Hyperthyroidism is associated with work disability and loss of labour market income. A Danish register-based study in singletons and disease-discordant twin pairs

Frans Brandt, Marianne Thvilum, Laszlo Hegedüs and Thomas Heiberg Brix
Department of Endocrinology and Metabolism, Elite Endocrine Research Centre, Odense University Hospital, Sønder Boulevard 29, DK-5000 Odense C, Denmark

Abstract

Objective: To examine the risk of disability pension and changes in labour market income in patients with hyperthyroidism.

Methods: From a 5% random sample of the Danish population and twins from the Danish Twin Registry we identified 1942 hyperthyroid singletons and 7768 non-hyperthyroid (matched 1:4) controls as well as 584 same-sex twin pairs discordant for hyperthyroidism. Singletons and twins were followed for a mean of 9 years (range 1–20). Cox regression analysis was used to examine the risk of disability pension and a difference-in-differences model was used to evaluate changes in labour market income.

Results: Hyperthyroid individuals had an increased risk of receiving disability pension: hazard ratio (HR) was 1.88, (95% CI: 1.57–2.24). Subdividing as to the cause of hyperthyroidism did not change this finding: Graves' disease (GD) HR was 1.51 (95% CI: 0.87–2.63) and toxic nodular goitre (TNG) HR was 2.10 (95% CI: 1.02–4.36). With respect to labour market income, the income of hyperthyroid individuals increased on average 1189 € less than their controls (P<0.001). This difference in income was more pronounced in GD (2539 €) than in TNG (132 €). Essentially similar results, with respect to disability pension and labour market income, were seen within monozygotic twin pairs discordant for hyperthyroidism.

Conclusion: Hyperthyroidism is associated with severe work disability as reflected by an 88% increased risk of receiving disability pension and a significant loss of labour market income. Similar results in monozygotic twins discordant for hyperthyroidism suggest that genetic confounding is unlikely.

Introduction

Hyperthyroidism is a common endocrine disorder with a life-time risk of 5–10% (1). Regardless of its cause, the development depends on a complex interplay between gender, age, genetics and environmental exposures (2, 3). Hyperthyroidism is associated with an increased somatic morbidity, such as cardiovascular diseases, diabetes mellitus and rheumatic diseases (4, 5, 6, 7). Also, psychiatric morbidity, such as psychosis, anxiety disorders and bipolar disease (8), is overrepresented among patients with hyperthyroidism. Hyperthyroid individuals have been reported to have a reduced quality of life (9) and problems with everyday routines, such as housekeeping (10). However, less is known about whether, and if so to which degree, the patients with hyperthyroidism have decreased work ability.

In studies of self-reported work role functioning, more than 30% of patients with hyperthyroidism have reported to be completely or partially work-disabled (11), especially...
right after the thyroid diagnosis (12, 13). However, the presence of recall-bias questions the validity of these findings. In a recent study, where 262 hyperthyroid patients were recruited from outpatient clinics of two Danish University Hospitals, subjects with hyperthyroidism had within the first year after the diagnosis some degree of work disability and an increased risk of sickness absence (14). Importantly, that study did not have the power to evaluate whether the findings were influenced by the cause of hyperthyroidism and whether the observed consequences of hyperthyroidism on work disability persisted years after the diagnosis. In the present study, using a random 5% sample of the Danish population and applying record linkage between administrative registers, we investigated the risk of receiving disability pension in patients with Graves’ disease (GD) and nodular toxic goitre (NTG) followed for up to 20 years. For the first time in the literature on hyperthyroidism, we calculated the difference in income between individuals with hyperthyroidism and euthyroid controls, testing the hypothesis that hyperthyroid individuals have a decline in labour market income. Additionally, we investigated the same variables in twin pairs discordant for hyperthyroidism. Using the latter approach, we were able to match not only for genetic factors but also for a number of non-measured factors that could influence adult socio-economic status, such as early life environmental exposures and family socio-economic background (15).

**Subjects and methods**

Denmark has a longstanding tradition for storing health information as well as information regarding socio-economic factors, such as income and employment, from all citizens in central databases (16). Connecting these data opens a unique possibility to study the socio-economic consequences of having hyperthyroidism. On this basis it is possible to adjust for potential confounding covariates, such as educational level and relevant co-morbidities.

**Data sources**

The Danish Civil Registration System (DCRS) (17), the Danish National Patient Registry (DNPR) (18) and the Danish National Prescription Registry (DNPrR) (19) are nationwide registers covering information such as demographic data, social factors, incomes, pensions, hospital treatments and prescriptions of drugs, on an individual level. The Danish Twin Registry (DTR) holds information on all Danish twin births, including a variable for zygosity (20). All registers are hosted at Statistics Denmark (16) and have previously been described in detail (8). The ten-digit personal identification number (CPR-number), assigned to all Danish citizens, enables record-linkage between all the mentioned databases on an individual level.

**Diagnosis of hyperthyroidism**

Information on thyroid status was obtained from DNPR and/or DNPrR. In DNPR, hyperthyroidism was defined by ICD-8 codes 242.00–242.99 (1977–1994) and the ICD-10 codes E05–E05.9 (1995–2008). GD was defined by the ICD-8 codes 242.08, 242.09, 242.00 or 242.01 as well as by the ICD-10 codes E05.0, H05.2 or H06.2. TNG was defined by the ICD-8 code 242.19 and the ICD-10 codes E05.1 or E05.2. In DNPrR, hyperthyroidism was defined by at least two dispensed prescriptions of anti-thyroid medication (ATC H03B). Either the first date of registration with a hyperthyroid diagnosis in DNPR, or the first date of collecting anti-thyroid medication registered in DNPrR, whichever occurred first, was chosen as the date of diagnosis of hyperthyroidism (index-date).

**Socio-economic parameters**

Information on socio-economic parameters was drawn from the DCRS. The occupational status for each citizen in Denmark is established at the end of November each year, and describes the primary occupational status, e.g. white-collar, self-employed, student or retiree. For many years, Danish citizens aged 60 years or more have been able to retire voluntarily, even without any work disability. In contrast, pensions under the age of 60 years is related to some degree to work disability. Therefore, in this study, disability pension was defined as retirement before the age of 60.

Income was based on the registration of annual labour market income of each individual. Therefore, individuals not available on the labour market, e.g., early-retired individuals, were excluded in all income analyses. All data on income are given in Euros and converted to fixed 2012 prices using the consumer price index from Statistics Denmark (16).

**Study population**

Singleton cases were selected from a random 5% sample of all Danes, identified from DCRS. Only incident cases diagnosed with hyperthyroidism between 31 December
1978 and 31 December 2006 and older than 18 years and younger than 60 years at the time of diagnosis were eligible for the present study. Each hyperthyroid singleton individual was matched for age and gender with four non-hyperthyroid control individuals, after the principles of density sampling (21). From DTR, same-sexed twin pairs discordant for hyperthyroidism were identified. Date of debut of hyperthyroidism (index-date) was chosen as the first date of registration in either DNPR or DNPrR. Cases and controls were followed until the age of 60, death, migration, or 31 December 2006, whichever came first.

Data analyses

Group frequencies were compared with the Pearson $\chi^2$ test, whereas group means and medians were compared by a $t$-test and the Mann–Whitney $U$ test respectively. In the case of paired comparisons, the paired $t$-test was used.

The relationship between hyperthyroidism and disability pension was evaluated using a Cox regression model. Age was chosen as the underlying time variable and outcome was defined by retirement before the age of 60. Person years of follow-up, in both cases and controls, were accumulated from the date of diagnosis of the case and terminated on the date of retirement, age of 60, date of death or end of follow-up (31 December 2006), whichever came first. In all analyses, the variable ‘pair’ was used as a stratum variable, fixing the baseline hazard within a matched pair, while at the same time allowing this baseline hazard to vary freely between pairs. Subsequently, the analyses were adjusted for sex, age at diagnosis and educational status, the latter categorized into three categories: primary and lower secondary, upper- and post secondary and tertiary, according to the International Standard Classification of Education (ISCED). Pre-existing co-morbidity was adjusted for using the Charlson score (CS), which 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, leukaemia, liver failure and AIDS) by creating a weighted score on an individual level, to optimize the prediction of the 1-year mortality risk within each disease category (22). Although the CS was designed to estimate the 1-year mortality in breast cancer patients, it has been validated in non-malignant phenotypes as well (23). In both cases and controls the CS was calculated from individual records in DNPR using relevant ICD-codes. As many patients in Denmark with diabetes, cardiovascular disease (i.e., hypertension) and lung diseases (i.e. chronic obstructive lung diseases) are diagnosed and treated solely in primary care, we classified all users of antidiabetics (ATC code A10), cardiovascular-related drugs (ATC codes B01, C01, C03, C07, C08, C09 and N02) and drugs for obstructive airway disease (ATC codes R03) registered in DNPrR as having diabetes, cardiovascular disease, or lung disease respectively.

To evaluate the effect on labour market income of a diagnosis of hyperthyroidism, we used a difference-in-differences model (DID) (24). Therefore, progress in labour market income for cases and controls was assessed by evaluating the income 2 years before the diagnosis of hyperthyroidism and 2 years after the diagnosis. Further analyses, i.e., 4 years after the thyroid diagnosis or later, was not meaningful since power diminished. The intraperson variation in labour market income among cases and controls respectively was thereby compared individually among these two groups using linear regression analysis. Subsequently, all analyses were adjusted for sex, age at diagnosis, educational level and the history of co-morbidity, as evaluated by the CS. In addition, all analyses were restricted to individuals with a CS of 0.

We also performed intra-pair analyses in the twin population. In these analyses, the hyperthyroid twin was matched with the corresponding euthyroid co-twin. All twin analyses were stratified according to zygosity.

Significant differences were defined as a $P$ value below 0.05 using two-tailed tests. All analyses were conducted using STATA version 13.0 (StataCorp. 2013. Stata Statistical Software: Release 13. College Station, TX, USA: StataCorp LP).

Results

Baseline characteristics of the study population

We included 1942 singletons with hyperthyroidism and 582 disease-discordant twin pairs. The mean follow-up time for cases and controls was 9 years (range 1–20 years). The baseline characteristics of the 1942 singletons diagnosed with hyperthyroidism and their corresponding controls are presented in Table 1. Based on information from DNPR it was possible to further sub-classify 637 as to the cause of hyperthyroidism, splitting the group into 442 with GD and 195 with TNG. Overall the annual number of
incident hyperthyroid cases as identified from DNPR did not change significantly.

Subjects with hyperthyroidism had a significantly higher degree of co-morbidity ($P!0.001$) and a significantly lower education level than their non-hyperthyroid controls ($P!0.001$).

Risk of disability pension

The results regarding disability pension in the singleton population are shown in Table 2. Hyperthyroid cases had a significantly higher risk of receiving disability pension, with a hazard ratio (HR) of 1.88 (95% CI 1.57–2.24).

Adjusting for possible confounders such as age, sex and level of education (multivariate analysis I) or the burden of co-morbidity prior to the diagnosis of hyperthyroidism (multivariate analysis II) did not change the results significantly. Evaluating individuals with no co-morbidity (CS=0) did not significantly change the results (HR 1.87, 95% CI 1.52–2.30). When stratifying according to the cause of hyperthyroidism (GD=422 and TNG=195), the size of the risk estimate was essentially unchanged but the association did not reach statistical significance (Table 2).

Labour market income

Labour market income differed between cases and control, with cases having a significantly lower mean income before as well as after the diagnosis of hyperthyroidism (Table 1).

The effect of a diagnosis of hyperthyroidism on labour market income is evident from Table 3. Hyperthyroid individuals remaining on the labour market had a significantly lower progress in income, measured from two years before to two years after the diagnosis of hyperthyroidism as calculated by DID (24). In other words, the income of the euthyroid individuals increased 1189 € more than that for hyperthyroid individuals ($P<0.05$). In GD individuals the difference was even more pronounced (2539 €), while it attenuated in those with TNG (132 €). These results did not change significantly when evaluated in multivariate models adjusted for sex, age, level of education and CS before the diagnosis of hyperthyroidism (multivariate analysis I and II). Restricting the analyses to individuals with a CS=0 did not significantly change the results (data not shown).

Twin analyses

Twin individuals with hyperthyroidism had an increased risk of disability pension as compared to their euthyroid

### Table 1

Baseline characteristics of the hyperthyroid singleton cases compared with their controls.

<table>
<thead>
<tr>
<th></th>
<th>Cases (n=1942)</th>
<th>Controls (n=7768)</th>
<th>$P$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ratio of females</td>
<td>83%</td>
<td>83%</td>
<td>1.00</td>
</tr>
<tr>
<td>Mean age at diagnosis (years)</td>
<td>44.5</td>
<td>44.5</td>
<td>0.9248</td>
</tr>
<tr>
<td>Mean age at disability pension (years)</td>
<td>47.4</td>
<td>47.9</td>
<td>0.3725</td>
</tr>
<tr>
<td>Persons retiring during follow-up (%)</td>
<td>9.93</td>
<td>5.84</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mean income 2 years before diagnosis (€)</td>
<td>23425</td>
<td>27799</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mean income 2 years after diagnosis (€)</td>
<td>26151</td>
<td>28601</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Frequency of persons with a Charlson score=0</td>
<td>78%</td>
<td>83%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Frequency of persons with a Charlson score = 1</td>
<td>15%</td>
<td>12%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Frequency of persons with a Charlson score &gt;1</td>
<td>7%</td>
<td>5%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Education level &gt;2a</td>
<td>19%</td>
<td>26%</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

*aUpper and postsecondary, according to the International Standard Classification of Education.

### Table 2

Risk of disability pension in singletons and twins diagnosed with hyperthyroidism compared with their controls.

<table>
<thead>
<tr>
<th>Population</th>
<th>Phenotype</th>
<th>Crude</th>
<th>Multivariate analysis Ia</th>
<th>Multivariate analysis IIb</th>
</tr>
</thead>
<tbody>
<tr>
<td>Singletons</td>
<td>Hyperthyroidism</td>
<td>1.88 (1.57–2.24)</td>
<td>1.70 (1.41–2.04)</td>
<td>1.69 (1.40–2.03)</td>
</tr>
<tr>
<td>Singletons</td>
<td>Graves’ disease</td>
<td>1.51 (0.87–2.63)</td>
<td>1.42 (0.78–2.59)</td>
<td>1.33 (0.71–2.48)</td>
</tr>
<tr>
<td>Singletons</td>
<td>Toxic nodular goitre</td>
<td>2.10 (1.02–4.36)</td>
<td>1.76 (0.77–4.03)</td>
<td>1.81 (0.78–4.18)</td>
</tr>
<tr>
<td>Singletons</td>
<td>Hyperthyroidism</td>
<td>1.50 (0.76–2.95)</td>
<td>1.70 (0.78–3.71)</td>
<td>1.92 (0.83–4.42)</td>
</tr>
<tr>
<td>All twin pairs</td>
<td>Hyperthyroidism</td>
<td>1.50 (0.42–5.32)</td>
<td>1.25 (0.34–4.65)</td>
<td>1.17 (0.30–4.54)</td>
</tr>
<tr>
<td>Monozygotic twin-pairs</td>
<td>Hyperthyroidism</td>
<td>1.50 (0.67–3.33)</td>
<td>2.00 (0.75–5.33)</td>
<td>2.73 (0.88–8.47)</td>
</tr>
<tr>
<td>Dizygotic twin-pairs</td>
<td>Hyperthyroidism</td>
<td>1.50 (0.67–3.33)</td>
<td>2.00 (0.75–5.33)</td>
<td>2.73 (0.88–8.47)</td>
</tr>
</tbody>
</table>

*aSex, age at diagnosis, level of education and 5-year intervals.

bSex, age at diagnosis, level of education, 5-year intervals and the Charlson score.
co-twins (Table 2). This remained unchanged after stratification for zygosity or controlling for covariates (multivariate analysis I), including co-morbidity (multivariate analysis II). In line with this, analyses of twin pairs discordant for hyperthyroidism demonstrated a significant difference in income increase favouring the euthyroid twin in monozygotic twins (difference in income: 6021 €, 95% CI: 1721 €-10321 €).

### Discussion

Based on record linkage between nation-wide Danish health registers we have shown that individuals diagnosed with hyperthyroidism before the age of 60 have an 88% increased risk of receiving disability pension compared to controls. This seems to be the case for both GD and TNG patients. In addition, we have shown that even in individuals remaining on the labour market, hyperthyroid patients have a lower progression in income compared to controls. This effect persisted after controlling for co-morbidity and the level of education, indicating a causal link between the diagnosis of hyperthyroidism and risk of receiving disability pension and having a lower progression in income. On the other hand, it is well accepted that hyperthyroid patients have an increased burden of somatic as well as psychiatric diseases following the diagnosis of hyperthyroidism (4, 8), suggesting that the impact on disability pension and income is not necessarily a direct consequence of hyperthyroidism, but could be facilitated via various other diseases following the diagnosis of hyperthyroidism. However, when restricting our analyses to individuals without co-morbidity both before and after the diagnosis of hyperthyroidism, our results did not change, pointing towards a genuine causal relationship between hyperthyroidism and work disability. The similar findings in twin pairs discordant for hyperthyroidism adds strength to this interpretation.

In contrast to the few other studies evaluating the risk of disability pension in patients with hyperthyroidism, we included, in a population-based setting, both major phenotypes, GD and TNG, independent of whether diagnosed in a hospital setting or in primary care. Our results are at large in line with what has been suggested by previous smaller studies. Using similar methodology to the one used here, a smaller Danish study showed that hyperthyroid individuals have a significantly higher risk of disability pension (HR = 4.15) within the first year after the diagnosis of hyperthyroidism (14). A German study found that 4% of younger individuals with Graves’ ophthalmopathy are early retired while 6% are permanently work-disabled (25). We, with the advantageous design just described, found a rate of early retirement of nearly 10% (Table 1).

Interestingly, hypothyroidism is associated with an 89% increased risk of disability pension (95% CI: 1.42–2.51) (25). To offer a recognisable perspective, smoking predicts a 69% increased risk of disability pension (95% CI: 1.46–1.97) (26), while obesity (BMI of 30–34.9) is associated with an 87% increased risk (95% CI: 1.76–1.99) (27). Thus, an 88% increased risk of disability pension in patients diagnosed with hyperthyroidism seems to be of the same magnitude as exposures to risk factors with well-established adverse socio-economic consequences.

To our knowledge, this is the first study to evaluate changes in income associated with a diagnosis of hyperthyroidism. While Ponto et al. (28) have estimated that the annual costs due to sick leave and work impairment in cases with Graves’ ophthalmopathy is up to 6683 €, they have not calculated the loss of income on an individual level. We show that hyperthyroid individuals have a lower income both before and after the thyroid diagnosis when compared to controls, and we demonstrate a lower progression in income in hyperthyroid individuals capable of retaining a job as compared to their respective controls. This seems plausible, since hyperthyroid individuals had a lower education level and studies on health-related quality of life in patients with thyroid disease show problems with everyday routines such as housekeeping (10) and a decreased quality of life.

**Table 3** Changes in labour market income in hyperthyroid singleton individuals compared with their controls from 2 years before the thyroid diagnosis until 2 years after, measured in Euros (€).

<table>
<thead>
<tr>
<th>Population</th>
<th>Crude</th>
<th>Multivariate analysis I*</th>
<th>Multivariate analysis IIb</th>
</tr>
</thead>
<tbody>
<tr>
<td>All singletons</td>
<td>1189 (86–2291)</td>
<td>1126 (32–2219)</td>
<td>1109 (15–2203)</td>
</tr>
<tr>
<td>Graves’ disease</td>
<td>2539 (187–4890)</td>
<td>2380 (105–4654)</td>
<td>2284 (6–4561)</td>
</tr>
<tr>
<td>Toxic nodular goitre</td>
<td>132 (–2840–3103)</td>
<td>173 (–2775–3120)</td>
<td>197 (–2754–3147)</td>
</tr>
</tbody>
</table>

*aSex, age at diagnosis, level of education, 5-year intervals.

*bSex, age at diagnosis, level of education, 5-year intervals and the Charlson score.
life (9), which is improved but not normalized after therapy (29). Therefore, work disability may impact work productivity and work role function among hyperthyroid patients staying on the labour market. Following this line of thought, these individuals are most likely not the first in line for promotion or wage increase, which could explain income disparities between cases and controls in the present study. Interestingly, the relative increase in income seems to be higher in patients with hyperthyroidism than in the control population (11.6% vs 2.9%), which could indicate a beneficial effect of treatment. Unfortunately, the present study does not allow further evaluation of this hypothesis.

Importantly, and in contrast to our findings regarding disability pension, the thyroid phenotype, GD or TNG, had a substantial effect on the results from the income analyses. Overall hyperthyroidism was associated with an 1189 € lower increase in income compared to the controls, but it was much higher in GD than in TNG. This difference is most likely explained by the more acute and severe toxic state in GD (7) and/or accompanying ophthalmopathy. In addition, as GD primarily affects younger individuals at higher risk of missing work-associated training or receiving a promotion, this could explain the more pronounced loss of income in GD compared to TNG patients.

As with disability pension, wages differ between countries and consequently a direct comparison between countries is difficult. Because Denmark has a regulated labour market, including a statutory minimum wage, the income differences are likely to be more pronounced in less regulated countries. However, the decreased progress in labour market income found in our study is of the same magnitude as that seen in North American patients with rheumatoid arthritis. In the latter group, the annual income of affected individuals was found to be 1666 US $ (1254 €) less than the expected earnings, based on job type and working hours (30).

Since hyperthyroidism (2, 3) and social parameters such as disability pension (31) and education-level (32) are under genetic control, our findings could be due to genetic confounding. Uniquely, we were able to evaluate the findings from the singleton case population in twin pairs discordant for hyperthyroidism. Although the twin analyses were characterized by relatively few discordant pairs, especially with respect to disability pension, and rather imprecise risk estimates, the finding of comparable risk estimates for disability pension between the singleton and twin population indicates that our results most likely are unaffected by genetic confounding (33, 34). As for income, the marked difference in income seen in disease-discordant MZ twin pairs also minimizes the risk of genetic confounding.

The strengths of the present study include a large sample size, ascertainment of participants from nationwide population-based registers, use of standardized and validated procedures for evaluating the degree of co-morbidity, education level, employment and a mean follow-up period of 9 years. The long-standing tradition of treating thyroid patients in a hospital setting in Denmark minimizes the risk of selection bias. On the other hand, our findings should be interpreted in the context of a number of potential limitations. First, hyperthyroidism is a graded phenomenon, ranging from subclinical hyperthyroidism to the extreme thyroid storm. Due to the lack of both clinical and biochemical information, our data do not allow for stratification of patients in an attempt to evaluate whether the severity of the hyperthyroid state, the presence of Graves’ orbitopathy, the therapy given and the rate of relapses, which inevitably lead to more prolonged periods of treatment and follow-up, influence our findings. Second, when compared with the control population, patients with hyperthyroidism had a lower education level. This finding probably explains much of the observed income differences, even though multivariate analysis II includes level of education.

Clearly, a lower education level could explain a higher risk of disability pension. Low-income jobs more often include hard physical work, allowing speculations on whether these individuals more often receive disability pension. On the other hand, the comparison among twins seems to discard this bias since a similar education level between twins is likely. Third, accepting that hypothyroidism is linked with work disability (25), it can be speculated that the development of hypothyroidism as a consequence of the treatment for hyperthyroidism may affect the association between hyperthyroidism and income level as well as the risk of disability pension. Unfortunately, due to lack of biochemical data, we are not able to further explore the possible impact of this bias on the risk estimates. Fourth, the data in this study were obtained from persons 95% of whom were white Caucasians living in Denmark, among whom cultural background and living conditions are generally homogeneous. Migration may have affected the incidence of hyperthyroidism over time, but our data source did not allow further speculation as to this point. Also worth mentioning is the risk of overmatching, which is clearly the case in the twin population. This phenomenon may well explain why no statistically significant association
was found in the twin analyses. This limitation of the co-twin case–control method may serve as a reminder that no method is ideal for all circumstances.

In conclusion, individuals diagnosed with hyperthyroidism before the age of 60 years had an 88% increased risk of receiving disability pension. They also had a lower progression in income compared to controls, even when remaining on the labour market. Replicating the same trend within twin pairs discordant for hyperthyroidism indicates that these findings are not based on genetic confounding.

Declaration of interest
The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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Author contribution statement
All authors have had full access to all of the data in the study and take responsibility for the integrity and the accuracy of the data analyses.

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