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Estimating incidence and case fatality of thyroid storm in Germany between 2007 and 2017: A claims data analysis

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Abstract

Background: Given the paucity of epidemiological studies on thyroid storm, we aimed to estimate the incidence rate and case fatality of thyroid storm in Germany based on a large claims database.

Methods: Using the German Pharmacoepidemiological Research Database (GePaRD) we identified patients with at least one inpatient discharge diagnosis of thyroid storm (International Statistical Classification of Diseases and Related Health Problems, 10th revision, German modification; ICD-10-GM E05.5) between 2007 and 2017 and calculated age-standardized and age-specific incidence rates in males and females (no age restriction). We defined deaths occurring within 30 days of the diagnosis as thyroid storm-associated and determined case fatality by sex and age group. Point estimates were reported with 95% confidence intervals (CI).

Results: We identified 1,690 patients with an incident diagnosis of thyroid storm. Of these, 72% were females (n=1,212). The mean age was 60 years (standard deviation: 18.6 years). The age-standardized incidence rate per 100,000 persons per year was 1.4 (95% CI 1.2 to 1.7) in females and 0.7 (95% CI 0.5 to 0.9) in males. In females ≤60 and >60 years of age, the incidence rate was 0.9 (95% CI 0.9 to 1.0) (males: 0.4 (95% CI 0.3 to 0.4)) and 2.7 (95% CI 2.5 to 2.9) (males: 1.7 (95% CI 1.5 to 1.9)), respectively. The case fatality of thyroid storm was 1.4% (95% CI 0.6% to 2.8%) in females ≤60 years and 10.9% (95% CI 8.6% to 13.7%) in females >60 years. In males, the case fatality was 1.0% (95% CI 0.2% to 4.0%) in those aged ≤60 years and 16.7% (95% CI 12.6% to 21.7%) in those >60 years.

Conclusions: Incidence rates of thyroid storm were markedly higher in females than in males and were three times higher in persons >60 years compared to younger age groups. Case fatality was below 2% in persons aged ≤60 years and markedly higher in older persons (males: 17 times, females: 8 times).

Background

Thyroid storm is a rare and life-threatening condition characterized by an acute exacerbation of thyrotoxicosis (elevated free triiodothyronine or free thyroxine and suppressed thyrotropin) with severe clinical symptoms. It often results in multi-organ failure involving one or more organ systems such as the central nervous, cardiac, hepatic, pulmonary, respiratory, digestive, and gastrointestinal excretory systems. The diagnosis is based on clinical signs using scoring classifications suggested by Burch and Wartofsky[1] or by the Japan Thyroid Association.[2] Surgeries, infections, trauma, amiodarone use, and acute iodine exposures (by radiocontrast agents) have been identified as the most common potential triggers of thyroid storm in a hospital setting.[3,4] The underlying conditions causing thyroid storm include Graves' disease, toxic multinodular goiter, and solitary toxic adenoma.[5,6]

Globally, only three studies have reported on the epidemiology of thyroid storm using population-based databases. The incidence rate of thyroid storm has been estimated to range from 0.20 to 0.76 per 100,000 persons per year.[2,7,8] Females have been reported to be more susceptible to this condition (female-to-male ratio: 3:1), as were individuals >40 years of age.[8] Four studies have provided estimates for the case fatality of thyroid storm. These estimates, which were mostly based on small sample sizes, varied between 8% (2 out of 25 patients),[9] 10% (134 out of 1324 patients),[10] 11% (38 out of 356 patients),[2] and 25% (7 out of 28 patients).[11]

In Germany, the current knowledge on the incidence and case fatality of thyroid storm is limited to the results of a questionnaire-based retrospective multi-center study conducted in 1992.[12] However, interpretation of this study is difficult as neither the underlying method is clearly described nor it is clear whether the study population was representative for Germany. Apart from this, only case studies published between 1970 and 1989 are available from Germany.[13-15] Given the general lack of descriptive epidemiological studies on thyroid storm, we aimed to estimate the incidence rate and case fatality of thyroid storm using data from a large German claims database.

Materials and Methods

Data source

We used the German Pharmacoepidemiological Research Database (GePaRD), which contains claims data from four statutory health insurance providers in Germany.[16] This database includes approximately 25 million persons who have been insured with one of the four health insurance providers since 2004 or later.[17] GePaRD covers approximately 20% of the general German population and it includes persons from all geographical regions of Germany. Diagnoses in GePaRD are coded according to the International Statistical Classification of Diseases and Related Health Problems, 10th revision, German Modification (ICD-10 GM). For this study, we used data from the years 2007 to 2017.

The use of GePaRD data for this study was approved by all four health insurance providers as well as the German Federal Office for Social Security and the Senator for Health, Women and Consumer Protection in Bremen as their responsible authorities. Informed consent for studies based on claims data is required by law unless obtaining consent appears unacceptable and would bias results, which was the case in this study. According to the Ethics Committee of the University of Bremen studies based on GePaRD are exempt from institutional board review. The study was performed according to the institutional guidelines of the Leibniz Institute for Prevention Research and Epidemiology – BIPS. All data was analyzed anonymously and the authors did not have access to identifying information.

Around 90% of the general population in Germany are covered by statutory health insurances.[18] The main characteristics of the German health insurance system are uniform access to all levels of care and free choice of providers. It has been shown that the data in GePaRD is representative of the German population regarding drug prescriptions, hospital admissions and hospital diagnoses.[19,20]

Study population and study design

To identify cases with incident thyroid storm, we considered all patients (irrespective of age) with at least one inpatient diagnosis code (main or secondary hospital discharge diagnosis) of thyroid storm (ICD-10 GM E05.5) within the study period (2007–2017). The admission date of the hospital stay for which “thyroid storm” has been coded as discharge diagnosis. was assigned as the index date (i.e., date of first diagnosis). We excluded patients with missing information on sex or gender diverse, age, and those who do not live in Germany. Furthermore, we excluded patients who were not continuously insured for at least one year prior to the index date. We used this exclusion criterion because shorter pre-observation periods would not allow to assess whether patients were newly diagnosed or still under treatment for a former diagnosis of thyroid storm. Patients were followed until end of the study period (i.e., 31 December 2017), end of the insurance period or death, whichever occurred first. We also determined whether patients had more than one inpatient diagnosis of thyroid storm during the study period. Patients dying within 30 days following an inpatient diagnosis of thyroid storm were defined as cases of death associated with thyroid storm. In sensitivity analyses, the maximum permissible time period from the date of diagnosis to the date of death was varied (15 days, 45 days).

To determine the incidence rate of thyroid storm for each calendar year between 2007 and 2017, a denominator was required as well. For the denominator, we included all individuals represented in GePaRD in the respective calendar year, excluding those with missing information on sex or gender diverse, age, and those who do not live in Germany as well as those with continuous insurance of less than one year before the first day they were insured in the respective calendar year.

Data analysis

We stratified the patients with thyroid storm by sex and described them regarding age at index date, type of admission and the number of inpatient diagnoses of thyroid storm during the study period. Type of admission is an information recorded by hospitals that distinguishes between admission for “usual care” vs. admission for “emergency care” vs. “others”. Analogously, we described the cases of death associated with thyroid storm.

In addition, we assessed relevant comorbidities coded in the year prior to the incident diagnosis of thyroid storm for all patients with thyroid storm and additionally for the subgroup of patients dying within 30 days after the diagnosis. The comorbidities were defined based on algorithms that combine information from diagnoses codes, procedures and drug dispensations.[21] We also examined concurrent diagnoses i.e., discharge diagnoses of the hospital stay coded in addition to thyroid storm.

We calculated incidence rates stratified by sex and age group for each calendar year between 2007 and 2017, using the number of incident cases with thyroid storm of the respective calendar year as the numerator and the number of persons in GePaRD (see "study population and study design") as the denominator. To calculate overall incidence rates for the whole study period (2007–2017), we summed up the numerators and the denominators of each calendar year. We determined both crude and age-standardized incidence rates per 100,000 persons per year with corresponding 95% confidence intervals based on exact Poisson confidence limits. Age-standardized incidence rates were calculated using the age distribution of the German population in 2017 as standard.[22]

We also calculated the case fatality of thyroid storm for each calendar year by considering the number of thyroid storm-associated deaths in the respective calendar year as the numerator and the total number of patients with a thyroid storm diagnosis (only incident diagnosis) identified in the same calendar year as the denominator. The corresponding 95% confidence intervals were calculated based on the Wilson score method.[23]

We performed all analyses using SAS 9.4 (SAS Institute, Inc., Cary, North Carolina, USA).[24]

Results

Patient characteristics

We identified 1,690 patients with an incident diagnosis of thyroid storm during the study period. Two patients were excluded due to missing information on sex or gender diverse, five patients because

they did not live in Germany and 83 patients were excluded because they were not continuously insured for at least one year prior to the index date (Supplementary figure 1). As shown in Table 1, mean age was 60 years (standard deviation: 18.6 years) and 77% (1,310/1,690) of patients were ≥ 46 years of age. The female-to-male ratio in the age groups <18 years, 18 to 30 years, 31 to 45 years, 46 to 60 years, 61 to 70 years, 71 to 80 years, and >80 years was 2.8, 4.2, 3.7, 2.5, 2.1, 1.9, and 2.9, respectively. In about 38% (635/1,690) of patients, the type of admission to the hospital was coded as "usual care". In 6.7% (114/1,690) of patients, there was more than one inpatient diagnosis of thyroid storm during the study period. The characteristics of these patients were similar to those of the overall group of thyroid storm patients (see Supplementary table 1). The median time between the first and second inpatient diagnosis of thyroid storm was 25 days with an interquartile range from 8 to 57.

As shown in Table 2, there were 125 cases of death associated with thyroid storm. Mean age at death was 77 years (standard deviation: 11.7 years) and 92% of the deceased patients were >60 years. In a sensitivity analysis using a maximum permissible time period of 14 days (instead of 30 days) between the date of diagnosis and the date of death, the number of cases decreased to 87. The number of cases increased to 166 when a time period of 45 days was used (see Table 6).

As shown in Table 3, 66% (1,123/1,690) of all thyroid storm patients and 87% (109/125) of those who died had any of the selected comorbidities. In 48% (805/1,690) of all patients had any medical treatment for cardiovascular disease. Other common comorbidities were medically treated diabetes (12% of all patients [201/1,690]) and obesity (14% of all patients [228/1,690]). Graves' disease was coded in 4% (67/1,690) of all patients. Most comorbidities were more common in the subgroup who died as compared to all patients. For example, prevalence in those who died was more than twice as high as compared to all patients for several cardiovascular comorbidities such as acute myocardial infarction (5% [6/125] vs. 2% [38/1,690]), dementia (13% [16/125] vs. 5% [83/1,690]) and chronic obstructive pulmonary disease (15% [19/125] vs. 7% [119/1,690]). With regard to hospital discharge diagnoses coded in addition to the thyroid storm diagnosis, 41% (688/1,690) of all patients and 65%

(81/125) of those who died had a code for atrial fibrillation and flutter. Heart failure was coded in 27% (456/1,690) of all patients and 57% (72/125) of those who died. Most other conditions were also coded more often in those who died (Table 4). For the results presented in Tables 3 and 4, a stratification by sex is provided in Supplementary tables 2 and 3 and a restriction to patients older than 60 years is provided in Supplementary tables 4 and 5.

Incidence rates of thyroid storm

The overall age-standardized incidence rate of thyroid storm was 1.1 (95% CI 0.9 to 1.3) per 100,000 persons per year. In females and males, the age-standardized incidence rate was 1.4 (95% CI 1.2 to 1.7) and 0.7 (95% CI 0.5 to 0.9) per 100,000 persons per year, respectively. Stratification of the age-standardized incidence rates by calendar year showed little variation over time from 2010 to 2017 with overlapping confidence intervals across the calendar years (Figure 1). Age-standardized and crude incidence rates were almost identical (see Supplementary figure 2). As shown in Table 5, the incidence rate (per 100,000 persons per year) increased with age. It was lowest in patients aged <18 years (females: 0.1 (95% CI 0.1 to 0.2), males: 0.04 (95% CI 0.01 to 0.1)) and highest in those aged >80 years (females: 4.0 (95% CI 3.4 to 4.7), males: 2.6 (95% CI 1.9 to 3.4)).

Case fatality of thyroid storm

As shown in Table 6A, case fatality of thyroid storm varied by sex (lower in females than in males) and was higher in older than in younger age groups. The overall case fatality was 6.3% (95% CI 5.0% to 7.8%) in females and 10.3% (95% CI 7.8% to 13.3%) in males. In females, it ranged between 1.7% and 24.3% across age groups; in males, it ranged between 0.9% to 31.0%. Both males and females >80 years of age showed the highest case fatality. A similar pattern by age and sex was observed in sensitivity analyses using different time periods for the definition of thyroid storm-associated deaths (15 days, 45 days; see Table 6B, 6C). The overall case fatality increased was 7.8% (95% CI 6.5% to 9.5%) in females and 14.9% (95% CI 11.9% to 18.3%) in males when the maximum permissible time period was extended from 30 days to 45 days. Figure 2 shows case fatality in men and women

stratified by calendar year between 2010 and 2017 with largely overlapping confidence intervals across years.

Discussion

To the best of our knowledge, this is the first study reporting population-based data on incidence and case fatality of thyroid storm in Germany. Our findings suggest that every year there was about one case of thyroid storm per 100,000 persons in Germany during the study period (2007–2017). However, incidence strongly varies with age and sex. In our study, the age-standardized incidence rate of thyroid storm was two times higher in females than in males (1.4 vs. 0.7 per 100,000 persons per year) and it was three times higher in persons >60 years compared to younger individuals. For example, in females >60 years of age, the incidence rate was 3 per 100,000 persons per year. Also, case fatality of thyroid storm strongly varied with age and sex. While it was below 2% in persons aged ≤60 years, it was 17% in males and 11% in females > 60 years of age.

Our finding that the age-standardized incidence rate of thyroid storm in females was twice as high as in males is consistent with other population-based studies conducted in Japan, Taiwan, and the United States.[2,7,8] In these studies, about two thirds to three quarters of all cases with thyroid storm occurred in females. This is consistent with the fact that also certain risk factors of thyroid storm are more common in females. For example, for Graves' disease a female-to-male ratio of 5:1 has been reported.[25] The overall incidence rate observed in our study (one per 100,000 persons per year) was higher than in the above-mentioned studies. For Japan, an incidence rate of 0.2 cases per 100,000 persons per year was reported based on data from 2004-2008.[2] In the study from Taiwan using data from 2005–2014, an incidence rate of 0.6 cases per 100,000 persons per year was estimated.[7] In the study from the USA, the incidence rate varied from 0.6 to 0.8 per 100,000 persons per year over the 10-year study period (2004–2013).[8] A higher incidence of thyroid storm in Germany may be plausible given that Germany used to be a region with mild-to-moderate iodine deficiency. Accordingly, Germany used to have a high prevalence of thyroid disorders that increase the risk of thyroid

storm.[26] Even though the iodine fortification program implemented in 1993 has substantially improved the iodine status in Germany,[27] it may still differ from the status in countries such as Japan or Taiwan.[28] However, caution is needed for the interpretation of between-country differences since they could also result from different data sources and coding practices.

In our study, case fatality of thyroid storm strongly varied with age. A study from Japan investigating factors associated with death from thyroid storm also reported a seven times higher risk of death among patients with thyroid storm aged 60–79 and a twelve times higher risk among those aged ≥80 years compared to patients >20 years of age.[10] A higher risk of death was reported for patients developing cardiovascular complications[29] and also for those with cardiovascular comorbidities.[7,10] We observed that concomitant cardiovascular events and cardiovascular comorbidities as well as other comorbidities were markedly more common in patients >60 years than in all patients, which may explain the higher case fatality. The study from Japan also reported a higher risk of death among male compared to female patients even though this difference was not statistically significant.[10] In our study, we observed a higher case fatality in older males than in older females. Given that other studies did not report absolute values of case fatality stratified by age and sex, a direct comparison to our findings is not possible. Furthermore, the absolute value depends on the definition of case fatality. In our base case analysis, we defined patients dying within 30 days following an inpatient diagnosis of thyroid storm as cases of death associated with thyroid storm. Our sensitivity analyses illustrated that case fatality gradually increased when the permissible time period between the date of diagnosis and the date of death was extended. In agreement with this, a study from Taiwan also found an increase in case fatality when this time period was increased from 14 days to 90 days.[7]

Considering the severe complications and potential fatality of thyroid storm, the extent to which and how it is preventable is a key question. Regarding underlying conditions, most patients with thyroid storm present either a subclinical hyperthyroidism or irregular use of antithyroid drugs with previously diagnosed hyperthyroidism.[2,30,31] With respect to subclinical hyperthyroidism, patient screening for thyroid disorders before major medical procedures, particularly in those >60 years of

age, could play a significant role in preventing thyroid storm. This would be particularly relevant in regions with former or current iodine deficiency. For patients with previously diagnosed hyperthyroidism stopping treatment with antithyroid drugs, the European Thyroid Association recommends regular follow-up including medical examination and thyroid function tests.[32] This would be beneficial in controlling the blood thyroid level and lower the risk of developing thyroid storm in these patients.[32] In 38% of patients with thyroid storm in our study, the type of admission was coded as "inpatient, usual care". If coding is correct this would imply that these patients likely developed thyroid storm after their admission to the hospital. Thyroid storm in these patients may have been potentially preventable if a screening for thyroid disorders had occurred in the hospital prior to exposure to a triggering factor.

Our study has several strengths and limitations. The large claims database allowed us to estimate population-based incidence and case fatality of this rare condition without non-responder or recall bias. The almost identical age-standardized and crude incidence rates in our study (see Supplementary figure 1) suggests a lack of relevant differences between the age distribution in GePaRD and the German population as a whole. Our study also allowed us to investigate incidence and case fatality of thyroid storm stratified by age and sex, which was insufficiently addressed in previous studies. Furthermore, our database also contains information on other diseases, so we could describe comorbidities and concomitant diagnoses in patients with thyroid storm. There are also limitations to be considered in the interpretation of our results. Our study used health insurance claims data, i.e., data collected for reimbursement rather than for research purposes. The quality of such data may not be optimal. This applies especially to diagnoses coded in the outpatient setting as medical records and laboratory parameters for confirmation of thyroid storm diagnoses based on diagnostic criteria (i.e., Burch and Wartofsky Score[1] or score from the Japan Thyroid Association[2]) are not available in GePaRD. In our study, however, we only considered hospital discharge diagnoses which are considered to have a very high validity due to strict coding guidelines and regular audits. To describe comorbidities, we used algorithms combining different types of information to maximize

validity of the definitions. We could not describe the treatment during thyroid storm because GePaRD does not contain information on medications dispensed in the hospital (except for certain very expensive drugs, which are not relevant for the treatment of thyroid storm). While our study focused on describing population-based incidence and case fatality of thyroid storm in Germany, it will also be interesting to investigate risk factors of thyroid storm in future analyses using a study design that is appropriate for this research question. Also, exploring factors that may explain the observed differences in case fatality between males and females in future studies would be of value.

In conclusion, our study found incidence rates of thyroid storm to be markedly higher in females than in males and three times higher in persons >60 years compared to younger age groups. Case fatality was below 2% in persons aged ≤60 years and markedly higher in older persons (males: 17 times, females: 8 times).

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Authors' disclosure statement

AT, KP and UH are working at an independent, non-profit research institute, the Leibniz Institute for Prevention Research and Epidemiology – BIPS. Unrelated to this study, BIPS occasionally conducts studies financed by the pharmaceutical industry. Almost exclusively, these are post-authorization safety studies (PASS) requested by health authorities. The design and conduct of these studies as well as the interpretation and publication are not influenced by the pharmaceutical industry. The study presented was not funded by the pharmaceutical industry and was performed in line with the ENCePP Code of Conduct. TI and HV have no conflict of interest to disclose.

Authors' contribution statement

AT: conception and design of the research; formal analysis; writing – original draft. KP: conception and design of the research; writing – review and editing. TI: writing – review and editing. HV: writing – review and editing. UH: conception and design of the research; review and editing; supervision. All authors have read and approved the manuscript.

References

1. Burch HB, Wartofsky L. Life-threatening thyrotoxicosis. Thyroid storm. Endocrinol Metab Clin North Am 1993;22(2):263-77
2. Akamizu T, Satoh T, Isozaki O, et al. Diagnostic criteria, clinical features, and incidence of thyroid storm based on nationwide surveys. Thyroid 2012;22(7):661-79, doi:10.1089/thy.2011.0334
3. Pokhrel B, Aiman W, Bhusal K. Thyroid Storm. In: StatPearls. StatPearls Publishing, Copyright © 2020, StatPearls Publishing LLC.: Treasure Island (FL); 2020.
4. Nayak B, Burman K. Thyrotoxicosis and thyroid storm. Endocrinol Metab Clin North Am 2006;35(4):663-86, vii, doi:10.1016/j.ecl.2006.09.008
5. Bourcier S, Coutrot M, Kimmoun A, et al. Thyroid storm in the ICU: A retrospective multicenter study. Critical Care Medicine 2020;48(1):83-90, doi:10.1097/CCM.0000000000004078
6. Isozaki O, Satoh T, Wakino S, et al. Treatment and management of thyroid storm: analysis of the nationwide surveys: The taskforce committee of the Japan Thyroid Association and Japan Endocrine Society for the establishment of diagnostic criteria and nationwide surveys for thyroid storm. Clinical Endocrinology 2016;84(6):912-918, doi:10.1111/cen.12949
7. Kornelius E, Chang KL, Yang YS, et al. Epidemiology and factors associated with mortality of thyroid storm in Taiwan: a nationwide population-based study. Intern Emerg Med 2020, doi:10.1007/s11739-020-02445-6
8. Galindo RJ, Hurtado CR, Pasquel FJ, et al. National trends in incidence, mortality, and clinical outcomes of patients hospitalized for thyrotoxicosis with and without thyroid storm in the United States, 2004-2013. Thyroid 2019;29(1):36-43, doi:10.1089/thy.2018.0275
9. Angell TE, Lechner MG, Nguyen CT, et al. Clinical features and hospital outcomes in thyroid storm: a retrospective cohort study. J Clin Endocrinol Metab 2015;100(2):451-9, doi:10.1210/jc.2014-2850
10. Ono Y, Ono S, Yasunaga H, et al. Factors associated with mortality of thyroid storm: Analysis using a national inpatient database in Japan. Medicine (Baltimore) 2016;95(7):e2848-e2848, doi:10.1097/MD.0000000000002848
11. Swee du S, Chng CL, Lim A. Clinical characteristics and outcome of thyroid storm: a case series and review of neuropsychiatric derangements in thyrotoxicosis. Endocr Pract 2015;21(2):182-9, doi:10.4158/ep14023.Or
12. Lederbogen S, Reinwein D. Epidemiologische Daten zur thyreotoxischen Krise, eine retrospektive Untersuchung. Akt Endokrin Stoffw 1992;13(1):82-86
13. Kallee E, Wahl R, Secker KH, et al. Thyrotoxic crisis: symptoms and therapy (author's transl). Med Klin 1973;68(51):1689-96
14. Steidle B. Iodine-induced hyperthyroidism after contrast media: animal experimental and clinical studies. Fortschr Geb Rontgenstrahlen Nuklearmed Erganzungsbd 1989;128(1):6-14
15. Herrmann J, Krüskemper HL. Risk to patients with latent or manifest hyperthyroidism through iodine-containing contrast media and drugs (author's transl). Dtsch Med Wochenschr 1978;103(37):1434, 1437-43, doi:10.1055/s-0028-1129278
16. Pigeot I, Ahrens W. Establishment of a pharmacoepidemiological database in Germany: methodological potential, scientific value and practical limitations. Pharmacoepidemiology and Drug Safety 2008;17(3):215-223, doi:10.1002/pds.1545
17. Haug U, Schink T. German Pharmacoepidemiological Research Database (GePaRD). In: Databases for pharmacoepidemiological research. (Sturkenboom M, Schink T. eds.) Springer International Publishing: Cham; 2021; pp. 119-124.
18. Statista: GKV und PKV - Mitglieder- und Versichertenzahl im Vergleich bis 2020. 2022. Available from: https://de.statista.com/statistik/daten/studie/155823/umfrage/gkv-pkv-mitglieder-und-versichertenzahl-im-vergleich.
19. Fassmer A ST. Repräsentativität von ambulanten Arzneiverordnungen in der German Pharmacoepidemiological ResearchDatabase (GePaRD). 9. Jahrestagung der Deutschen Gesellschaft fürEpidemiologie (DGEpi); 17.-20. September 2014, Ulm.
20. Schink T, Garbe E. Assessment of the representativity of in-patient hospital diagnoses in the German Pharmacoepidemiological Research Database. Gesundheitswesen 2010;72(10), doi:10.1055/s-0030-1266518
21. Helmut Schröder GB, Katrin Schüssel, Jan Breitkreuz, Andreas Schlotmann, Christian Günster. Monitor: Vorerkrankungen mit erhöhtem Risiko für schwere COVID-19-Verläufe. Wissenschaftliches Institut der AOK (WldO): 2020.
22. Statistisches Bundesamt Deutschland - GENESIS-Online. 2021. Available from: https://www-genesis.destatis.de/genesis/online?operation=previous&levelindex=0&step=0&titel=Hilfe&levelid=1625048206172&acceptscookies=false#abreadcrumb] (Online; accessed 30. Jun. 2021).

392 23. Wilson EB. Probable inference, the law of succession, and statistical inference. Journal of the American
393 Statistical Association 1927;22(158):209-212, doi:10.1080/01621459.1927.10502953
394 24. SAS I. The SAS system for Windows. Release 9.4. SAS Inst. Cary, NC, USA.: 2009.
395 25. Blick C NM, Jialal I. Thyrotoxicosis. In: StatPearls [Internet] Treasure Island (FL): StatPearls
396 Publishing; 2021;
397 26. Heinisch M, Kumnig G, Asböck D, et al. Goiter prevalence and urinary iodide excretion in a formerly
398 iodine-deficient region after introduction of statutory Iodization of common salt. Thyroid 2002;12(9):809-14,
399 doi:10.1089/105072502760339389
400 27. Khattak RM, Ittermann T, Nauck M, et al. Monitoring the prevalence of thyroid disorders in the adult
401 population of Northeast Germany. Population Health Metrics 2016;14(1):39, doi:10.1186/s12963-016-0111-3
402 28. Zimmermann MB, Andersson M. Update on iodine status worldwide. Curr Opin Endocrinol Diabetes
403 Obes 2012;19(5):382-7, doi:10.1097/MED.0b013e328357271a
404 29. Waqar Z, Avula S, Shah J, et al. Cardiovascular events in patients with thyroid storm. J Endocr Soc
405 2021;5(6):bvab040, doi:10.1210/jendso/bvab040
406 30. Bartalena L, Bogazzi F, Chiovato L, et al. European Thyroid Association (ETA) guidelines for the
407 management of amiodarone-associated thyroid dysfunction. European Thyroid Journal 2018;7(2):55-66,
408 doi:10.1159/000486957
409 31. De Leo S, Lee SY, Braverman LE. Hyperthyroidism. Lancet 2016;388(10047):906-918,
410 doi:10.1016/S0140-6736(16)00278-6
411 32. Kahaly GJ, Bartalena L, Hegedüs L, et al. European thyroid association guideline for the management
412 of Graves' hyperthyroidism. European Thyroid Journal 2018;7(4):167-186, doi:10.1159/000490384
413

Figure 1: Annual age-standardized incidence rates of thyroid storm stratified by sex

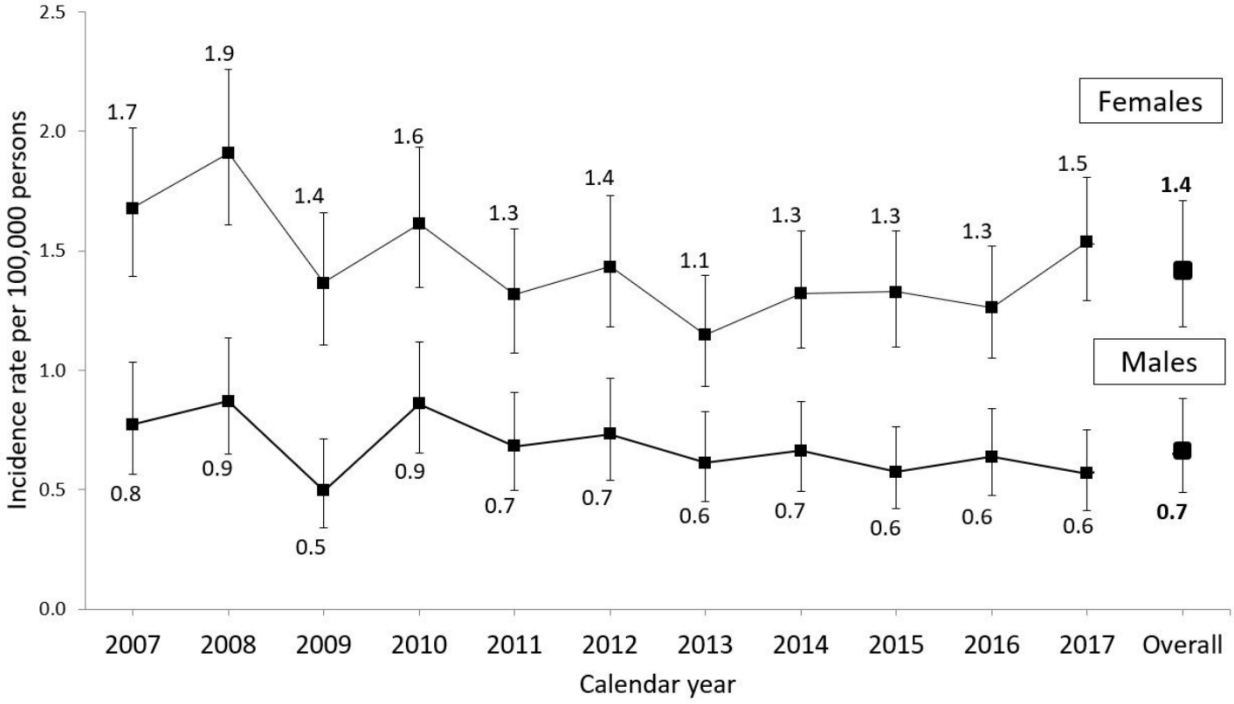
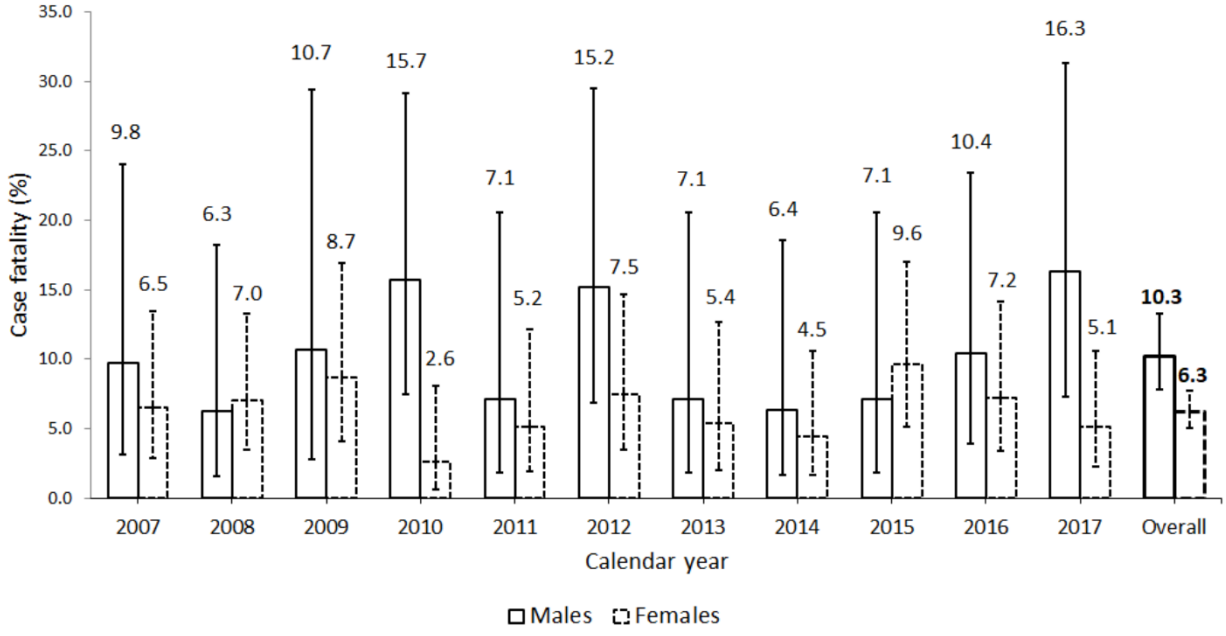


Figure 2: Annual case fatality[a] of thyroid storm stratified by sex



[a]death within 30 days of a diagnosis of thyroid storm was considered to be associated with thyroid storm

Table 1: Characteristics of patients with an incident diagnosis of thyroid storm during the study period 2007–2017

Characteristics	Male n=478	Female n=1,212	Total n=1,690
Age at first diagnosis			
Mean ± SD	62.2±17.1	59.2±19.1	60.1±18.6
Median [IQR]	65 [52–76]	62 [46–75]	63 [48–75]
Age group, n (%)			
< 18 years	5 (1.0)	14 (1.2)	19 (1.1)
18–30 years	26 (5.4)	108 (8.9)	134 (7.9)
31–45 years	48 (10.0)	179 (14.8)	227 (13.4)
46–60 years	117 (24.5)	289 (23.9)	406 (24.0)
61–70 years	96 (20.1)	205 (16.9)	301 (17.8)
71–80 years	128 (26.8)	248 (20.5)	376 (22.3)
> 80 years	58 (12.1)	169 (13.9)	227 (13.4)
≤ 60 years	196 (41.0)	590 (48.7)	786 (46.5)
> 60 years	282 (58.9)	622 (51.3)	904 (53.5)
Type of (index) admission, n (%)			
Inpatient, usual care	189 (39.5)	446 (36.9)	635 (37.6)
Inpatient, emergency care	287 (60.0)	760 (62.7)	1,047 (61.9)
Others	2 (0.4)	6 (0.4)	8 (0.4)

SD: standard deviation; IQR: interquartile range

Table 2: Characteristics of cases of death[a] associated with thyroid storm

Characteristics	Male n=49	Female n=76	Total n=125
Age at first diagnosis			
Mean ± SD	76.3±10.6	76.9±12.4	76.7±11.7
Median [IQR]	78 [73–83]	81 [73–85]	80 [73–84]
Age group, n (%)			
≤ 60 years	2 (4.1)	8 (10.5)	10 (8.0)
61–70 years	7 (14.3)	9 (11.8)	16 (12.8)
71–80 years	22 (44.9)	18 (23.7)	40 (32.0)
> 80 years	18 (36.7)	41 (53.9)	59 (47.2)
> 60 years	47 (95.9)	68 (89.4)	115 (92.0)

SD: standard deviation; IQR: interquartile range;

[a]death within 30 days of a diagnosis of thyroid storm was considered to be associated with thyroid storm

Table 3: Comorbidities recorded one year prior to diagnosis of thyroid storm in all patients with incident thyroid storm and in those with thyroid-storm associated death

Comorbidities	Patients with incident diagnosis of thyroid storm n=1,690	Cases of death[a] associated with thyroid storm n=125
Cardiovascular diseases, n (%)		
Acute myocardial infarction	38 (2.3)	6 (4.8)
Acute stroke	27 (1.6)	4 (3.2)
Arterial hypertension with antihypertensive therapy	633 (37.5)	76 (60.8)
Coronary artery disease	256 (15.1)	31 (24.8)
Congestive heart failure	162 (9.6)	25 (20.0)
Any medication for cardiovascular disease	805 (47.6)	93 (74.4)
Endocrine disorders, n (%)		
Diabetes treated with medications	201 (11.9)	18 (14.4)
Diabetes with end organ damage	12 (0.7)	0
Graves' disease	67 (3.9)	4 (3.2)
Hepatic diseases, n (%)		
Liver diseases including chronic viral hepatitis	115 (6.8)	9 (7.2)
Hepatitis B or Hepatitis C	4 (0.2)	0
Serious liver disease	6 (0.4)	1 (0.8)
Renal diseases, n (%)		
End-stage renal disease	39 (2.3)	3 (2.4)
Immune disorders, n (%)		
Immunosuppressive therapy	85 (5.0)	5 (4.0)
HIV therapy	1 (0.1)	0
Neuropsychiatric disorders, n (%)		
Dementia	83 (4.9)	16 (12.8)
Hemiplegia	36 (2.1)	6 (4.8)
Therapy with antidepressants	97 (5.7)	8 (6.4)
Therapy with antipsychotics	24 (1.4)	4 (3.2)
Life-style related comorbidities, n (%)		
Alcohol abuse	57 (3.4)	7 (5.6)
Drug abuse	33 (1.9)	2 (1.6)
Obesity	228 (13.5)	15 (12.0)
Respiratory diseases, n (%)		
Asthma	98 (5.8)	7 (5.6)
Chronic obstructive pulmonary disease	119 (7.0)	19 (15.2)
Any of the above comorbidities, n (%)	1,123 (66.4)	109 (87.2)

Number of patients (% of group total) are shown for each category

[a]*death within 30 days of a diagnosis of thyroid storm was considered to be associated with thyroid storm*

Table 4: Hospital discharge diagnoses coded in addition to thyroid storm diagnosis

Discharge diagnoses	Patients with incident diagnosis of thyroid storm n=1,690	Cases of death[a] associated with thyroid storm n=125
Cardiovascular diseases, n (%)		
Atrial fibrillation and flutter	688 (40.7)	81 (64.8)
Myocardial infarction	88 (5.2)	19 (15.2)
Chronic ischemic heart disease	257 (15.2)	36 (28.8)
Cardiogenic shock	39 (2.3)	16 (12.8)
Heart failure	456 (26.9)	72 (57.6)
Hypertension	736 (43.6)	68 (54.4)
Other cardiac arrhythmias	87 (5.2)	10 (8.0)
Stroke	5 (0.3)	2 (1.6)
Endocrine disorders, n (%)		
Adrenal gland disorders	11 (0.7)	1 (0.8)
Thyroiditis	115 (6.8)	1 (0.8)
Type 1 diabetes mellitus	23 (1.4)	0
Type 2 diabetes mellitus	263 (15.6)	24 (19.2)
Hepatic diseases, n (%)		
Acute renal failure	135 (7.9)	37 (29.6)
Chronic kidney disease	203 (12.0)	28 (22.4)
Fibrosis and cirrhosis of liver	7 (0.4)	1 (0.8)
Hepatic failure	24 (1.4)	10 (8)
Hyperbilirubinemia	2 (0.1)	1 (0.8)
Toxic liver disease	17 (1.0)	1 (0.8)
Renal diseases, n (%)		
Acute renal failure	135 (7.9)	37 (29.6)
Chronic kidney disease	203 (12.0)	28 (22.4)
Respiratory diseases, n (%)		
Acute respiratory failure	226 (13.4)	51 (40.8)
Pulmonary embolism	20 (1.2)	5 (4.0)
Neuropsychiatric disorders, n (%)		
Dementia	7 (0.4)	0
Patients with any of the above diagnoses, n (%)	1,248 (73.8)	118 (94.4)

Number of patients (% of group total) are shown for each category

[a]*death within 30 days of a diagnosis of thyroid storm was considered to be associated with thyroid storm*

Table 5: Incidence rates (per 100,000 persons per year) of thyroid storm, overall and stratified by age group and sex

	Incidence rate per 100,000 persons per year [95% CI]		
	Male	Female	Total
	n=478	n=1,212	n=1,690
Overall	0.7 [0.5–0.9]	1.4 [1.2–1.7]	1.1 [0.9–1.3]
Age group			
< 18 years	0.04 [0.01–0.1]	0.1 [0.1–0.2]	0.08 [0.1–0.1]
18–30 years	0.2 [0.1–0.3]	0.9 [0.7–1.1]	0.6 [0.5–0.7]
31–45 years	0.3 [0.3–0.5]	1.1 [0.9–1.2]	0.7 [0.6–0.8]
46–60 years	0.7 [0.6–0.9]	1.4 [1.2–1.6]	1.1 [0.9–1.2]
61–70 years	1.2 [0.9–1.4]	1.9 [1.7–2.2]	1.6 [1.4–1.8]
71–80 years	1.9 [1.7–2.4]	2.9 [2.6–3.4]	2.5 [2.3–2.8]
> 80 years	2.6 [1.9–3.4]	4.0 [3.4–4.7]	3.5 [3.1–4.0]
≤ 60 years	0.4 [0.3–0.4]	0.9 [0.9–1.0]	0.7 [0.6–0.7]
> 60 years	1.7 [1.5–1.9]	2.7 [2.5–2.9]	2.3 [2.1–2.4]

CI: confidence interval

Table 6: Case fatality of thyroid storm, overall and stratified by age group and sex: Maximum permissible time period of 30 days (base case analysis)

	Case fatality, % [95% CI]		
	Male	Female	Total
	n=49	n=76	n=125
Overall	10.3 [7.8–13.3]	6.3 [5.0–7.8]	7.4 [6.2–8.7]
Age group			
< 18 years	0	0	0
18–30 years	3.8 [0.2–21.6]	0	0.7 [0.04–4.7]
31–45 years	0	1.7 [0.4–5.2]	1.3 [0.3–4.1]
46–60 years	0.9 [0.1–5.4]	1.7 [0.6–4.2]	1.5 [0.6–3.4]
61–70 years	7.3 [3.2–14.9]	4.4 [2.2–8.4]	5.3 [3.2–8.7]
71–80 years	17.2 [11.3–25.1]	7.3 [4.5–11.4]	10.6 [7.8–14.3]
> 80 years	31.0 [19.9–44.7]	24.3 [18.2–31.6]	25.9 [20.5–32.3]
≤ 60 years	1.0 [0.2–4.0]	1.4 [0.6–2.8]	1.3 [0.6–2.4]
> 60 years	16.7 [12.6–21.7]	10.9 [8.6–13.7]	12.7 [10.7–15.1]

CI: confidence interval

Table 7: Case fatality of thyroid storm, overall and stratified by age group and sex: Maximum permissible time period of 15 days (sensitivity analysis)

	Case fatality, % [95% CI]		
	Male	Female	Total
	n=34	n=53	n=87
Overall	7.1 [5.1–9.8]	4.4 [3.4–5.7]	5.2 [4.2–6.3]
Age group			
< 18 years	0	0	0
18–30 years	3.8 [0.6–18.8]	0	0.7 [0.04–4.7]
31–45 years	0	1.7 [0.4–5.2]	1.3 [0.3–4.1]
46–60 years	0.9 [0.04–5.4]	1.7 [0.6–4.2]	1.5 [0.6–3.4]
61–70 years	4.2 [1.3–10.9]	2.9 [1.2–6.6]	3.3 [1.7–6.2]
71–80 years	10.9 [6.3–17.9]	4.4 [2.4–8.0]	6.7 [4.4–9.8]
> 80 years	24.1 [14.3–37.5]	16.6 [11.5–23.2]	18.5 [13.8–24.3]
≤ 60 years	1.0 [0.2–3.6]	1.4 [0.6–2.8]	1.3 [0.6–2.4]
> 60 years	11.3 [8.0–15.8]	7.2 [5.4–9.6]	8.5 [6.8–10.6]

CI: confidence interval

Table 8: Case fatality of thyroid storm, overall and stratified by age group and sex: Maximum permissible time period of 45 days (sensitivity analysis)

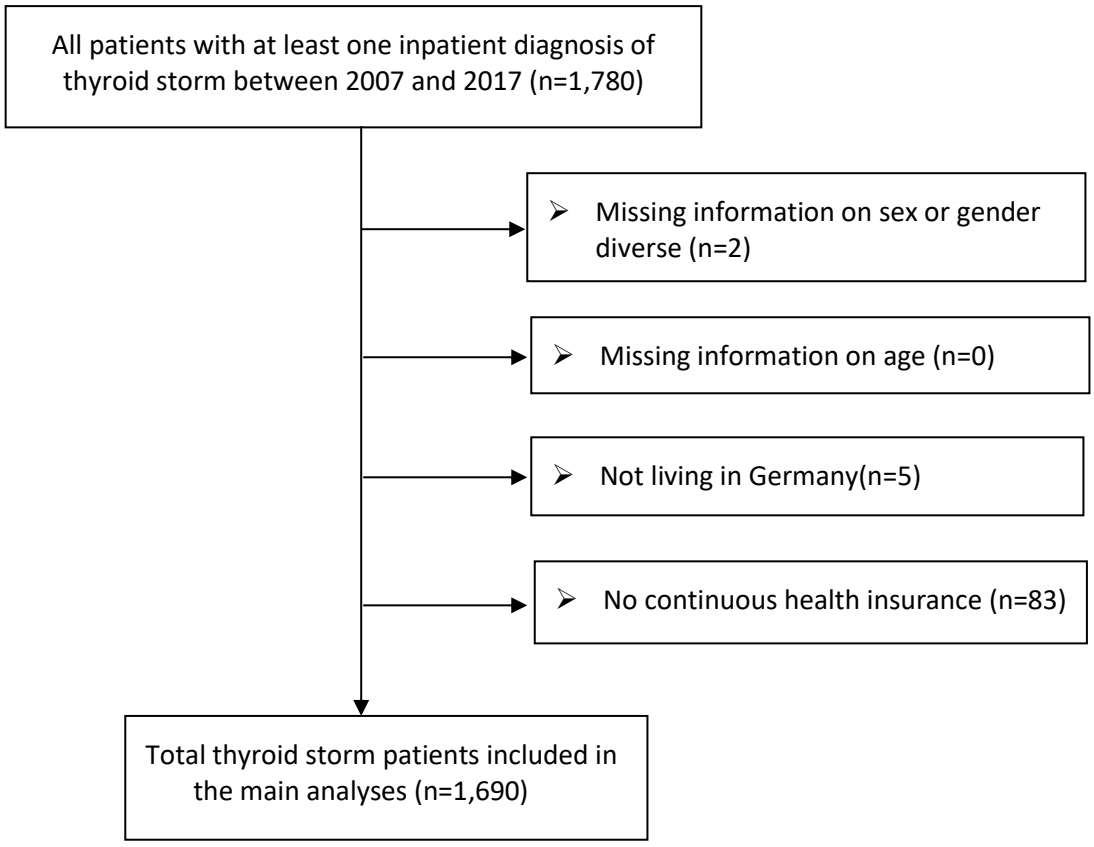
	Case fatality, % [95% CI]		
	Male	Female	Total
	n=71	n=95	n=166
Overall	14.9 [11.9–18.3]	7.8 [6.5–9.5]	9.8 [8.5–11.3]
Age group			
< 18 years	0	0	0
18–30 years	3.8 [0.6–18.9]	0	0.7 [0.04–4.7]
31–45 years	2.1 [0.1–12.5]	1.7 [0.4–5.2]	1.8 [0.6–4.7]
46–60 years	4.3 [1.6–10.2]	2.1 [0.8–4.7]	2.7 [1.4–4.9]
61–70 years	13.6 [7.7–22.4]	7.3 [4.3–12.0]	9.3 [6.4–13.3]
71–80 years	23.4 [16.6–31.9]	9.7 [6.4–14.2]	14.4 [11.1–18.4]
> 80 years	36.2 [24.3–49.9]	27.8 [21.3–35.3]	29.9 [24.2–36.4]
≤ 60 years	3.6 [1.7–7.2]	1.5 [0.7–2.9]	2.0 [1.2–3.3]
> 60 years	22.7 [18.0–28.1]	13.8 [11.3–16.8]	16.6 [14.3–19.2]

CI: confidence interval

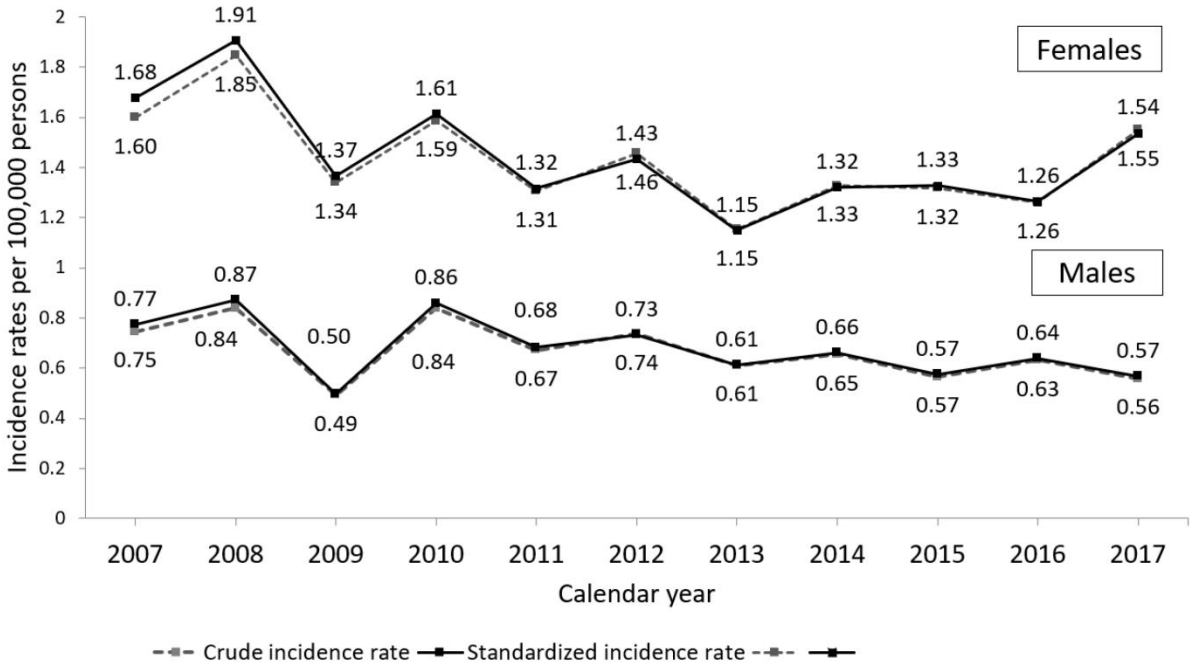
Supplementary file to: Estimating incidence and case fatality of thyroid storm in Germany between 2007 and 2017: A claims data analysis

Arulmani Thiyagarajan, Katharina Platzbecker, Till Ittermann, Henry Völzke, Ulrike Haug

Supplementary figure 1: Patient flow diagram



Supplementary figure 2: Annual crude and age-standardized incidence rates[a] of thyroid storm in males and females during the study period (2007–2017)



[a]*Incidence rates were standardized using the standard German population, 2017*

Supplementary table 1: Characteristics of thyroid storm patients with more than one inpatient diagnosis of thyroid storm during the study period (2007–2017)

Characteristics	Male (n=41)	Female (n=73)	Total (n=114)
Age at first diagnosis			
Mean ± SD	63.2±12.4	61.5±17.9	61.9±16.2
Median [IQR]	67 [27–73]	63 [50–75]	64 [52–73]
Age group, n (%)			
< 18 years	0	0	0
18–30 years	1 (2.4)	6 (8.2)	7 (6.1)
31–45 years	2 (4.9)	7 (9.6)	9 (7.9)
46–60 years	11 (26.8)	20 (27.4)	31 (27.2)
61–70 years	13 (31.7)	15 (20.6)	28 (24.6)
71–80 years	12 (29.3)	15 (20.6)	27 (23.7)
> 80 years	2 (4.9)	10 (13.7)	12 (10.5)
Number of inpatient diagnoses of thyroid storm, n (%)			
2 diagnoses	36 (87.8)	66 (90.4)	102 (89.5)
3 diagnoses	5 (12.2)	7 (9.6)	12 (10.5)
Time between first and second inpatient thyroid storm diagnosis (in days)			
Mean ± SD	137.9±441.7	165.3±440.2	157.6±437.7
Median [IQR]	31 [12–57]	21 [8–49]	25 [8–57]
Range [Min-Max]	2728 [1-2729]	2573 [1-2574]	2728 [1-2729]
Type of admission, n (%)			
Inpatient, usual care	27 (65.8)	37 (50.6)	64 (56.1)
Inpatient, emergency care	14 (35.9)	36 (49.3)	51 (43.8)

SD: standard deviation; IQR: interquartile range

Supplementary table 2: Comorbidities recorded one year prior to diagnosis of thyroid storm in all patients with incident thyroid storm and those with thyroid-storm associated death stratified by sex

Comorbidities	Patients with incident diagnosis of thyroid storm		Cases of death[a] associated with thyroid storm	
	Male n=478	Female n=1,212	Male n=49	Female n=76
Cardiovascular diseases, n (%)				
Acute myocardial infarction	20 (4.2)	18 (1.5)	3 (6.1)	3 (3.9)
Acute stroke	9 (1.9)	18 (1.5)	0	4 (5.3)
Arterial hypertension with antihypertensive therapy	218 (45.6)	415 (34.2)	33 (67.4)	43 (56.6)
Coronary artery disease	119 (24.9)	137 (11.3)	19 (38.8)	12 (15.8)
Congestive heart failure	73 (15.3)	89 (7.3)	12 (24.5)	13 (17.1)
Any medications for cardiovascular disease	282 (59.0)	523 (43.2)	38 (77.6)	55 (72.4)
Endocrine disorders, n (%)				
Diabetes treated with medications	86 (17.9)	115 (9.5)	13 (26.5)	5 (6.6)
Diabetes with end organ damage	4 (0.8)	8 (0.7)	0	0
Graves' disease	13 (2.7)	54 (4.5)	0	4 (5.3)
Hepatic diseases, n (%)				
Liver diseases including chronic viral hepatitis	47 (9.8)	68 (5.6)	3 (6.1)	0
Hepatitis B or Hepatitis C	0	4 (0.3)	5 (10.2)	4 (5.3)
Serious liver disease	3 (0.6)	3 (0.3)	1 (2.0)	0
Renal diseases, n (%)				
End-stage renal disease	21 (4.4)	18 (1.5)	0	0
Immune disorders, n (%)				
Immunosuppressive therapy	26 (5.4)	59 (4.9)	3 (6.1)	2 (2.6)
HIV therapy	1 (0.2)	0	0	0
Neuropsychiatric disorders, n (%)				
Dementia	19 (3.9)	64 (5.3)	8 (16.3)	8 (23.7)
Hemiplegia	11 (2.3)	25 (2.1)	3 (6.1)	3 (3.9)
Therapy with antidepressants	16 (3.4)	81 (6.7)	1 (2.0)	7 (9.2)
Therapy with antipsychotics	6 (1.3)	18 (1.5)	0	4 (5.3)
Life-style related comorbidities, n (%)				
Alcohol abuse	27 (5.7)	30 (2.5)	4 (8.2)	3 (3.9)
Drug abuse	11 (2.3)	22 (1.8)	1 (2.0)	1 (1.3)
Obesity	69 (14.4)	159 (13.1)	7 (14.3)	8 (10.5)
Respiratory diseases, n (%)				
Asthma	17 (3.4)	81 (6.7)	3 (6.1)	4 (5.3)
Chronic obstructive pulmonary disease	43 (9.0)	76 (6.3)	10 (20.4)	9 (11.8)
Any of the above comorbidities, n (%)	351 (73.4)	772(63.7)	44 (99.8)	65 (85.5)

Number of patients (% of group total) are shown for each category

[a]death within 30 days of a diagnosis of thyroid storm was considered to be associated with thyroid storm

Supplementary table 3: Hospital discharge diagnoses coded in addition to thyroid storm diagnosis stratified by sex

Discharge diagnoses	Patients with incident diagnosis of thyroid storm		Cases of death[a] associated with thyroid storm	
	Male n=478	Female n=1,212	Male n=49	Female n=76
Cardiovascular diseases, n (%)				
Atrial fibrillation and flutter	240 (50.2)	448 (36.9)	32 (65.3)	49 (64.5)
Myocardial infarction	34 (7.1)	54 (4.5)	7 (14.3)	12 (15.8)
Chronic ischemic heart disease	127 (26.6)	130 (10.7)	18 (36.7)	18 (23.7)
Cardiogenic shock	18 (3.8)	21 (1.7)	7 (14.3)	9 (11.8)
Heart failure	162 (33.9)	294 (24.3)	29 (59.2)	43 (56.6)
Hypertension	238 (49.8)	498 (41.1)	31 (63.3)	37 (48.7)
Other cardiac arrhythmias	29 (6.1)	58 (4.8)	4 (8.2)	6 (7.9)
Stroke	3 (0.6)	2 (0.2)	1 (2.0)	1 (1.3)
Endocrine disorders, n (%)				
Adrenal gland disorders	2 (0.4)	9 (0.7)	1 (2.0)	0
Thyroiditis	27 (5.7)	88 (7.3)	0	1 (1.3)
Type 1 diabetes mellitus	7 (1.5)	16 (1.3)	0	0
Type 2 diabetes mellitus	99 (20.7)	164 (13.5)	15 (30.6)	9 (11.8)
Hepatic diseases, n (%)				
Fibrosis and cirrhosis of liver	2 (0.4)	5 (0.4)	1 (0.8)	0
Hepatic failure	10 (2.1)	14 (1.2)	3 (6.1)	7 (9.2)
Hyperbilirubinemia	0	2 (0.2)	0	1 (1.3)
Toxic liver disease	7 (1.5)	10 (0.8)	1 (2.0)	0
Renal diseases, n (%)				
Acute renal failure	59 (12.3)	76 (6.3)	13 (26.5)	24 (31.6)
Chronic kidney disease	81 (16.9)	122 (10.1)	12 (24.5)	16 (21.1)
Respiratory diseases, n (%)				
Acute respiratory failure	81 (16.9)	145 (11.9)	17 (34.7)	34 (44.7)
Pulmonary embolism	6 (1.3)	14 (1.2)	2 (4.1)	3 (3.9)
Neuropsychiatric disorders, n (%)				
Dementia	0	7 (0.6)	0	0
Patients with any of the above diagnosis, n (%)	401 (83.9)	847 (69.9)	46 (93.9)	72 (94.7)

Number of patients (% of group total) are shown for each category

[a]death within 30 days of a diagnosis of thyroid storm was considered to be associated with thyroid storm

Supplementary table 4: Comorbidities recorded one year prior to diagnosis of thyroid storm in all patients with incident thyroid storm and those with thyroid-storm associated death restricted to patients >60 years of age

Comorbidities	Patients with incident diagnosis of thyroid storm n=904	Cases of death[a] associated with thyroid storm n=115
Cardiovascular diseases, n (%)		
Acute myocardial infarction	30 (3.3)	5 (4.4)
Acute stroke	22 (2.4)	4 (3.5)
Arterial hypertension with antihypertensive therapy	514 (56.9)	72 (62.6)
Coronary artery disease	220 (24.3)	28 (24.4)
Congestive heart failure	133 (14.7)	25 (21.7)
Any medications for cardiovascular disease	629 (69.6)	89 (77.4)
Endocrine disorders, n (%)		
Diabetes treated with medications	151 (16.7)	18 (15.7)
Diabetes with end organ damage	8 (0.9)	0
Graves' disease	27 (3.0)	4 (3.5)
Hepatic diseases, n (%)		
Liver diseases including chronic viral hepatitis	94 (10.4)	9 (7.8)
Hepatitis B or Hepatitis C	1 (0.1)	0
Serious liver disease	5 (0.6)	1 (0.9)
Renal diseases, n (%)		
End-stage renal disease	26 (2.9)	2 (1.7)
Neuropsychiatric disorders, n (%)		
Dementia	82 (9.1)	26 (22.6)
Hemiplegia	28 (3.1)	6 (5.2)
Therapy with antidepressants	54 (5.9)	7 (6.1)
Therapy with antipsychotics	17 (1.9)	3 (2.6)
Immune disorders, n (%)		
Immunosuppressive therapy	50 (5.5)	4 (3.5)
Life-style related comorbidities, n (%)		
Alcohol abuse	35 (3.9)	6 (5.2)
Drug abuse	18 (1.9)	2 (1.7)
Obesity	144 (15.9)	14 (12.2)
Respiratory diseases, n (%)		
Asthma	47 (5.2)	7 (6.1)
Chronic obstructive pulmonary disease	95 (10.5)	19 (16.5)
Any of the above comorbidities, n (%)	754 (83.4)	104 (90.4)

Number of patients (% of group total) are shown for each category

[a]*death within 30 days of a diagnosis of thyroid storm was considered to be associated with thyroid storm*

Supplementary table 5: Hospital discharge diagnoses coded in addition to thyroid storm diagnosis restricted to patients >60 years of age

Discharge diagnoses	Patients with incident diagnosis of thyroid storm n=904	Cases of death[a] associated with thyroid storm n=115
Cardiovascular diseases, n (%)		
Atrial fibrillation and flutter	511 (56.5)	77 (66.9)
Myocardial infarction	63 (7.0)	15 (13.0)
Chronic ischemic heart disease	214 (23.7)	30 (26.1)
Cardiogenic shock	27 (3.0)	13 (11.3)
Heart failure	348 (38.5)	65 (56.5)
Hypertension	539 (59.6)	65 (56.5)
Other cardiac arrhythmias	60 (6.6)	7 (6.1)
Stroke	4 (0.4)	2 (1.7)
Endocrine disorders, n (%)		
Adrenal gland disorders	5 (0.6)	1 (0.9)
Thyroiditis	42 (4.6)	1 (0.9)
Type 1 diabetes mellitus	1 (0.1)	0
Type 2 diabetes mellitus	215 (23.8)	23 (20)
Hepatic diseases, n (%)		
Fibrosis and cirrhosis of liver	6 (0.7)	1 (0.9)
Hepatic failure	14 (1.5)	6 (5.2)
Hyperbilirubinemia	2 (0.2)	1 (0.9)
Toxic liver disease	10 (1.1)	1 (0.9)
Renal diseases, n (%)		
Acute renal failure	105 (11.6)	32 (27.8)
Chronic kidney disease	171 (18.9)	26 (22.6)
Respiratory diseases, n (%)		
Acute respiratory failure	165 (18.3)	43 (37.4)
Pulmonary embolism	17 (1.9)	5 (4.4)
Neuropsychiatric disorder, n (%)		
Dementia	7 (0.8)	0
Patients with any of the above diagnosis, n (%)	816 (90.3)	109 (94.8)

Number of patients (% of group total) are shown for each category

[a]*death within 30 days of a diagnosis of thyroid storm was considered to be associated with thyroid storm*