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Death by suicide in Graves’ disease and Graves’ orbitopathy. A nationwide Danish register study. *

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Abstract

**Background.** Graves’ disease (GD) is associated with excess morbidity and mortality, but little is known about unnatural manners of death and the potential relation with Graves’ orbitopathy (GO). Here we investigate the risk of unnatural death in Graves’ patients with and without orbitopathy, compared to matched control populations.

**Methods.** Cohort study covering all adult Danes (≥18 years) diagnosed with GD or GO during 1995-2012. Median follow-up time was 7.9 years (range, 0-17.5). Utilizing the Danish Register of Causes of Death and the Danish National Patient Registry, 28,461 subjects with GD, and 3965 with GO were identified and matched for age and sex with four subjects from the background population. Manner of death was identified and hazard ratios (HR) for mortality due to unnatural deaths (accident, suicide, violence/homicide, and unknown) were calculated using Cox regression analyses, adjusted for pre-existing somatic and psychiatric morbidity.

**Results.** In GD overall there was an increased risk of death from unknown unnatural manners [HR: 2.01 (95% confidence interval: 1.17-3.45); P=0.012] and of suicide, although the latter difference was not with certainty statistically significant [HR 1.43 (1.00-2.04); P=0.053]. There was no significant difference in risk of death from suicide in GD subjects compared to their controls [HR 1.27 (0.85-1.89); P=0.253]. However, GO patients had a significantly higher risk of death from suicide [HR 2.71 (1.16-6.32); p=0.022].

**Conclusions.** Mortality by suicide was increased in GD, most significantly in patients with GO, also after adjustment for pre-existing somatic and psychiatric disease. These findings indicate that GD and GO may have a significant role in the pathophysiological mechanisms of suicidal behavior. Beyond independent confirmation, reasons for this need to be explored in order to introduce preventive measures.
Introduction

Graves’ disease is associated with an increased somatic (1) as well as psychiatric co-morbidity (2), with possible profound effects on the mental health. In fact, the majority of GD patients experience some psychiatric symptoms, such as anxiety, nervousness, irritability, anger and sadness, poor concentration, and sometimes even changes in personality (3, 4). Quality of life impairments, as determined by disease-specific and generic health related quality of life instruments, persist also after therapy (5). In GD patients with involvement of the eyes, which is clinically the most severe manifestation of hyperthyroidism (6), studies have demonstrated a significantly reduced quality of life (7), increased psychosocial morbidity (8), and have also reported psychotic symptoms (9). Moreover, GD patients, both with and without orbitopathy (10), have an increased risk of long-term sickness absence, work disability, unemployment, loss of labour market income, and receiving a disability pension (10-12).

In a recent study of the entire Danish population (13), we found an increased mortality in patients with a history of GD, compared to a matched control population, whether with (23%) or without orbitopathy (19%). The negative impact on quality of life with an increased somatic and psychiatric morbidity raises the question whether these patients could have an increased risk of unnatural death due to suicide, accidents or violence/homicide. As for suicides, this has previously been shown in other chronic diseases with major impact on quality of life, such as diabetes mellitus (14, 15). However, little is known about unnatural deaths in GD and GO patients. To our knowledge, there is only one prior study on this subject, which found no significantly increased risk of suicide in hyperthyroid patients (16).

Denmark’s long tradition for storing information on its citizens in nation-wide registers (17), provides a unique opportunity for large scale, population-based investigations. In this study we aimed to address i) the risk of unnatural death in GD overall compared to an adequately matched control population, ii) the risk of unnatural death in GD patients without and with GO separately, compared to their respective control populations.
Materials and methods

Data sources

In this register-based cohort study, data were retrieved from the Danish health registers listed below. By means of a unique personal identification number, the registers were linked and information was recovered on an individual level.

The Danish Civil Registration System (DCRS) contains information on demographics, vital status, date of death and residence of all persons living or having lived in Denmark (18). The Danish National Patient Registry (DNPR) holds information on all diagnoses given at all hospital in- and outpatient visits in Denmark (19). Registration of diagnoses is based on the Danish edition of the International Classification of Diseases, using the 10th revision (ICD-10) from 1994 and up until now. The DNPR has high validity, with misclassification of thyroid diagnoses occurring in less than 2% (20, 21). The quality of data on psychiatric diagnoses, based on register-based information, has also been found to be acceptable (22). The Danish National Prescription Registry (DNPrR) holds information on prescriptions of drugs dispensed from Danish pharmacies since 1995 (20). Danish pharmacies are required by law to register all prescriptions dispensed at an individual level. The registry holds, amongst other things, information on medical products coded according to the Anatomic Therapeutical Chemical (ATC) classification system and the date of dispensing. Because antithyroid, as well as antipsychotic, antidepressant and anxiolytic drugs are prescribed drugs, the DNPrR is a highly valid source of information for our purpose (1). The Danish Register of Causes of Death (DRCD) covers all deaths among citizens dying in Denmark (23). It holds information on date, manner and cause of death.

Study population

Admissions to hospital wards have been registered in the DNPR since 1977. However, registration of outpatient visits did not start until 1995. The DNPrR, with information on prescriptions of drugs, was also first established in 1995. Since GD patients, as well as the majority of patients with psychiatric disorders, are often solely treated as outpatients, the start date for inclusion in this study was set to the year 1995.

Subjects with GD were defined by an ICD-10 code E050, in the DNPR. GO-subjects were retrieved from the subjects with GD, and defined by the ICD-10 codes H052 and/or H062. Control subjects were defined by lack of thyroid or orbitopathy related ICD-
10 codes in DNPR and no evidence of dispensed prescriptions of thyroid hormone or antithyroid drugs in the DNPrR. The first six months of 1995 were used as a washout period, to ensure inclusion of only incident cases. Therefore, all cases appearing with a thyroid diagnosis in this period were excluded from the study. We identified 32,426 individuals with GD, out of whom 28,461 had GD without orbitopathy, and 3965 had GO. Each case was randomly matched for age and sex with four control subjects.

**Mortality and manners of death.**

Information on date and manner of death was obtained from the DRCD (23). Manners of unnatural death were categorized into accidental, suicidal, violence/homicide, and unknown.

**Pre-existing morbidity.**

The Charlson score (CS) was used as a measure of pre-existing somatic morbidity, in order to adjust for confounding. It includes 19 disease categories (vascular disease, heart failure, myocardial infarction, cerebrovascular disease, dementia, hemiplegia, chronic lung disease, rheumatic disease, liver disease, liver failure, gastric ulcer, kidney disease, diabetes mellitus without complication, diabetes mellitus with complications, cancer without metastases, cancer with metastases, lymphoma, leukaemia and AIDS); each assigned a score from 1 to 6, depending on severity. For each individual, the CS is the sum of scores for all their conditions. Each increment in the CS level has been associated with a 2.3-fold (95% confidence interval: 1.9-2.8) increase in the 10-year mortality risk in a cohort of 685 breast cancer patients (24). The CS has been validated for different morbidities including non-malignancies (25). We based the CS primarily on information from the DNPR. However, to ensure inclusion of patients with diabetes, cardiovascular diseases, and lung diseases, many of whom are solely seen in primary care, we also used information from the DNPrR for these disease categories. Thus, we classified users of anti-diabetics (ATC code: A10), cardiovascular-related drugs (ATC: B01, C01, C03, C07, C08, C09 or N02), and drugs for obstructive airway diseases (ATC: R03), as having diabetes, cardiovascular diseases, or lung diseases, respectively.

In order to adjust for pre-existing psychiatric morbidity, all individuals with a prior psychiatric diagnosis in the DNPR, or with evidence of treatment with antipsychotic
(ATC: N05A), antidepressant (ATC: N06A) or anxiolytic (ATC: N05BA) medication in the DNPrR were classified as having had a 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 unnatural death in GD overall, and GD and GO separately, was evaluated by Cox’s proportional hazard model, and time since diagnosis was 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 (December 31, 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). 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).

**Ethical considerations.**

There was no patient involvement in the design or analysis of this study. The data used in the study are anonymized so that the identity of all patients remained unknown to the investigators, and the project has been approved by the Danish Data Protection Agency. Project number: 704047.

**Results**

The baseline characteristics of GD and GO cases, as well as their control subjects are summarized in table 1. Compared to their controls, both GD and GO subjects had a significantly higher pre-existing morbidity and shorter time of follow-up ($P<0.001$). There was no significant difference in CS between GD and GO individuals ($P=0.248$), but the median age at time of diagnosis was higher in the GD- than in the GO-group (Table 1). The median time of follow-up was 7.9 years (range 0-17.5).

**Risk and manners of unnatural death in GD overall (GD and GO).**

There was a significantly higher overall incidence of unnatural deaths, and specifically of suicide and unknown manners of death in individuals with GD compared to
controls (Table 2). The hazard ratios (HR) for the different manners of death (Table 3) showed an increased risk of unknown manners of death in GD, also after adjustment for pre-existing somatic and psychiatric morbidity [HR: 2.01 (95% confidence interval: 1.17-3.45); P=0.012]. There was also an increased risk of suicide, although this effect attenuated after adjustment [HR: 1.43 (95% confidence interval: 1.00-2.04); P=0.053].

**Risk and manners of unnatural death in GD.**

GD patients had a significantly higher overall incidence of unnatural deaths, and specifically of unknown manners of death, than their controls (Table 2). The adjusted HR for the different manners of death showed a significantly increased risk of unknown manners of death, but not of suicide in GD [HR: 1.84 (1.02-3.32); P=0.044 and HR 1.27 (0.85-1.89); P=0.253, respectively] (Table 3).

**Risk and manners of unnatural death in GO.**

GO individuals had a significantly higher overall incidence of unnatural deaths, and specifically of suicide, compared to controls (Table 2). There was also a significantly higher risk of suicide in GO compared to controls, both before [HR 3.30 (1.45-7.52); P=0.005], and after adjusting for pre-existing somatic and psychiatric morbidity [HR 2.71 (1.16-6.32); P=0.022] (Table 3).

**Discussion**

In this large scale, population- and register-based, long-term follow-up study of more than 30,000 Danish patients with GD, we explored type and magnitude of unnatural deaths. The most striking finding was that of a 101% increased risk of death by unknown manners as compared to a sex and age matched control population. There was also a 43% increased risk of death from suicide. However, despite the huge numbers investigated, this increased risk was not with certainty statistically significant (P=0.053) after adjustment for pre-existing somatic and psychiatric morbidity. After subdivision according to presence of GO there was an excess mortality of 84% by unknown unnatural manners in individuals with GD, and an 171% increased risk of suicide in GO patients. Excess mortality from suicide, in this range or higher, has also been found in other autoimmune conditions such as type 1 diabetes (26), inflammatory bowel disease (27), and rheumatoid arthritis (28). Having access to data on deaths from accidents, violence/homicide, and a group labeled
“unknown”, we included these although the groups were small and the manners of death more uncertain. As in previous register-based studies from Denmark (29), we did not include death by accidents, violence/homicide, and unknown manners of death in the suicide category, as these cannot be classified as certain suicides. It could be speculated that these three groups, especially the unknown group also include some deaths from suicide. Clearly, if some of the deaths registered as unknown manners of death were due to suicides, the reported risk rates for suicides in this study would be even higher.

At variance with us, in the only other study on this topic, Abraham-Nordling et al. (16), in a similar sized group of hyperthyroid patients who were selected on the basis of having had radioiodine or thyroid surgery, did not find an increased risk of death from suicide. Reasons for this discrepancy are not obvious. Their findings concerned both GD and toxic nodular goitre, but without specific data on GO. The Swedish study (16) included individuals diagnosed between 1950 and 2005 at a time when diagnostic tools were less sophisticated and therapy more ablative, that is surgery or radioactive iodine, than the current propensity of offering antithyroid drug therapy in our patients, diagnosed between 1995 and 2012 (6, 30). We included all Graves’ patients, on a national level, and employed validated Danish registries (18-20, 23), while the Swedish study mainly included individuals from one region, Stockholm (16), and in contrast to our four matched controls, took advantage of one cohort hospitalized due to non-toxic goitre, and one undergoing cholecystectomy without control for pre-existing morbidity. Thus, we suggest that the disease burden of the control groups in the two studies may well have differed and that the studies are de facto incomparable. Neither of the studies adequately accounted for a number of pertinent variables, such as smoking behavior (31), length of hyperthyroidism before diagnosis (32), and long-term thyroid function control (33), all of which significantly impact morbidity and mortality.

Are our findings plausible? Pointing towards a biological mechanism, the development of mood disorders and suicide has been linked to inflammation caused by infection and/or autoimmunity (34-36). On top of that, it is currently accepted that morbidity, both before and after the diagnosis of GD, is increased (1). Moreover, although discussed until recently (32), it is beyond doubt that mortality is also increased (37), especially if the disease is poorly controlled (33). Furthermore, in addition to the
psychiatric manifestations of early and untreated GD (9), the condition is also associated with a diagnosis of psychiatric disorders (anxiety disorders, depression and psychoses) in the long-term, all of which lead to excess mortality (2). Based on the aforementioned, accepting that our study does not prove causality, we consider our findings plausible. Also the strong association of GO with deaths from suicide can intuitively be understood, in view of the huge impact of GO on quality of life, appearance, work disability, and early retirement (8, 10, 11).

Classification of the thyroid diagnosis of GD may be inaccurate. However, as mentioned previously, it has been shown that misclassification occurs in less than 2% (20, 21). Undoubtedly, not all GO cases were classified as such. But it has been shown that the cases with moderate to severe GO are correctly classified (38). It is generally accepted that the quality and validity of register-based data on somatic and psychiatric diagnoses are reliable (19, 22). Although our study is nationwide, the data is based on rather crude register-based material, and we lack information about life-style, smoking, and drinking habits. Thus we are unable to further disentangle the relative importance of these confounders. It is also important to point out that our control population only includes individuals who during the study period had at least one in- or outpatient contact. Accepting that these individuals may have an increased risk of unnatural death as compared to the general background population, our results may in fact underestimate the risk for unnatural death in GD.

We conclude that mortality by suicide seems to be increased in GD, most significantly in patients with GO. In addition to independent confirmation of our data, there are ways of extending the insight provided here. Understanding the potential role of thyroid dysfunction versus thyroid autoimmunity could be advanced by incorporating another case group suffering from nodular toxic goiter. As recently done for overall mortality in hyperthyroidism (33), analyzing the consequences for mortality of the length of thyroid dysfunction before and during therapy would offer insight into a potential dose-response relationship and thereby touch upon causality. The fact that divergent conclusions have been reached, as for the association between hyperthyroidism and mortality from suicide, suggests that type of thyroid therapy may be crucial and needs further study. Equally important is the understanding of the link between psychosocial
consequences of GO (8, 10, 11) and therapy with immunosuppressant drugs, including glucocorticoids, for the excess risk of suicide.

Acknowledgments

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Author disclosure statement

No competing financial interests exist.
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Table 1: Baseline characteristics for Graves’ disease individuals without (GD) and with Graves’ orbitopathy (GO), as well as their controls.

<table>
<thead>
<tr>
<th></th>
<th>GD</th>
<th>GO</th>
<th>GO vs. GD</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cases</td>
<td>Control</td>
<td>P</td>
</tr>
<tr>
<td>Number</td>
<td>28,461</td>
<td>113,844</td>
<td>-</td>
</tr>
<tr>
<td>Median age at diagnosis (range)</td>
<td>55 (18-102)</td>
<td>55 (18-102)</td>
<td>-</td>
</tr>
<tr>
<td>Number of females</td>
<td>23,268 (82%)</td>
<td>93,072 (82%)</td>
<td>-</td>
</tr>
<tr>
<td>Number with CS(^a) = 0</td>
<td>7,056 (25%)</td>
<td>50,116 (44%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Number with CS(^a) = 1</td>
<td>11,967 (42%)</td>
<td>39,140 (34%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Number with CS(^a) = 2</td>
<td>5,586 (20%)</td>
<td>15,372 (14%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Number with CS(^a) &gt; 2</td>
<td>3,852 (14%)</td>
<td>9,216 (8%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Median time of follow-up (range)</td>
<td>7.1 (0-17.5)</td>
<td>8.0 (0-17.5)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

\(^a\) CS: Charlson score, as a measure of co-morbidity.
Table 2: Mortality in relation to the manner of unnatural deaths, in Graves’ disease overall, in Graves’ disease without (GD) and with orbitopathy (GO), compared to their respective controls.

<table>
<thead>
<tr>
<th>Manners of unnatural death</th>
<th>Number dead</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cases (%)</td>
<td>Controls (%)</td>
<td>P</td>
<td></td>
</tr>
<tr>
<td>Accident</td>
<td>156 (0.48)</td>
<td>532 (0.41)</td>
<td>0.085</td>
<td></td>
</tr>
<tr>
<td>Suicide</td>
<td>43 (0.13)</td>
<td>103 (0.08)</td>
<td>0.007</td>
<td></td>
</tr>
<tr>
<td>Violence/homicide</td>
<td>0 (0)</td>
<td>5 (0.00)</td>
<td>0.590</td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>21 (0.06)</td>
<td>37 (0.03)</td>
<td>0.004</td>
<td></td>
</tr>
<tr>
<td>All</td>
<td>220 (0.68)</td>
<td>677 (0.52)</td>
<td>0.001</td>
<td></td>
</tr>
</tbody>
</table>

| Accident                   | 145 (0.51)  | 498 (0.44) | 0.114 |
| Suicide                    | 33 (0.12)   | 90 (0.08)  | 0.070 |
| Violence/homicide          | 0 (0)       | 5 (0.00)  | 0.590 |
| Unknown                    | 17 (0.06)   | 33 (0.03) | 0.020 |
| All                        | 195 (0.69)  | 626 (0.55) | 0.009 |

| Accident                   | 11 (0.28)   | 34 (0.21) | 0.456 |
| Suicide                    | 10 (0.25)   | 13 (0.08) | 0.015 |
| Violence/homicide          | 0 (0)       | 0 (0)     | -     |
| Unknown                    | 4 (0.10)    | 4 (0.03)  | 0.056 |
| All                        | 25 (0.63)   | 51 (0.32) | 0.009 |
Table 3: Hazard ratios (HR) for different manners of unnatural death, in Graves’ disease overall, in Graves’ disease without (GD) and with orbitopathy (GO), compared to their respective controls.

<table>
<thead>
<tr>
<th>Manners of unnatural death</th>
<th>Unadjusted</th>
<th>P</th>
<th>Adjusted (^a)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>GD+GO vs. controls</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Accident</td>
<td>1.26 (1.05-1.51)</td>
<td>0.011</td>
<td>0.96 (0.80-1.15)</td>
<td>0.672</td>
</tr>
<tr>
<td>Suicide</td>
<td>1.79 (1.25-2.55)</td>
<td>0.001</td>
<td>1.43 (1.00-2.04)</td>
<td>0.053</td>
</tr>
<tr>
<td>Unknown</td>
<td>2.39 (1.40-4.01)</td>
<td>0.001</td>
<td>2.01 (1.17-3.45)</td>
<td>0.012</td>
</tr>
<tr>
<td>All</td>
<td>1.39 (1.20-1.62)</td>
<td>&lt;0.001</td>
<td>1.08 (0.93-1.26)</td>
<td>0.322</td>
</tr>
<tr>
<td>GD vs. controls</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Accident</td>
<td>1.27 (1.06-1.53)</td>
<td>0.011</td>
<td>0.98 (0.82-1.18)</td>
<td>0.849</td>
</tr>
<tr>
<td>Suicide</td>
<td>1.59 (1.07-2.37)</td>
<td>0.022</td>
<td>1.27 (0.85-1.89)</td>
<td>0.253</td>
</tr>
<tr>
<td>Unknown</td>
<td>2.20 (1.22-3.95)</td>
<td>0.008</td>
<td>1.84 (1.02-3.32)</td>
<td>0.044</td>
</tr>
<tr>
<td>All</td>
<td>1.36 (1.15-1.59)</td>
<td>&lt;0.001</td>
<td>1.06 (0.90-1.25)</td>
<td>0.477</td>
</tr>
<tr>
<td>GO vs. controls</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Accident</td>
<td>1.39 (0.70-2.74)</td>
<td>0.345</td>
<td>0.94 (0.47-1.87)</td>
<td>0.861</td>
</tr>
<tr>
<td>Suicide</td>
<td>3.30 (1.45-7.52)</td>
<td>0.005</td>
<td>2.71 (1.16-6.32)</td>
<td>0.022</td>
</tr>
<tr>
<td>Unknown</td>
<td>4.20 (1.05-16.79)</td>
<td>0.042</td>
<td>3.79 (0.90-15.85)</td>
<td>0.068</td>
</tr>
<tr>
<td>All</td>
<td>2.10 (1.30-3.38)</td>
<td>0.002</td>
<td>1.54 (0.95-2.52)</td>
<td>0.081</td>
</tr>
</tbody>
</table>

\(^a\) Adjusted for both somatic morbidity (using the Charlson score) and for psychiatric morbidity prior to the thyroid diagnosis.

Although we provide data on violence/homicide in table 2, the fact that numbers are very low (n=5) prohibit us from calculating hazard ratios in table 3.