



# Death by unnatural causes, mainly suicide, is increased in patients with Hashimoto's thyroiditis. A nationwide Danish register study

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## Abstract

**Purpose** Hashimoto's thyroiditis (HT) is associated with excess psychiatric in addition to reduced quality of life. However, little is known about risk of unnatural manners of death in HT. We investigated the risk of death by accidents, suicide, violence/homicide, and unknown causes in patients with HT, compared to a matched control population.

**Methods** Register study covering all adult Danes diagnosed with HT during 1995–2012. In total, 111,565 HT cases were identified and matched for age and sex with four euthyroid controls. The hazard ratios (HR) for mortality were calculated using Cox regression analyses, adjusted for pre-existing morbidity. Median follow-up time was 5.9 years (range 0–17.5).

**Results** Compared to controls, HT patients had an increased frequency of death by suicide (0.10% vs 0.07%,  $p < 0.001$ ) and unknown manners (0.05% vs 0.02%,  $p < 0.001$ ). There were no significant differences between controls and HT patients in risk of death by accidents (0.36% vs 0.37%,  $p = 0.384$ ) or violence (0.004% vs 0.005%,  $p = 0.749$ ). After adjustment for pre-existing somatic and psychiatric morbidity HT patients still had an increased risk of suicide and death by unknown causes, whereas risk of death caused by accidents was reduced.

**Conclusions** Mortality due to suicide and unknown causes, but not accidents and violence, was increased in HT. This indicates that HT may have a significant role in the pathophysiological mechanisms of suicidal behavior. This suggests that physicians caring for HT patients should be vigilant when facing expressions of suicidal ideation or signs and symptoms of self-harm as a first step towards prevention.

**Keywords** Hashimoto's thyroiditis · Hypothyroidism · Mortality · Unnatural death · Suicide · Population-based

## Introduction

The possible relationship between thyroid dysfunction, mood disorders, and brain dysfunction has been observed since the earliest descriptions of hypothyroidism and hyperthyroidism [1]. The crucial role of thyroid hormones for the development and differentiation of neurons and neuroglia and hence for the development and function of the central nervous system is well recognized [2, 3]. It is also widely accepted that mood disturbances, cognitive impairment and a number of other psychiatric symptoms can emerge due to dysregulation of thyroid function [2]. In fact, the majority of patients with hypothyroidism (whether of

autoimmune origin or not) experience a number of psychiatric symptoms such as sadness, poor concentration, anxiety, and sometimes even altered personality with psychotic symptoms [4, 5]. Quality of life impairment, as evaluated by both disease specific and generic health related quality of life questionnaires, may persist in many during therapy [6–8]. The high frequency of long-term sickness absence, unemployment, and disability pension reported in patients with hypothyroidism, reflects that this group of patients also has reduced working capacity [9, 10]. In line with the observed clinical symptoms and the associated socio-economic consequences, most [11, 12], but not all [13], large scale clinical studies report an association between hypothyroidism and psychiatric morbidity.

The combination of the profound impact on quality of life and increased burden of psychiatric [12] and somatic morbidity [14], as well as increased all-cause mortality [15, 16] raises the question whether patients with hypothyroidism could have an increased risk of unnatural death due to accidents, suicide, or violence/homicide. An

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increased risk of suicide has previously been reported in other diseases with impact on quality of life, such as Graves' disease [17], diabetes [18], and multiple sclerosis [19], to name but a few. However, little is known about the risk and manner of unnatural death in patients with hypothyroidism. To our knowledge, only one study has reported data on this subject [20]. However, due to lack of power, that study [20] (which reported no significantly increased risk of suicide or other external causes of death in a group of female patients with hypothyroidism) could not provide evidence for or against an increased risk of unnatural death in patients with hypothyroidism. In the present study, we have utilized a number of Danish health registers in order to explore the risk and manner of unnatural deaths in a nationwide sample of 111,565 patients with Hashimoto's thyroiditis (HT).

## Materials and methods

### Data sources

The Danish Civil Registration System harbors information on demographics, vital status, date of death, and residence of all persons living or having lived in Denmark [21]. The Danish National Patient Registry (DNPR) contains information on diagnoses given at all hospital in- and outpatient visits since 1977 and 1995, respectively [22]. All registrations within the DNPR are according to the International Classification of Diseases (ICD), using the ICD-8 codes for diagnoses before 1994 and the ICD-10 codes from 1994 up until now. The Danish National Prescription Registry (DNPrR) covers information on all prescription drugs dispensed from Danish pharmacies since 1995 [23]. DNPrR holds, among other things, information on medical products coded according to the Anatomic Therapeutic Chemical (ATC) classification system and the date of dispensing. The Danish Register of Causes of Death (DRCD) contains information on date, manner, and cause of death for all citizens dying in Denmark [24].

By means of a unique 10-digit personal identification number given to all persons living/having lived in Denmark, the above registers were linked, and information was extracted on an individual level.

### Study population

In order to obtain the same time frame of observation in our different data sources (DNPR, DNPrR, and DRCD) only patients diagnosed with hypothyroidism after 31 December 1994 were eligible for this study. Thus, cases were ascertained from 2,634,844 Danish persons who had at least one registration within DNPR or DNPrR between 1995 and

2012 (Fig. 1). Subjects with no thyroid related diagnosis, as well as patients with present or previous hyperthyroidism (defined by the ICD-10 codes E05.0-E05.9 in DNPR or having received prescriptions of antithyroid drugs (ATC: HO3B in DNPrR) were excluded. Patients with goiter (ICD-10: E04.0-E04.2 and E07.8), thyroid cancer (ICD-10: C73), congenital hypothyroidism (ICD-10: E00.0-E00.9 and E03.0-E03.3), pituitary disease (ICD-10: E22.0-E22.9, E23.0-E23.7 and E24.0), hypothyroidism due to thyroid surgery (ICD-10: E89.0), or treatment with lithium (ATC: CO1BD01) or amiodarone (ATC: NO5AN), were also excluded. Finally, in order to ensure inclusion of only incident cases, the first 12 months of the study period were used as a washout period and all cases diagnosed with hypothyroidism within this period were also excluded. A total of 111,565 patients with Hashimoto's thyroiditis, as defined by ICD-10 codes E03.4-E03.9 and E06.3 in DNPR, or by at least two prescriptions of thyroid hormone (ATC: HO3A, in DNPrR), and no obvious other cause of hypothyroidism (see above) were identified.

Each of the 111,565 cases with HT was matched for age and sex with 4 subjects from the background population. To be considered as a control, individuals should be alive on the date of diagnosis of the corresponding case and euthyroid, which was defined as no thyroid related diagnoses in the DNPR and no record of thyroid hormone and/or antithyroid drug use in DNPrR.

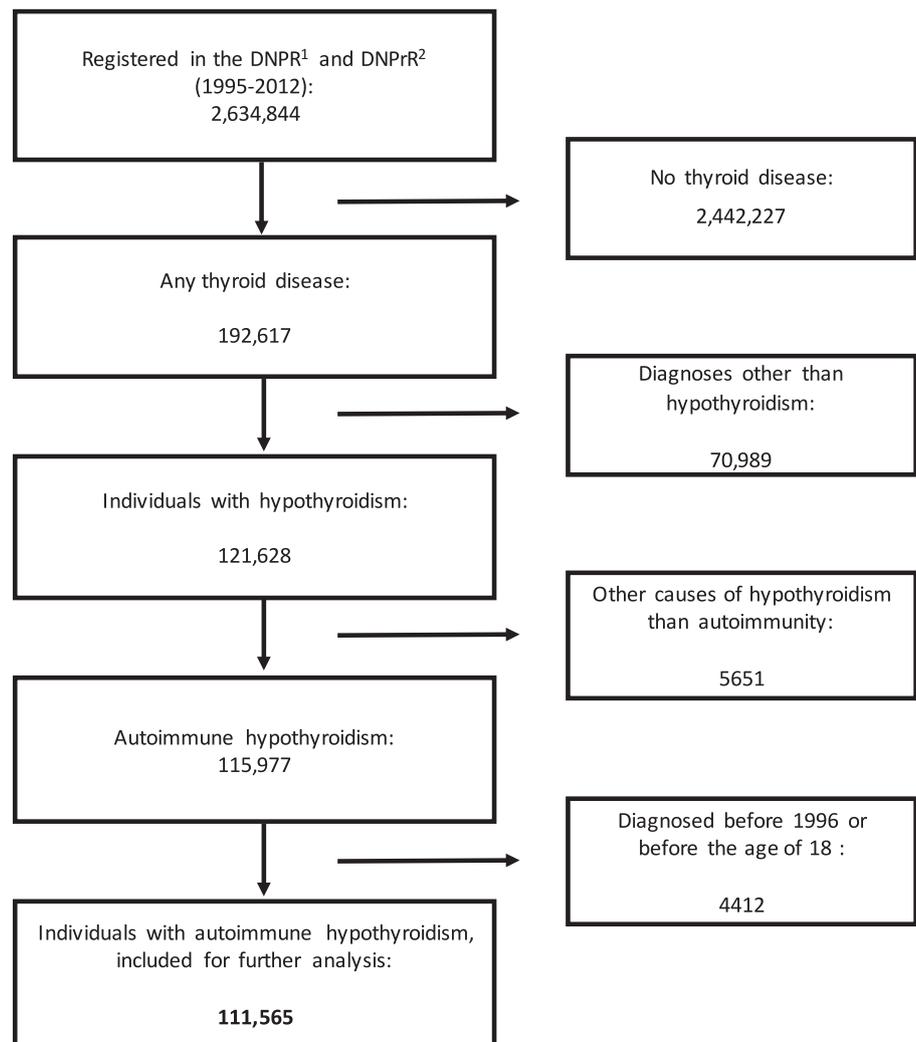
### Outcome – manners of death

Manners of unnatural death were extracted from DRCD and subcategorized further into accidental, suicidal, violence/homicide, or unknown causes of death.

### Pre-existing morbidity

The burden of somatic morbidity was evaluated by using the Charlson score (CS). CS accounts for 19 disease groups (myocardial infarction, heart failure, vascular disease, cerebrovascular disease, dementia, chronic lung disease, rheumatic disease, gastric ulcer, liver disease, diabetes mellitus without complications, diabetes mellitus with complications, hemiplegia, kidney disease, cancer, cancer with metastases, lymphoma, leukemia, liver failure, and AIDS) by creating a weighted score on an individual level, to optimize the prediction of the one-year mortality risk [25]. The CS has been used in a large number of studies and in a number of different phenotypes, including non-malignant diseases [26–28]. The CS was mainly based on records in DNPR. However, many patients with diabetes, cardiovascular diseases, and chronic lung diseases are primarily seen and treated in a primary care setting and therefore do not have a record in this register. In order to

**Fig. 1** Flowchart showing the selection of cases with autoimmune hypothyroidism. **a** The Danish National Patient Registry; **b** The Danish National Prescription Registry



classify these subjects correctly, pre-existing morbidity was also evaluated by using information from DNPrR. Hereby, users of antidiabetic drugs (ATC: A10), cardiovascular-related drugs (ATC: B01, C01, C03, C07, C08, C09, and N02) and drugs used for obstructive airway disease (ATC: R03) were classified as having pre-existing diabetes, cardiovascular disease, or lung disease, respectively.

All persons with a psychiatric diagnosis in DNPR (ICD-10: F20-F25, F28-F34, F38-F39, and F41), or registered in DNPrR as users of antipsychotic (ATC: N05A), antidepressant (ATC: N06A), or anxiolytic (ATC: N05BA) drugs before the date of inclusion in the study, were classified as having or having had pre-existing psychiatric morbidity.

### Statistical analyses

Group frequencies were compared with the Pearson  $\chi^2$  test or Fisher's exact test, when one or more of the cells had an

expected frequency of  $\leq 5$ . Group means were compared by a t-test and group medians by the Mann–Whitney-test. Risk of different manners of unnatural death in HT compared to controls was evaluated by Cox's proportional hazard model, with time since diagnosis as the underlying time variable. Hence, person years of follow-up were accumulated from the date of diagnosis, and terminated at the date of death, emigration, or end of follow-up (31 December 2012), whichever came first. The validity of the proportional hazards assumption was evaluated by inspection of Schoenfeld residuals versus follow-up time (no significant associations were found). To estimate differences in fluctuations of time of death by unnatural causes across the time period after the diagnosis of HT, the Walter-Elwood test for seasonality was used. Significant differences were defined as a  $p$ -value  $< 0.05$ , using two-tailed tests. All analyses were conducted using STATA version 14.1 (2015; Stata Corporation, College Station, TX, USA).

**Table 1** Baseline characteristics for individuals with Hashimoto's thyroiditis and their controls

	Cases	Controls	<i>p</i> -value
Number	111,565	446,260	–
Median age at diagnosis (range), years	56 (18–104)	56 (18–104)	–
Number of females	91,891 (82%)	367,564 (82%)	–
Number with CS <sup>a</sup> = 0	18,909 (17%)	178,865 (40%)	<0.001
Number with CS <sup>a</sup> = 1	39,873 (36%)	160,955 (36%)	0.040
Number with CS <sup>a</sup> = 2	25,978 (23%)	65,864 (15%)	<0.001
Number with CS <sup>a</sup> > 2	26,805 (24%)	40,576 (9%)	<0.001
Number with pre-existing psychiatric morbidity <sup>b</sup>	38,194 (34%)	122,974 (28%)	<0.001
Median time of follow-up (range), years	5.9 (0.0–17.5)	6.2 (0.0–17.5)	<0.001

<sup>a</sup>Charlson score, a measure of pre-existing somatic morbidity.

<sup>b</sup> Defined by all in- and outpatient visits with a psychiatric diagnosis in DNPR, or with a track record in DNPrR of use of antipsychotic, antidepressant, or anxiolytic medication

**Table 2** Mortality in relation to the manner of unnatural death in individuals with Hashimoto's thyroiditis compared to their controls

Manner of death	Cases	Controls	<i>p</i> -value
Accident Number (%)	418 (0.37)	1594 (0.36)	0.384
Suicide Number (%)	111 (0.10)	301 (0.07)	<0.001
Violence/homicide Number (%)	5 (0.00)	17 (0.00)	0.749
Unknown Number (%)	53 (0.05)	106 (0.02)	<0.001

## Ethical considerations

Due to the register-based design, utilizing historical, anonymized register-data, there has been no direct patient involvement in the study, thus no patient consent had to be obtained. The study has been approved by the Danish Data Protection Agency (project number: 704047).

## Results

The baseline characteristics of the HT and the control population are outlined in Table 1. Compared to their controls, HT cases had a significantly higher burden of both somatic and psychiatric pre-existing morbidity and a shorter follow-up time than the control population.

### Risk and manners of unnatural death in HT

Compared to controls there was a significantly higher rate of suicide and death by unknown manners in patients with HT, but not death due to accidents or violence (Table 2). After adjustment for pre-existing somatic and psychiatric

**Table 3** Hazard ratios (HR) and confidence intervals (CI) for different manners of unnatural death in individuals with Hashimoto's thyroiditis compared to their controls

Manner of death	HR, unadjusted	<i>p</i> -value	HR, adjusted <sup>a</sup>	<i>p</i> -value
Accident	1.08 (0.97–1.20)	0.146	0.68 (0.61–0.77)	<0.001
Females	1.05 (0.93–1.19)	0.440	0.67 (0.59–0.76)	<0.001
Males	1.24 (0.98–1.55)	0.070	0.73 (0.57–0.93)	0.010
Suicide	1.53 (1.23–1.90)	<0.001	1.31 (1.04–1.65)	0.024
Females	1.60 (1.22–2.09)	0.001	1.35 (1.01–1.79)	0.041
Males	1.45 (0.99–2.13)	0.055	1.25 (0.83–1.89)	0.277
Violence/homicide	1.21 (0.45–3.29)	0.705	0.87 (0.31–2.48)	0.796
Females	1.17 (0.38–3.55)	0.784	0.85 (0.26–2.77)	0.787
Males	1.37 (0.14–13.19)	0.783	0.92 (0.09–8.93)	0.943
Unknown	2.04 (1.47–2.84)	<0.001	1.65 (1.17–2.34)	0.005
Females	1.68 (1.13–2.51)	0.011	1.36 (0.89–2.06)	0.152
Males	3.34 (1.83–6.09)	<0.001	2.76 (1.45–5.26)	0.002

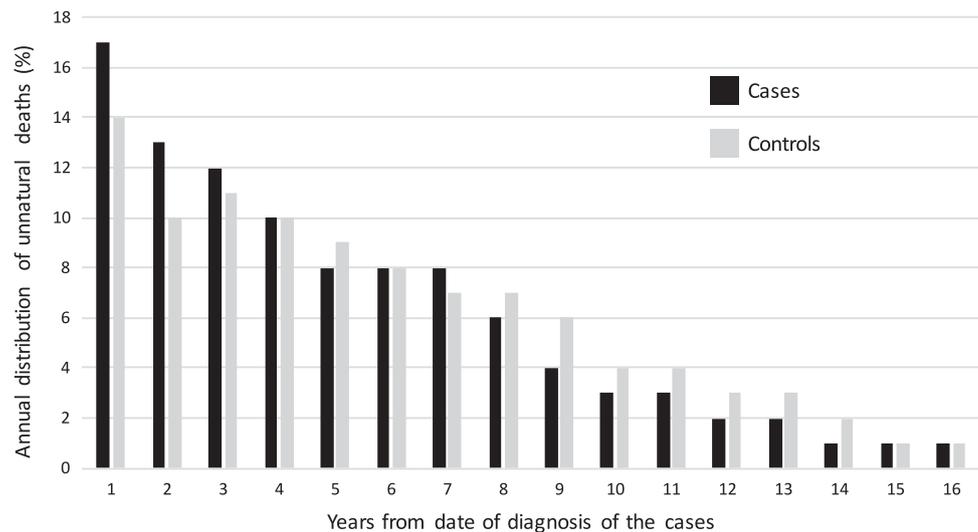
<sup>a</sup>Adjusted for both somatic and psychiatric morbidity prior to the date of the thyroid diagnosis or date of inclusion in the study for cases and controls, respectively.

morbidity, the hazard ratios (HR) for the different manners of death showed a statistically significant increased risk of death by suicide (HR 1.31; 95% confidence interval (CI):1.04–1.65) and unknown manners (HR 1.65; 95% CI: 1.17–2.34) in HT, whereas risk of death due to accidents was significantly decreased (HR 0.68; 95% CI: 0.61–0.77). Stratification into females and males essentially yielded the same results as the main analysis, although the results were influenced by low power (Table 3). Results based on the Walter Elwood test showed significant differences in fluctuations of time of death by unnatural causes, overall, across the time period after the diagnosis of HT ( $p < 0.001$ ; Fig. 2). This was also true when subdividing into the categories death by suicide ( $p = 0.001$ ), death by unknown manners ( $p = 0.032$ ), death by accidents ( $p < 0.001$ ) or death by violence ( $p < 0.001$ ). As visualized in Fig. 2, the increase in unnatural deaths occurred in the early period after diagnosis in cases compared to controls. After diagnosis of HT, the median time to death by unnatural causes was 3 years for cases versus 4 years for controls ( $p < 0.001$ ).

## Discussion

In this nationwide population- and register-based follow-up study of more than 110,000 Danish patients with HT, the risk and manners of unnatural death were scrutinized. We found that, compared to a sex and age matched control population, patients with HT had a 65 and 31% increased risk of death due to unknown manners and suicide,

**Fig. 2** Distribution of deaths by unnatural causes in cases and their controls over time. From date of diagnosis among cases



respectively. In line with other Danish and Scandinavian register-based studies exploring the risk and manners of unnatural deaths in different disease populations [17, 29], deaths from accidents, violence/homicide, and unknown manners were not included in the suicide group, as these cannot be labelled as evident suicides. Accepting, that it is not always straight forward to classify correctly the manners of unnatural deaths, these three groups, especially the unknown group, may very well also include many deaths from suicide. If some of the deaths registered as unknown manner of death were in fact due to suicide, the reported risk rate for suicides in this study would most likely be even higher. Suicide, for a number of reasons, is a sensitive issue, and very likely to be under-reported [30]. Whether the under-reporting or misclassification differs between the background population and those with hypothyroidism/Hashimoto's thyroiditis remains unknown. However, we cannot imagine why this would be the case.

In line with our findings, a higher risk of suicide has been observed in a number of other organ specific autoimmune diseases such as Graves' disease [17], diabetes [18], and inflammatory bowel disease [31]. At variance, the only other study reporting data on unnatural deaths in patients with hypothyroidism, did not find an increased risk of dying from suicide or external manners [20]. The reason for this divergence is most likely the lack of power in the study by Journy et al. [20], who reported 28 cases of death by suicide/external manners out of a population of 4,456 patients with hypothyroidism (0.6%) compared to 0.4% in the control population. Although these prevalences are almost identical to ours (0.5% and 0.4% in cases with HT and controls, respectively), only our study has sufficient power to show a statistically significant difference. Thus, a power calculation estimates that it is necessary with a sample size of more than 20,000 cases and controls, to show a 40%

increased frequency of unnatural death with a power of 80%. As suicide as a cause of death is often under-reported, our data may be "only" the top of the iceberg, which underlines the clinical relevance for these findings.

Another interesting finding in our study is that the risk of death due to accidents was reduced by 32% in patients with HT as compared to the control population. The present study does not allow any firm conclusions regarding the reason(s) for this observation. However, it could be speculated that the negative impact of HT on quality of life and problems associated with everyday life and work disability are contributing factors [6, 10]. Following this line of thought, HT individuals may be less inclined to participate in activities which could be linked to an increased risk of accidents.

Our study lacks information on smoking habits [32] and use of alcohol [33] both of which are linked to excess mortality and thyroid diseases. However, including control for pulmonary as well as hepatic diseases by the CS, partly compensates for this and we consider our findings biologically plausible. First, it is well accepted that thyroid hormones interact with the distribution of important neurotransmitters, such as serotonin and norepinephrine<sup>2</sup>, both linked with the development of depression and mood disorders [34]. Second, the development of mood disorders and suicide has recently been associated with autoimmune diseases [35], including thyroid autoimmunity [36]. In fact, several studies have reported a possible relationship between circulating thyroid autoantibodies, especially anti-thyroperoxidase, and outcomes such as affective disorders and alterations in brain structure and function, even in the absence of thyroid hormone abnormalities [37, 38]. Due to unavailability of biochemical variables in this register-based study, we cannot explore whether the increased risk of unnatural death in HT is due to the thyroid dysfunction

*per se* or is related to the presence of thyroid autoantibodies. The fact that the excess risk of death mainly occurs in the first three years after diagnosis of HT might suggest that thyroid dysfunction in the early phase of the disease is a contributing factor. Further interrogation of the potential role of the level of thyroid hormones versus thyroid autoimmunity could be accomplished by including a case population suffering from hypothyroidism of non-autoimmune origin. However, despite our huge number of hypothyroid individuals, 111,565 with HT and 5,651 with non-autoimmune hypothyroidism (Fig. 1), we lack power to further dissect this issue.

The major strengths of our study are the size and the limited selection bias by ascertaining from the entire Danish population in combination with a high validity of the Danish health related registers. As an example, the validity of the DNPR has been found to be high and misclassification of thyroid dysfunction has been shown to occur in <2% of cases [39]. In addition, our definition of HT, even in the light of lacking biochemical variables, is quite robust. As evident from Fig. 1, all patients with a non-autoimmune cause of thyroid dysfunction were excluded and out of all hypothyroid subjects identified in this study, 95% were classified as having autoimmune hypothyroidism, which is in line with previous reporting from Denmark [40].

In conclusion, mortality due to suicide and unknown manners, but not accidents and violence, was increased in HT. These findings indicate that HT may have a significant role in the pathophysiological mechanisms underlying suicidal behavior. The current study suggests that physicians treating HT patients should be vigilant about expressions of suicidal ideation or signs and symptoms of self-harm as a step towards prevention.

### Compliance with ethical standards

**Conflict of interest** The authors declare that they have no conflict of interest.

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