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Incidence of Graves' Disease with Validation and Completeness of the Diagnosis for Registry Extracts in the Danish National Patient Register

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Purpose: Graves' disease (GD) is one of the most common causes of thyrotoxicosis. It has been proposed to identify incident GD by using the GD-specific code, E05.0, of the 10th revision of the International Classification of Disease (ICD-10) in the Danish National Patient Register (DNPR). We aimed to report the incidence of GD and to investigate the validity and completeness of E05.0 registration using Aalborg University Hospital (AaUH) as a single centre-sample.

Patients and Methods: The study included registry data from 2020 to 2022. The study population (n=2,893) comprised all people (15–99 years) in the catchment area of AaUH (n=244,872) with either positive anti-thyroid stimulating hormone receptor antibodies (TRAb), or registered with a thyroid disease related ICD-10 code E03.0-E07.9, O99.2 or O90.5 at the Department of Endocrinology, AaUH. To identify incident cases, all subjects occurring for the first time in 2020 were excluded (n=2,339). The incident subjects were categorized into a general practice (n=63) or hospital care group (n=491) and underwent GD verification by biochemical tests and thyroid imaging. Validity was evaluated by positive (PPV) and negative (NPV) predictive values and completeness of E05.0 registration was estimated to the total number of verified GD subjects in hospital care only and in overall (groups combined).

Results: One hundred thirty-one incident GD subjects were identified corresponding to an incidence of 26.8 per 100,000/year. E05.0 had a PPV of 90% [95% CI: 81;96] and a NPV of 90% [95% CI: 85;93] to identify incident cases of GD. Completeness was estimated to be 73% [95% CI: 63;82] in hospital care and 50–60% [95% CI: 41;68] in overall.

Conclusion: We report on a similar incidence of GD as previous studies in Denmark. Despite a high PPV, incident cases of GD could not adequately be identified by E05.0 in DNPR due to low completeness. Researchers should rely on biochemical test results to identify incident GD.

Keywords: E05.0, epidemiology, hyperthyroid disease, validation, ICD, DNPR

Introduction

Graves' disease (GD) is one of the most common causes of thyrotoxicosis with incidence rates of 20–50 cases per 100,000 person-years and an estimated prevalence of 1.3–6.4 per 1,000.[1–5] Depending on the severity of the hyperthyroidism, nearly all organ systems can be affected resulting in reduced quality of life, severe morbidity and increased risk of death.[2,6–8] The diagnosis is based on biochemical tests and to various degrees ultrasound and thyroid scintigraphy.[9] The biochemical tests consist of thyroid stimulating hormone (TSH), triiodothyronine (T3), thyroxine (T4) or the free forms of T3 and T4, and the anti TSH-receptor antibody (TRAb) which is the driver of the disease and pathognomonic for GD.[2,3] Ultrasound and thyroid scintigraphy can be used to diagnose the rare cases of TRAb-negative GD.[9] The course of GD is highly heterogeneous from a one-time event with lifelong remission to multiple periods of active disease, remission and frequent relapses, or life-long thyroid hormone substitution therapy after definitive ablative management.[9,10] For most research purposes, only incident or active GD is relevant as patients not undergoing active

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management with sustained normalised thyroid function as well as patients managed with a definitive treatment may be considered cured or unaffected.

Denmark has several national health registries that continuously collect patient data for administrative and quality surveillance purposes. Central is the Danish National Patient Register (DNPR) which links information from every patient interaction, defined as contacts, with public services in the secondary care sector such as hospitals and laboratories.[11,12] The patient contacts are classified according to an appropriate code by the 10th revision of the International Classification of Disease (ICD-10) by a hospital physician.[12,13] Studies have shown a high validity of the coding in DNPR.[14] However, referral rates from general practice to hospital care can become a limiting factor for completeness of registration in DNPR as referral to hospital facilities from a general practitioner is mandatory in non-emergency situations.

Register-based studies have used the GD specific ICD-10 code E05.0 - thyrotoxicosis with diffuse goitre to assemble national cohorts of GD patients.[7,8,15,16] However, the literature is lacking investigation of the validity and completeness of E05.0 in DNPR. Biochemical test results have formerly been used with 100% sensitivity and specificity to automatically identify hyper- and hypothyroidism from registries.[17] Thus, a similar approach could be conducted to identify GD patients for reference. Automatic 3rd generation TRAb immunoassays has a sensitivity and specificity of GD of 97.6% and 99.1%, respectively.[18]

Using Aalborg University Hospital (AaUH), Aalborg, Denmark, as a single centre-sample, we aimed 1) to identify all incident subjects with GD (15–99 years) by specific biochemical test and imaging criteria in the catchment area of AaUH and to report the incidence and 2) to validate and estimate the completeness of the ICD-10 code E05.0 for registry extracts of incident GD in DNPR using the identified GD cohort as reference. We specifically validated E05.0 in patients registered with any thyroid disease at the Department of Endocrinology at AaUH (DEAaUH).

Materials and Methods

Study Population

We performed a combined cross-sectional and retrospective cohort study based on registry data collected between the 1st of January 2020 and the 31st of December 2022 of people aged 15–99 years in the catchment area of AaUH in Northern Jutland, Denmark (municipality codes: 851, 840 and 849). The mean population size for the period was 244,872 inhabitants in the specified age group.[19] We included all people in the area with GD and all people registered with a thyroid disease at DEAaUH in the specified age group based on a TRAb measurement ≥1 IU/L (locally applied cut-off) or a registration at DEAaUH with a thyroid related ICD-10 code E03.0-E07.9, O99.2 or O90.5. All analyses were conducted on incident subjects defined as subjects occurring for the first time in the data sets in 2021 and 2022 by excluding 2020 subjects (n=2,292) from all three years. The incident subjects underwent verification as verified GD (GD-verified) or not GD (GD-not) by biochemical tests and imaging (Table 1) and were categorised either in a general practice (GP) group or if registered at DEAaUH in a hospital care (HC) group.

The hospitals in the North Denmark Region approved the retrospective, observational study design with a waiver of patient informed consent. The Scientific Ethics Committee for the North Denmark Region deemed the study exempt from review. The study was registered according to the General Data Protection Regulation in the North Denmark Region (2021–077).

Data Sources

The included data comprised 1) all TRAb measurements (n=6,141) in the catchment area, 2) all patient contacts at DEAaUH registered with a thyroid related ICD-10 code E03.0-E07.9, O99.2 or O90.5 (n=3,122), 3) all thyroid function tests containing TSH (n=31,199), T3 (n=27,818), T4 (n=28,332), Thyroxine-binding globulin(TBG)-corrected T4 (n=2,934) and free T4 (n=604) for all the included subjects as well as 4) thyroid scintigraphies and ultrasound for relevant HC subjects.

TRAb (ref. value ≥1 IU/L [15–99] yrs.) was analysed by TRAK Human (Thermo scientific, B.R.A.H.M.S GmBH, Hennigsdorf, Germany). TSH (ref. value 0.60–4.5 mIU/L [15–18) yrs., 0.30–4.5 mIU/L [18–99] yrs)., T3 (ref. value 1.3–3.4 nmol/L [15–18) yrs., 1.1–2.5 nmol/L [18–99] yrs)., T4 (ref. value 68–185 nmol/L [15–18) yrs., 60–140 nmol/L [18–99] yrs.) and

Table 1 Verification of Graves' Disease

GD-verified	
Overt TRAb+ hyperthyroidism	TRAb ≥1 IU/L and TSH <0.01 mIU/L.
	TRAb ≥1 IU/L, and TSH below the lower limit in 2 blood samples min. 1 month apart with the first TSH of the two accompanied by T3 and/or T4/TBG corrected T4/free T4 elevated above the upper limits.
Subclinical TRAb+ hyperthyroidism	TRAb ≥1 IU/L, and TSH below the lower limit + normal T3 and T4/TBG corrected T4/free T4 in 2 blood samples min. 1 month apart.
Image-verified TRAb-negative GD	TRAb <1 UI/L, TSH <0.01 + diffuse, symmetrical increased activity on thyroidal Tc-99m-pertechnetat or I-123 scintigraphy and/or diffuse, symmetrical increased blood flow without nodules on ultrasound.
In the event a subject met the criteria for more than one classification, the subject was classified by the first classification met.	
GD-not	Did not meet any of the classifications above.

Notes: The latest biochemical test was regarded as valid in up to 90 days to handle different combinations of dates with only selected thyroid blood tests analysed. All units follow the Système international d'unités.
Abbreviations: GD, Graves' disease; TRAb, anti TSH-receptor antibody; TRAb+, TRAb ≥1 IU/L; TSH, thyroid stimulating hormone; T3, triiodothyronine; T4, thyroxine; TBG, thyroxine-binding globulin.

free T4 (ref. value 10.0–16.0 pmol/L [15–19) yrs., 10.8–16.8 pmol/L [19–99] yrs.) were analysed by Cobas (Roche Diagnostics, Basel Switzerland) until the 15th of February 2022 and thereafter by Alinity (Abbott Diagnostics, Des Plaines, IL, USA). Few GP subjects had TSH, T3 and T4 analysed by Atellica (Siemens Healthineers, Forchheim, Germany). TBG for TBG-corrected T4 (ref. value 70–140 nmol/L [15–99] yrs.) was analysed by TBG Radioimmunoassay (Thermo scientific, B.R.A.H.M.S GmBH, Hennigsdorf, Germany).

Data from the registries were linked by CPR-numbers (unique national identification numbers), which also provided age and sex. To ensure correct identification, all people registered with a temporary CPR-number were excluded (n=15) (Figure 1).

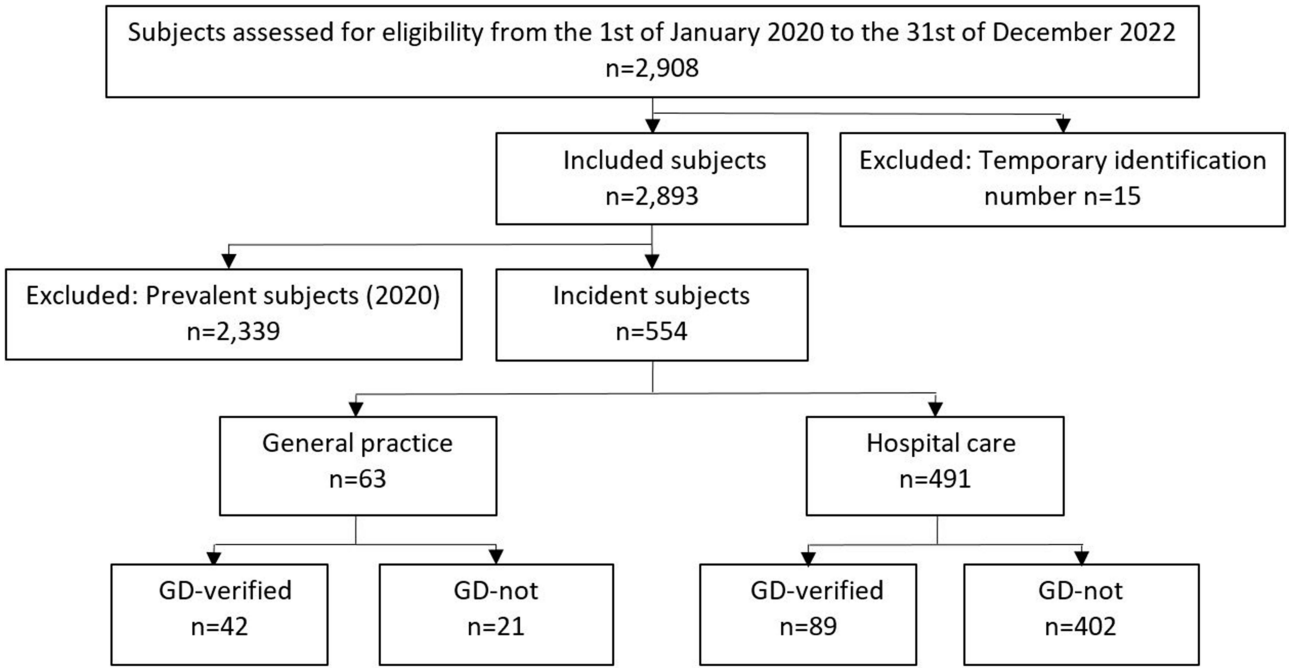

Figure 1 Flowchart of Subject Identification with Biochemical and Thyroid Image Verification of Graves' disease (GD).

Validation and Completeness

Validation of E05.0 was conducted in the HC group of thyroid patients at DEAaUH as general practice was not covered by DNPR. All HC subjects linked with E05.0 registration were labelled E05.0+. E05.0 validity was assessed by positive (PPV) and negative (NPV) predictive values using the specified biochemical test and imaging criteria as the gold standard of GD.[14] Registrations of other thyroid disease codes than E05.0 were summarised for false negative HC subjects.

Completeness was assessed by the sensitivity of E05.0 in identifying GD in the HC group alone as well as in overall (GP and HC combined).[14] The latter was calculated both as a minimal and a maximal overall completeness. The minimal overall completeness was calculated as the proportion of GD-verified subjects registered with E05.0 at DEAaUH to the total number of GD-verified GP and HC subjects in the catchment area. To encompass that this might underestimate the completeness of registration in DNPR, a maximal overall completeness was estimated. This was calculated as the proportion of GD-verified GP subjects with relevant contacts in hospital care facilities in addition to the GD-verified HC subjects registered with E05.0 at DEAaUH to the total number of GD-verified subjects in the catchment area. This incorporated that some GD-verified subjects in the GP group could be registered with E05.0 in DNPR and not at DEAaUH if they had one or more relevant contacts with other hospital care facilities. The contacts were regarded as relevant if TRAb or thyroid function tests were measured.

Statistical Analysis

Stata (StataCorp. 2021. Stata Statistical Software: Release 17. College Station, TX: StataCorp LLC) was used for data management and statistical calculations. Normality was tested by histograms and QQ-plots. Normally distributed data were described by means and standard deviations (SD) and non-normally distributed data by median and interquartile range [IQR]. For inferential statistics, a Student's *t*-test was used when data were normally distributed or when sample sizes were >30 applying the central limit theorem. Otherwise, a corresponding non-parametric Mann–Whitney *U*-test was used. Ninety-five percent confidence intervals were reported as [95% CI:]. Loss to follow-up could not be actively managed within the data extracts.

Incidence was calculated as the weighted averages of yearly incidence proportions of 2021 and 2022 to the background population in the catchment area.

Results

A total of 2,908 unique subjects were identified in the data extracts and screened for eligibility by the inclusion criteria. Fifteen were excluded due to temporary CPR-numbers. By excluding 2020-subjects as prevalent cases, 554 subjects were identified as incident cases (Figure 1). Of the incident cases were 131 verified with GD. This corresponded to an incidence of 26.8 per 100,000/year.

The incident GD-verified subjects were 44 ± 15 years and 82% were women. Median TSH was fully suppressed and T3 and T4 elevated (Table 2). Forty-two of the GD-verified subjects were identified in general practice with 38 having overt TRAb+ hyperthyroidism and 4 having subclinical TRAb+ hyperthyroidism. Nineteen (45%) of them had one or more relevant contacts with the hospital care sector, but not DEAaUH. The other 89 GD-verified subjects were identified in hospital care with 87 having overt TRAb+ hyperthyroidism, 2 having subclinical TRAb+ hyperthyroidism and 0 having image-verified TRAb-negative hyperthyroidism. No clinical relevant differences existed between the GD-verified subjects in general practice and hospital care (Table 2).

Validity and Completeness

Using biochemical test and imaging criteria as reference standard, E05.0 had a PPV of 90% [95% CI: 81;96] and a NPV of 90% [95% CI: 85;93]. The 10% false positive subjects registered with E05.0 were characterized by negative TRAb (median 0.5 [0.3;0.9] IU/L) and normal TSH, T3 and T4, and thus had no biochemical evidence of hyperthyroidism or GD (Table 3). The GD-verified subjects not registered with E05.0 in hospital care (27%) were missing proper registration despite having clear biochemical evidence of GD with a median TRAb of 5.6 [3.2;11.0] IU/L, a fully suppressed TSH

Table 2 Demographical and Biochemical Overview of Incident Subjects with Verified Graves' Disease

GD-verified	Total	GP	HC	Mean Diff
N Subjects	131	42	89	47
Sex - female (%)	82 [CI: 75;88]	83 [CI: 72;94]	82 [CI: 72;89]	0 [CI: −15;12]
Mean Age (years)	44 ± 15	41 ± 17	45 ± 14	4 [CI: −2;9]
Median TRAb (IU/L)	5.8 [2.8;11.0]	3.6 [2.2;12.0]	6.9 [3.5;11.0]	3.1 [CI: −0.9;7.1]
Median TSH (mIU/L)	0.01 [0.01;0.01]	0.01 [0.01;0.01]	0.01 [0.01;0.01]	0.01 [CI: −0.02;0.00]
Median T3 (nmol/L)	3.9 [2.7;5.7]	3.5 [2.0;5.8]	4.0 [2.8;5.6]	0.1 [CI: −0.7;1.0]
Median T4 (nmol/L)	156 [124;204]	154 [121;194]	156 [128;205]	3 [CI: −17;23]

Notes: Cells are reported by median ± standard deviation, median [interquartile range] or mean [95% confidence interval]. All units follow the Système international d'unités.
Abbreviations: GD-verified, subjects verified with Graves' disease; GP, general practice group; HC, hospital care group; Mean Diff, GP minus HC; CI, 95% confidence interval; TRAb, anti TSH-receptor antibody; TSH, thyroid stimulating hormone; T3, triiodothyronine; T4, thyroxine.

Table 3 Comparison of Incident Subjects in Hospital Care with Verified Graves' Disease

	GD-verified HC	E05.0+	True positive	False positive	False negative
N subjects	89	72	65	7	24
Sex -female (%)	82 [CI: 72;89]	85 [CI: 74;91]	83 [CI: 72;90]	100	79 [CI: 57;91]
Mean Age (years)	45 ± 14	44 ± 15	43 ± 14	55 ± 22	50 ± 15
Median TRAb (IU/L)	6.9 [3.5;11.0]	7.0 [2.8;11.0]	7.5 [3.3;11.0]	0.5 [0.3;0.9]	5.6 [3.2;11.0]
Median TSH (mIU/L)	0.01 [0.01;0.01]	0.01 [0.01;0.01]	0.01 [0.01;0.01]	0.44 [0.07;2.10]	0.01 [0.01;0.01]
Median T3 (nmol/L)	4.0 [2.8;5.6]	2.3 [1.8;3.4]	2.5 [1.8;3.5]	1.7 [1.6;2.0]	3.3 [2.5;4.1]
Median T4 (nmol/L)	156 [128;205]	111 [84;149]	111 [81;149]	94 [88;97]	156 [120;204]

Notes: Comparison of demographical and biochemical variables of GD-verified HC and E05.0+ subjects at the time of classification, labelling or as close to in ± 90 days. E05.0+ is referenced against GD-verified in true positive, false positive and false negative. Each subject was represented only one time within each cell but could be represented multiple times between cells. Cells are reported by median ± standard deviation, median [interquartile range] or mean [95% confidence interval]. All units follow the Système international d'unités.
Abbreviations: GD-verified HC, subjects in hospital care verified with Graves' disease; E05.0+, subjects linked with a E05.0 registration in the Danish National Patient Register; CI, 95% confidence interval; TRAb, anti TSH-receptor antibody; TSH, thyroid stimulating hormone; T3, triiodothyronine; T4, thyroxine.

and a high T3 (median 3.3 [2.3;4.1] nmol/L) (Table 3). They were instead registered with E05.9 - Thyrotoxicosis, unspecified (n=18; 75%), E05.2 - Thyrotoxicosis with toxic single thyroid nodule (n=4; 17%) and E05.8 - Other thyrotoxicosis (n=1; 4%).

HC completeness was 73% [95% CI: 63;82] over a 2-year period. Minimal and maximal overall completeness was estimated to 50% [95% CI: 41;58] and 60% [95% CI: 51;68], respectively, with up to 64% of the GD-verified subjects not registered with E05.0 being in the GP group.

Discussion

We estimated the incidence of GD and evaluated the validity and completeness of E05.0 in DNPR by identifying the census of GD patients in the catchment area of AaUH. We identified the GD patients in blood sample register data through automatic criteria-based identification as have been done with success in hyper- and hypothyroidism.[17] This was combined with highly sensitive and specific TRAb measurements for the diagnosis of GD.[18] The identified GD subjects

had a female to male ratio of 5:1 and a mean age of 44 ± 15 years closely resembling the expected demographics of GD.[3,4] The incidence of GD was estimated to be 26.8 per 100,000/year. This was a little higher than the previously estimated standardised incidence rate of 22.2 per 100,000/year by Petersen et al for the same catchment area.[1] The overall standardised incidence rate of GD in Denmark has formerly been estimated by Carlé et al to 30.7 per 100,000 person years from 1997–2000.[4] Compared to our study 20 years later the incidence seemed stationary or mildly declining. The incidence in our study fitted with the incidences reported from other countries between 20 and 50 cases per 100,000 person-years with most reports around 20–30.[3]

Incident E05.0 had a PPV of 90% of true GD. This matched the PPVs of other thyrotoxic diseases in DNPR of 62% to 97.5% as reported by Houmøller et al and Kjellerup et al as well as of endocrine diseases in general as reported by Schmidt et al of 54% to 96%.[14,20,21] It did fall short of a 2% misclassification proportion found in the study by Vestergaard and Mosekilde.[22] However, in their study, misclassification might have been less likely by design, as the proportion was estimated for thyroid diseases collectively including unspecific coding.

In estimating completeness, it was unexpected that 27% of GD subjects within hospital care were lacking proper E05.0 registration despite having clear biochemical evidence of GD. They were instead registered with an unspecified coding of thyrotoxic disease or other thyroid disease. This suggested that GD registration practice did not stringently use E05.0 even in a department specialising in endocrine disorders. Due to the low overall completeness of 50–60%, researchers of GD should be aware of discrepancies in population characteristics between the patient population registered with E05.0 and the true GD patient population. The population registered with E05.0 had a similar age and sex distribution as well as TRAb levels as the true GD population. However, the E05.0 population had a higher mean TSH (mean diff. 0.37 [95% CI: 0.16;0.59] mIU/L), lower T3 (mean diff. −1.6 [95% CI: −2.2;-1.0] nmol/L) and lower T4 (mean diff. −44 [95% CI: −60;-29] nmol/L) than the verified GD population. Researchers should, thus, rely on biochemical tests rather than E05.0 to identify incident GD subjects. Adding data on thyroid scintigraphies and ultrasound did not add information as no image-verified, TRAb-negative patients were identified.

High overall completeness of E05.0 was limited by the 18–32% of incident GD subjects who were only seen in general practice despite general recommendations of referral to hospital care at the first biochemical evidence of thyrotoxicosis.[23] Aside from a 3.1 IU/L lower mean TRAb, they were no different in age, sex distribution or thyroid function tests compared to the GD subjects in hospital care. Demographics and biochemical tests could thus not readily explain the difference in referral. Compared to the results of a study by Carlé et al of referral patterns around 2000, referral seemed, however, to have improved.[24] Carlé et al found that up to 52% of GD patients were not referred from primary to hospital care.[24] In contrast to our findings, they also found that lower T3 and T4 as well as higher age were predictors of less referral.

The study was limited by a short observation period. This resulted in less control with appropriate exclusion of prevalent cases of GD with a relapse in 2021 or 2022 years after the initial onset. These subjects would appear as incident in the data sets and be included in the analyses.

Conclusion

We identified by register data of biochemical tests and thyroid imaging all incident GD subjects in the catchment area of Aalborg University Hospital, Denmark, between 2021 and 2022. This corresponded to an incidence of GD of 26.8 per 100,000/year. We also investigated the GD specific ICD-10 code E05.0 for register extracts in the Danish National Patient Register. Despite excellent positive and negative predictive values of 90%, incident cases of GD could not adequately be identified by E05.0 due to low completeness in hospital care and overall completeness of 73% and 50–60%, respectively. The population identified by E05.0 differed phenotypically from the true GD population as the E05.0 population had milder biochemical test results. Researchers should, thus, rely on biochemical tests to identify GD subjects. Adding thyroid imaging to biochemical test data did not improve results.

Disclosure

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