Increased risk of dementia in hypothyroidism.
A Danish nationwide register-based study

Short title: Hypothyroidism and dementia

Authors: Marianne Thvilum¹,², Frans Brandt³,⁴, Mads Lillevang-Johansen²,⁵, Lars Folkestad²,⁵, Thomas H. Brix²,⁵, Laszlo Hegedüs²,⁵

1) Department of Endocrinology and Internal Medicine, Aarhus University Hospital, Aarhus, Denmark
2) Department of Endocrinology, Odense University Hospital, Odense, Denmark
3) Department of Internal Medicine, Hospital of Southern Jutland, Sønderborg, Denmark
4) Institute of Regional Health Research, University of Southern Denmark, Odense, Denmark
5) Institute of Clinical Research, University of Southern Denmark, Odense, Denmark

Key terms: Hypothyroidism; Hashimoto’s disease; vascular dementia; Alzheimer’s disease; register study; autoimmunity

Word count (excluding abstract, figure captions and references): 3227
Word count in summary: 250
Number of references: 33
Number of tables: 3

This is the author manuscript accepted for publication and has undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/CEN.14424

This article is protected by copyright. All rights reserved
Summary

Objective: Globally, the prevalence of individuals with dementia is increasing, and identification of risk factors is of paramount interest. Using population-based registers, we evaluated whether hypothyroidism is a risk factor for dementia.

Design: Register-based cohort study.

Patients and Methods: Risk of dementia was evaluated in two cohorts. The DNPR cohort comprises 111,565 hypothyroid patients, diagnosed between 1995 and 2012, and 446,260 euthyroid age and sex matched individuals (median follow-up 6.2 years). The OPENTHYRO cohort comprises 233,844 individuals with at least one measurement of serum thyrotropin (TSH) between 1995 and 2011, of whom 2,894 had hypothyroidism (median follow-up 7.2 years). Primary outcome was dementia defined as an International Classification of Diseases 10 code, or prescription of medicine for dementia.

Results: In the DNPR cohort, risk of dementia was significantly increased in subjects with hypothyroidism (HR 1.22; 95% CI: 1.17-1.27), which attenuated after adjusting for pre-existing comorbidity (HR 0.82; 95% CI: 0.79-0.86). Stratification of age into ≤ 56 and > 56 years showed an inverse relationship between age and risk of dementia (HR ≤56 yrs. 2.03; 95% CI: 1.62-2.53 and HR >56
In the OPENTHYRO cohort, the risk of dementia was significantly increased for each 6 months of elevated TSH (HR 1.12; 95% CI: 1.07-1.16).

**Conclusions:** Hypothyroidism is associated with increased risk of dementia. The association is influenced by co-morbidity and age. Every 6 months of elevated TSH increased the risk of dementia by 12%, suggesting that also the length of hypothyroidism influences the risk of dementia.

**Introduction**

Hypothyroidism is a common chronic endocrine disorder, with a multifactorial aetiology, a lifetime risk of 2-3%\(^1\), and female preponderance\(^2\). Irrespective of its cause, hypothyroidism has repeatedly been linked to various somatic morbidities\(^3\), especially cardiovascular diseases\(^4\), as well as psychiatric morbidities\(^5\), including cognitive impairment\(^6\). Whether this increased burden of co-morbidities also includes dementia is currently debated\(^7\). Some studies indicate an increased risk of Alzheimer’s disease (AD)\(^8,9\), and while others found no association to AD, a significantly higher risk of vascular dementia has been found in hypothyroid individuals (VD)\(^10\). Nonetheless, others failed to show any association between dementia and hypothyroidism\(^11\). To further complicate interpretation, it has been indicated that slightly elevated levels of thyrotropin (TSH) might be beneficial in the elderly\(^12\). Whether this potential antagonistic pleiotropic effect\(^13\) of the thyroid hormones is at play with respect to dementia is unknown. The conflicting data concerning the relation between hypothyroidism and dementia may depend on lack of statistical power but also variations in the definition of thyroid dysfunction and dementia. This is additionally complicated by the fact that both hypothyroidism and dementia comprise a cluster of different diagnoses with different aetiologies\(^2,14\). This by itself highlights the need of large-scale and long-term follow-up cohort studies using clinical operational definitions of both hypothyroidism and dementia.

Based on the aforementioned, we hypothesized that hypothyroid individuals have an increased risk of dementia compared to euthyroid individuals. We utilized population-based Danish health registers to determine this potential association. In addition, having access to longitudinal biochemical data from a subpopulation allowed evaluation of the cumulative effect of elevated serum TSH and risk of being diagnosed with dementia.

**Materials and methods**

This article is protected by copyright. All rights reserved
Data sources

Data were collected utilizing various Danish health registers. The Danish Civil Registration System (DCRS) and the Danish Demographic Database (DDB) cover information on demographics and date of death of all persons living or having lived in Denmark from 1968\textsuperscript{15}. The Danish National Patient Registry (DNPR) and The Danish National Prescription Registry (DNPrR) cover information on diagnoses from hospital treatments (both in- and outpatient visits) and prescriptions of drugs in all persons in Denmark since 1995\textsuperscript{15}. All databases are hosted at Statistics Denmark. Further details of each database used in the present study are described elsewhere\textsuperscript{16}. Due to a unique personal identification number, assigned to all persons living in Denmark, records can be linked across the databases at the level of the individual.

In addition to the above-mentioned registers, we used the Odense Patient data Explorative Network Thyroid Status and Register Outcomes (OPENTHYRO) register cohort, which has been described in detail previously\textsuperscript{17}. In summary, the OPENTHYRO cohort includes all individuals on the Island of Funen with a TSH measurement analysed at the Department of Clinical Biochemistry, Odense University Hospital, between 1 January 1995 and 1 January 2011. The participants were followed from their first-ever TSH determination until death or end of study (30 November 2012). In this period, 275,467 individuals had at least one serum TSH measurement.

Two cohorts were identified – the DNPR cohort and the OPENTHYRO cohort. In the DNPR cohort, we identified all hypothyroid patients evaluated within the secondary health care system in Denmark. This offered a cohort with a high number of cases with complete follow-up, at the expense of having no information on biochemical variables. In the OPENTHYRO cohort we identified hypothyroid patients evaluated within the primary health care system on the Island of Funen, Denmark. This offered a cohort of patients with biochemical verification of hypothyroidism, and information on duration of thyroid dysfunction, but at the expense of a lower number of patients. In both cohorts, we lacked information as to the severity of hypothyroidism (overt and/or subclinical) and the dose of levothyroxine.

Definition and identification of hypothyroidism and dementia

All incident cases above the age of 18 with primary hypothyroidism diagnosed after December 31, 1995 were eligible for this study. Excluded were individuals diagnosed with malignant thyroid
diseases, congenital hypothyroidism or pituitary hypothyroidism, represented by the International Classification of Diseases 10th revision (ICD-10) codes C73, E00.0-E00.9, E03.0-E03.1, E22.0-E22.9, E23.0-E23.7 and E24.0. Furthermore, hypothyroid individuals diagnosed with hyperthyroidism (defined by ICD-10: E05.0 to E05.9), or having filled prescriptions of antithyroid drugs (Anatomical Therapeutic Chemical Classification System (ATC)=H03B)), prior to the diagnosis of hypothyroidism, were excluded. Excluded were also individuals diagnosed with dementia before the diagnosis of hypothyroidism. If a hypothyroid individual was excluded due to dementia prior to a diagnosis of hypothyroidism, all corresponding matched reference individuals were excluded as well. In case of a reference individual being diagnosed with dementia before the index date (date of the diagnosis of hypothyroidism), this individual was excluded from further analyses. Table 1 covers data sources and codes used in the identification and classification of individuals with hypothyroidism and the reference population.

In the DNPR cohort individuals were classified as hypothyroid if they had a ICD-10 code for hypothyroidism (E03.9) in the DNPR or at least two dispensed prescriptions of thyroid hormone (ATC = H03A), recorded in the DNPrR. In all, 111,565 individuals with a diagnosis of hypothyroidism were identified and matched, 1:4 according to age and gender, with 446,260 non-hypothyroid reference individuals. The reference individuals had to be alive on the index date of the hypothyroid individuals. All included individuals were followed prospectively from the index date until migration, death, a registered diagnosis of dementia in the DNPR or a relevant drug to treat dementia was dispensed and registered in the DNPrR, or December 31, 2013, whichever came first.

In the OPENTHYRO cohort individuals were classified as hypothyroid if they had a minimum of two consecutive elevated TSH values (>4.0mIU/L) within a period of 6 months from the first ever measurement, with at least 14 days between measurements. In all, we identified 2,894 individuals with hypothyroidism. The reference population for the OPENTHYRO cohort included 230,950 individuals with initial TSH measurements within the reference range.

The identification of dementia was based on relevant ICD-10 codes and ATC codes (Table 1).

Pre-existing morbidity
Pre-existing morbidity was evaluated by the Charlson Comorbidity Index (CCI) (Table 1) as described by Christensen et al.\textsuperscript{18}. For subjects with hypothyroidism and reference individuals, the CCI reflects the maximum CCI on the index-date.

**Statistical Analyses**

Group frequencies were compared with the Pearson $X^2$ test, whereas group means and medians were compared by a t-test and the Wilcoxon Rank Sum Test, respectively. In case of paired comparisons, the paired t-test was used. Significant differences were defined as a p-value below 0.05, using two-tailed tests. All analyses were conducted using Stata version 16.0 (2013; Stata Corporation, College Station, TX, USA) and SAS version 9.4 (SAS Institute, Inc., Cary, NC, USA).

In the DNPR cohort, the risk of dementia was evaluated by a Cox Proportional Hazards regression model. Age was chosen as the underlying time variable. In both hypothyroid as well as reference individuals, person years of follow-up were accumulated from the index-date of the hypothyroid individual and terminated on the date of diagnosis of dementia, migration, death, or end of follow-up, whichever came first. All Cox Proportional Hazards model regression analyses were adjusted for the degree of pre-existing morbidity, using the CCI. In order to evaluate a potential effect of age, the data were stratified into being younger than or 56 years or older, corresponding to the median age at diagnosis of hypothyroidism. The assumption of proportional hazards was evaluated by the log-log plot of survival for each group within each used model, accepting that the proportionality assumption held if the plots did not cross.

As hypothyroidism is associated with increased mortality\textsuperscript{16}, hypothyroid individuals, \textit{a priori}, have a shorter observation period than the reference individuals and, at least theoretically, a lower risk of being diagnosed with dementia. To account for a potential influence of competing risk of death, the risk of dementia was re-evaluated by the competing risk regression model described by Fine and Gray\textsuperscript{19}.

Additionally, we performed a sensitivity analysis evaluating only cases diagnosed with dementia at least one year after the diagnosis of hypothyroidism, in order to take Berkson’s bias into account\textsuperscript{20}. Berkson’s bias may be present when the diagnosis of one disease influences the risk of being diagnosed with another disease at the same time\textsuperscript{20}.
For the OPENTHYRO cohort the TSH level as a time-dependent covariate was used. The number of 6-month periods with a TSH level > 4.0 mIU/L was incorporated as a cumulative time-dependent covariate in a Cox Proportional Hazards regression model, thereby taking alterations in thyroid status over time into account. Any 6-month period in which no TSH measurement had been performed was considered a period with normal TSH.

**Ethical considerations**

The study has been approved by the Danish Data Protection Agency (project 704047).

**Results**

**Baseline characteristics**

The baseline characteristics from the DNPR cohort are given in table 2A. Females comprised 82% of the included individuals and the median age at diagnosis of hypothyroidism was 56 years [interquartile range (IQR) 43-69]. Median time of follow-up was 6.2 years (IQR 3.1-10.4), corresponding to 747,906 person years of observation for the hypothyroid cohort and 3,068,041 person years for the reference population. Overall, the hypothyroid individuals had a higher burden of pre-existing morbidity, as evaluated by CCI (Table 2A).

The baseline characteristics of the OPENTHYRO cohort are presented in table 2B. 79.3% were females and the mean age at time of the first TSH measurement was 56.4 years (IQR 42.6-69.2) for hypothyroid individuals and 50.3 years (IQR 36.4-64.2) for the reference population. Individuals were followed for a median of 7.2 years (IQR 4.3-10.6), corresponding to 22,461 person years of observation for the hypothyroid cohort and 1,703,167 person years for the reference population. The hypothyroid individuals and the reference population had similar burden of morbidity prior to the index date, as determined by CCI.

**Risk of dementia in hypothyroid individuals in the DNPR cohort**

Risk of dementia is summarized in table 3. The cumulative hazard estimates (risk of dementia, at a certain point in time) is shown in figure 1. Overall, there was a higher prevalence of dementia among hypothyroid individuals, as compared to the reference population (3.7% vs. 2.7%, p<0.001). The risk of dementia over time was significantly increased among the hypothyroid individuals.
compared to the reference population (HR 1.22; 95% CI: 1.17-1.27), which did not change significantly after stratification for gender. Neither did adjusting for competing risk of death nor did Berkson’s bias change the risk estimates significantly. However, when adjusting for degree of pre-existing morbidity the association between hypothyroidism and dementia was significantly reduced (HR 0.82; 95% CI: 0.79-0.86).

Stratification of age of the cases into \( \leq 56 \) and > 56 years demonstrated a higher prevalence of dementia in both age groups as compared with the reference population (0.3% vs. 0.1%, \( p<0.001 \) and 5.4% vs 4.7%, \( p<0.001 \), in age groups \( \leq 56 \) and >56 years old, respectively). There was a significantly higher risk of dementia among the younger hypothyroid individuals, which persisted after adjusting for CCI (HR 2.03; 95% CI: 1.62-2.53). Among the older individuals, there was an increased risk of dementia in the crude analysis (HR 1.21; 95% CI: 1.16-1.26) which regressed towards the null when adjusting for CCI (HR 1.00; 95% CI: 0.96-1.05).

Although the risk estimates became imprecise, subdividing dementia into AD or VD yielded essentially similar results (Table 3). The cumulative hazard estimates stratified for age are shown in figure 2.

Effect of cumulative exposure to increased TSH

In the OPENTHYRO cohort the prevalence of dementia was higher among the hypothyroid individuals than among the reference population (3.7% vs. 2.7%, \( p < 0.001 \)). Compared to the reference population, hypothyroid individuals demonstrated a significantly increased risk of being diagnosed with dementia for each 6 months of elevated TSH (HR 1.12; 95% CI: 1.07-1.16), which illustrates the effect of the cumulative exposure of elevated TSH. Due to lack of power, these data did not allow further stratification into gender, age or severity of hypothyroidism.

Discussion

The relationship between hypothyroidism and subsequent dementia is currently under debate. Based on population-based register data we found a significantly increased risk of dementia in patients with hypothyroidism. Unique to our investigation, we showed a 12% increased risk of dementia for each 6 months of TSH above 4.0 IU/L. Since the levels of thyroid hormones are important for the distribution of amyloid-\( \beta \) as well as of the regulation of the amyloid-\( \beta \) precursor...
genes within the brain, both suggested contributing to the development of AD\textsuperscript{21}, the observed association between hypothyroidism and dementia is biologically plausible. Furthermore, thyroid hormones regulate hippocampal function and neurogenesis which have been suggested as one explanation for the reduced learning ability, cognitive performance and memory function observed in patients with thyroid dysfunction\textsuperscript{22,23}.

A major strength of our study is the inclusion of two cohorts (DNPR and OPENTHYRO) with validated definitions of both hypothyroidism and dementia but with different ascertainment procedures, thereby limiting some of the shortcomings of other studies\textsuperscript{8-11,24}. In the DNPR cohort, we identified all hypothyroid patients evaluated within the secondary health care system in Denmark. This offered a cohort with a high number of cases with complete follow-up, at the expense of having no information on biochemical variables. Therefore, we also included a cohort based on availability of biochemical data, including patients evaluated within the primary health care system on the Island of Funen (OPENTHYRO). This offered a cohort of patients with biochemical verification of hypothyroidism, and duration of thyroid dysfunction, but at the expense of a lower number of patients. By including patients and controls evaluated and managed in the primary (OPENTHYRO) as well as in the secondary health care system (DNPR), our study sample, unlike many other studies, covers the entire clinical spectrum of patients with hypothyroidism.

While our finding of an increased risk of dementia in overtly hypothyroid individuals is in line with the observations of George et al.\textsuperscript{24} other studies have been less clear. The Framingham Study, evaluating a slightly older study population with a mean age of 71, found an increased risk of AD associated with high TSH levels in women, but not in men\textsuperscript{8}. In contrast, Chaker et al. failed to demonstrate an association between elevated levels of TSH and risk of dementia among individuals with a mean age of 65\textsuperscript{11}. This discrepancy may be due to the fact that these studies only used a single point estimate of thyroid status\textsuperscript{8,11}. Up to 50\% of abnormal thyroid function tests will be normalized when re-tested after 3 months\textsuperscript{25}. In the present study, the hypothyroid diagnoses were based on a relevant ICD-10 diagnosis or at least two prescriptions of levothyroxine in the DNPR-cohort, or at least two measurements of TSH > 4 MIU/l in the OPENTHYRO cohort, thereby reducing the risk of erroneous classification.
Accepting that the influence of thyroid hormones on brain function may differ over a lifetime\textsuperscript{11}, we performed sub-analyses stratifying for age at diagnosis. The difference in the relative risk between the two groups, being younger or older than 56 years, was especially evident after adjusting for comorbidity. Thus, the increased risk of dementia persisted among individuals ≤56 years, but went towards the null among persons >56 years of age. However, it is important to point out that the relative effect of hypothyroidism on the risk of a given disease decreases when the probability of the disease increases with age. In other words, the huge relative risk of dementia in the young is partly due to the otherwise very low probability of being diagnosed with dementia before the age of 56 years. This finding is in analogy with what has been observed with respect to risk of cardiovascular disease in diabetes\textsuperscript{26}, where the absolute risk of cardiovascular events is increased by age, but the relative excess decreases by age. Although our results are based on observational register data, making it impossible to make any firm conclusions regarding causality, this observation indicates that hypothyroidism is an independent modifiable risk factor for dementia in young persons, whereas the effect of hypothyroidism on dementia in older persons is diluted by the higher burden of comorbidity. Unfortunately, due to lack of power, we could not meaningfully stratify our biochemical data according to age.

Hypothyroidism\textsuperscript{1} as well as dementia\textsuperscript{27} have multifactorial aetiologies, and represent a number of different diseases with distinct pathology and risk factors\textsuperscript{13}. A wide range of environmental factors (e.g. smoking-, drinking- and physical activity-habits) are involved in the development of dementia\textsuperscript{27}. Some of these factors have also been shown to influence the development of hypothyroidism\textsuperscript{28}, implying that an association between the two could be due to common exposure(s). Hence, residual confounding may be present to some extent. However, since we have adjusted for lung and liver diseases, mirroring exposure to smoking and alcohol, respectively, the impact of this is most likely minimized.

Surprisingly, we found a decreased risk of dementia in hypothyroid individuals after adjusting for pre-existing morbidity. A potential explanation could be an indirect link, driven by comorbidities such as cardiovascular disease or presence of unmeasured environmental exposures more or less accounted for in the CCI. As cardiovascular disease increases the risk of both hypothyroidism and dementia\textsuperscript{4,29}, cardiovascular disease may actually act as a mediator of the risk between hypothyroidism and dementia. In other words, controlling for conditions that may occur
on the pathophysiological pathway for both hypothyroidism and dementia, may introduce excessive correction not in line with the study design.

The present study has some limitations. First, the risk of Berkson’s bias, that is the diagnosis of one disease (dementia) leading to the risk of being diagnosed with another (hypothyroidism), is high in the present study, as according to current guidelines the diagnosis of dementia is based on excluding other causes of cognitive failure, such as hypothyroidism\(^30\). However, this was addressed and ruled out as a confounding factor by applying a 365 day censoring window demonstrating no significant influence on our findings. Second, we were unable to stratify our analyses according to overt versus subclinical hypothyroidism, and therefore cannot shed light on any potential relationship between degree of hypothyroidism and dementia. Third, we did not have statistical power to stratify for cause of hypothyroidism (autoimmune versus iatrogenic hypothyroidism, as induced by radioiodine therapy, thyroid surgery or treatment with amiodarone or lithium), which would have been of interest in order to discuss the specificity of the association. Fourth, all included patients were diagnosed with hypothyroidism but Information on treatment, including dose of thyroid hormone, is lacking. Thus it is impossible to explore whether treatment influences the risk of dementia in patients with hypothyroidism as has been suggested previously\(^31\). Fifth, the fact that both hypothyroidism and dementia are conditions that typically progress over time challenges our possibility to define the exact time of onset of disease. However, applying a 365 day censoring window did not significantly influence our findings indicating that the impact of this potential misclassification is negligible. Finally, register based research in general depends highly on correct diagnoses by the clinicians, and a potential high degree of misclassification would be a major limitation. However, the validity of the diagnoses of both the dementia syndrome and hypothyroidism have been evaluated in Denmark and shown to be high, and therefore found suitable for epidemiological research\(^32,33\).

In conclusion, investigation of two large population based Danish cohorts of hypothyroid individuals demonstrate an increased risk of dementia associated with hypothyroidism. This association was influenced by pre-existing morbidity and age. However, even though pre-existing morbidity impacted our findings, a cumulative effect of elevated TSH on the risk of development of dementia.
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.

Funding
The research did not receive any specific grant from any funding agency in the public, commercial or not-for-profit sector.

Author contributions
MT, FB, LF, MLJ, TB and LH designed the study. MT, FB, LF and MLJ carried out the calculations. All authors provided critical feedback and helped shape the research, analysis and manuscript.

Availability of data
The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

References


<table>
<thead>
<tr>
<th>Table 1: Variables of exposure and outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Data source</td>
</tr>
</tbody>
</table>

This article is protected by copyright. All rights reserved.
# Exposure

<table>
<thead>
<tr>
<th>Hypothyroidism</th>
<th>DNPR&lt;sup&gt;a&lt;/sup&gt;</th>
<th>ICD-10&lt;sup&gt;b&lt;/sup&gt;</th>
<th>E03.2-E03.9</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>DNPrR&lt;sup&gt;c&lt;/sup&gt;</td>
<td>ATC&lt;sup&gt;d&lt;/sup&gt;</td>
<td>H03A</td>
</tr>
<tr>
<td></td>
<td>OPENTHYRO&lt;sup&gt;e&lt;/sup&gt;</td>
<td>-</td>
<td>TSH contration</td>
</tr>
</tbody>
</table>

# Primary outcome

<table>
<thead>
<tr>
<th>All cause dementia</th>
<th>DNPR</th>
<th>ICD-10</th>
<th>F0.00-F0.02, F0.09-F0.13, F0.18-F0.20, F0.39, G3.00, G3.01, G3.08, G3.09</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>DNPrR</td>
<td>ATC</td>
<td>N06DA02-N06DA04, N06DX01</td>
</tr>
</tbody>
</table>

# Secondary outcomes

<table>
<thead>
<tr>
<th>Alzheimer’s disease</th>
<th>DNPR</th>
<th>ICD-10</th>
<th>F0.00-F0.02, F0.09, G3.00, G3.01, G3.08, G3.09</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>DNPrR</td>
<td>ATC</td>
<td>N06DA02-N06DA04, N06DX01</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Vascular dementia</th>
<th>DNPR</th>
<th>ICD-10</th>
<th>F0.10-F0.13, F0.18-F0.19,</th>
</tr>
</thead>
</table>

# Variables adjusted for

<table>
<thead>
<tr>
<th>Charlson Comorbidity Index</th>
<th>DNPR</th>
<th>ICD-10</th>
<th>As described by Christensen et al.(18)</th>
</tr>
</thead>
</table>

<sup>a</sup> The Danish National Patient Registry. <sup>b</sup>International Classification of Diseases 10th revision. <sup>c</sup>The Danish National Prescription Registry. <sup>d</sup>Anatomical Therapeutic Chemical Classification System. <sup>e</sup>Odense Patient data Explorative Network Thyroid Status and Register Outcomes.
### Table 2A: Participant characteristics in the DNPR<sup>a</sup> cohort

<table>
<thead>
<tr>
<th></th>
<th>Hypothyroid individuals</th>
<th>Reference individuals</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Number</strong></td>
<td>111,565</td>
<td>446,260</td>
<td>-</td>
</tr>
<tr>
<td><strong>Females (%)</strong></td>
<td>91,891 (82)</td>
<td>371,224 (82)</td>
<td>-</td>
</tr>
<tr>
<td><strong>Median age at diagnosis (IQR)</strong></td>
<td>55.8 (43.3-68.5)</td>
<td>55.8 (43.3-68.5)</td>
<td>-</td>
</tr>
<tr>
<td><strong>Median follow-up time (IQR)</strong></td>
<td>6.0 (2.9-10.2)</td>
<td>6.2 (3.1-10.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Number with dementia (%)</strong></td>
<td>4,110 (3.7)</td>
<td>14,828 (3.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Vascular dementia (%)</td>
<td>379 (0.3)</td>
<td>1281 (0.3)</td>
<td>0.329</td>
</tr>
<tr>
<td>Alzheimer’s dementia (%)</td>
<td>823 (0.7)</td>
<td>3209 (0.7)</td>
<td>0.009</td>
</tr>
<tr>
<td>Other dementia</td>
<td>2,908 (2.5)</td>
<td>10,338 (2.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Charlson Comorbidity Index = 0 (%)</strong></td>
<td>18,909 (16.9)</td>
<td>178,260 (39.9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Charlson Comorbidity Index = 1 (%)</strong></td>
<td>39,873 (35.7)</td>
<td>160,955 (36.1)</td>
<td>0.04</td>
</tr>
<tr>
<td><strong>Charlson Comorbidity Index = 2 (%)</strong></td>
<td>25,978 (23.3)</td>
<td>65,864 (14.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Charlson Comorbidity Index ≥ 3 (%)</strong></td>
<td>26,805 (24.1)</td>
<td>40,576 (9.2)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

### Table 2B: Participant characteristics in the OPENTHYRO<sup>d</sup> cohort

<table>
<thead>
<tr>
<th></th>
<th>Hypothyroid individuals</th>
<th>Reference individuals</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Number</strong></td>
<td>2,894</td>
<td>230,950</td>
<td>-</td>
</tr>
<tr>
<td><strong>Females (%)</strong></td>
<td>2,295 (79)</td>
<td>128,711 (55)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td><strong>Median age at first TSH-measurement (IQR)</strong></td>
<td>56.4 (42.6-69.2)</td>
<td>50.3 (36.4-64.2)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td><strong>Median follow-up time (IQR)</strong></td>
<td>7.6 (4.6-11.2)</td>
<td>7.2 (4.3-10.6)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td><strong>Number with dementia (%)</strong></td>
<td>108 (3.7)</td>
<td>6,420 (2.7)</td>
<td>0.002</td>
</tr>
<tr>
<td><strong>Charlson Comorbidity Index = 0 (%)</strong></td>
<td>2,297 (79.4)</td>
<td>184,830 (80.3)</td>
<td>0.376</td>
</tr>
<tr>
<td><strong>Charlson Comorbidity Index = 1 (%)</strong></td>
<td>403 (13.9)</td>
<td>31,707 (13.7)</td>
<td>0.760</td>
</tr>
<tr>
<td><strong>Charlson Comorbidity Index = 2 (%)</strong></td>
<td>105 (3.6)</td>
<td>8,083 (3.5)</td>
<td>0.709</td>
</tr>
<tr>
<td><strong>Charlson Comorbidity Index ≥ 3 (%)</strong></td>
<td>89 (3.1)</td>
<td>6,330 (2.7)</td>
<td>0.274</td>
</tr>
</tbody>
</table>

<sup>a</sup>The Danish National Patient Registry  
<sup>b</sup>Round off from 0.74,  
<sup>c</sup>Round off from 0.72,  
<sup>d</sup>Odense Patient data
Table 3: Hazard ratios with 95% confidence intervals for being diagnosed with dementia in patients with hypothyroidism, in the DNPR<sup>a</sup> cohort

<table>
<thead>
<tr>
<th></th>
<th>Risk of dementia, all types</th>
<th>Risk of Alzheimer’s disease</th>
<th>Risk of vascular dementia</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All</td>
<td>Females</td>
<td>Males</td>
</tr>
<tr>
<td>Crude</td>
<td>1.22 (1.17-1.27)</td>
<td>1.21 (1.16-1.26)</td>
<td>1.30 (1.18-1.43)</td>
</tr>
<tr>
<td>Adjusted&lt;sup&gt;b&lt;/sup&gt;</td>
<td>0.82 (0.79-0.86)</td>
<td>0.82 (0.79-0.86)</td>
<td>0.82 (0.74-0.91)</td>
</tr>
<tr>
<td>365 days</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>censoring</td>
<td>1.05 (1.01-1.10)</td>
<td>1.05 (1.00-1.10)</td>
<td>1.07 (0.96-1.20)</td>
</tr>
<tr>
<td>≥ 56 yr&lt;sup&gt;c&lt;/sup&gt;</td>
<td>1.21 (1.16-1.26)</td>
<td>1.19 (1.14-1.25)</td>
<td>1.29 (1.17-1.42)</td>
</tr>
<tr>
<td>Adjusted&lt;sup&gt;b&lt;/sup&gt;</td>
<td>1.00 (0.96-1.05)</td>
<td>1.00 (0.95-1.04)</td>
<td>1.03 (0.93-1.15)</td>
</tr>
<tr>
<td>&lt;56 yr</td>
<td>2.29 (2.20-3.29)</td>
<td>2.46 (1.95-3.10)</td>
<td>3.58 (2.39-5.35)</td>
</tr>
<tr>
<td>Adjusted&lt;sup&gt;b&lt;/sup&gt;</td>
<td>2.03 (1.62-2.53)</td>
<td>1.79 (1.39-2.31)</td>
<td>2.90 (1.83-4.59)</td>
</tr>
<tr>
<td>Competing</td>
<td>1.12 (1.05-1.20)</td>
<td>1.21 (1.16-1.26)</td>
<td>1.30 (1.18-1.43)</td>
</tr>
<tr>
<td>risk</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup> The Danish National Patient Registry, <sup>b</sup> adjusted for Charlson Comorbidity Index, <sup>c</sup> Years of age at diagnosis of hypothyroidism, <sup>d</sup> Too few outcomes to perform Cox Proportional Hazards Regression.
Legends to figures

Legends figure 1.
Cumulative hazard estimates, comparing the hypothyroid individuals in the DNPR Cohort with the reference population. The cumulative hazard estimates depict the likelihood of having the event (dementia) at a given time. The data arise from the Nelson-Aalen cumulative hazard estimate model. The y-axis indicates the probability of dementia at a given analysis time (x-axis).

Legends figure 2.
Cumulative hazard estimates, comparing the hypothyroid individuals in the DNPR Cohort with the reference population, stratified for age. The cumulative hazard estimates illustrate the likelihood of having the event (dementia) at a given time. The data arise from the Nelson-Aalen cumulative hazard estimate model. The y-axis indicates the probability of dementia at a given analysis time (x-axis).
Figure 2.

Cumulative hazard estimates

- Hypothyroid individuals, <56
- Hypothyroid individuals, ≥56
- Reference population, <56
- Reference population, ≥56