DANISH MEDICAL JOURNAL

Original Article

Validity of a thyrotoxicosis diagnosis code among women of fertile age

Nanna Maria Uldall Torp[1], Signe Kirkegaard[1], Karoline Schack[1] & Stine Linding Andersen[1, 2]

1) Department of Clinical Biochemistry, Aalborg University Hospital, 2) Department of Clinical Medicine, Aalborg University, Denmark

Dan Med J 2025;72(10):A04250296. doi: 10.61409/A04250296

ABSTRACT

INTRODUCTION. Graves' disease (GD) is the leading cause of hyperthyroidism in women of fertile age. Register-based studies rely on diagnostic codes; this study examined the validity of diagnosed thyrotoxicosis among women of fertile age in the Danish National Hospital Register (DNHR).

METHODS. All women in the North Denmark Region aged 18-45 years with a diagnosis of thyrotoxicosis (Tenth International Classification of Diseases: E05.0-05.9) in the DNHR from 2017-2018 were identified and medical records reviewed.

RESULTS. Among 263 women included, thyrotoxicosis was confirmed in 249 cases with a positive predictive value (PPV) of 94.7% (95% **confidence interval** (CI): 91.2-97.1%) for the diagnostic group (E05.0-05.9). Autoimmune hypothyroidism was the leading cause of misclassification. GD was the aetiology in 150 women, resulting in a PPV for GD of 57.0% (95% CI: 50.8-63.1%) in the diagnostic group (E05.0-05.9), increasing to 83.6% (95% CI: 76.4-89.3%) when restricted to women who were prescribed an antithyroid drug (ATD). The PPV for GD was highest when the specific diagnosis (DE05.0) was considered (PPV 91.1% (95% CI: 84.7-95.5%); however, 42 women with GD (28.0%) were first given a diagnosis of unspecified thyrotoxicosis (E05.9).

CONCLUSIONS. The validity of thyrotoxicosis identified in the DNHR among women of fertile age was high. Results emphasise the importance of how subtypes of thyrotoxicosis are defined and show that the combined use of diagnoses and prescriptions of ATD is warranted to define GD.

FUNDING. Novo Nordisk Foundation (grant no: NNF20OC0059465).

TRIAL REGISTRATION. Not relevant.

In women of fertile age, thyroid disorders are predominantly of autoimmune origin [1]. Knowledge of thyroid disease in this patient group is important, as normal thyroid function during pregnancy is essential for foetal neurodevelopment, and any disturbance in maternal thyroid function carries a risk of adverse obstetric outcomes [2]. The autoimmune Graves' disease (GD) is the most common cause of hyperthyroidism in women of fertile age, while gestational hyperthyroidism is another common cause of hyperthyroidism during pregnancy [2, 3]. Observational, register-based studies have investigated the occurrence of hyperthyroidism in Denmark in the general population and among pregnant women [4, 5]. These studies utilised information from hospital diagnoses of disease registered in the Danish National Hospital Register (DNHR) and redeemed prescriptions from Danish pharmacies registered in the Danish National Prescription Register [6, 7]. To specifically identify GD in and around the time of pregnancy, information on prescriptions and hospital diagnoses is often combined [5, 8]. In the DNHR, hospital diagnoses are coded according to the tenth edition of the International Classification of Diseases (ICD-10) [7]. However, the validity of the diagnostic codes for thyrotoxicosis in women

of fertile age remains unclear.

This study aimed to investigate the validity of the diagnostic codes for thyrotoxicosis in the DNHR with a focus on the identification of GD among women of fertile age.

Methods

This was a retrospective cohort study including women of fertile age diagnosed in the two public hospitals covering patients of the North Denmark Region (Aalborg University Hospital and the North Denmark Regional Hospital). All women aged 18-45 years with a diagnosis of thyrotoxicosis during the two-year period from 1 January 2017 to 31 December 2018 were identified in the DNHR and were coded according to the ICD-10 [7]. For this study, primary or secondary diagnoses of thyrotoxicosis (ICD-10: E05.0-0.5.9) registered in the DNHR for in- or outpatients were selected. The hospitals approved the retrospective, observational study design with a waiver of informed consent, and the study was registered according to the General Data Protection Regulation in the North Denmark Region (2021-077).

Medical records were reviewed by the authors (medical specialists not involved in the clinical care of the enrolled patients) for all women with a thyrotoxicosis diagnosis. From the medical records, information was available on hospital visits, while information from visits in general practice was unavailable. From the medical records, we extracted information regarding prescribed medicine, pregnancy, thyroid symptoms, clinical findings, biochemical results and thyroid imaging. The information from each medical record was reviewed by at least two of the authors to ensure consistency. Thyrotoxicosis was defined as the presence of excess thyroid hormone in the blood; hyperthyroidism, as an excess production of thyroid hormone in the thyroid gland. Consequently, thyroiditis and thyrotoxicosis factitia were included in the definition of thyrotoxicosis but excluded from that of hyperthyroidism. The diagnoses were established according to the current clinical guidelines [9, 10] and retrospectively confirmed by findings consistent with GD, namely thyroid-stimulating hormone (TSH)-receptor antibodies and/or a scintigraphy with diffuse, high uptake. Among the hyperthyroid women without GD, a diagnosis of multinodular toxic goitre (MNTG) or solitary toxic adenoma was based on the results of the thyroid scintigraphy or ultrasound, while gestational hyperthyroidism was characterised by the transient occurrence in pregnancy.

A group of women (n = 134) had a registered pregnancy during the study period. Information from the pregnancy period was retrieved if a diagnosis was registered in the DNHR between one year before and one year after the end of the pregnancy. The pregnancy period was determined from the ultrasound-confirmed gestational age documented in the medical records. A diagnosis was classified as pregnancy-related if the diagnostic code was registered between the first date of the last menstrual period and the end of the pregnancy.

Data were collected and managed using Research Electronic Data Capture (REDCap) hosted at Aalborg University Hospital [11, 12]. The positive predictive value (PPV) of hyperthyroidism was calculated in the overall diagnostic group as the number of verified cases of hyperthyroidism divided by the number of patients given a diagnosis in the diagnostic group. The PPV of GD was calculated as the number of verified cases of GD divided by the total number of individuals in the group examined. Analyses were performed using STATA 18.0 (StataCorp, College Station, Texas, USA).

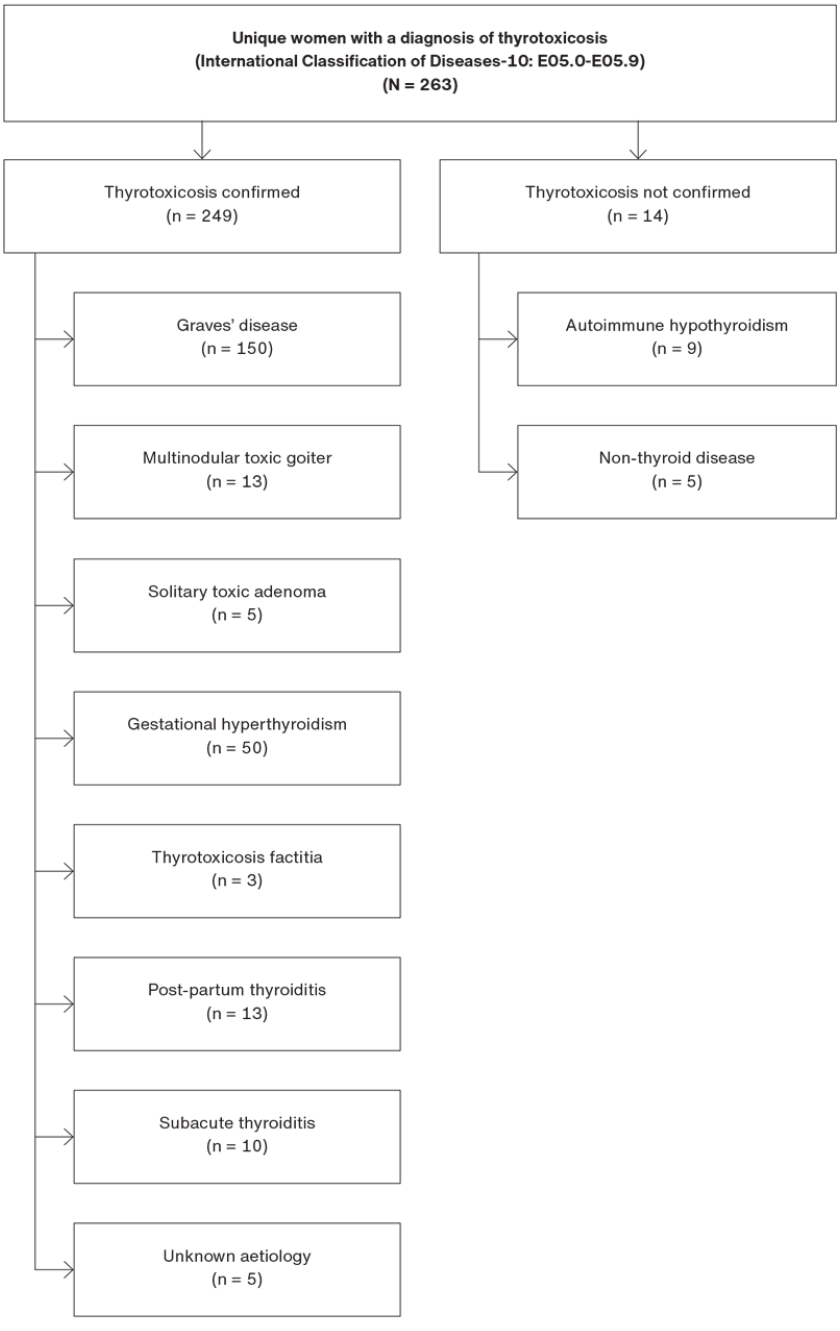
Trial registration: not relevant.

Results

A total of 337 diagnostic codes of thyrotoxicosis (ICD-10: E05.0-05.9) were given to 263 unique women of fertile

age. Thyrotoxicosis was confirmed in 249 of the 263 women, resulting in a PPV for thyrotoxicosis in the overall diagnostic group (ICD-10: E05.0-05.9) of 94.7% (95% **confidence interval** (CI): 91.2-97.1%). Among the 14 misclassified women, the most common cause of misclassification was autoimmune hypothyroidism, seen in 3.4% of the study population (**Figure 1**). Hyperthyroidism was confirmed in 213 women with thyrotoxicosis after excluding those with thyroiditis and thyrotoxicosis factitia, resulting in a PPV of 81.0% (95% CI: 75.7-85.5%) for hyperthyroidism in the overall diagnostic group (ICD-10: E05.0-0.5.9). In confirmed cases, the aetiology of hyperthyroidism was predominantly GD (ICD-10: E05.0) or gestational hyperthyroidism (Figure 1). The third most common cause was MNTG, and the PPV when using the specific diagnostic code (ICD-10: E05.2) was 50.0% (95% CI: 24.7-75.3%).

FIGURE 1 Confirmed diagnoses among women with a diagnosis of thyrotoxicosis in the Danish National Hospital Register.



The PPV of GD within the overall diagnostic group (ICD-10: E05.0-05.9) was 57.0%. This percentage rose to 83.6% when data were restricted to women who also redeemed a prescription of an antithyroid drug (ATD) (**Table 1**). The PPVs were similar when excluding women given a secondary diagnostic code (Table 1). The PPV for GD was above 90% when the specific diagnostic code for GD was used (ICD-10: E05.0) (Table 1). However, not all confirmed cases of GD were detected when the specific diagnostic code was used (Table 1). In total, 52 of the 150 women with confirmed GD were initially given another diagnostic code; for 42 (28.0%), this first diagnostic code was thyrotoxicosis unspecified (ICD-10: E05.9). Subsequently, when only the first diagnostic code assigned to each woman was considered, the total number of women identified with GD was lower than when all codes at any time point were included, but the PPVs were similar (Table 1 and **Table 2**).

TABLE 1 Positive predictive values of Graves' disease for diagnoses registered at any given time point in the Danish National Hospital Register among all women and women prescribed an antithyroid drug.

	All women			Women with a prescription of an ATD		
	n	GD confirmed	PPV (95% CI)	n	GD confirmed	PPV (95% CI)
Diagnosis given at any given time point[a]						
E05 Thyrotoxicosis	263	150	57.0 (50.8-63.1)	140	117	83.6 (76.4-89.3)
E05.0 Thyrotoxicosis with diffuse goitre	124	113	91.1 (84.7-95.5)	94	88	93.6 (86.6-97.6)
E05.9 Thyrotoxicosis unspecified	145	53	36.6 (28.7-44.9)	57	40	70.2 (56.6-81.6)
Primary diagnosis at any given time point[b]						
E05 Thyrotoxicosis	229	129	56.3 (49.6-62.9)	118	98	83.1 (75.0-89.3)
E05.0 Thyrotoxicosis with diffuse goitre	117	107	91.5 (84.8-95.8)	89	83	93.3 (85.9-97.5)
E05.9 Thyrotoxicosis unspecified	110	30	27.3 (19.2-36.6)	33	19	57.6 (39.2-74.5)

ATD = antithyroid drug; CI = confidence interval; GD = Graves' disease; PPV = positive predictive value.
a) All unique women with the diagnostic code registered, regardless of whether it was the 1st diagnosis recorded.
b) All unique women with the diagnostic code registered as a primary diagnosis, regardless of whether it was the 1st primary diagnosis recorded.

TABLE 2 Positive predictive values of Graves' disease for the first individual diagnosis in the Danish National Hospital Register among all women and women prescribed an antithyroid drug.

	All women			Women with a prescription of an ATD		
	n	GD confirmed	PPV (95% CI)	n	GD confirmed	PPV (95% CI)
1st diagnosis given[a]						
E05.0 Thyrotoxicosis with diffuse goitre	108	98	90.7 (83.6-95.5)	83	78	94.0 (86.5-98.0)
E05.9 Thyrotoxicosis unspecified	129	42	32.6 (24.6-41.4)	44	31	70.5 (54.8-83.2)
1st primary diagnosis given[b]						
E05.0 Thyrotoxicosis with diffuse goitre	102	93	91.2 (83.9-95.9)	79	74	93.7 (85.8-97.9)
E05.9 Thyrotoxicosis unspecified	102	26	25.5 (17.4-35.1)	27	16	59.3 (38.8-77.6)

ATD = antithyroid drug; CI = confidence interval; GD = Graves' disease; PPV = positive predictive value.
a) Groups include only the 1st diagnostic code of thyrotoxicosis assigned to each unique woman.
b) Groups include only the 1st primary diagnostic code of thyrotoxicosis assigned to each unique woman.

Among 134 women who were pregnant in the study period, thyrotoxicosis was confirmed in 125, resulting in an overall PPV of thyrotoxicosis of 93.3% (95% CI: 87.6-96.9%). GD was confirmed in 56 pregnant women (**Table 3**), yielding a lower PPV of GD (42.6% (95% CI: 33.3-50.6%)) than the overall findings. However, the PPVs of GD increased when analyses were restricted to women prescribed an ATD (Table 3). Of the 263 women, six (2.3%) received definitive treatment with radioiodine or surgery at some point. Three had MNTG and three had GD.

TABLE 3 Positive predictive values of Graves' disease for diagnoses registered in the period from three months prior to a pregnancy and until one year after the birth (n = 134) or only diagnoses given in pregnancy (n = 87).

	All women			Women with a prescription of an ATD		
	n	GD confirmed	PPV (95% CI)	n	GD confirmed	PPV (95% CI)
Diagnosis given in or around pregnancy[a]						
E05 Thyrotoxicosis	134	56	41.8 (33.3-50.6)	57	44	77.2 (64.2-87.3)
E05.0 Thyrotoxicosis with diffuse goiter	38	33	86.8 (71.9-95.6)	30	28	93.3 (77.9-99.2)
E05.9 Thyrotoxicosis unspecified	92	22	23.9 (15.6-33.9)	26	16	61.5 (40.6-79.8)
Diagnosis given in pregnancy[b]						
E05 Thyrotoxicosis	87	31	35.6 (25.6-46.6)	32	27	84.4 (67.2-94.7)

ATD = antithyroid drug; CI = confidence interval; GD = Graves' disease; PPV = positive predictive value.
a) The period from 3 mos. prior to a pregnancy and until 1 yr after the birth.
b) The period from the 1st day of the last menstrual period to the date of birth.

Discussion

In a Danish regional investigation of women of fertile age, a diagnosis of thyrotoxicosis was verified in 95%. GD was the most common cause, and as a result, the PPV of GD in the overall diagnostic group was 57%, which increased to 84% when combined with ATD prescriptions. The PPV for GD was higher when a specific diagnosis (ICD-10: E05.0) was used, but this approach risked overlooking some cases.

Pregnancy is a vulnerable state, and in this patient group, observational register-based studies are an important source of evidence. The quality of register-based studies relies on the validity of the information provided on exposures and outcomes. In this study, we report an overall 5% rate of misclassification for thyrotoxicosis in the DNHR among women of fertile age. Previously, a misclassification rate of 2% for hyperthyroidism and hypothyroidism was reported by screening 900 medical records [13]. In this previous study, the fracture risk in non-pregnant adult patients with hyperthyroidism was studied, and these patients were identified using the diagnostic codes for GD and MNTG (ICD-10: E05.0 and E05.2) [13].

Our study specifically focused on women of fertile age. We found a higher rate of misclassification for both thyrotoxicosis and hyperthyroidism in the overall diagnostic group (ICD-10: E05.0-05.9), with the main cause of misclassification for hyperthyroidism being thyroiditis in the initial hyperthyroid stage. Another previous study evaluated the validity of the specific diagnostic code for subacute thyroiditis (SAT) in a Danish population and confirmed the risk of misclassifying the thyrotoxic phase of SAT [14]. This was corroborated in our study, in which seven of the 23 women (30.4%) with thyroiditis were subsequently given a specific diagnosis of SAT (ICD-10: E06.1) or postpartum thyroiditis (ICD-10: O90.5) following their initial thyrotoxic diagnosis.

In our study, GD was the primary cause of hyperthyroidism. A recent investigation conducted within the North Denmark Region studied the validity of the specific diagnostic code for GD in adults (males and females) in the DNHR [15]. This study found a PPV for GD of 90% when using the specific diagnostic code (ICD-10: E05.0), identical to the 91% observed in this study specifically among women of fertile age. In the study by Klit et al., the completeness of the diagnostic code was assessed via linkage to blood samples drawn as part of routine care in general practitioners and hospitals and was found to be 50-60% [15]. Completeness could not be assessed in our study, and some women may have been diagnosed by their general practitioner without being referred to the hospital. However, we consider the risk of referral bias low as younger patients are generally referred to the hospital for management, and as it is recommended that women with hyperthyroidism are referred to a specialised endocrine department when a pregnancy is planned or as soon as it is detected [16-18]. Several strategies can be utilised when aiming to identify GD in a register-based study.

We found that the PPV of GD was highest when the specific diagnostic code for GD was used (ICD-10: E05.0) and

that the PPV increased regardless of whether the diagnostic code was combined with information on redeemed prescriptions of an ATD. On the other hand, the PPV for GD did not depend on the order of the diagnosis given and whether the diagnosis was primary or secondary. Whereas the PPV of GD was higher using the specific diagnostic code (ICD-10: E05.0) than when using those of the diagnostic group (ICD-10: E05.0-05.9), it should be emphasised that this approach would increase the likelihood that the women identified actually suffered from GD. On the other hand, some women with GD would be missed as they would be diagnosed with a more nonspecific diagnostic code of thyrotoxicosis. This important fact should inform strategies for the definition of disease and thereby exposure in register-based studies.

Regarding diagnoses in and around pregnancy, a previous study found that the diagnosis was verified in 64.1% of women with an obstetric diagnostic code of thyrotoxicosis (O992C) [19]. In our study, the PPV for GD decreased when the analyses were restricted to diagnoses given in or around pregnancy. This was mainly due to gestational hyperthyroidism along with the thyrotoxic phase of postpartum thyroiditis. However, the PPVs for GD in and around pregnancy increased markedly when the analyses were restricted to women prescribed an ATD, which aligns with the fact that neither gestational hyperthyroidism nor the thyrotoxic phase of postpartum thyroiditis should be treated with ATDs [20]. This emphasises that population-specific characteristics may influence the identification of GD using ICD-10 diagnostic codes, and that, in pregnancy, accurate identification requires combining diagnostic codes with ATD prescriptions.

This was a retrospective cohort study covering public hospitals in the North Denmark Region. This population is expected to be similar to the general Danish population, as national guidelines for the management of hyperthyroidism are in place [18]. Still, the possibility of regional differences needs to be acknowledged. Diagnostic codes from 2017 and 2018 were evaluated, and the validity reported in this study pertains to this specific period. Consequently, changes in diagnostic practices in the subsequent years cannot be ruled out. Our study cohort was consecutively established from the entire North Denmark Region with a low risk of selection bias. Our study entry was the DNHR, which allowed for the calculation of PPV; however, negative predictive values or completeness could not be assessed. The validity of the diagnoses was assessed from review of medical records and was performed by researchers who were not involved in the patient management; thus, we consider any information bias regarding the subtype of thyrotoxicosis to be non-differential.

Conclusions

This is the first study to assess the validity of thyrotoxicosis diagnoses in the DNHR among women of reproductive age, and the results indicate that diagnostic validity is high. The study provides insights into strategies for identifying women with a diagnosis of GD specifically. It provides evidence that a combined approach using diagnostic codes and prescriptions of ATDs is needed to define GD in this population.

Correspondence *Nanna Maria Uldall Torp*. E-mail: nanna.torp@rn.dk

Accepted 23 July 2025

Published 9 September 2025

Conflicts of interest: SLA reports financial support from or interest in the Novo Nordisk Foundation. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. These are available together with the article at ugeskriftet.dk/dmj

References can be found with the article at ugeskriftet.dk/dmj

Cite this as Dan Med J 2025;72(10):A04250296

doi 10.61409/A04250296

REFERENCES

1. Lee SY, Pearce EN. Assessment and treatment of thyroid disorders in pregnancy and the postpartum period. Nat Rev Endocrinol. 2022;18(3):158-171. https://doi.org/10.1038/s41574-021-00604-z
2. Cooper DS, Laurberg P. Hyperthyroidism in pregnancy. Lancet Diabetes Endocrinol. 2013;1(3):238-249. https://doi.org/10.1016/S2213-8587(13)70086-X
3. Carle A, Pedersen IB, Knudsen N, et al. Epidemiology of subtypes of hyperthyroidism in Denmark: a population-based study. Eur J Endocrinol. 2011;164(5):801-809. https://doi.org/10.1530/EJE-10-1155
4. Petersen M, Knudsen N, Carlé A, et al. Thyrotoxicosis after iodine fortification. A 21-year Danish population-based study. Clin Endocrinol (Oxf). 2018;89(3):360-366. https://doi.org/10.1111/cen.13751
5. Torp NMU, Liew Z, Carlé A, et al. Hyperthyroidism in Danish pregnant women during a 20-year period. J Clin Endocrinol Metab. 2023;109(1):e370-e378. https://doi.org/10.1210/clinem/dgad410
6. Kildemoes HW, Sørensen HT, Hallas J. The Danish National Prescription Registry. Scand J Public Health. 2011;39(7 suppl):38-41. https://doi.org/10.1177/1403494810394717
7. Andersen TF, Madsen M, Jørgensen J, et al. The Danish National Hospital Register: a valuable source of data for modern health sciences. Dan Med Bull. 1999;46(3):263-268
8. Andersen SL, Olsen J, Carlé A, Laurberg P. Hyperthyroidism incidence fluctuates widely in and around pregnancy and is at variance with some other autoimmune diseases: a Danish population-based study. J Clin Endocrinol Metab. 2015;100(3):1164-1171. https://doi.org/10.1210/jc.2014-3588
9. Kahaly GJ, Bartalena L, Hegedüs L, et al. 2018 European Thyroid Association guideline for the management of Graves' hyperthyroidism. Eur Thyroid J. 2018;7(4):167-186. https://doi.org/10.1159/000490384
10. Ross DS, Burch HB, Cooper DS, et al. 2016 American Thyroid Association guidelines for diagnosis and management of hyperthyroidism and other causes of thyrotoxicosis. Thyroid. 2016;26(10):1343-1421. https://doi.org/10.1089/thy.2016.0229
11. Harris PA, Taylor R, Thielke R, et al. Research electronic data capture (REDCap) - a metadata-driven methodology and workflow process for providing translational research informatics support. J Biomed Inform. 2009;42(2):377-381. https://doi.org/10.1016/j.jbi.2008.08.010
12. Harris PA, Taylor R, Minor BL, et al. The REDCap consortium: building an international community of software platform partners. J Biomed Inform. 2019;95:103208. https://doi.org/10.1016/j.jbi.2019.103208
13. Vestergaard P, Mosekilde L. Fractures in patients with hyperthyroidism and hypothyroidism: a nationwide follow-up study in 16,249 patients. Thyroid. 2002;12(5):411-419. https://doi.org/10.1089/105072502760043503
14. Kjellerup CR, Thomsen MJ, Torp NMU, et al. Characteristics of patients with subacute thyroiditis. Dan Med J. 2023;70(11):A05230318
15. Klit FØ, Dal J, Andersen SL, et al. Incidence of Graves' disease with validation and completeness of the diagnosis for registry extracts in the Danish National Patient Register. Clin Epidemiol. 2024;16:699-705. https://doi.org/10.2147/CLEP.S484335
16. Carlé A, Pedersen IB, Perrild H, et al. High age predicts low referral of hyperthyroid patients to specialized hospital departments: evidence for referral bias. Thyroid. 2013;23(12):1518-1524. https://doi.org/10.1089/thy.2013.0074
17. Carle A, Laurberg P, Pedersen IB, et al. Mainly the younger hypothyroid patients are referred to hospital - evidence for referral bias. J Clin Epidemiol. 2009;62(4):446-451. https://doi.org/10.1016/j.jclinepi.2008.06.016
18. Dansk Endokrinologisk Selskab. Thyrotoxicose. Dansk Endokrinologisk Selskab, 2024.

https://endocrinology.dk/nbv/thyroideasygdomme/thyrotoksikose/ (Apr 2025)

19. Houmøller AM, Gerlif K, Torp NMU, Andersen SL. Diagnoses of obstetric and postpartum thyroid disease: a Danish validation study. Sci Rep. 2024;14(1):8777 . https://doi.org/10.1038/s41598-024-59636-w

20. Alexander EK, Pearce EN, Brent GA, et al. 2017 guidelines of the American Thyroid Association for the diagnosis and management of thyroid disease during pregnancy and the postpartum. Thyroid. 2017;27(3):315-389. https://doi.org/10.1089/thy.2016.0457

