on non-malignant diseases were selected based upon hypothesized associations with ALL at the time of data collection and included allergic diseases (food and drug allergies, asthma, hay fever, and hives), anemia, autoimmune diseases (multiple sclerosis, rheumatoid arthritis, psoriasis, ulcerative colitis, celiac disease, lupus, sarcoidosis, ankylosing spondylitis, and diabetes), birth defects, and thyroid diseases (hyperthyroidism or Grave's disease, thyroiditis or Hashimoto's disease, and hypothyroidism).

2.3. Statistical analysis

Dichotomous variables were created to designate any or no family history of cancer and non-malignant disease. Categorical variables were created to assess dose-response for the number of relatives with cancer and selected non-malignant diseases. Cut points were determined such that each category contained sufficient data with five being the maximum number of categories. Using dichotomous variables, we further examined family history among parents only, grandparents only, maternal relatives only (i.e., risk in maternal relatives regardless of occurrence in paternal relatives including proband's mother, maternal grandmother, and paternal grandfather), family history among paternal relatives only, family history among male relatives only and female relatives only.

The covariates maternal age at birth of the proband, birth weight and total number of relatives were chosen a priori for inclusion in regression models. Increased maternal age and high birth weight have been associated with increased risk of ALL [25–27].

Conditional logistical regression was used to calculate odds ratios (OR) and 95% confidence intervals (CI) to evaluate the potential associations between family history of disease and risk of ALL. Analyses for cancers and selected non-malignant disease were adjusted for maternal age, birth weight and total number of relatives (Table 1). Personal history of allergies was also adjusted for in the disease specific analysis. Additional analyses examined family history of disease occurring among parents, grandparents, maternal, paternal, male and female relatives separately. Sensitivity analyses were completed to exclude data from cancers diagnosed after the primary cancer and data from paternal proxy interviews. Exclusion of multiple primary cancers permitted the analysis of solely primary cancers separate from multiple cancer diagnoses which could be mistaken for metastases or treatment-related secondary cancers. For the analysis dropping paternal proxy data, matched pairs were broken to allow unconditional logistic regression. Categorical data for the number of affected relatives were analyzed using a test for trend. SAS statistical software (Version 9.2, Cary, NC) was used to perform all data analyses.

3. Results

3.1. Demographics

Cases were mainly 2–5 years of age at ALL diagnosis, primarily white, with a somewhat greater proportion being male. Compared to cases, controls were more likely to be white and of higher socioeconomic status based on differences in income and maternal education (Table 1). The mean number of siblings (1.5), parents (1.9), grandparents (3.7), and total relatives (7.1) was the same in cases and controls.

3.2. Family history of cancer

Having a reported family history of any type of cancer in one or more relatives was borderline associated with childhood ALL (OR = 0.98, 95%CI = 0.93, 1.00) but did risk increase significantly with an increasing number of relatives with cancer (Table 2). The origin of cancer in parents, grandparents, maternal or paternal relatives only showed no associations (OR = 0.85, 95%CI = 0.56, 1.29, OR = 0.91, 95%CI = 0.77, 1.07, OR = 0.97, 95%CI = 0.83, 1.13 and OR = 1.01, 95%CI = 0.86, 1.18 respectively). Risk of ALL was not associated with family history of cancer when considering female or male relatives only (OR = 1.00, 95%CI = 0.86, 1.16 and OR = 0.91, 95%CI = 0.78, 1.06, respectively). Younger age at cancer diagnosis (i.e., cancer <40 years of age) was not different in family members of cases compared to controls (OR = 0.92, 95%CI = 0.78, 2.31). Family history of malignancy and ALL associations did not differ based upon inclusion of multiple primary cancer diagnoses or exclusion of paternal proxy interviews (data not shown).

Family history of 18 cancer sites or grouping of sites categorized by ICD-9 site was assessed for associations with ALL (Table 3). With the exception of esophageal cancer, which showed an inverse association with risk of ALL (OR = 0.22, 95%CI = 0.07, 0.80), there were no significant associations between cancers sites and the risk of ALL.

3.3. Family history of non-malignant disease

Significant inverse associations were found for family history of allergic diseases (OR = 0.86, 95%CI = 0.73, 1.00) and specifically food and drug allergies (OR = 0.83, 95%CI = 0.73, 0.95), but not other allergic conditions (Table 4). The association was predominantly seen in families with five or more relatives with allergic diseases (OR = 0.75, 95%CI = 0.61, 0.92). Maternal family history of allergic diseases was negatively associated (OR = 0.86, 95%CI = 0.76, 0.98), whereas paternal family history was positively associated with ALL (OR = 1.23, 95%CI = 1.07, 1.41).

Family history of any autoimmune disease was not associated with increased risk of ALL (OR = 0.92, 95%CI = 0.80, 1.06), nor were specific autoimmune diseases associated with an evaluated risk including multiple sclerosis, psoriasis, ulcerative colitits, celiac disease, lupus, sarcoidosis, ankylosing spondylitits, and diabetes. Only rheumatoid arthritis showed a significant association (OR = 0.79, 95%CI = 0.65, 0.96).

Birth defects, immunodeficiency/recurrent infections, and thyroid disease among family members were not significantly associated with risk of ALL (OR = 0.87, 95%CI = 0.65, 1.16, OR = 0.97, 95%CI = 0.81, 1.17, OR = 1.16, 95%CI = 0.67, 2.00, respectively). Family history of anemia was also acquired but was not included in the analysis due to concerns of ambiguity ranging from the acute myeloid precursor myelodysplastic syndromes (MDS) to iron deficiency, hemolytic, autoimmune and other disorders causing anemia. Associations of family history of non-malignant disease with ALL did not materially differ after exclusion of paternal proxy interviews (data not shown).

4. Discussion

This study is one of the largest case–control studies of family history of cancer and selected non-malignant conditions in childhood ALL to date. The large sample size permitted analysis of relatively rare cancer sites and specific allergic, autoimmune, and thyroid diseases. The current study suggested some novel associations between family history of malignant and benign diseases and childhood ALL.

In this study, family history of cancer was not significantly more frequent among ALL cases compared to controls. No significant associations were noted for family history of 17 specific cancer sites, maternal or paternal cancer only, male or female cancer only, or cancer in relatives less than 40 years of age. Interestingly, the likelihood of family history of esophageal cancer was lower in cases compared to controls but the number of affected relatives was small and multiple comparisons performed. For selected non-malignant conditions, significant inverse associations with family history of allergic disease, food and drug allergy, rheumatoid arthritis and risk of ALL were observed. Below we will compare our results with those of previous published reports.

Epidemiological studies investigating family history of cancer have not provided conclusive evidence for any associations with ALL. Six case–control studies have been completed almost exclusively by interview based questionnaires with the exception of one hospital based case–control study which verified cancer diagnoses via medical records [16–18,28–30]. Five population based registries and one cancer survivor cohort study assessed family history of cancer and ALL [19,20,31–34]. Positive family history of hematological cancers in second degree relatives of ALL cases has been reported in one population based case–control study [16]. Specific cancer site associations that have been reported in one study but have not been replicated include brain, breast, colon/rectum, genital lip/oral, kidney cancer, and testicular teratomas [16–20].

We did not find associations between any family history of cancer, hematological cancers, or any other previously reported solid tumor (i.e., brain, breast, colon/rectum, genital, lip/oral, kidney cancer, and testicular teratomas). An inverse association was noted for the risk of ALL and family history of esophageal cancer, based on small numbers, which to our knowledge has not been analyzed separate from stomach cancer. Studies have investigated esophageal and stomach cancer combined and not seen any significant associations. Notably, risk factors are quite different for esophageal and stomach cancers [17,18]. By dividing esophageal and stomach cancer, the analysis is limited by a small number of esophageal cases. Other explanations for the significant result are unknown confounding factors or an artifact of multiple comparisons. It is possible that individuals with a family history of ALL may be less likely to smoke. Inclusion of smoking status, a known risk factor for esophageal cancer, in our model was desired but not possible to examine smoking as a confounder.

Two reports support a protective effect of family history of allergies and risk of ALL [6]. Schuz et al. [7] investigated first degree relatives' medical histories of hay fever, neurodermatitis, asthma, contact eczema, hives, and food/drug allergies in a case–control study. Parents and siblings showed an underrepresentation of atopic disease. In a separate case–control study, Rosenbaum et al. [8] investigated personal and parental allergy histories and found a borderline non-significant inverse association between parental allergies and ALL risk. Previously, siblings of the ALL cases in our study had been shown to have a significant inverse association with risk of ALL (OR = 0.9, 95%CI = 0.8, 1.0) [9]. The current study expanded the analysis to include family history of allergies in parents and

grandparents and finds an inverse association with allergic diseases. Risk was predominantly related to food and drug allergies rather than asthma, hay fever, eczema, or hives.

Several associations have been described between family history of autoimmune diseases and ALL. Till et al. [10] first suggested that first and second degree relatives of children with leukemia were slightly more likely to have autoimmune disease than controls. Buckley et al. [11] reported an association with maternal diagnosis of multiple sclerosis and childhood ALL [18]. Perrillat et al. [18] conducted a case–control study which found a significant association with increased autoimmune disease in first and second degree relatives and ALL as well as any thyroid disease. Family history of autoimmune thyroid diseases such as Grave's disease or hyperthyroidism and Hashimoto's disease and/or hyperthyroidism was specifically associated with risk, while associations were not found for ALL risk and diabetes mellitus, psoriasis, rheumatoid arthritis or multiple sclerosis. Cohort studies in Sweden and Denmark have attempted to determine if children born to parents with autoimmune disease are at increased risk of childhood cancers. In Sweden, mothers with autoimmune conditions did not have an increased risk of childhood cancer with the exception of maternal diabetes [35]. In a similar Danish cohort study, parents with any autoimmune diseases showed a borderline significant association with childhood ALL [12].

We found no association with ALL and general autoimmune diseases or specific types. Of note, we found a modest decreased likelihood of family history of rheumatoid arthritis in ALL cases (OR = 0.79, 95%CI = 0.65, 0.96). Studies of rheumatoid arthritis and adult acute myeloid leukemia show an increased risk of adult leukemia but it is unclear whether the association is with rheumatoid arthritis or with the medications used to treat the disease [36–38].

Three out of four reports have suggested an association with leukemia and congenital anomalies in siblings and/or more distant family members of patients with childhood ALL. Savitz et al. [13] and Mann et al. [14] both reported increased risk of congenital anomalies in siblings and first, second, and third degree relatives. A more recent study showed borderline increased risk of congenital anomalies in siblings and increased risk for family history of congenital anomalies in first and second degree relatives [15]. An expanded analysis of 2117 ALL cases, including our 1842 cases, and their siblings did not find an increased risk of congenital anomalies with the exception of pancreas-digestive tract anomalies [39]. We have additionally analyzed information on parents and grandparents and did not find a significant association between birth defects and family history in siblings, parents, and grandparents.

There are several strengths and limitations to the current study. This is one of the largest case–control studies of ALL to investigate family history of cancer and the selected non-malignant diseases. Our large national sample permitted the study of many rare diseases among relatives. Even with this large of a study, the analysis of family history of some conditions had limited power to detect associations.

Data collected by self-report in a case–control study raise concern of misclassification [40]. Validation studies of cancer diagnoses show sensitivities of 30–83% depending on the type of cancer with highest sensitivity for breast, colorectal and prostate cancers and lower sensitivities for uterine cancers [41–43]. Minimal recall bias was reported in one study carried out in Utah, but genealogy is notably more important in Utah than in other geographic locations [42]. Accuracy of self-report of family history of autoimmune diseases is mixed. Confirmation of autoimmune diseases with medical records shows a sensitivity of 76%, with sensitivity highest for systemic lupus erthematosus patients and lowest for rheumatoid arthritis patients [44]. There is a substantial problem with self-report or family

history report based on questionnaire only with rheumatoid arthritis. Rheumatoid arthritis may easily be confused with the more common and unrelated condition of osteoarthritis. We did see an inverse association with rheumatoid arthritis but this result must be viewed skeptically as the validity of self-report may have compromised the analysis [45,46].

Family history was obtained rapidly following diagnosis from first degree relatives (i.e. mothers and fathers) who completed surveys for their parents and children. The accuracy of information collected from first degree relatives is improved compared to data collected from second degree relatives [43]. The collection of data shortly following diagnosis however made the age of parents and grandparents fairly young. Null results of family history of cancer may thus be related to the relatively young age of family members. Another possible concern of misclassification bias arises in the use of maternal surrogates for paternal interviews. The exclusion of surrogate interviews in our sensitivity analysis did not reveal any differences from data obtained solely for mothers.

Selection of hospital-based cases may give rise to mismatch when controls are selected in a population-based manner. In this study, random digit dialing selected from the exchange of the case's residence at diagnosis acted as a marker for similar geography. Although the possibility for a mismatch in the enrolled controls to the source population may exist, using exchange to match cases and controls may serve to better match the source population [24]. To minimize possible confounders, we choose a set of covariates a priori known to be associated with childhood cancer including maternal age, maternal education, family income, birth weight and total number of relatives. Covariates are not known to be associated with family history of cancer or non-malignant diseases but were still chosen to be included in the analysis. We are mindful that unknown confounders, such as smoking exposure, which was unknown for relatives, may still exist producing erroneous associations.

In summary, this study examining the association of family history of cancer and non-malignant diseases on the risk of ALL did not observe an association with a family history of cancer in first and second degree relatives. Most previously reported cancer associations were not confirmed by our analysis providing additional evidence that family history of cancer is not an important risk factor for childhood ALL. More studies regarding family history of non-malignant diseases are needed to validate the accuracy of disease reporting and provide insight into the true nature of potential associations, as well as mechanisms for the development of ALL.

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Table 1

Characteristics of cases and controls.

	Cases	Controls	*P*-value
Gender-male	1018 (55.2%)	1076 (54.2%)	0.54
Age			
<12 months	64 (3.5%)	81 (4.1%)	0.07
12–23 months	138 (7.5%)	189 (9.5%)	
2–5 years	1020 (55.4%)	1038 (52.3%)	
6–10 years	408 (22.2%)	466 (23.5%)	
11–15 years	212 (11.5%)	212 (10.7%)	
Race			
White	1492 (81.0%)	1720 (86.6%)	<0.01
Black	109 (5.9%)	94 (4.7%)	
Hispanic	153 (8.3%)	121 (6.1%)	
Other	88 (4.8%)	51 (2.6%)	
Maternal age			
<20	159 (8.6%)	117 (5.9%)	0.01
20–29	1127 (61.2%)	1257 (63.3%)	
30–39	540 (29.3%)	598 (30.1%)	
40+	16 (0.9%)	14 (0.7%)	
Birth weight			
<2500 g	99 (5.4%)	110 (5.5%)	0.04
2500–4000	1465 (79.5%)	1632 (82.2%)	
>4000	278 (15.1%)	244 (12.3%)	
Mean number of relatives with disease history	Mean (SD)	Mean (SD)	
Siblings	1.5 (1.2)	1.5 (1.2)	
Parents	1.9 (0.2)	1.9 (0.3)	
Grandparents	3.7 (0.7)	3.7 (0.7)	
Total	7.1 (1.5)	7.1 (1.5)	

Table 2

Family history of cancer and risk of childhood ALL.

Family cancer history characteristics	Case number (*n* =1842)	Control number (*n*=1986)	Adjusted OR[a]	95%CI	*P*-value (test for trend)
Any relative with cancer[b]	730	833	0.98	0.93, 1.00	
Any relative with cancer according to the number of relatives with cancer					
0	1112	1153	1.00		*P* = 0.25
1	542	640	0.89	0.77, 1.03	
2	161	160	1.09	0.86, 1.39	
3+	27	33	0.83	0.50, 1.40	
Parents only	45	58	0.85	0.56, 1.29	
Grandparents only	607	693	0.91	0.77, 1.07	
Maternal relatives only[b]	445	501	0.96	0.83, 1.12	
Paternal relatives only[b]	397	438	0.98	0.83, 1.15	
Female relatives only[b]	454	492	1.00	0.86, 1.16	
Male relatives only[b]	408	484	0.91	0.78, 1.06	
Any relative developing cancer at age less than 40 years old	641	737	0.92	0.78, 2.31	

[a] Odds ratios were derived from conditional logistical regression analysis and are adjusted for maternal age, birth weight and total number of relatives.

[b] Any relative with cancer includes mother, father, maternal grandparents, paternal grandparents, and siblings. Family history among maternal relatives only includes the proband's mother, maternal grandmother, and paternal grandfather, family history among paternal relatives only includes proband's father, paternal grandfather, and paternal grandmother, family history among male relatives only includes father, paternal grandfather, and maternal grandfather, family history among female relatives includes mother, paternal grandmother, and maternal grandmother.

Table 3

Family history of malignancy classified by cancer site and risk of childhood ALL.

Family history of cancer by cancer site	ICD-9 codes	Case number (n = 1842)	Control number (n = 1986)	Adjusted OR[a]	(95%CI)
Lip, oral cavity, pharynx	140–149	23	21	1.15	(0.64, 2.06)
Esophageal	150.9	3	14	0.22	(0.07, 0.80)
Stomach	151.9–152.9	19	33	0.61	(0.35, 1.05)
Colon, rectum	153–154	75	87	0.94	(0.69, 1.30)
Liver	155	44	34	1.37	(0.88, 2.14)
Respiratory and intrathoracic organs (including lung)	160–164	106	133	0.86	(0.66, 1.12)
Lung	162	97	124	0.85	(0.65, 1.12)
Bone, connective tissue	170–171	38	33	1.30	(0.84, 2.00)
Melanoma	172	14	18	0.81	(0.40, 1.64)
Skin	173	93	111	0.94	(0.71, 1.24)
Breast	174	134	142	1.02	(0.80, 1.31)
Uterine, ovarian	179–184	92	86	1.16	(0.86, 1.54)
Prostate	185	50	58	0.89	(0.61, 1.29)
Kidney	189	15	15	1.02	(0.52, 2.01)
Brain	191	24	32	0.80	(0.49, 1.32)
Thyroid	193	16	17	0.93	(0.47, 1.84)
Lymphoma	200.1–202	31	31	0.96	(0.60, 1.55)
Multiple Myeloma	203	4	8	0.54	(0.16, 1.83)
Leukemia	204–208	28	36	0.85	(0.51, 1.43)

[a]Odds ratios were derived from conditional logistical regression analysis and are adjusted for maternal age, birth weight and total number of relatives.

Table 4

Medical family history of selected non-malignant diseases.

	Case number (n = 1842)	Control number (n = 1986)	Adjusted OR[a]	(95%CI)	*P*-value (test for trend)
Allergic diseases[b]	1436	1610	0.86	0.73, 1.00	
Food and drug allergies	1068	1231	0.83	0.73, 0.95	
Asthma	542	586	0.99	0.86, 1.13	
Hay fever	754	863	0.89	0.78, 1.01	
Hives	473	522	0.98	0.85, 1.14	
Eczema	296	354	0.87	0.73, 1.04	
Number of relatives with allergic diseases					
0	1351	1425	1.00		*P* = 0.14
1	338	263	0.86	0.70, 1.05	
2	306	342	0.83	0.67, 1.03	
3	237	273	0.79	0.63, 1.00	
4	196	201	0.89	0.69, 1.14	
5+	359	431	0.75	0.61, 0.92	
Parents only	967	1020	0.97	0.83, 1.12	
Grandparents only	727	769	1.09	0.92,1.30	
Maternal side only	937	1097	0.86	0.76, 0.98	
Paternal side only	870	844	1.23	1.07, 1.41	
Female relatives only	1007	1100	1.00	0.88, 1.14	
Male relatives only	869	915	1.06	0.93, 1.21	
Autoimmune diseases	491	461	0.92	0.80, 1.06	
Multiple sclerosis	20	27	0.81	0.45, 1.46	
Rheumatoid arthritis	220	286	0.79	0.65, 0.96	
Psoriasis	143	146	1.07	0.84, 1.36	
Ulcerative colitis	81	81	1.07	0.78, 1.47	
Celiac disease	6	7	1.06	0.35, 3.20	
Lupus	24	19	1.40	0.76, 2.55	
Sarcoidosis	5	7	0.80	0.25, 2.54	
Ankylosing spondylitis	4	4	1.17	0.29, 4.82	

	Case number (n = 1842)	Control number (n = 1986)	Adjusted OR[a]	(95%CI)	*P*-value (test for trend)
Diabetes	91	81	1.20	0.88, 1.64	
Number of relatives with autoimmune diseases					
0	1351	1425	1.00		*P* = 0.32
1	351	421	0.88	0.74, 1.03	
2	102	100	1.08	0.81, 1.44	
3	22	29	0.79	0.45, 1.40	
4+	16	11	1.47	0.67, 3.23	
Parents only	120	161	0.79	0.61, 1.04	
Grandparents only	326	328	1.10	0.90, 1.35	
Maternal side only	301	340	0.94	0.80, 1.12	
Paternal side only	232	266	0.93	0.77, 1.13	
Female relatives only	335	382	0.93	0.79, 1.10	
Male relatives only	223	242	0.98	0.81, 1.19	
Birth defects	105	127	0.87	0.66, 1.14	
Number of relatives with birth defects					
0	1737	1859	1.00		*P* = 0.59
1	93	112	0.87	0.65, 1.16	
2+	12	15	0.85	0.40, 1.82	
Parents only	79	88	0.96	0.69, 1.34	
Grandparents only	27	43	0.63	0.37, 1.05	
Maternal side only	58	80	0.77	0.54, 1.09	
Paternal side only	54	50	1.17	0.78, 1.74	
Female relatives only	54	75	0.76	0.53, 1.08	
Male relatives only	61	59	1.11	0.76, 1.61	
Immunodeficiency and recurrent infections	268	297	0.97	0.81, 1.17	
Number of relatives with immunodeficiency and recurrent infections					
0	1574	1689	1.00		*P* = 0.36
1	203	243	0.90	0.73, 1.10	
2	54	45	1.29	0.86, 1.92	
3+	11	9	1.34	0.55, 3.28	
Parents only	8	9	0.98	0.35, 2.73	

	Case number (n = 1842)	Control number (n = 1986)	Adjusted OR[a]	(95%CI)	*P*-value (test for trend)
Grandparents only	7	8	0.75	0.26, 2.18	
Maternal side only	203	228	0.99	0.97, 1.00	
Paternal side only	82	82	1.09	0.79, 1.51	
Female relatives only	204	237	0.92	0.75, 1.12	
Male relatives only	95	86	1.23	0.90, 1.68	
Thyroid	231	236	1.16	0.67, 2.00	
Hyperthyroidism or Grave's disease	92	90	1.12	0.83, 1.51	
Thyroiditis or Hashimoto's	27	25	1.16	0.67, 2.00	
Hypothyroidism	130	151	0.95	0.74, 1.22	
Number of relatives with thyroid disease					
0	1611	1750	1.00		*P* = 0.41
1	197	193	1.16	0.92, 1.41	
2+	34	43	0.87	0.55, 1.37	
Parents only	69	65	1.17	0.82, 1.67	
Grandparents only	153	152	1.10	0.85, 1.44	
Maternal side only	169	177	1.05	0.84, 1.31	
Paternal side only	65	67	1.08	0.76, 1.53	
Female relatives only	201	216	1.03	0.84, 1.26	
Male relatives only	30	26	1.22	0.72, 2.07	

[a] Odds ratios were derived from conditional logistical regression analysis and are adjusted for maternal age, birth weight and total number of relatives.

[b] All analyses including allergic diseases have been adjusted for personal history of allergies. In addition to the variables listed above.