Prediction of Progression to Overt Hypothyroidism or Hyperthyroidism in Female Relatives of Patients With Autoimmune Thyroid Disease Using the Thyroid Events Amsterdam (THEA) Score

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Background: Genetic and environmental factors are involved in the pathogenesis of autoimmune thyroid disease (AITD). Family members of patients with AITD are at increased risk for AITD, but not all will develop overt hypothyroidism or hyperthyroidism. Our goal was to develop a simple predictive score that has broad applicability and is easily calculated at presentation for progression to overt hypothyroidism or hyperthyroidism within 5 years in female relatives of patients with AITD.

Methods: We conducted a prospective observational cohort study of 790 healthy first- or second-degree female relatives of patients with documented Graves or Hashimoto disease in the Netherlands. Baseline assessment included measurement of serum thyrotropin (TSH), free thyroxine (FT_4), and thyroid peroxidase (TPO) antibody levels as well as evaluation for the presence and levels of *Yersinia enterocolitica* antibodies. We also gathered data on family background, smoking habits, use of estrogen medication, pregnancy, and exposure to high levels of iodine. In follow-up, thyroid function was investigated annually for 5 years. As main outcome measures, termed *events*, we looked for overt hypothyroidism (TSH levels >5.7 mIU/L and FT_4 levels <0.72 ng/dL) or overt hyperthyroidism (TSH levels <0.4 mIU/L and FT_4 levels >1.56 ng/dL).

Results: The cumulative event rate was 7.5% over 5 years. The mean annual event rate was 1.5%. There were 38 hypothyroid and 13 hyperthyroid events. Independent risk factors for events were baseline findings for TSH and TPO antibodies in a level-dependent relationship (for TSH the risk already starts to increase at values >2.0 mIU/L) and family background (with the greatest risk attached to subjects having 2 relatives with Hashimoto disease). A numerical score, the Thyroid Events Amsterdam (THEA) score, was designed to predict events by weighting these 3 risk factors proportionately to their relative risks (maximum score, 21): low (0-7), medium (8-10), high (11-15), and very high (16-21). These THEA scores were associated with observed event rates of 2.7%, 14.6%, 27.1%, and 76.9%, respectively.

Conclusions: An accurate simple predictive score was developed to estimate the 5-year risk of overt hypothyroidism or hyperthyroidism in female relatives of patients with AITD. However, in view of the small number of observed events, independent validation of the THEA score is called for.

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AUTOIMMUNE THYROID DISEASE (AITD) occurs more often in women than in men and frequently runs in families. Siblings of patients with AITD are clearly at risk, as evident from a sibling risk ratio (λs) ranging from 5.9 to higher than 10 (λs represents the ratio of the risk for developing AITD in a sibling of a patient with AITD beyond the risk for AITD present in the general population).[1,2] Twin studies suggest that genetic factors account for about 70% of the risk of contracting AITD and that environmental factors contribute about 30% to the risk.[3-6] Subjects with family members who have AITD are obviously at increased risk for AITD. It is thus understandable that a frequently asked question by patients with AITD is "Will my daughter or my sister also get this disease?" The physician is likely to answer that indeed the risk in family members—especially in women—is increased, but the physician will have difficulties in giving a more precise estimate of the risk. To obtain a quantitative risk estimate, we undertook a prospective observational study in a cohort of healthy first- or second-degree female relatives of patients with AITD who were observed for 5 years. The baseline characteristics of this cohort have been reported previously.[7] We aimed to design a simple score to predict the risk for developing overt hypothyroidism or hyperthyroidism based on the results of thyroid function tests, family history, and exposure to some environmental insults at study entrance.

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Table 1. Baseline Characteristics of the Prospective Euthyroid[a] Cohort of 790 Women With First- or Second-Degree Relatives With Proven AITD

Characteristic	Numerical Data[b]
Total subjects, No.	790
Age, mean (SD), y	36 (12)
TSH, mean (SD), mIU/L	2.1 (1.8)
FT_4, mean (SD), ng/dL	1.0 (0.2)
TPO Ab positive[c]	206 (26.1)
Tg Ab positive[c]	65 (8.2)
TBII positive[c]	2 (0.3)
Relative 1–Relative 2[d]	
Graves–Indeterminate	131 (16.6)
Graves–Graves	273 (34.6)
Graves–Hashimoto	195 (24.7)
Hashimoto–Indeterminate	49 (6.1)
Hashimoto–Hashimoto	142 (18.0)
Smoking habits	
Never smoker	337 (42.7)
Former smoker	179 (22.6)
Current smoker	274 (34.7)
Estrogen medication	
Never used	65 (8.2)
Formerly used	368 (46.6)
Currently use	357 (45.2)
Pregnancies	
None	382 (48.4)
≥1	408 (51.6)
YOP IgG	
Negative	472 (59.8)
Positive	318 (40.2)
YOP IgA	
Negative	617 (78.1)
Positive	173 (21.9)
High iodine exposure	
Absent	732 (92.7)
Present	58 (7.3)

Abbreviations: Ab, antibody; AITD, autoimmune thyroid disease; FT_4, free thyroxine; TBII, TSH-binding inhibitory immunoglobulins; Tg, thyroglobulin; TPO, thyroid peroxidase; TSH, thyrotropin; YOP, *Yersinia enterocolitica* outer membrane protein.

SI conversion factor: To convert FT_4 to picomoles per liter, multiply by 12.871.

[a] For the definition of normal thyroid function, see the "Methods" section.

[b] Unless otherwise indicated, data are reported as number (percentage) of subjects.

[c] For the definitions of positive findings, see the "Methods" section.

[d] Presence and type of AITD in 2 of the subject's first- or second-degree relatives.

METHODS

STUDY DESIGN AND PARTICIPANTS

The study was approved by the institutional review board of the Academic Medical Center, University of Amsterdam, Amsterdam, the Netherlands. The original cohort consisted of 803 healthy female subjects who had at least 1 first- or second-degree relative with documented autoimmune hyperthyroidism or hypothyroidism. All subjects were in self-proclaimed good health with no history of thyroid disease and were between 18 and 65 years old. The autoimmune nature of the thyroid disease in the subjects' relatives was ascertained by letters from their treating physicians. Results of thyroid function tests revealed overt hypothyroidism in 10 subjects and overt hyperthyroidism in 3 subjects, leaving 790 subjects to be included in the present study.[7]

All subjects were seen at our institution. After informed consent was obtained, blood was drawn for thyroid function tests, thyroid autoantibody assays, and assays for antibodies against *Yersinia enterocolitica* outer membrane proteins (YOPs). The rationale for determining the presence and/or levels of YOP antibodies is that *Y enterocolitica* membranes have specific thyrotropin (TSH) binding sites. Infection with *Y enterocolitica* induces the production of antibodies against these sites that recognize and stimulate TSH receptors in human thyrocytes. All subjects completed questionnaires on smoking habits (current and past), use of oral contraceptives or other estrogens (current and past), number of pregnancies, and exposure to high levels of iodine in the previous year. Current smoking was defined as smoking at the time of the study visit or having stopped smoking within 1 year of the study visit.

Participants were asked to return annually to our institution for evaluation of TSH and free thyroxine (FT_4) levels in their serum. Study follow-up time was 5 years, and all events reported in this study occurred within this 5-year period. *Event* in this study is defined as the development of overt hypothyroidism (TSH levels >5.7 mIU/L and FT_4 levels <0.72 ng/dL) or overt hyperthyroidism (TSH levels <0.4 mIU/L and FT_4 >1.56 ng/dL). To convert FT_4 to picomoles per liter, multiply by 12.871.

LABORATORY MEASUREMENTS

Serum TSH and FT_4 levels were measured using time-resolved fluoroimmunoassay (Delphia, Turku, Finland). Reference levels were 0.4 to 5.7 mIU/L for TSH and 0.72 to 1.56 ng/dL for FT_4.[7] Total triiodothyronine (T_3) levels were measured by an in-house radioimmunoassay (reference values, 84.4-178.6 ng/dL) to exclude T_3 toxicosis in subjects with TSH levels lower than 0.4 mIU/L but normal FT_4 levels. Presence and/or levels of antibodies against thyroid peroxidase (TPO) and thyroglobulin were measured using a chemiluminescence immunoassay (LUMI-Test; Brahms, Berlin, Germany), and results were considered positive at levels higher than 100 kU/L. Thyrotropin-receptor antibodies were measured by radioreceptor assay as TSH-binding inhibitory immunoglobulins (TBII) (first generation TRAK assay; Brahms), and results were considered positive at higher than 12 U/L. The presence and/or levels of specific IgG and IgA antibodies against purified plasmid-encoded associated YOPs of *Y enterocolitica* serotype 09 in serum samples were demonstrated by immunoblotting with a YOP antibody assay (AID, Strassberg, Germany), as described previously.[8] To convert T_3 to nanomoles per liter, multiply by 0.0154.

STATISTICAL ANALYSIS

Statistical analysis was carried out with the SPSS software, version 10 (Chicago, Illinois). To compare event rates among groups, we used Cox regression analysis. Multiple logistic regression analysis was carried out to identify independent risk factors for events. A multivariate model for prognostication of risk for an event was initially developed incorporating baseline characteristics that tested independently in a univariate logistic regression model. Variables associated with $P < .05$ were retained in the final model. From the logistic regression model, a simplified model was obtained by putting weights to individual risk factors proportional to regression coefficients. The simplified model, called the Thyroid Events Amsterdam (THEA) score, allowed easy calculation of a predictive score.

RESULTS

Baseline characteristics of the cohort are summarized in **Table 1**. All participants had serum FT_4 concentrations

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within the reference range, but 19 subjects had subclinical hypothyroidism (2.4%), and 13 subjects had subclinical hyperthyroidism (1.6%). With respect to family background, 608 of the 790 participants came from families with 2 proven patients with AITD (77%); both of these first- or second-degree relatives in each case had either the same AITD (either Graves hyperthyroidism or Hashimoto hypothyroidism for both relatives), or one had Graves disease, and the other had Hashimoto disease. In 182 of the 790 participants, we obtained proof of AITD in only 1 first- or second-degree relative (23%). Although each of these participants reported 2 relatives with thyroid disease, information obtained from the treating physician of the second relative indicated either non-AITD (eg, nontoxic goiter or thyroid cancer) or hypothyroidism or hyperthyroidism of unspecified cause, and these cases were labeled as *indeterminate*. Seven participants used antihypertensive drugs, and 1 used oral antidiabetic agents; none used lithium salts or amiodarone.

During the 5-year observation period, 136 of the 790 participants were lost to follow-up (17.2%), the loss occurring rather evenly over the whole study period, with an average annual loss of 27 participants. Characteristics of the dropouts were similar to those of the whole group (data not shown).

OCCURRENCE OF EVENTS

Events occurred in 51 of the 790 participants (6.5%): 38 developed overt hypothyroidism (4.8%), and 13 developed overt hyperthyroidism (1.7%). The cause of hypothyroidism was Hashimoto disease in 34 cases and postpartum thyroiditis in 4 subjects. At the time of diagnosis of hypothyroidism, the median (range) concentration of serum TSH was 14.8 (6.3-16.9) mIU/L, and for FT_4, it was 0.55 (0.15-0.71) ng/dL. At baseline, 7 of the 38 subjects with hypothyroidism had serum TSH levels higher than 5.7 mIU/L; 30 had TPO antibody levels higher than 100 kU/L; and none had TBII levels higher than 12 U/L. The cause of hyperthyroidism was Graves disease in 11 subjects (1 had Graves ophthalmopathy), postpartum thyroiditis in 1 subject, and silent thyroiditis in 1 subject. No cases of T_3 toxicosis were encountered.

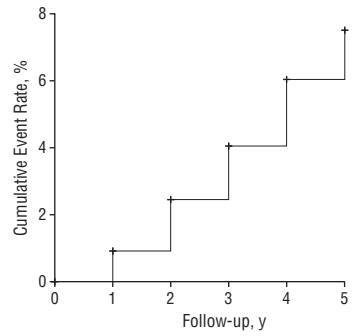
At the time of diagnosis of hyperthyroidism, the median (range) serum TSH level was 0.02 (<0.01 to 0.13) mIU/L, and for FT_4, it was 3.2 (1.6 to >5.4) mg/dL. At baseline, 2 of the 13 subjects with hyperthyroidism had serum TSH levels lower than 0.4 mIU/L; 9 had TPO antibody concentrations higher than 100 kU/L; and none had TBII levels higher than 12 U/L. Hypothyroid events occurred more often in subjects having 1 or 2 relatives with Hashimoto disease (28 of 386 [7.3%]) than in subjects having 1 or 2 relatives with Graves disease (19 of 599 [3.2%]) (P=.004). Hyperthyroid events, however, did not occur more often in subjects having 1 or 2 relatives with Graves disease (10 of 599 [1.7%]) than in subjects having 1 or 2 relatives with Hashimoto disease (6 of 386 [[1.6%]) (P>.10) (**Table 2**).

Figure 1 depicts the cumulative event rate in the population at risk, which was 7.5% over 5 years. The mean annual event rate was 1.5%.

Table 2. Hypothyroid and Hyperthyroid Events During 5-Year Follow-up of the Euthyroid[a] Cohort of 790 Women With First- or Second-Degree Relatives With Proven AITD According to Family History of AITD[b]

Family History	Hypothyroid Events	Hyperthyroid Events	All Events
Relative 1–Relative 2[c]			
Graves–Indeterminate	1/131 (0.8)	0/131 (0)	1/131 (0.8)
Graves–Graves	9/273 (3.3)	7/273 (2.6)	16/273 (5.9)
Graves–Hashimoto	9/195 (4.6)	3/195 (1.5)	12/195 (6.1)
Hashimoto–Indeterminate	2/49 (4.1)	2/49 (4.1)	4/49 (8.2)
Hashimoto–Hashimoto	17/142 (12.0)	1/142 (0.7)	18/142 (12.7)
Total	**38/790** (4.8)	**13/790** (1.7)	**51/790** (6.5)

Abbreviation: AITD, autoimmune thyroid disease.
[a] For the definition of normal thyroid function, see the "Methods" section.
[b] All data are reported as number of applicable subjects/total number of possible subjects (percentage).
[c] Presence and type of AITD in 2 of the subject's first- or second-degree relatives.



Subjects at risk, No.	790	750	720	685	647	603
Events, No.	0	7	11	11	13	9
Hypothyroid events, No.	0	3	9	8	10	8
Hyperthyroid events, No.	0	4	2	3	3	1

Figure 1. Cumulative event rate over 5 years in a euthyroid cohort of 790 women with first- or second-degree relatives with proven autoimmune thyroid disease.

RISK FACTORS FOR EVENTS

Table 3 lists hazard ratios of baseline characteristics for the occurrence of an event, as determined by Cox regression analysis. Identified risk factors are serum TSH level, TPO antibody concentration, and family background. A TSH outside the reference range of 0.4 to 5.7 mIU/L at study entrance clearly constituted a risk, but the risk started to increase already at TSH levels above 2.0 mIU/L. A level-dependent effect was also observed for TPO antibody concentrations: the higher the concentration, the greater the hazard ratio. Having 2 relatives with Hashimoto disease also enhances the risk. Increasing age might be associated with a higher event rate, but this trend was not significant. Age, according to multiple logistic regression analysis, was not an independent risk factor; nor was thyroglobulin antibody presence or concentration. The 2 subjects with positive TBII findings had normal TSH values at baseline and remained euthyroid. No environmental factors significantly affected hazard ratios.

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Table 3. Event Rates During 5-Year Follow-up of the Euthyroid[a] Cohort of 790 Women With First- or Second-Degree Relatives With Proven AITD

Characteristic at Study Entry	Event Rate[b]	HR (95% CI)[c]	*P* Value[c]
Age, y			.16 For trend
20-30	5.6 (16/288)	1 [Reference]	NA
>30-40	5.1 (11/215)	0.9 (0.42-1.95)	.80
>40-50	7.2 (12/166)	1.3 (0.61-2.72)	.51
>50-60	12.1 (11/91)	2.3 (1.05-4.90)	.04
>60	3.3 (1/30)	0.6 (0.08-4.40)	.60
TSH, mIU/L			<.001 For trend[d]
<0.4	23.1 (3/13)	9.6 (2.76-33.40)	<.001
0.4-2.0	2.7 (13/484)	1 [Reference]	NA
>2.0-4.0	6.0 (14/233)	2.2 (1.05-4.76)	.04
>4.0-5.7	29.3 (12/41)	11.6 (5.29-25.42)	<.001
>5.7	47.4 (9/19)	22.0 (9.47-52.04)	<.001
TPO antibodies, kU/L			<.001 For trend
≤100	2.1 (12/584)	1 [Reference]	NA
>100-1000	8.6 (9/105)	4.5 (1.89-10.64)	.001
>1000-10 000	27.6 (24/87)	14.4 (7.18-29.00)	<.001
>10 000	42.9 (6/14)	25.7 (9.60-68.40)	<.001
Relative 1–Relative 2[e]			<.001 For trend
Graves–Indeterminate	0.8 (1/131)	0.14 (0.02-1.05)	.06
Graves–Graves	5.9 (16/273)	1 [Reference]	NA
Graves–Hashimoto	6.2 (12/195)	1.1 (0.51-2.30)	.86
Hashimoto–Indeterminate	8.2 (4/49)	1.5 (0.52-4.60)	.44
Hashimoto–Hashimoto	12.7 (18/142)	2.2 (1.11-4.25)	.02
Smoking habits			
Never smoker	7.4 (25/337)	1 [Reference]	NA
Former smoker	7.3 (13/179)	1.1 (0.55-2.10)	.84
Current smoker	4.8 (13/274)	0.7 (0.33-1.28)	.21
Estrogen medication			
Never used	6.2 (4/65)	1 [Reference]	NA
Formerly used	6.3 (23/368)	1.0 (0.35-2.96)	.98
Currently use	6.7 (24/357)	1.1 (0.39-3.20)	.85
Pregnancies			
None	6.3 (24/382)	1 [Reference]	NA
≥1	6.6 (27/408)	1.0 (0.55-1.64)	.85
YOP IgG			
Negative	6.1 (29/472)	1 [Reference]	NA
Positive	6.9 (22/318)	1.2 (0.66-2.01)	.62
YOP IgA			
Negative	6.3 (39/617)	1 [Reference]	NA
Positive	6.9 (12/173)	1.1 (0.58-2.12)	.75
High iodine exposure			
Absent	6.6 (48/732)	1 [Reference]	NA
Present	5.2 (3/58)	0.8 (0.25-2.54)	.70

Abbreviations: AITD, autoimmune thyroid disease; CI, confidence interval; HR, hazard ratio; NA, not applicable; TPO, thyroid peroxidase; TSH, thyrotropin; YOP, *Yersinia enterocolitica* outer membrane protein.

[a] For the definition of normal thyroid function, see the "Methods" section.

[b] Data are reported as percentage (number of applicable subjects/total number of possible subjects); the overall event rate for all subjects was 6.5% (51 of 790).

[c] By Cox regression analysis.

[d] Excluding the lowest TSH category (<0.4 mIU/L).

[e] Presence and type of AITD in 2 of the subject's first- or second-degree relatives.

PREDICTIVE SCORE FOR EVENTS

A simplified model was obtained from the logistic regression model by putting weights to individual risk factors proportional to their relative risks. This model allowed the calculation of a predictive score called the THEA score (**Table 4**). The operational value of the THEA score was evaluated by comparison of the observed and expected event rates (**Table 5**). The good agreement between both event rates is taken as a measure for the validity of the THEA score. Event rates increased significantly as the THEA score increased ($P < .001$ for trend by χ^2 analysis) (**Figure 2**).

COMMENT

We observed in our at-risk female population a cumulative event rate of 7.5%, with an annual incidence rate of 1.5%. Overt hypothyroidism occurred in 38 subjects, and overt hyperthyroidism in 13 subjects during the 5-year follow-up of the 790 participants. The hypothyroidism

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Table 4. Calculation of the THEA Score, a Predictive Score for the Occurrence of Events in a Euthyroid[a] Cohort of 790 Women With First- or Second-Degree Relatives With Proven AITD

Characteristic	Hypothyroid Event	Hyperthyroid Event	Any Event
TSH, mIU/L			
<0.4	0	2	2
0.4-2.0	0	0	0
>2.0-4.0	3	–1	2
>4.0-5.7	6	–2	4
>5.7	9	–3	6
TPO antibodies, kU/L			
≤100	0	0	0
>100-1000	3	1	4
>1000-10 000	6	2	8
>10 000	9	3	12
Family background			
2 Relatives with Graves	0	1	1
2 Relatives with Hashimoto	3	0	3
Maximum THEA score	21	6	21

Abbreviations: AITD, autoimmune thyroid disease; THEA, Thyroid Events Amsterdam; TPO, thyroid peroxidase; TSH, thyrotropin.
[a] For the definition of normal thyroid function, see the "Methods" section.

Table 5. Comparison of Observed and Expected Event Rates in a Euthyroid[a] Cohort of 790 Women With First- or Second-Degree Relatives With Proven AITD According to the THEA Score

THEA Score	Event Rate	
	Observed[b]	Expected, %
Hypothyroid event rate		
0-7 (Low)	1.6 (11/690)	1.6
8-10 (Medium)	12.2 (5/41)	10.8
11-15 (High)	30.8 (16/52)	34.2
16-21 (Very high)	85.7 (6/7)	70.1
Hyperthyroid event rate		
≤0 (Low)	0.6 (3/497)	0.7
1-2 (Medium)	3.0 (8/296)	2.3
3-6 (High)	9.5 (2/21)	16.6
Any event rate		
0-7 (Low)	2.7 (18/670)	2.6
8-10 (Medium)	14.6 (7/48)	13.1
11-15 (High)	27.1 (16/59)	32.9
16-21 (Very high)	76.9 (10/13)	59.4

Abbreviations: AITD, autoimmune thyroid disease; THEA, Thyroid Events Amsterdam; TPO, thyroid peroxidase; TSH, thyrotropin.
[a] For the definition of normal thyroid function, see the "Methods" section.
[b] Data are reported as percentage (number of applicable subjects/total number of possible subjects).

incidence rate in our population was 9.6/1000/y; the hyperthyroidism incidence rate was 3.3/1000/y. Incidence rates in the general female population have been reported in the prospective DanThyr study by Bülow Pedersen et al[9] (comparing 2 regions of Denmark with moderate and mild iodine deficiency [urinary iodine levels, 45 µg/L in Aalborg and 61 µg/L in Copenhagen]) in the prospective Whickham study by Vanderpump et al,[10] and in the retrospective Tayside study by Flynn et al.[11] Both the Whickham and the Tayside studies were conducted in England, a country considered to be iodine sufficient (mean urinary iodine excretion level, 141 µg/L).[12] The incidence rates of hypothyroidism in these 4 areas were 0.44, 0.61, 3.5, and 4.98 per 1000 women per year, respectively. Incidence rates of hyperthyroidism were 1.49, 1.02, 0.80, and 0.77 per 1000 women per year, respectively. To convert iodine to nanomoles per liter, multiply by 7.880.

These epidemiologic data support the notion that higher levels of dietary iodine decrease the incidence of hyperthyroidism at the expense of an increased incidence of hypothyroidism. The Netherlands is considered to be a country of dietary iodine sufficiency, with a median urinary iodine excretion level of 154 µg/L.[13] Our incidence figures are therefore best compared with those in the United Kingdom: in our at-risk female population, the incidence rate of overt hypothyroidism is 1.9 to 2.7 times higher than that in the general female population in the United Kingdom, and the incidence rate of hyperthyroidism is 4.1 to 4.3 times higher. These figures once again demonstrate that subjects with a family history of AITD are at increased risk for thyroid disease.

The risk in siblings of parents with AITD is much higher than that observed in the present study (with reported λs as high as 11.6 for Graves disease and 28.0 for Hashimoto thyroiditis).[2] This finding is understandable

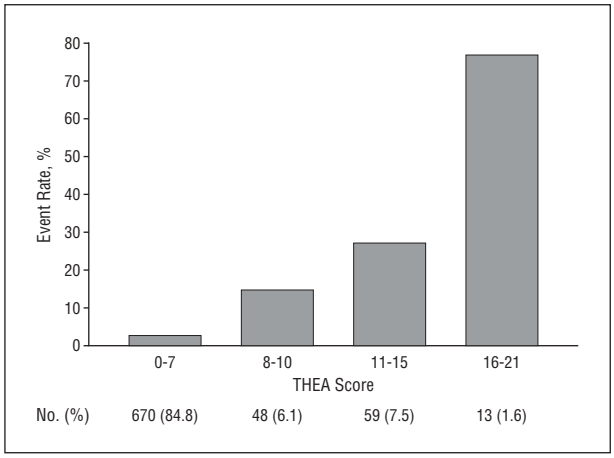

Figure 2. The Thyroid Events Amsterdam (THEA) score used to predict hypothyroid and hyperthyroid events over 5 years in a euthyroid cohort of 790 women with first- or second-degree relatives with proven autoimmune thyroid disease. Event rates increased significantly, as measured by the χ^2 test, as the THEA score increased ($P<.001$ for trend).

because relatives with AITD in our study could be children, brothers, sisters, parents, grandparents, uncles, or aunts of the participants. Our figures thus fit nicely between the lower risk in the general population and the higher risk in siblings.

In the present study, we found that independent risk factors are serum TSH level (increased risk at TSH values <0.4 mIU/L and >2.0 mIU/L, still within the reference range), high TPO antibody concentration, and presence of a family history of AITD (with the greatest risk attached to subjects having 2 relatives with Hashimoto disease). These findings are in perfect agreement with the prospective Whickham study,[10] which reported that the risk to develop hypothyroidism sharply increased at TSH levels above 2 mIU/L, independently of TPO antibody lev-

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els. The agreement in these findings underscores the notion that TSH levels between 0.4 and 2.0 mIU/L are associated with optimal thyroid health.[14,15] The progressively increasing risk with increasing TPO antibody concentrations, independent of TSH levels, has also been observed in the Whickham study.[10] Advancing age is associated with a higher concentration of TPO antibodies,[10] which likely explains why age in our study was not an independent risk factor. In the Whickham study, the age-specific hazard rates for the development of hypothyroidism (but not for hyperthyroidism) sharply increase when the patients are older than 60 years.[10] In our study, the trend of a higher event rate in older age was nonsignificant, probably owing to the small number of subjects in the age group 60 to 65 years (only 30 subjects).

In the Whickham study,[10] a positive family history of thyroid disease was not associated with increased odds of developing hypothyroidism. This absent relationship might be explained by evaluation of the general population in that study and by the fact that not all patients with AITD have a positive family history of thyroid disease (eg, in Graves disease, family history of AITD is reported in only 60% of cases).[1] In our study, limited to families with first- or second-degree relatives with AITD, we observed the greatest risk for hypothyroid events in participants with 2 relatives with Hashimoto disease; this was not the case for hyperthyroid events, nor did participants with 2 relatives with Graves disease represent such a high risk.

A baseline concentration of higher than 100 kU/L for TPO antibodies was found with equal frequency in subjects having hypothyroid and hyperthyroid events (79% vs 69%) ($P>.10$), just as the median (range) baseline TPO antibody concentration was similar in the 2 groups: 1890 (370 to >10 000) kU/L vs 1060 (340 to >10 000) kU/L ($P>.10$). Regarded as early markers of thyroid autoimmunity, the presence of TPO antibodies is common to both Graves and Hashimoto disease. In healthy euthyroid women, genetic factors account for 72% of the risk for positive TPO antibody findings[6]; according to this estimate, 28% of the liability should be caused by environmental factors. However, none of the environmental factors to which the participants of our study were exposed at study entrance contributed to the risk for developing an event.

This is not to deny that the investigated environmental factors might have played a role in developing overt hypothyroidism or hyperthyroidism. Exposure might have changed between the time of study entrance and time of the event. However, given the similarity in the baseline prevalence of TPO antibodies in subjects developing hypothyroid and hyperthyroid events, and in view of the dependency of the hypothyroid event rate on family background (3 times higher in cases of 2 relatives with Hashimoto disease)—and keeping in mind that the hyperthyroid event rate was not preferentially influenced by the number of relatives with Graves or Hashimoto disease—it is tempting to speculate that subjects genetically predisposed to AITD first develop TPO antibodies and then develop hypothyroidism unless exposure to smoking and stressful life events provokes development of Graves hyperthyroidism.

The 3 independent risk factors for events allowed us to compose a predictive score for the development of overt hypothyroidism or hyperthyroidism within 5 years in euthyroid women with first- or second-degree relatives with AITD. This THEA score apparently gives a fairly accurate estimate of the risk. Its advantages are the easy calculation and the broad applicability. The family members of patients with AITD can be reassured of a very high likelihood of maintaining euthyroidism in the next 5 years if they have a low score (0-7). If the THEA score is higher, reassessment after 1 year might be warranted. The THEA score might be very useful for young women of AITD families who want to become pregnant in the next few years.[16] Screening seems to be indicated for these women in view of the high abortion rate associated with the presence of TPO antibodies. The abortion rate can be lowered by treatment with levothyroxine.[17]

Our study has several limitations. The THEA score is derived from a female population and may be not applicable to men. Although a large sex difference is unlikely, the score should be validated in a male population. Prediction of events by the THEA score is restricted to a time span of 5 years, but undoubtedly many more events will occur after that period. In clinical practice, reassessment of the THEA score after 5 years might be indicated.

Another important limitation of our study is the relatively low number of events, especially hyperthyroid events, which probably renders the THEA score less accurate. The small number of observed events may raise concern about possible overfitting of our model. Consequently, there is a need to validate the THEA score in other populations.

Finally, the precise genetic background in 182 of the 1580 relatives could not be ascertained (11.5%); an unknown proportion of these indeterminate relatives might still have Graves or Hashimoto disease, thereby affecting the weights assigned to family background in the THEA score. This bias is likely to be small in view of its limited contribution to the maximum THEA score. The uncertainty is acceptable because it reflects the reality of day-to-day practice in which it is not always possible to determine with certainty the autoimmune nature of thyroid disease in family members. Inclusion of indeterminate relatives in our study permits application of the THEA score also in subjects with only 1 known relative with AITD.

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Author Contributions: Drs Wiersinga and Tijssen had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Dr Endert was responsible primarily for the laboratory tests of thyroid function and thyroid antibodies, and Dr Wenzel performed the serologic tests for *Yersinia enterocolitica*. *Study concept and design:* Tijssen, Endert, and Wiersinga. *Acquisition of data:* Strieder,

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