

# Familial aggregation and heritability of type 1 diabetes mellitus and coaggregation of chronic diseases in affected families

Chang-Fu Kuo<sup>1,2,\*</sup>  
I-Jun Chou<sup>3,4,\*</sup>  
Matthew J Grainge<sup>5</sup>  
Shue-Fen Luo<sup>2</sup>  
Lai-Chu See<sup>2,6,7</sup>  
Kuang-Hui Yu<sup>2</sup>  
Weiya Zhang<sup>1</sup>  
Michael Doherty<sup>1</sup>  
Ana M Valdes<sup>1</sup>

<sup>1</sup>Division of Rheumatology, Orthopaedics and Dermatology, School of Medicine, University of Nottingham, Nottingham, UK;

<sup>2</sup>Division of Rheumatology, Allergy and Immunology, Chang Gung Memorial Hospital, Taoyuan, Taiwan; <sup>3</sup>Division of Clinical Neuroscience, School of Medicine, University of Nottingham, Nottingham, UK; <sup>4</sup>Division of Paediatric Neurology, Chang Gung Memorial Hospital, Taoyuan, Taiwan;

<sup>5</sup>Division of Epidemiology and Public Health, School of Medicine, University of Nottingham, Nottingham, UK;

<sup>6</sup>Biostatistics Core Laboratory, Molecular Medicine Research Centre, Chang Gung University, Taoyuan, Taiwan; <sup>7</sup>Department of Public Health, College of Medicine, Chang Gung University, Taoyuan, Taiwan

\*These authors contributed equally to this work

Correspondence: Ana M Valdes  
Clinical Sciences Building, Nottingham City Hospital, Hucknall Road, Nottingham, NG5 1PB, UK  
Tel/fax +44 115 823 1115  
Email ana.valdes@nottingham.ac.uk

**Purpose:** To estimate the extent of familial aggregation of type 1 diabetes (T1D) and coaggregation of related chronic diseases and assess the relative contribution of environmental and genetic factors on the risks.

**Patients and methods:** This population-based study used the Taiwan National Health Insurance database to reconstruct family structure and identify people with T1D and other chronic diseases between 1999 and 2015. Relative risks (RRs) for T1D and other chronic diseases and heritability of T1D were estimated. Heritability was estimated using the polygenic liability model.

**Results:** Validation of family structure found the positive predictive value to be 98.7% for maternal links and 98.6% for paternal links. Having an affected twin, first-degree relative, or spouse was associated with an adjusted RR (95% CI) of 553.66 (427.59–716.89), 32.49 (28.66–36.84), and 2.17 (0.31–15.40) for T1D, respectively. Based on the polygenic liability model, heritability, shared and non-shared contributions to T1D, and variances were 66.50%, 10.86%, and 22.64%, respectively. A family history of T1D was associated with an RR (95% CI) of 1.51 (1.20–1.89) for rheumatoid arthritis, 1.66 (1.21–2.26) for Sjögren's syndrome, 1.48 (1.09–2.01) for systemic lupus erythematosus, 1.24 (1.14–1.35) for simple goiter, 1.16 (1.04–1.31) for non-toxic nodular goiter, 1.61 (1.49–1.74) for thyrotoxicosis, 1.78 (1.57–2.01) for acquired hypothyroidism, 1.66 (1.40–1.98) for thyroiditis, and 1.15 (0.97–1.37) for epilepsy.

**Conclusion:** These data highlight the importance of the genetic contribution to T1D and confirm the coaggregation of autoimmune and metabolic diseases with T1D.

**Keywords:** type 1 diabetes mellitus, familial aggregation, co-aggregation, autoimmune diseases, endocrine diseases

## Introduction

Type 1 diabetes mellitus is an autoimmune disorder caused by the destruction of pancreatic  $\beta$  cells in people with a genetic predisposition, and it is characterized by absolute insulin deficiency.<sup>1,2</sup> Although type 1 diabetes has a relatively low prevalence, epidemiologic studies have reported that the incidence of type 1 diabetes is increasing by 3% per year worldwide.<sup>3</sup> It is one of the most common autoimmune diseases in childhood with an estimated incidence rate of 6.4/100,000 for 0- to 9-year-old Asians and Pacific Islanders.<sup>4</sup> A recent population-based estimate of the incidence of type 1 diabetes in Taiwan was 5.6/1,000,000 for 0- to 14-year-olds,<sup>5</sup> with a two- to three-fold higher mortality rate than age-matched individuals.<sup>6</sup>

Positive family history is one of the strongest risk factors for type 1 diabetes, and the genetic contribution to the susceptibility to type 1 diabetes is substantial.<sup>7</sup> For example, the human leukocyte antigen (HLA) region has been found to be one of the major genetic determinants of type 1 diabetes.<sup>1,8</sup> Strong ethnic differences in the HLA haplotypes present in this region,<sup>9</sup> such as those between European and East Asian populations,<sup>10</sup> are likely to explain some of the large variations in the prevalence and incidence of type 1 diabetes. To date, heritability estimates for type 1 diabetes have been derived only for populations of European origin,<sup>11,12</sup> and the results have suggested an additive genetic contribution of 72%–88%. The heritability in East Asian populations has not been investigated to date. In addition, it is well known that type 1 diabetes coaggregates with other autoimmune diseases such as autoimmune thyroid disease and celiac disease.<sup>13</sup> Recently, Chou et al reported that individuals with type 1 diabetes were more likely to develop epilepsy than controls,<sup>14</sup> a finding that was later confirmed in a European cohort.<sup>15</sup> Therefore, there may be a common root for type 1 diabetes with these chronic conditions.

This nationwide study used data on the entire population of Taiwan in 2015 to construct nationwide genealogy linking to health information derived from a large comprehensive database. We aimed to estimate the relative risks (RRs) of type 1 diabetes in individuals with affected relatives of specific kinship, and assess the relative contribution of genetic, and shared and non-shared environmental factors to the susceptibility to type 1 diabetes. In addition, we estimated the RRs of other chronic diseases in people with a family history of type 1 diabetes.

## Materials and methods

### Study population

Ethical approval was obtained from the Institutional Review Board of Chang Gung Memorial Hospital and the National Health Research Institute (IRB No 104-8042B), the data holder of the National Health Insurance (NHI) database. The NHI database was provided by the Administration of National Health Insurance, Ministry of Health and Welfare. The database is fully anonymized, and no trackable data were available. To protect confidentiality, the conduct of the research and use of the data within the database are restricted to the specialized data center operated by the administration. We constructed a cohort comprising all beneficiaries of the Taiwan NHI program who were registered in 2015 and had valid insurance status using data from the Registry for NHI beneficiaries.

The Taiwan NHI program was initiated in 1995 as a single-payer insurance system co-funded by the government, employers, and beneficiaries. As a single-payer system and as enrollment is required by law,<sup>16</sup> almost all residents in Taiwan are enrolled, and the majority of medical facilities in Taiwan are contracted with the NHI to provide a comprehensive package of health care. The NHI database contains all registration and original claims data, including gender, date of birth, place of residence, details of insurance, family relationships, dates of inpatient and outpatient visits, medical diagnoses, medical expenditure, prescription details, examinations, operations, and procedures. All information in the database and other government-held data such as the death registry are linked using a unique personal identifier assigned to each resident in Taiwan. The personal identifier is encrypted; however, the identification remains unique for each beneficiary in the database to facilitate internal and external linkage of records.

### Methods of nationwide genealogy reconstruction

We have reported methods for genealogy reconstruction using family relationships recorded in the NHI database in our previous publications.<sup>17–19</sup> The registry of beneficiaries records the insurance status of all people covered by the NHI program, and also contains information regarding relationships between the insured person (who paid the insurance fee) and his/her dependents. Both blood relatives and spouses are eligible as dependents of the insured. A birth certificate is required for a child to be registered as a dependent of their parents. The family identifiers and unique personal identifiers allowed us to establish family relationships (parents, offspring, full siblings, twins, and spouse). We used an algorithm to identify parent–offspring relationships indirectly and to maximize possible family links.<sup>17–19</sup> Full siblings were defined as those with the same parents. Twins were defined as full siblings with the same date of birth ( $\pm 1$  day). However, twin zygosity could not be derived from the database. Changes in residence, employment, insurance status (insurant or dependent), and relationships between the insurant and dependents are recorded in the registry. Overall, there were ~364 million records in the registry in 2015. We used this dynamic nature to maximize the identification of possible family links by incorporating the entire registry of records from 1999 to 2015. We used family relationships to reconstruct genealogy. Overall, we classified 4,373,116 families of 2–5 generations with a mean family size of 5.8 persons. Each may have appeared multiple times in different categories of family relationships depending on the family structure.

## Validation of family relationships

To validate the accuracy of the family identification method, we linked the NHI data to the civil registration system governed by the Ministry of Internal Affairs, which records the original data of the birth certificate. We identified 2,171,765 children born between 2001 and 2014 and found that the maternal and paternal links identified by our methods were highly consistent with the original birth certificate records. The positive predictive value was 98.7% for maternal links and 98.6% for paternal links.

## Ascertainment of type 1 diabetes and other autoimmune diseases

In Taiwan, patients with suspected autoimmune diseases and severe endocrine diseases are referred to specialists for diagnosis and treatment. Patients with diagnoses of type 1 diabetes and other autoimmune diseases are entitled to a waiver for medical co-payments. Clinical information is sent to the insurance administration for review by commissioned expert panels to confirm the diagnosis before approving such waivers. The approval of co-payment waivers for type 1 diabetes requires further confirmation of the diagnosis such as the presence of autoantibodies. The Registry for Catastrophic Illness Patients contains clinical and registration information of these patients. We used this registry to identify patients with type 1 diabetes mellitus (ICD-9 codes 250.01, 250.03, 250.11, 250.13, 250.21, 250.23, 250.31, 250.33, 250.41, 250.43, 250.51, 250.53, 250.61, 250.63, 250.71, 250.73, 250.81, 250.83, 250.91, and 250.93). Therefore, all patients who had type 1 diabetes between 1999 and 2015 and were alive in 2015 were identified. The diagnosis of diabetes in the NHI database has previously been validated, with a positive predictive value of type 1 diabetes of 98.3%.<sup>6,20</sup> The case definition of type 1 diabetes was also validated by a retrospective chart review.

The details of case definitions for other chronic conditions are shown in Table S1, and included rheumatoid arthritis, Sjögren's syndrome, systemic lupus erythematosus, systemic sclerosis, polymyositis/dermatomyositis, Behçet's disease, vasculitis, inflammatory bowel disease, multiple sclerosis, myasthenia gravis, simple goiter, non-toxic nodular goiter, thyrotoxicosis, acquired hypothyroidism, thyroiditis, and epilepsy.

## Covariates

We considered that age, sex, occupation, income, level of urbanization of residence, and family size may have confounded or modified the familial associations. Therefore, these factors were used as covariates in the estimation of familial RRs.

## Statistical analysis

The prevalence of type 1 diabetes for the general population was calculated as the number of people who were alive and diagnosed with type 1 diabetes between 1999 and 2015 divided by the number of mid-year population in Taiwan in 2015. This prevalence estimate was the basis for the calculations of heritability and familial transmission. The RRs of type 1 diabetes were the adjusted prevalence ratios between first-degree relatives of an individual with type 1 diabetes and the general population.<sup>21</sup> Of the several established methods available for the estimation of prevalence ratios, we used Breslow–Cox models to estimate prevalence rate ratios in a cross-sectional study by setting an equal follow-up time for all subjects.<sup>22</sup> This method has been shown to produce consistent estimates of prevalence ratios close to true parameters.<sup>23,24</sup> The Breslow–Cox model assumes independence between subjects; however, family members form natural clusters. Bias caused by within-family clustering can be overcome by using the marginal model or shared frailty model.<sup>25</sup> Previous studies have documented the comparability of point estimates and 95% CIs between the frailty model<sup>25</sup> and marginal model with a robust sandwich method.<sup>26</sup> In addition, a previous study suggested that the marginal model produces a more precise parameter.<sup>27</sup> The RRs were adjusted for age, sex, socioeconomic factors, and family size.<sup>28</sup> We fitted the models separately according to the kinship and sex of the affected relatives. Twins were excluded from the sibling analyses. The RR was estimated for the number of affected first-degree kinships. In this model, we compared the risk of type 1 diabetes in individuals with one or two affected first-degree relatives with the general population.

Based on the polygenic liability model,<sup>17–19,29</sup> heritability was defined as the proportion of phenotypic variance attributable to genetic factors, and familial transmission was defined as the sum of genetic and shared environmental contributions. Familial transmission and heritability can be calculated using the polygenic liability model to calculate both measures.<sup>30–32</sup> As in the original formula developed by Reich and Yang,<sup>29</sup> we used the population prevalence and sibling RR to calculate familial transmission. We further used spouses as controls, assuming that they shared the family environment but had no genetic similarity with blood family members. We could thus calculate heritability, as reported in our previous publications.<sup>17–19</sup>

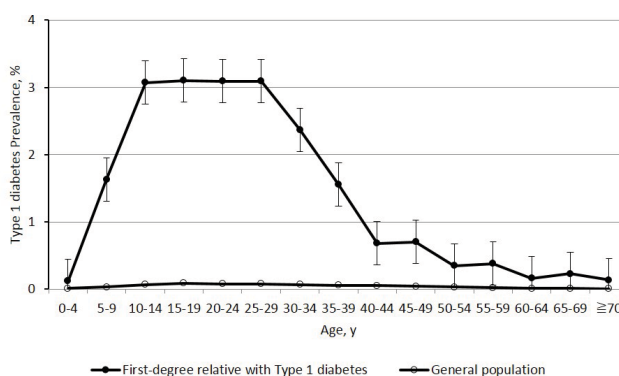
The extent of familial coaggregation with other chronic diseases in the families affected by type 1 diabetes was estimated using a marginal Cox proportional hazards regression

model with an equal follow-up time for all subjects adjusting for age, sex, place of residence, income level, occupation, and family size. RRs were estimated as the adjusted prevalence ratio of the specified autoimmune disease between individuals with a first-degree relative with type 1 diabetes mellitus and those without a family history of type 1 diabetes mellitus. A two-sided *P*-value of less than 0.05 was considered to indicate statistical significance. All analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC, USA).

## Results

### The prevalence of type 1 diabetes in individuals with affected first-degree family members versus the general population

We identified 10,723 patients with a diagnosis of type 1 diabetes, giving a crude prevalence of 0.04% (Table 1). Women had a slightly higher prevalence than men. In the general population of Taiwan in 2015, 28,163 (0.12%) individuals had at least one first-degree relative with type 1 diabetes, including 4,872 with affected parents, 12,493 with affected offspring, 10,755 with an affected sibling, and 123 with an affected twin. The age-specific prevalence of type 1 diabe-



**Figure 1** Age-specific prevalence of type 1 diabetes in individuals with an affected first-degree relative and the general population in Taiwan in 2015.

tes was higher in the individuals with affected first-degree relatives with type 1 diabetes than in the general population (Figure 1).

### Relative risks for type 1 diabetes in individuals with affected first-degree relatives

The prevalence of type 1 diabetes in individuals with affected first-degree relatives of specific types is shown in Table 2. The RRs (95% CIs) for type 1 diabetes were associated with the

**Table 1** Baseline characteristics of the individuals with affected first-degree relatives with type 1 diabetes and the general population

Characteristics	Women		<i>P</i> -value	Men		<i>P</i> -value
	≥1 Affected relative	General population		≥1 Affected relative	General population	
No	14,339	12,262,442		13,824	12,087,157	
Age, mean (SD), years	36.73 (17.87)	40.26 (21.02)	<0.0001	36.63 (19.14)	38.86 (20.92)	<0.0001
Type 1 diabetes, n (%)	227 (1.58)	5,839 (0.05)	<0.0001	224 (1.62)	4,884 (0.04)	<0.0001
Place of residence, n (%)			<0.0001			0.0313
Urban	9,096 (63.44)	7,733,956 (63.07)		8,352 (60.42)	7,308,878 (60.47)	
Suburban	4,332 (30.21)	3,621,892 (29.54)		4,455 (32.23)	3,848,284 (31.84)	
Rural	859 (5.99)	871,433 (7.11)		964 (6.97)	895,513 (7.41)	
Unknown	52 (0.36)	35,161 (0.29)		53 (0.38)	34,482 (0.29)	
Income level, n (%)			<0.0001			<0.0001
Quintile 1	2,273 (15.85)	2,060,626 (16.80)		2,522 (18.24)	23,102,94 (19.11)	
Quintile 2	2,233 (15.57)	1,837,544 (14.99)		1,729 (12.51)	15,063,39 (12.46)	
Quintile 3	4,191 (29.23)	3,655,373 (29.81)		3,738 (27.04)	32,065,35 (26.53)	
Quintile 4	3,142 (21.91)	2,409,990 (19.65)		2,799 (20.25)	22,409,37 (18.54)	
Quintile 5	2,498 (17.42)	2,296,692 (18.73)		3,034 (21.95)	28,123,33 (23.34)	
Unknown	2 (0.01)	2,217 (0.02)		2 (0.01)	1,819 (0.02)	
Occupation, n (%)			<0.0001			<0.0001
Dependents of the insured individuals	5,454 (38.04)	4,531,055 (36.95)		4,712 (34.09)	3,746,218 (30.99)	
Civil servants, teachers, military personnel, and veterans	402 (2.80)	343,648 (2.80)		731 (5.29)	570,777 (4.72)	
Non-manual workers and professionals	4,489 (31.31)	3,641,661 (29.70)		4,258 (30.80)	3,933,917 (32.55)	
Manual workers	2,921 (20.37)	2,606,844 (21.26)		2,674 (19.34)	2,285,790 (18.91)	
Other	1,073 (7.48)	1,139,234 (9.29)		1,449 (10.48)	1,550,455 (12.83)	

**Table 2** Relative risks for type 1 diabetes in first-degree relatives

Type of affected relative	Sex of affected relative	Sex of the individual	No of cases	Prevalence (%)	Relative risk (95% CI) <sup>a</sup>
<b>Any</b>	Male	Male	132	2.15	50.01 (39.74–62.93)
		Female	98	1.47	27.33 (22.41–33.33)
		All	230	1.79	36.97 (31.47–43.42)
	Female	Male	102	1.31	29.44 (24.12–35.92)
		Female	133	1.71	30.97 (24.66–38.90)
		All	235	1.51	30.29 (25.91–35.40)
	All	Male	224	1.62	36.97 (31.59–43.27)
		Female	227	1.58	29.00 (24.82–33.88)
		All	451	1.60	32.49 (28.66–36.84)
<b>Parent</b>	Male	Male	15	1.36	25.18 (15.30–41.45)
		Female	14	1.36	20.09 (11.99–33.66)
		All	29	1.36	22.47 (15.34–32.93)
	Female	Male	15	1.03	19.43 (11.81–32.00)
		Female	16	1.25	19.01 (11.73–30.79)
		All	31	1.13	19.18 (13.28–27.71)
	All	Male	30	1.17	21.93 (15.44–31.16)
		Female	30	1.30	19.52 (13.73–27.74)
		All	60	1.23	20.65 (15.86–26.89)
<b>Offspring</b>	Male	Male	15	0.55	22.31 (13.55–36.76)
		Female	13	0.41	12.81 (7.46–21.99)
		All	28	0.48	16.50 (11.44–23.81)
	Female	Male	12	0.38	15.12 (8.63–26.49)
		Female	15	0.42	12.65 (7.65–20.90)
		All	27	0.40	13.60 (9.36–19.76)
	All	Male	25	0.43	17.19 (11.69–25.30)
		Female	26	0.39	11.94 (8.16–17.47)
		All	51	0.41	13.98 (10.67–18.33)
<b>Sibling</b>	Male	Male	78	3.44	58.09 (42.89–78.68)
		Female	73	2.92	39.05 (31.22–48.85)
		All	151	3.17	47.11 (38.73–57.29)
	Female	Male	76	2.42	40.1 (31.9–50.3)
		Female	81	2.78	36.3 (27.0–48.7)
		All	157	2.59	38.1 (31.6–45.9)
	All	Male	148	2.75	46.07 (38.03–55.81)
		Female	154	2.86	37.80 (31.35–45.56)
		All	302	2.81	41.50 (35.57–48.43)
<b>Twin</b>	Male	Male	27	50.00	768.48 (545.83–1081.94)
		Female	1	10.00	107.54 (17.37–665.90)
		All	28	43.75	640.40 (445.06–921.49)
	Female	Male	1	6.67	112.76 (17.46–728.21)
		Female	21	47.73	557.54 (396.23–784.54)
		All	22	37.29	471.47 (328.77–676.10)
	All	Male	28	40.58	636.13 (446.10–907.12)
		Female	22	40.74	468.29 (324.39–676.01)
		All	50	40.65	553.66 (427.59–716.89)
<b>Spouse</b>	All	All	2	0.09	2.17 (0.31–15.40)

**Note:** <sup>a</sup>Adjusted for age, gender, place of residence, quintile of income level, occupation, and family size.

degree of genetic distance between family relatives. Overall, having an affected co-twin (50% or 100% genetic similarity depending on zygosity), first-degree relative (on average 50% genetic similarity), or spouse (no genetic similarity) was associated with adjusted RRs of 553.66 (427.59–716.89), 32.49 (28.66–36.84), and 2.17 (0.31–15.40), respectively.

In addition, the RRs increased with the number of types of affected first-degree relatives. The individuals with one type of affected first-degree relative had an RR (95% CI) of 31.19 (27.45–35.44), and those with two or more types of affected first-degree relatives had an RR of 173.84 (95.63–316.01) for type 1 diabetes.

## Familial resemblance and heritability of type I diabetes

Using a threshold liability model, we estimated that the accountability for phenotypic variance in type 1 diabetes was 66.50% for genetic factors (heritability), 10.86% for shared environmental factors, and 22.64% for non-shared environmental factors.

## Coaggregation of other autoimmune diseases, thyroid diseases, and epilepsy

We examined the RRs of ten other autoimmune diseases (Table 3), three of which (rheumatoid arthritis, Sjögren's syndrome, and systemic lupus erythematosus) showed a significant familial coaggregation associated with type 1 diabetes. A family history of type 1 diabetes was associated with thyroid diseases, specifically, a RR (95% CI) of 1.24 (1.14–1.35) for simple goiter, 1.16 (1.04–1.31) for non-toxic nodular goiter, 1.61 (1.49–1.74) for thyrotoxicosis, 1.78 (1.57–2.01) for acquired hypothyroidism, and 1.66 (1.40–1.98) for thyroiditis. We further tested the coaggregation of type 1 diabetes with epilepsy, as an association was reported in a recent study. However, we found that the RR of epilepsy was not significantly increased (RR, 1.15; 95% CI, 0.97–1.37) in relatives of people with type 1 diabetes compared to the general population (Table 3).

## Discussion

This is the first study to report the heritability of type 1 diabetes in an East Asian population. Type 1 diabetes was more common in people with a family history, and the risk was associated with the genetic distance of affected relatives. The familial RR was

30 times higher than that of individuals with an affected first-degree relative compared to the general population. We also confirmed the strong genetic contribution to type 1 diabetes with a heritability of 66.5%, and our results showed that one-third of phenotypic variance was attributable to environmental factors. Furthermore, autoimmune diseases such as rheumatoid arthritis and thyroid diseases were more common in people with a family history of type 1 diabetes, suggesting that type 1 diabetes has a strong genetic association or shares common pathogenetic roots with autoimmune and thyroid diseases.

Several previous studies have investigated the heritability of type 1 diabetes in northern Europe,<sup>11,12</sup> with heritability estimates ranging from 70% to 88%, which is slightly higher than our estimate of 66.5%. A key difference is that we found that shared environmental factors also contributed to phenotypic variance, whereas no effect was estimated by Hyttinen et al.<sup>11</sup> We also found significant coaggregation with three autoimmune diseases, rheumatoid arthritis, Sjögren's syndrome, and systemic lupus erythematosus, and also a trend toward an increased risk of systemic sclerosis, polymyositis/dermatomyositis, Behçet's disease, vasculitis, and myasthenia gravis in the relatives of the patients with type 1 diabetes. The very low prevalence of these disorders in Taiwan means that the study may not be powered sufficiently to detect significant coaggregation with these disorders. However, a previous study found familial coaggregation of type 1 diabetes with autoimmune thyroiditis and celiac disease.<sup>33</sup> Our data also showed that family members of patients with type 1 diabetes tended to have a higher risk of goiter, hypothyroidism, and thyroiditis. Therefore, type 1 diabetes probably shares pathogenetic roots with autoimmune and thyroid diseases.

**Table 3** Relative risks of other diseases in first-degree relatives of patients with type I diabetes

Associated conditions	With affected relatives		General population		Relative risk (95% CI) <sup>a</sup>
	No of cases	Prevalence (%)	No of cases	Prevalence (%)	
Rheumatoid arthritis	77	0.27	44,103	0.18	1.51 (1.20–1.89)
Sjögren's syndrome	30	0.11	22,652	0.09	1.66 (1.21–2.26)
Systemic lupus erythematosus	36	0.13	21,603	0.09	1.48 (1.09–2.01)
Systemic sclerosis	4	0.01	2,071	0.01	1.49 (0.56–3.97)
Polymyositis/dermatomyositis	5	0.02	2,113	0.01	1.79 (0.75–4.30)
Behçet's disease	4	0.01	2,064	0.01	1.38 (0.52–3.67)
Vasculitis	1	0.00	5,044	0.02	0.42 (0.13–1.29)
Inflammatory bowel disease	3	0.01	2,805	0.01	0.81 (0.30–2.14)
Multiple sclerosis	2	0.01	1,586	0.01	0.88 (0.28–2.71)
Myasthenia gravis	11	0.04	7,114	0.03	1.15 (0.62–2.13)
Simple goiter	617	2.19	431,452	1.77	1.24 (1.14–1.35)
Non-toxic nodular goiter	361	1.28	283,735	1.17	1.16 (1.04–1.31)
Thyrotoxicosis	891	3.16	449,904	1.85	1.61 (1.49–1.74)
Acquired hypothyroidism	294	1.04	155,515	0.64	1.78 (1.57–2.01)
Thyroiditis	149	0.53	74,893	0.31	1.66 (1.40–1.98)
Epilepsy	287	1.02	244,967	1.01	1.15 (0.97–1.37)

We did not find a significant familial coaggregation of type 1 diabetes with epilepsy, even though the risk of developing epilepsy among patients with type 1 diabetes has been shown to be ~ 3 times that of the general population both in Taiwan<sup>14</sup> and Europe.<sup>15</sup> Moreover, a four- to five-fold increased risk of epilepsy has been associated with autoimmune diseases in general, and particularly in children.<sup>34</sup> The fact that we failed to detect any familial coaggregation between type 1 diabetes and epilepsy, unlike that seen with other autoimmune disorders, suggests that epilepsy may be a consequence of autoimmune diseases. Our familial aggregation data did not support a common etiology, at least not for genetic factors, between these two disorders.

There are several limitations to the present study. First, the case definition of type 1 diabetes was based purely on diagnoses made by physicians. Nevertheless, the accuracy of the diagnosis of diabetes in the NHI database has previously been validated,<sup>20</sup> with one previous study reporting a positive predictive value of type 1 diabetes in the NHI database of 98.3%.<sup>6</sup> Therefore, our case definitions are stringent. Second, zygosity of twins is not recorded in the database, so we could not estimate heritability using a classic twin study design. Instead, we used a population-based design to assess the extent of familial aggregation in first-degree relatives. Furthermore, we conducted a validation study which confirmed the accuracy of our method to reconstruct family structure. Third, because we estimated heritability using the threshold liability model which assumes that underlying liability is normally distributed in the population, the results are subject to this assumption. Fourth, assortative mating was not considered in our model. If this assortment was not negligible, heritability could have been underestimated.<sup>35</sup> Fifth, this study was restricted to Taiwan, and different findings may occur in different populations and different environments. Therefore, further studies in other countries are required to determine the generalizability of our findings.

## Conclusion

This nationwide family study suggests that, in Taiwan, a family history of type 1 diabetes is one of the strongest risk factors for this disease. The differential risk associated with different kinships suggests a strong genetic component to the susceptibility to type 1 diabetes. A family history of type 1 diabetes also exerted an increased risk of other autoimmune and thyroid diseases. This may be useful information when counseling families with one or more affected relatives.

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## Disclosure

The authors report no conflicts of interest in this work.

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## Supplementary material

**Table S1** ICD-9 codes of diseases in first-degree relatives of patients with type I diabetes

Diseases	ICD-9 code	Definition
Type I diabetes	250	Catastrophic illness certificates
Simple goiter	240	Two outpatient records
Non-toxic nodular goiter	241	Two outpatient records
Thyrotoxicosis	242	Two outpatient records
Acquired hypothyroidism	244	Two outpatient records
Thyroiditis	245	Two outpatient records
Rheumatoid arthritis	7140	Catastrophic illness certificates
Sjögren's syndrome	7102	Catastrophic illness certificates
Systemic lupus erythematosus	7100	Catastrophic illness certificates
Systemic sclerosis	7101	Catastrophic illness certificates
Polymyositis/dermatomyositis	7103, 7104	Catastrophic illness certificates
Behçet's disease	1361	Catastrophic illness certificates
Vasculitis	4431, 4460, 4461, 4462, 4464, 4465, 4467	Catastrophic illness certificates
Inflammatory bowel disease	555, 5560, 5561, 5562, 5563, 5564, 5565 5566, 5567, 5568, 5569	Catastrophic illness certificates
Multiple sclerosis	340	Catastrophic illness certificates
Myasthenia gravis	358	Catastrophic illness certificates
Epilepsy	345	Two outpatient records of hospitalization records

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