CLINICAL STUDY

Increased risk of affective disorder following hospitalisation with hyperthyroidism – a register-based study

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Abstract

Objective: The pattern of co-morbidity between thyroid disorders and affective disorder is not fully known. We assessed whether hospitalisation with hyperthyroidism was a risk factor for hospitalisation with affective disorder and evaluated the temporal relationship between these events.

Design: A historical prospective cohort study comparing patients with hyperthyroidism with patients with non-toxic goitre or osteoarthritis, using existing data from Danish registers. The observational period was from 1 January 1977 to 31 December 1999.

Methods: Three study cohorts were identified by their International Classification of Diseases (ICD) diagnoses at discharge from hospital and consisted of all patients with a first hospital admission with the index diagnoses of hyperthyroidism, osteoarthritis, or non-toxic goitre. Later admissions to psychiatric hospital wards with discharge ICD diagnoses of affective disorder were used as events of interest. Rates of re-admission were estimated using competing risks models in survival analyses. Age, sex, substance abuse, and calendar time were included as co-variables.

Results: A study sample of 183,647 patients discharged with an index diagnosis was identified. In total 1,374 events occurred in the observational period. An index diagnosis of hyperthyroidism was associated with an increased risk of hospitalisation with affective disorder for both sexes and for all age-bands investigated, compared with the other index diagnoses. The risk was greatest in the first six months after index hospitalisation (rate ratio, 95% confidence interval: 3.60 (2.58 – 5.04)).

Conclusions: Patients hospitalised with hyperthyroidism are at greater risk of re-admission with depressive disorder or bipolar disorder than control patients. This suggests that hyperthyroidism is associated with long-term mood disturbances.

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Introduction

Mental symptoms are often prominent in the syndrome of hyperthyroidism (1), especially in the form of anxiety and mood disturbances (2). Thyroid hormones influence adult brain functioning (3, 4), and may interact with mood regulation via targets in specific brain circuits (5, 6). Cross-sectional studies show that psychiatric symptoms often accompany hyperthyroidism in patients admitted to hospital (7), and that a substantial number of patients with hyperthyroidism display a clinical picture of depressive disorder (8). Sub-clinical hyperthyroidism occurs among patients with melancholic depression (9), and case reports suggest that thyrotoxicosis may precipitate mania in susceptible individuals (10, 11). However, other studies have failed to demonstrate any association between hyperthyroidism and affective disorder in outpatients with major depression (12), or within a large unselected population (13).

Cross-sectional studies suggest that there may be long-term effects on cognitive function and affective modulation following hyperthyroidism. Stern et al. (1996), in a retrospective survey among 137 patients treated for Graves’ disease, found that 24% described problems in cognitive functioning and that 37% described altered mood and personality, commonly involving depression or mood swings (14). Perrild et al. (1986) reported a frequency of neuropsychological deficits of 40% in a follow-up study of 26 patients who had been successfully treated for hyperthyroidism 10 years earlier (15). Fahrenfort et al. (2000) found that euthyroid patients recovering from hyperthyroidism had long-term residual complaints, and that one third of the patients were reporting persistent symptoms of depression and anxiety (16).

Contrary to this, the studies investigating the long-term effect of hyperthyroidism on mental functioning in prospective designs indicate that symptoms of anxiety, depression and cognitive dysfunction are
present while patients are hyperthyroid, but tend to disappear parallel with the successful treatment of thyroid hyperactivity (8, 17, 18). Thus, Paschke et al. (1990), in a sequential psychological testing of 16 patients with Graves’ disease, found resolution of depressive symptoms within a month after normalisation of hormone levels (19). However, few prospective studies of affective symptoms of patients with hyperthyroidism exist, and they have been conducted with relatively short follow-up times. Also, because of small numbers of patients prospective studies have been sensitive to bias due to drop-out (8, 20, 21) or to bias in the selection of patients (17).

We have addressed the question of whether hyperthyroidism is a risk factor for developing depressive disorder or bipolar disorder in a historical prospective cohort study based on data from Danish hospital registers. These hospital admission data covering an entire national population allow us to follow a large number of patients over a lengthy period of time.

We compared the risk for patients with hospital diagnoses of hyperthyroidism, non-toxic goitre or osteoarthritis of receiving a later diagnosis of affective disorder on re-admission to hospital. Our hypothesis was that patients with a hospital admission with hyperthyroidism would have higher risks of affective disorders, and hence higher risks of hospital admission with affective disorder diagnoses, than control patients. In a separate analysis, we also investigated the risk of affective disorder for hospitalised patients with hyperthyroidism that did not have diagnoses indicating Graves’ disease as the cause of hyperthyroidism. This was undertaken as Graves’ hyperthyroidism, including Graves’ ophthalmopathy, has in particular been associated with affective disorder (22, 23). We used patients who had passed the thresholds for hospitalisation as control patients in order to reduce the effect of Berkson’s bias (24). The control patients were selected as patients hospitalised with non-toxic goitre or osteoarthritis, as these diseases are not associated with an increased risk of affective disorder.

Materials and methods

Data from Danish hospital registers

We obtained data from three Danish registers after approval from the Danish Data Protection Agency.

In Denmark, hospital admissions to psychiatric wards have been recorded in a nationwide register, the Danish Psychiatric Central Research Register (DPCRR) (25) since 1 April 1970. In the period from 1 April 1970 to 31 December 1993 the Danish edition of the International Classification of Diseases 8 (ICD-8) (26) was used for registration. Since 1 January 1994 the updated International Classification of Diseases 10 (ICD-10) (27) has been in use. The admissions to somatic hospital wards have been registered separately in the Danish National Hospital Register (DNHR) (28) since 1 January 1977. The ICD-8 and ICD-10 systems have been used in the same manner as in the DPCRR.

All Danish hospitals are required to report to these public registers. Deaths in Denmark, in hospitals or elsewhere, are all registered in the Danish Register of Causes of Death (DRCD) (29).

All Danish citizens have a unique personal identification number, the central personal register number (CPR number). This number can be logically checked for errors, and it is used to identify the individual citizen in the various registers. Therefore, data on hospital admissions and deaths can be precisely registered irrespective of changes in name or address. The rate of migration from Denmark is low, and the use of foreign hospitals by citizens is negligible. The full pattern of hospital admissions in Denmark can thus be established with confidence.

The study sample

The three study cohorts were identified as all inpatients with a main diagnosis of (i) hyperthyroidism (exposed), (ii) non-toxic goitre (unexposed) and (iii) osteoarthritis (unexposed) at discharge after the first admission to hospital within the observational period from 1 January 1977 to 31 December 1999. Hyperthyroidism was defined by the ICD-8 codes 242.00–242.29, and the ICD-10 codes E05–E05.9. Additionally, hyperthyroidism from causes other than Graves’ disease was defined by the ICD-8 codes 242.02–242.29 and the ICD-10 codes E05 and E05.1–E05.9. Non-toxic goitre was defined by the ICD-8 codes 240.00–241.99 and the ICD-10 codes E04.0–E04.9. Osteoarthritis was defined by the ICD-8 codes 713.00–713.09 and the ICD-10 codes M15.0–M19.9.

The outcome of interest was admission to psychiatric hospital with a main diagnosis of affective disorder as registered in the DPCRR. Auxiliary diagnoses were disregarded as outcomes in order to ensure maximum validity. Affective disorder was defined as either depressive disorder, ICD-8 codes 296.09, 296.29, 286.89, 296.99 and ICD-10 codes F32.0–F33.31, F34.0–F34.9, F38.1–F39.9, or bipolar disorder, ICD-8 codes 296.19, 296.39 and ICD 10 codes F30.0–F31.6, F38.0.

Only incident exposed and unexposed patients were included in the analyses. Patients admitted to hospital at an age younger than 15 years and patients registered with a diagnosis of affective disorder or of schizophrenia prior to the index admission were excluded. All patients with a first-discharge auxiliary diagnosis of affective disorder, schizophrenia, or a diagnosis of one of the other cohorts were excluded. Patients registered in the DPCRR with main diagnoses of affective disorder or of schizophrenia (ICD-8 code 295.xx and ICD-10 code F20–F29) in the time period from 1 April 1970.
to 31 December 1976 were excluded. Similar principles of selection have been employed in previous studies from our group (30, 31).

Statistical analysis

The cohort of patients with hyperthyroidism was compared with the non-toxic goitre and osteoarthritis cohorts using Poisson regression analysis, with affective disorder as the event of interest. As death was a major hazard (see Table 1), affective disorder and death were both treated as outcomes in a competing risks model. Using estimated incidence rates of affective disorder and death, the probability of receiving a subsequent diagnosis of affective disorder was calculated for individuals alive and without affective illness at a given age.

When estimating the rate of hospital admissions with affective disorder, patients were censored (i.e. excluded from further participation in the study from this point of time) at the time of admission with schizophrenia, at the time of admission with one of the control cohort diagnoses, or at the time of death. If none of these events occurred patients were censored at the end of the study.

When estimating the rate of death, patients were censored at the time of admission with an affective disorder, schizophrenia, one of the control cohort diagnoses, or at the end of the study. Sex was included in the model as a fixed covariate. Age (divided into groups: 15–35, 35–40, . . . ; 80–85, 85+ years), duration of disease (0–0.5, 0.5–1, 1+ years), and calendar period (1977–1982, 1983–1988, 1989–1993, 1994–1999) were all included as time-dependent covariates.

Chronic alcohol abuse is associated with thyroid abnormalities (32). Substance abuse is also associated with an increased risk of affective disorder, so to estimate whether an effect of hyperthyroidism was mediated through substance abuse, this condition was included as a time-dependent covariate. Patients were classified as having substance abuse from the time of a first discharge from hospital with a substance abuse main diagnosis (ICD-8 codes 291.09–291.99, 303.09–303.99, 304.09–304.99 and ICD-10 codes DF10.0–DF16.9, DF18.0–DF19.9).

Using estimated rates, an approximation of the probability of receiving a diagnosis of affective disorder was made for individuals of both sexes who were alive, without affective disorder, and without diagnoses of substance abuse at a given age.

Results

Characteristics of the patients

The study sample included 183,647 patients of which 28,190 (15.3%) had hyperthyroidism, 122,770 (66.9%) had osteoarthritis and 32,687 (17.8%) had non-toxic goitre. Of the 28,190 patients with hyperthyroidism, 5573 patients had a diagnosis indicating Graves’ disease as the cause of hyperthyroidism. Table 1 shows the distribution of patients between cohorts, sex, median age at first discharge, number of events of interest, number of patients censored and causes of censoring, and number of patients admitted with a diagnosis of substance abuse. Among patients with hyperthyroidism who developed affective disorder leading to re-admission, 14% (n = 47) had a diagnosis of bipolar disorder, compared with 15% (n = 39) of patients with affective disorder following an index diagnosis of non-toxic goitre and with 13% (n = 99) of patients with affective disorder following an index diagnosis of osteoarthritis.

Predictions for re-admission

In the Poisson regression analysis three interactions were included in the model (sex and index diagnosis, sex and age group, index diagnosis and duration of

Table 1 The distribution of patients between cohorts, sex, median age at first discharge, number of events of interest, number of patients censored and causes of censoring, and number of patients admitted with a diagnosis of substance abuse.

<table>
<thead>
<tr>
<th></th>
<th>Hyperthyroidism (n = 28,190)</th>
<th>Non-toxic goitre (n = 32,687)</th>
<th>Osteoarthritis (n = 122,770)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Women</td>
<td>23,750 (84%)</td>
<td>27,867 (85%)</td>
<td>72,171 (58%)</td>
</tr>
<tr>
<td>Median age (years)</td>
<td>57.7</td>
<td>45.2</td>
<td>68.0</td>
</tr>
<tr>
<td>75th percentile</td>
<td>70.8</td>
<td>56.5</td>
<td>75.9</td>
</tr>
<tr>
<td>25th percentile</td>
<td>43.2</td>
<td>36.0</td>
<td>57.0</td>
</tr>
<tr>
<td>Event (percent of n)</td>
<td>32.8 (1.2%)</td>
<td>260 (0.8%)</td>
<td>786 (0.6%)</td>
</tr>
<tr>
<td>Depressive disorder</td>
<td>281 (86%)</td>
<td>221 (85%)</td>
<td>687 (87%)</td>
</tr>
<tr>
<td>Bipolar disorder</td>
<td>47 (14%)</td>
<td>39 (15%)</td>
<td>99 (13%)</td>
</tr>
<tr>
<td>Censored (n)</td>
<td>27,862</td>
<td>32,427</td>
<td>121,984</td>
</tr>
<tr>
<td>Schizophrenia (n)</td>
<td>35</td>
<td>31</td>
<td>40</td>
</tr>
<tr>
<td>Other index disease</td>
<td>2,098</td>
<td>1,957</td>
<td>1,427</td>
</tr>
<tr>
<td>End of study (n)</td>
<td>17,907</td>
<td>26,730</td>
<td>77,712</td>
</tr>
<tr>
<td>Death (n; %)</td>
<td>7,822 (27.7%)</td>
<td>3,709 (11.3%)</td>
<td>42,805 (34.4%)</td>
</tr>
<tr>
<td>Substance abuse (n; %)</td>
<td>393 (1.4%)</td>
<td>426 (1.3%)</td>
<td>2,453 (2.0%)</td>
</tr>
</tbody>
</table>
The covariates age group, substance abuse and calendar time were included only as main effects. The two interactions with sex were insignificant (results not shown). The interaction between index diagnosis and duration of disease was highly significant, as were the covariates included as main effects only (Table 2).

Women had a 1.71 times greater risk of hospitalisation with affective disorder than men. The risk of hospitalisation with affective disorder was greatest in the age groups between 70 and 85 years (results not shown). There was a significant effect of substance abuse, as the risk of affective disorder was 6.71 times greater if a patient also had a diagnosis of substance abuse. The incidence of affective diagnoses was greatest in the calendar period from 1994 to 1999.

### Incidence rates of re-admission with affected disorder

Table 3 shows, for different disease durations, the relative rates of hospitalisation with affective disorder after a first discharge from hospital with one of the index diagnoses. The duration time from index diagnosis was divided into three intervals: from 0–0.5 years, 0.5–1 years, and 1 year after discharge from hospital, and rate ratios were estimated for each of the intervals using Poisson regression models. The rate ratio for hospitalisation with affective disorder was increased 3.60 times (95% confidence interval (CI): 2.58–5.04) for patients with hyperthyroidism compared with patients with osteoarthritis in the first six months after discharge. Similarly, the rate ratio was increased 2.47 times (95% CI: 1.57–3.90) for patients with hyperthyroidism in the period between 0.5 and 1 year following discharge from hospital. After the first year and for the rest of the observational period (1 year +) the estimated rate ratio declined to 1.34 (95% CI: 1.14–1.56). Furthermore, we investigated the risk from 1 to 3 years after index discharge and the 3 years + separately, but no differences in risks beyond 1 year after index discharge were found (results not shown). The differences between the two control groups were insignificant in all time periods investigated (Table 3).

The same pattern of rate ratios was found when the analyses were performed with the cohort of patients with hyperthyroidism not caused by Graves’ disease. For these patients the rate ratios of affective disorder were 3.76 (95% CI: 2.65–5.34) in the first six months after index discharge, 2.89 (95% CI: 1.83–4.59) in the next six months, and 1.32 (95% CI: 1.12–1.55) for the rest of the observational period.

### Estimated probabilities of later admission

Figures 1 and 2 show the estimated probabilities of a later admission with a discharge diagnosis of affective disorder for patients hospitalised with either hyperthyroidism or one of the control diagnoses at the age of 60 years, for women and men respectively. The figures pertain to patients without diagnoses of substance abuse. The probabilities are adjusted for the competing risk of death. Patients discharged with a diagnosis of hyperthyroidism had an increased risk of psychiatric hospitalisation due to affective disorder throughout their lifetime. The probability curve for a patient with hyperthyroidism has the greatest gradient in the time immediately after index discharge. The gradient becomes reduced approximately one year after index discharge. The same pattern of estimated probabilities was found for patients aged 40, 50, 70 and 80 years.

### Discussion

Patients discharged from hospital with a diagnosis of hyperthyroidism had an increased risk of re-admission to hospital with affective disorder when compared with patients discharged with a diagnosis of non-toxic goitre or of osteoarthritis. This risk was similar whether or not patients with Graves’ disease were included in the hyperthyroidism cohort, indicating that the increased risk of hospitalisation with affective disorder was not

<table>
<thead>
<tr>
<th>Covariates</th>
<th>df</th>
<th>χ²</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td>1</td>
<td>64.63</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Age group</td>
<td>11</td>
<td>61.67</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Substance abuse</td>
<td>1</td>
<td>216.67</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Calendar period</td>
<td>3</td>
<td>144.00</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Interaction between index diagnosis and time period after index discharge</td>
<td>4</td>
<td>30.78</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

*df*, degrees of freedom.

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<table>
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<th>Covariates</th>
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<th>P</th>
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</thead>
<tbody>
<tr>
<td>Hyperthyroidism</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Non-toxic goitre</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Osteoarthritis</td>
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</tr>
</tbody>
</table>
specifically associated with Graves’ disease or with Graves’ ophthalmopathy, and that patients hospitalised with hyperthyroidism caused by Graves’ disease are at a similar risk of subsequent affective disorder as patients hospitalised with hyperthyroidism from other causes.

While Wallace et al. (1980) stated that ‘in hyperthyroidism the brain returns to normal more slowly than the blood’ (17), prospective studies of patients with hyperthyroidism suggest that remission of affective and cognitive symptoms usually occurs within a few months of patients becoming euthyroid. We found that the risk of affective disorder was greatest in the first half-year following discharge with hyperthyroidism, but a normalisation of affective symptoms within months is not concordant with our finding of a 2.47 (CI 95%: 1.57–3.90) rate ratio of admission with affective disorder in the time interval 0.5–1 year after a discharge diagnosis of hyperthyroidism. The risk of affective disorder continued to be significantly increased beyond the first year after index discharge, with a rate ratio of 1.34 (95% CI: 1.14–1.56) for the remainder of the patient’s lifetime.

This suggests that an episode of hyperthyroidism influences affective modulation in a time frame that extends the period of thyroid hormone excess.

A link between hyperthyroidism and affective disorder could consist of a direct co-morbidity between the disorders, with mood symptoms being present simultaneously with elevated thyroid hormone levels and gradually worsening to a degree that demanded hospitalisation with depressive disorder or mania. Alternatively, affective symptoms may have gradually developed in the wake of thyroid hormone excess, influenced by either changes in brain functioning induced by hyperthyroidism or by the medical or surgical treatment of hyperthyroidism (33). Also, common factors may have precipitated both disorders.

Fukao et al. (2003), in a study of sixty-nine patients with Graves’ disease in the euthyroid state, found that relapse of hyperthyroidism was significantly related to personality traits of hypochondriasis and depression, and that relapsing patients were more sensitive to stress and to the problems of daily life than patients that did not relapse into hyperthyroidism (34). Other studies have indicated that negative life events and emotional stress may play a role in the initiation of Graves’ disease (35, 36). The long-term increased risk of severe affective disorder found in our study might reflect the fact that dispositions, such as personality traits and coping style, negative life events, or autoimmunity, contribute to the development of both hyperthyroidism and affective disorder within different time frames. It may also be that residual cognitive and emotional deficits following hyperthyroidism (14–16, 37) make patients more prone to develop affective disorder.

It would have been interesting to estimate whether admission with hyperthyroidism caused differences in

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**Figure 1** Estimated probability of admission with a resulting discharge diagnosis of affective disorder for women from each of the study cohorts (osteoarthritis, non-toxic goitre, hyperthyroidism), hospitalised with an index episode at 60 years of age. The estimated probabilities relate to the calendar period 1 January 1994 to 31 December 1999.
risks of depressive disorder or bipolar disorder, but because of the small number of admissions with bipolar disorder diagnoses we found that a separate Poisson analysis of these events was not feasible. However, there was no shift in the distribution of bipolar disorder diagnoses and depressive disorder diagnoses in the three cohorts, with admissions with bipolar disorder diagnoses constituting 13–15% of the total number of affective disorder diagnoses. This is what would be expected in an unselected sample of patients with affective disorder (38).

It is not possible to give a single measure of the relative risk of admission with affective disorder, because the risk changes over time and varies with the age of primary admission with hyperthyroidism. This is illustrated in Figs 1 and 2. For a woman without substance abuse who is admitted with hyperthyroidism at the age of 60, an estimated lifetime risk of admission with affective disorder is approximately 3%. However, as an admission with affective disorder implies a clinically severe event, this must be considered a noteworthy risk.

Methodological considerations

The historical prospective cohort design used in this study has unique advantages but also several limitations.

The strength of the study is the use of register data covering an entire national population. The numerous patients under study enabled even relatively rare events to be detected with statistical significance. By comparing patients discharged from hospital with diagnoses of affective disorder with those having passed the threshold of hospital admission with other chronic disorders, we avoided biases that can otherwise affect epidemiological studies. Thus, recall bias, Berkson’s bias and selection bias due to non-participation or to geographic or socio-economic factors, is minimised in this study design. Physicians may have been more observant of the affective symptoms of patients with hyperthyroidism than of patients from the control groups, so referral bias may explain part of the elevated risk ratio in the immediate months after discharge. However, referral bias can hardly explain the long-term elevated risk of admission with affective disorder, as physician’s awareness of prior admissions with hyperthyroidism would decrease with time after index discharge.

We do not find it reasonable to believe that the pattern of prior admissions to somatic hospital wards has systematically influenced the subsequent distribution of affective diagnoses in ways other than by the possible referral bias discussed above. Misclassifications or flawed diagnoses are probably randomly distributed.
among the three cohorts, and in this way do not give rise to differential bias.

A limitation of the study is that it includes only patients who have been admitted to hospital at least once. This pertains to the selection of cohorts, and to the outcome of interest. We find it reasonable to assume that main discharge diagnoses of depression, bipolar disorder, osteoarthritis or hyperthyroidism denote that patients suffered from the respective diseases to degrees that made them un-manageable in outpatient settings. The results thus represent the most severe spectrums of the diseases under study. In Denmark, patients with newly discovered hyperthyroidism have traditionally been admitted to hospital for evaluation. This is reflected in the large number of patients registered with a main diagnosis of hyperthyroidism (39). However, in the last five years of the study period outpatient management became more common, and as even severe hyperthyroidism can be medically treated in an outpatient setting, it is possible that the study is biased by an overrepresentation of patients with hyperthyroidism with weak adherence to therapy. Patients with this trait could be prone to develop affective disorder at a greater rate than the patients who were selected into the control cohorts.

The data in the Danish registers are systematically collected for mainly administrative purposes, without specific emphasis on utility for scientific research. Therefore, the diagnoses were not standardised for research purposes but were based on the diagnostic practice of clinicians in Denmark in the observational period. The diagnostic validity of the DPCRR diagnoses has been compared with ICD-10 research criteria for affective disorder and was correct in 84% of cases (40). The diagnostic validity for thyroid disease in general and for bone and joint disease was 80% and 81% respectively (41). Also, in a screening of 900 hospital files of patients with diagnoses of hyperthyroidism and hypothyroidism only 2% of cases were misclassified in the DNHR (42).

The diagnostic validity decreases with the number of digits employed in the ICD-10, so to achieve a diagnostic validity of this size it is necessary to group the diagnoses into main categories such as ‘hyperthyroidism’, ‘osteoarthritis’ or ‘depression’, as these can be defined using the first three digits of the ICD diagnoses only. In this way we can investigate the associations between generic disease categories, but, for example, we cannot distinguish between the risk of re-admission with bipolar type 1 disorder or ‘rapid cycling’ disorder for patients with hyperthyroidism. However, we have attempted to identify patients with Graves’ disease by using all 5 digits in the ICD diagnoses. Because the literature about hyperthyroidism and affective disorder comorbidity suggests that this disease may, in particular, be associated with affective disorders. The study does not confirm that patients with Graves’ disease are more prone to develop affective disorder than are other patients with hyperthyroidism, but as the diagnostic validity of the Graves’ disorder diagnoses has not been specifically investigated, this result must be interpreted with caution.

Information on modes of treatment and medications, risk factors other than thyroid disease, or thyroid morbidity not leading to hospital admission, is not registered and is therefore not available for analysis.

**Osteoarthritis and non-toxic goitre as control diagnoses**

In previous published research on other diseases (30), we have argued that patients admitted with osteoarthritis are suitable controls if the aim is to compare rates of psychiatric disorder admissions between chronic disorders. Osteoarthritis, like hyperthyroidism, is a chronic condition that may require long-term medication and it may pose long-term psychological concerns for patients (43). No influence of mood regulation or other major brain functions have been associated with this control disease (44, 45).

In this study we included patients admitted with non-toxic goitre as an additional control group. This was done to match the characteristic sex distribution of the hyperthyroidism cohort. In previous investigations of mental symptoms, patients with non-toxic goitre have been used as controls to patients treated for other thyroid disorders (15). Moreover, patients with non-toxic goitre mimic patients with hyperthyroidism in that patients from the two groups undergo many of the same diagnostic procedures, they are admitted to similar types of hospital wards, and they are exposed to diagnosing clinicians from the same branches of the medical community. We note that the two control cohorts do not differ significantly from each other in the estimated rates of re-admission with affective disorder. This increases our confidence in the study design and in the validity of the increased risk ratio of affective disorder found among patients discharged from hospital with hyperthyroidism.

In conclusion, hospitalisation with the syndrome of hyperthyroidism is associated with a markedly increased immediate risk of severe affective disorder as well as a moderately increased long-term risk.

In absolute figures, only a small percentage of patients admitted with hyperthyroidism will later be admitted with depressive disorder or mania. However, it must be assumed that a substantial number of patients have less severe affective episodes that do not lead to hospitalisation. Clinicians should be aware of the pattern of risk of affective disorder among patients with a history of hyperthyroidism.

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