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Download date: 23-10-2023
Thyroid Disease and Type 1 Diabetes in Dutch Children: A Nationwide Study (Young Dudes-3)

Engelina Spaans, MD1,2, Eelco Schroor, MD, PhD2, Klaas Groenier, PhD1,3, Henk Bilo, MD, PhD1,4, Nanne Kleefstra, MD, PhD4,5, and Paul Brand, MD, PhD2,6

Objective To investigate the prevalence of overt thyroid disease in children in The Netherlands with and without type 1 diabetes mellitus (T1DM).

Study design Nationwide, retrospective cohort study in The Netherlands. Using the national registry of both healthcare reimbursement and pharmaceutical care, data of all Dutch children (aged 0-14 years) with a diagnosis of T1DM, or a diagnosis of hypothyroidism or hyperthyroidism in the period 2009-2011.

Results The prevalence of thyroid disease was 0.15% in children without T1DM, and 3.43% in children with T1DM (rate ratio 23.59; 95% CI 19.92-27.93; P < .001). Both hyperthyroidism and hypothyroidism were 24 times more likely in children with T1DM than in those without. Thyroid disease was more common in girls than in boys, both in children with T1DM (rate ratio of girls vs boys 3.07; 95% CI 2.10-4.49) and in children without T1DM (rate ratio 1.59; 95% CI 1.49-1.69). This sex difference was more pronounced for hypothyroidism than for hyperthyroidism.

Conclusions Children with T1DM in The Netherlands are 24 times more likely to develop thyroid disease than their peers without diabetes. Girls with T1DM were more prone to thyroid disease, particularly hypothyroidism. (J Pediatr 2017;187:189-93).

The incidence and prevalence of autoimmune diseases vary among the different diseases and between geographical regions.1 The prevalence of autoimmune thyroid disease (AITD) in a combined population of children and adults in Europe, for example, is estimated to be 3% for hypothyroidism and 0.75% for hyperthyroidism.2 The reported prevalence in the US population are slightly higher: 4.6% and 1.3% for hypothyroidism and hyperthyroidism, respectively.3 Autoimmune diseases tend to coincide, with the association between AITD and type 1 diabetes mellitus (T1DM) being the most common.4,5 Thyroid peroxidase antibodies have been found in 15%-30% of adults with T1DM in comparison with 2%-10% in matched controls.6 Approximately 50% of thyroid peroxidase antibody-positive patients with T1DM will develop overt AITD.6,7 In a Dutch population of adults with type T1DM, the average prevalence of AITD was 11.2%.8 The prevalence of AITD in children, however, is unknown, both in the general population and in children with T1DM. Studies from the previous decade reported detectable antithyroid antibodies in 15%-19% of children with T1DM.9,10 The prevalence of such antithyroid autoantibodies increases with age, especially in female adolescents.10,11 A recent study from Korea showed that 26% of children with newly diagnosed T1DM already had antithyroid autoantibodies, suggesting either that the prevalence of AITD in children with T1DM is increasing or that that this phenomenon is specific for Korea.12 Unfortunately, it is at present unknown what proportion of children with autothyroid autoantibodies will develop AITD, with estimates ranging from 3% to 60%.7,9,14-16

The aim of this nationwide cohort study was to investigate the prevalence of overt thyroid disease in children in The Netherlands with and without T1DM.

Methods

The present study is part of the Young DUDEs initiative (DUtch Diabetes Estimates), a project aimed at investigating the magnitude and impact of T1DM and its complications among children and adolescents in The Netherlands. A detailed description has been published previously.17

In The Netherlands, all children with T1DM are treated by hospital-based pediatricians. Over the time period 2009-2011, reimbursement of hospital care costs...
was handled nationwide through the registration as Diagnosis Treatment Combination (Diagnose-Behandeling Combinatie [DBC] in Dutch); physicians and hospitals are required to record the appropriate codes to allow reimbursement to proceed. Each DBC code contains information about the specialty of the attending physician, the patient’s diagnosis, and the type of care provided. All DBC codes and the MBC-associated reimbursements are stored in a national database, managed by Vektis (Zeist, The Netherlands). Vektis also manages other databases such as the Basic Health Insurance Information System, containing demographic information (like date of birth and sex) for all children registered as inhabitants in The Netherlands, and information on drug prescription. The coverage of this system is 98%. \(^1\) Claims records for pharmaceutical care with a coverage of 99% were derived from the Pharmacy Information System, containing information on the date the drug was supplied, who prescribed the drug, the specific drug that was supplied (including Anatomical Therapeutic Chemical [ATC] code), and the quantity supplied. Because all healthcare system records, including the Pharmacy Information System, use the same unique identifying number for each patient (the “Citizen Service Number”), it is possible to link all claims for any individual and thereby track each individual through all domains of healthcare and over time. \(^1\)

Children 14 years of age or younger on the first of July were selected for every single year of the study period (2009-2011). In this group, individuals with at least 1 DBC claim for diabetes (pediatrics code [0316] and diabetes code [7104], or internal medicine code [0313] and diabetes diagnosis code [221, 222, or 223]) were included. Patients were only classified as T1DM if pharmaceutical claims showed prescription and pick up of insulin (at least twice over the 4-year period 2008-2011). Patients with a diagnosis code of diabetes for whom no records of diabetes medication were found, or only records of medication except insulin, were excluded from further analysis in this study.

In the same study period (2009-2011) and cohort, we examined evidence of the presence of hyperthyroidism (based on 1 or more pharmaceutical claim[s] for carbimazole [ATC H03BB01], propylthiouracil [ATC H03BA02], thiamazole [ATC H03BB02], or DBC claim for hyperthyroidism [7107]), or hypothyroidism (based 1 or more pharmaceutical claim[s] for levothyroxine [ATC H03AA01] or liothyronine [ATC H03AA02] or DBC claim for hypothyroidism [7108], but not for ATC H03BB01, ATC H03BA02, ATC H03BB02, or DBC-[7107]).

Furthermore, the number, sex, and age of the whole population of children in The Netherlands were derived from the national Central Bureau of Statistics (CBS) (www.cbs.nl). Taken together, the collected data allowed us to estimate the nationwide prevalence of T1DM, thyroid disease, neither, either, or both.

Data selection, acquisition, and organization were performed within the Vektis electronic environment. Before analysis, all claims and personal data were stripped from identifying characteristics to ensure anonymity: the Citizen Service Number was encrypted, date of birth converted into the person’s age, and the postal code recoded to limit its identifying properties to the neighborhood level.

### Statistical Analyses

To examine whether the prevalence of thyroid disease is more common in children with T1DM compared with the general population of children aged 0-14 years in different age categories (0-4, 5-9, and 10-14 years), and for boys and girls separately, we used the CBS population statistics. We used the \(x^2\) goodness-of-fit test to compare the prevalence of thyroid disease in children with and without T1DM. In addition, the 95% CIs for the prevalences were computed. Statistical analyses were carried out using SPSS (IBM SPSS Statistics for Windows, Version 20.0.; IBM Corp, Armonk, New York) and OpenEpi, version 3.01 (www.OpenEpi.com). \(^2\)

Because retrospective studies using anonymized data are exempt from ethical review under Dutch law, medical ethics approval was not required for this study. A statement to that effect was issued by the Isala Hospital Ethical Review Board.

### Results

From 2009 to 2011, an average of 2 914 348 children 0-14 years of age (1 491 038 boys [51%] and 1 423 310 girls) lived in The Netherlands. There were 926 514 children 0-4 year of age (32%), 999 704 children 5-9 years of age (34%), and 988 130 children 10-14 years of age (34%). The cumulative prevalence of T1DM in children 0-14 years of age was 4186 (0.14%); 4107 known in 2009, 3947 in 2010, and 4089 in 2011.

Data on the prevalence of hyperthyroidism and hypothyroidism in children with and without T1DM are given in Tables I and II, respectively. Between 2009 and 2011, the overall prevalence of thyroid disease in children 0-14 years of age in The Netherlands was 0.15% (n = 4369).

The prevalence of thyroid disease was 0.15% (4230/2 905 932; 95% CI 0.14-0.15) in children without T1DM, compared with 3.43% (139/4048; 95% CI 2.90-4.04) in children with T1DM (rate ratio 23.59; 95% CI 19.92-27.93; \(P < .001\)). The prevalence of hyperthyroidism was 0.015% (95% CI 0.010-0.013) in children without T1DM vs 0.27% (95% CI 0.14-0.47) in children with T1DM (rate ratio 23.71; 95% CI 13.01-43.23; \(P < .001\)) (Table I). The prevalence of hypothyroidism was 0.134% (95% CI 0.1299-0.138) in children without diabetes vs 3.16% (95% CI 2.65-3.75) in children with T1DM (rate ratio 23.58; 95% CI 19.77-28.12; \(P < .0005\)) (Table II).

The rate ratio of thyroid disease in girls vs boys in children without T1DM was 1.59 (95% CI 1.49-1.69) vs 3.07 (95% CI 2.10-4.49) in children with T1DM. The rate ratio of girls vs boys for hyperthyroidism in children without T1DM was 2.37 (95% CI 1.88-3.00) vs 1.90 (95% CI 0.56-6.48) in children with T1DM.

The rate ratio of girls vs boys for hypothyroidism was 1.54 (95% CI 1.44-1.64) in children without T1DM compared with 3.12 (95% CI 2.10-4.63) in children with T1DM.

Overall, children with T1DM were 24 times as likely to have hyperthyroidism and 24 times as likely to have hypothyroidism as children without T1DM. The female preponderance for...
thyroid disease was more pronounced for hypothyroidism than for hyperthyroidism.

**Discussion**

In this Dutch nationwide study, we found that children with T1DM are much more likely to have thyroid disease compared with their peers without T1DM. The relative risk of thyroid disease in children 0-14 years of age with T1DM was 24 (3.43% vs 0.15%). This held true both for hyperthyroidism and hypothyroidism. Girls with T1DM were more likely to have thyroid disease than boys, in particular hypothyroidism.

A population-based study found orders for thyroxin prescriptions in 0.14% of subject 0-22 years of age from a database used to estimate population prevalence data on both T1DM and thyroid disease, allowing us to compare the prevalence of thyroid disease in children 0-14 years of age with and without T1DM. The 2 separate databases (healthcare insurance and pharmacy) used provide a 98%-99% coverage. As a limitation, some T1DM population was clinically diagnosed withAITD,3, which is slightly higher than the 3.43% found in our study. The difference is likely owing to the difference in age selection. A recent Taiwanese population-based case-control study showed a 6.65-fold increased incidence rate ratio of thyroid disease in T1DM compared with children without T1DM, with incidence rate ratios of 2.74 for simple and unspecified goiter, 6.95 for thyrotoxicosis, and 6.54 for unspecified hyperthyroidism.30

The prevalence of hyperthyroidism in children with T1DM found in this study (0.27%) is within the range of those reported in previous studies (0.20%-0.46%).31 Similarly, the 1:2.8 male:female ratio of thyroid disease in our study is comparable with that found in a previous study.31 The higher prevalence of thyroid disease in girls with T1DM has also been found in other autoimmune diseases. Unfortunately, there is no good explanation for this phenomenon.18

A major strength of this study is the nationwide coverage of population prevalence data on both T1DM and thyroid disease, allowing us to compare the prevalence of thyroid disease in children 0-14 years of age with and without T1DM. The 2 separate databases (healthcare insurance and pharmacy) used provide a 98%-99% coverage. As a limitation, some

<table>
<thead>
<tr>
<th>Year</th>
<th>Total, NBoys</th>
<th>Total, NGirls</th>
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<td>1570</td>
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<td>27 (2.07)</td>
<td>77 (6.17)</td>
<td>105 (0.01)</td>
<td>239 (0.02)</td>
<td>31 (0.20)</td>
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**Table I. Prevalence of hyperthyroidism in children with and without type 1 diabetes mellitus**

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<tr>
<th>Year</th>
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<th>Total, NGirls</th>
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<td>115 (0.86)</td>
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</table>
misclassification of T1DM through incorrect registration of diagnosis codes is always possible and, theoretically, we miss out on all information with regard to treatment and diagnoses not represented though reimbursement information.

Another limitation of this study is that we could not differentiate between congenital and acquired hypothyroidism because the DBC codes do not distinguish between these 2 types of hypothyroidism. Based on an annual incidence of 75 to 80 neonates with congenital hypothyroidism diagnosed through newborn screening in The Netherlands, the total group of children 0-14 years of age in our study will contain approximately 1200 children with congenital hypothyroidism. Re-analysis of our data, assuming that these patients with congenital hypothyroidism were divided equally between the groups of children with and without diabetes, showed that the malefemale ratio in diabetes related thyroid disease remained comparable (Appendix; available at www.jpeds.com). The International Society for Pediatric and Adolescent Diabetes suggests that thyroid function should be measured in every newly diagnosed child with T1DM, and this measurement should be repeated annually. This consensus is followed by Dutch pediatricians, strengthening the accuracy of the prevalence figure of thyroid disease in children with T1DM in our study. Underreporting of thyroid disease in children without diabetes cannot be excluded, however.

In conclusion, this study shows an overall prevalence of 3.43% for thyroid disease, and of 0.27% and 3.16% for hyperthyroidism and hypothyroidism, respectively, in children 0-14 years of age with T1DM. This shows that children with T1DM are approximately 24 times more likely to have thyroid disease (24 times both for hyperthyroidism and for hypothyroidism) compared with children without T1DM. The results of our study support recommendations for regular screening of thyroid function in children with T1DM.

References


Number of children with diabetes and hypothyroidism and children without diabetes and hypothyroidism

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<th>Girls (T1DM+/hypothyroidism+)</th>
<th>Boys (T1DM−/hypothyroidism+)</th>
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<td>2337</td>
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Number of children with diabetes and hypothyroidism and children without diabetes and hypothyroidism after leaving out the estimated number of children with congenital hypothyroidism

<table>
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<tr>
<th>Years</th>
<th>Boys (T1DM+/hypothyroidism+)</th>
<th>Girls (T1DM+/hypothyroidism+)</th>
<th>Boys (T1DM−/hypothyroidism+)</th>
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