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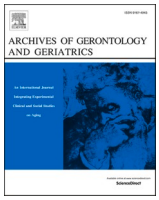

Association between thyroid function, nursing home admission and mortality in community-dwelling adults over 80 years

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ABSTRACT

Purpose: Thyroid deficiency may reduce mortality in older adults, but older adults prioritize independence over merely staying alive. We investigated the association between thyroid dysfunction and nursing home admission and all-cause mortality in community-dwelling older adults over 80.

Methods: We conducted a retrospective population-based open cohort study using data from laboratory registries covering 75% of Denmark supplemented by national registries. We included all community-dwelling older adults over 80 years with a first TSH measurement between 1996 and 2019. Participants with prior thyroid disorders or medication affecting the thyroid were excluded. Participants were followed from inclusion until nursing home admission, death or loss to follow-up due to emigration.

Results: We included 272,495 participants at baseline. Median follow-time was 3.71 years in analyses of nursing home admissions and 4.00 years for all-cause mortality. Hypothyroidism was associated with lower nursing home admission (TSH 5–10 mIU/l: HR 0.85, 95% CI: 0.80–0.91, $P < 0.001$); TSH >10 mIU/l HR 0.68, 95% CI: 0.54–0.85, $P = 0.001$) and with reduced all-cause mortality (TSH >10 mIU/l: HR 0.81, 95% CI: 0.70–0.93, $P = 0.002$). The association between hyperthyroidism and nursing home admission was of little clinical significance while hyperthyroidism was associated with increased all-cause mortality hazard both for low (HR 1.16, 95% CI 1.13–1.19, $P < 0.001$) and suppressed (HR 95% CI: 1.14 1.07–1.21, $P < 0.001$) TSH.

Conclusion: : Hypothyroidism is associated with a reduced nursing home admission hazard and to a lesser extent all-cause mortality in community-dwelling adults over 80 years, while hyperthyroidism is associated with increased all-cause mortality but not hazard of nursing home admission.

1. Introduction

Thyroid dysfunction is frequent and affects one in five older adults in the US, and it may influence mortality and morbidity (Canaris et al., 2000; Carlé et al., 2011). Symptoms of hypothyroidism lessen with age and treatment may not improve symptoms in subclinical hypothyroidism in old age (Carlé et al., 2016; Mooijaart et al., 2019; Stott et al., 2017). In contrast, hypothyroidism may improve longevity and health, though results are inconsistent (Atzmon et al., 2009; Du et al., 2021; Gussekloo et al., 2004; Mammen et al., 2017; Ogliari et al., 2017; Pearce et al., 2016; van den Beld et al., 2005; van et al., 2017). Adding to this end, the majority of older adults prioritize staying independent in activities of daily living (ADL) over staying alive or living without symptoms.

Thyroid dysfunction may cause muscle wasting and physical disability leading to loss of independence and nursing home admission (Du et al., 2021; Gussekloo et al., 2004; Pearce et al., 2016). However, there are no studies on the association between thyroid function and nursing home admission in older adults, and studies investigating thyroid function and disability are scarce (Gussekloo et al., 2004; Pearce et al., 2016). As this outcome may be the most important outcome for most older patients, information on prognosis is important when evaluation patients in clinical practice and if treatment is considered. This led us to investigate the association between thyroid function and nursing home admission and all-cause mortality in community-dwelling older adults. In addition, we explored the influence of treatment of

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hypothyroidism.

2. Methods

2.1. Study participants

This was an open cohort study with participants included consecutively during the study period. We included all adults having their first measurement of TSH after the age of 80 years in available laboratory databases between 1st of January 1996 and 31st of March 2019. We excluded samples taken from hospital inpatients. We followed participants from inclusion to date of nursing home admission, death, loss to follow-up due to emigration from Denmark or end of study at 31st of December 2019, which was the last date that nursing home admission data was available.

Laboratory databases used for inclusion covered most of Denmark with expanding coverage over time. All but one region of five regions was covered from 2008 and onwards, thereby covering more than 75% of the Danish population (supplementary figure 1). Laboratory, hospital, and general practitioner services in Denmark are free of charge, and most service utilizations are stored in national registries according to unique individual social security number. Participants were linked with other Danish registries and further information on comorbidity and medication was retrieved, as described in detail below. Diagnoses of comorbidities were recorded by International Classification of Disease 10th revision (ICD-10) codes and prescriptions of medication by Anatomical Therapeutic Chemical (ATC) codes. This information was used to exclude participants with prior thyroid conditions based on use of antithyroid medication, thyroid hormone therapy, prior diagnosis of hypo- or hyperthyroidism, diagnosis of thyroiditis, diagnosis of thyroid cancer, thyroid surgery, or radioiodine treatment for a thyroid condition. We further excluded participants with prescriptions of medications known to affect thyroid function in the year prior to inclusion: lithium, amiodarone, and systemic glucocorticoids. ICD-10 and ATC codes used in exclusion criteria can be found in supplementary Table 1. Finally, we excluded participants in nursing homes prior to inclusion.

2.2. Baseline covariates

Information on comorbidities was gathered from the Danish National Patient Register (DNPR) (Schmidt et al., 2015). The DNPR holds data on hospital admissions, emergency room contacts, and outpatient hospital contacts by dates and diagnoses, coded according to the ICD-10. The DNPR does not contain information on general practitioner contacts, and therefore we added the diagnoses of hypertension and diabetes using information on prescriptions from the Danish National Prescription Register. We defined hypertension by a validated method as the used of two or more antihypertensive agents in two or more consecutive quarters, as done previously (Krogager et al., 2017; Olesen et al., 2011). In accordance with previous studies, we defined diabetes as the use of any glucose lowering medication (Jensen et al., 2019; Krogager et al., 2017).

2.3. Thyroid function tests

Measurements of TSH came from laboratories across the country, which use different assays. Individual laboratories perform quality control to ensure precision of their measurements. As for thyroxine and triiodothyronine, measurements were of either free or total hormones, and differ by equipment and assays used. To avoid selection bias due to local differences when measuring peripheral hormones, groups were based on TSH only in the primary analysis. Participants were categorized by TSH: below 0.02 mIU/l, 0.02 – 0.3 mIU/l, 0.3 – 5 mIU/l, 5 – 10 mIU/l, or above 10 mIU/l. Classification of thyroid function by TSH was based on the scientific evidence available taking into consideration both biological variation and the, albeit limited, differences in reference ranges between laboratories (Andersen et al., 2003; Collet et al., 2012; Gencer et al., 2012; Gussekloo et al., 2004; Selmer et al., 2012) to establish categories that best described the individual's thyroid function. We opted to use the more abnormal value as group limit, and 5 mIU/l was chosen as the upper limit, and 0.02 was chosen to differentiate the two groups of hyperthyroidism.

A single laboratory, the Copenhagen General Practitioners Laboratory, covered approximately 30% of the Danish population. This laboratory measured TSH, free thyroxine (FT4), and total thyroxine (TT4) by the ADVIA Centaur TSH kit (Bayer/Siemens, Tarrytown, NY). Therefore, participants with samples from this laboratory were used in sensitivity analysis of the potential impact of combining participants with different assays.

2.4. Follow-up on nursing home admission

The association between thyroid function and nursing home admissions was determined with death as a competing risk factor. Data on nursing home admissions in Denmark are stored in a central registry covering the period from 1st of January 1994 to 31st of December 2016. Here, a validated method was used to capture all admissions in private and public nursing homes with a margin of error of 3% (Ældredokumentation, 2012). This method was supplemented by a method relying on report by municipalities from 2008 that fully replaced it from 2016 onwards. Both methods require a permanent change of address and therefore temporary stays in nursing facilities are not included. As such, nursing home admission according to this definition represents a considerable decline in function.

2.5. Association between treatment of hypothyroidism and outcomes

To explore the association between treatment of hypothyroidism and nursing home admission and all-cause mortality we performed two nested case control studies among participants with baseline TSH above 5 mIU/l within our cohort. In the first study we matched participants at time of nursing home admission and in the second at time of death from any cause. Participants were matched with up to 5 controls on sex and age in 5-year intervals in both studies using incidence density matching. Time of treatment was defined as the first redeemed prescription of thyroid hormone therapy. As initiation of thyroid hormone therapy in older adults can cause initial overtreatment, we explored early adverse effects of treatment on outcomes. Therefore, treatment during follow up was categorized by time from commencement in categories of below 6 months, 6–12 months and above 12 months.

3. Statistical analyses

When presenting characteristics, categorical variables were shown with numbers and percentages, normal continuous variables as means and standard deviations, and non-normal continuous variables as medians and interquartile range.

The associations between thyroid function and nursing home admission and all-cause mortality were determined by Aalen-Johansen cumulative incidence curves and multivariate Cox regression adjusted for age, year of inclusion, sex, ischemic heart disease, atrial fibrillation, heart failure, chronic kidney disease, chronic obstructive pulmonary disease, cancer, hypertension, and diabetes. Age was included as continuous variable modelled as restricted cubic splines with five knots to allow for non-linearity. All other variables were binary.

Likelihood ratio tests were used to test for interactions between thyroid function category and sex, age, and heart disease defined as a diagnosis of either atrial fibrillation, ischemic heart disease, or heart failure. These three indicators of heart disease were chosen for interaction analysis due to their relationship with thyroid disease (Collet et al., 2012; Gencer et al., 2012; Selmer et al., 2012).

The proportional hazards assumptions in the primary analyses were

checked using Schonefeld residuals. Testing of proportional hazards for the analysis of all-cause mortality indicated potential violation of the assumption. When follow-up was started after a 90-day grace period as in a similar previous study all analysis fulfilled the proportional hazards assumption (Selmer et al., 2012). There were no missing data.

Nested case control studies were analysed using time dependent Cox regression. Analyses were adjusted for the same covariates as primary Cox regression except for variables used in matching. All analyses were performed using R version 3.5.3 (Core Team, 2020).

4. Ethics

Ethical approval is not required for the conduct of registry-based studies in Denmark. The use of registry data was approved by the Data responsible unit in the Capital Region of Denmark (P-2019–191).

5. Results

A total of 272,495 community-dwelling older adults were eligible for the study (see Fig. 1 for selection process). Patients were followed for a median of 3.71 years for the outcome of nursing home admission and 4.00 years for all-cause mortality. Characteristics of participants is available in Supplementary Table 3. Generally, participants with thyroid dysfunction were more likely to be female and slightly older than euthyroid individuals. Likelihood ratio tests showed no interactions in statistical analysis.

5.1. Association between thyroid function and nursing home admission

Cumulative incidence curves for nursing home admission showed a distinct trend across TSH levels, with the highest risk of nursing home admission among participants with a low TSH, and the lowest risk among patients with a high TSH. A similar trend was seen for mortality, which was a competing risk in this analysis (Fig. 2).

In multivariate Cox regression, higher TSH levels were associated with lower nursing home admission hazard both in patients with TSH between 5 and 10 mIU/l (HR: 0.85, 95% CI: 0.80 to 0.91, $P < 0.001$) and above 10 mIU/l (HR: 0.68, 95% CI: 0.54 to 0.85, $P = 0.001$). There was an association with an increased hazard of nursing home admission among participants with TSH of 0.02–0.3 mIU/l (HR: 1.10, 95% CI: 1.05 to 1.15, $P < 0.001$), but not for patients with TSH < 0.02 mIU/l (HR: 1.04, 95% CI: 0.94 to 1.16, $P = 0.42$) (Fig. 3).

5.2. Association between thyroid function and all-cause mortality

Multivariate Cox regression for the outcome of all-cause mortality showed an association with lower mortality hazard for subjects with TSH above 10 mIU/l (HR: 0.70, 95% CI: 0.70 to 0.93, $P = 0.002$). There

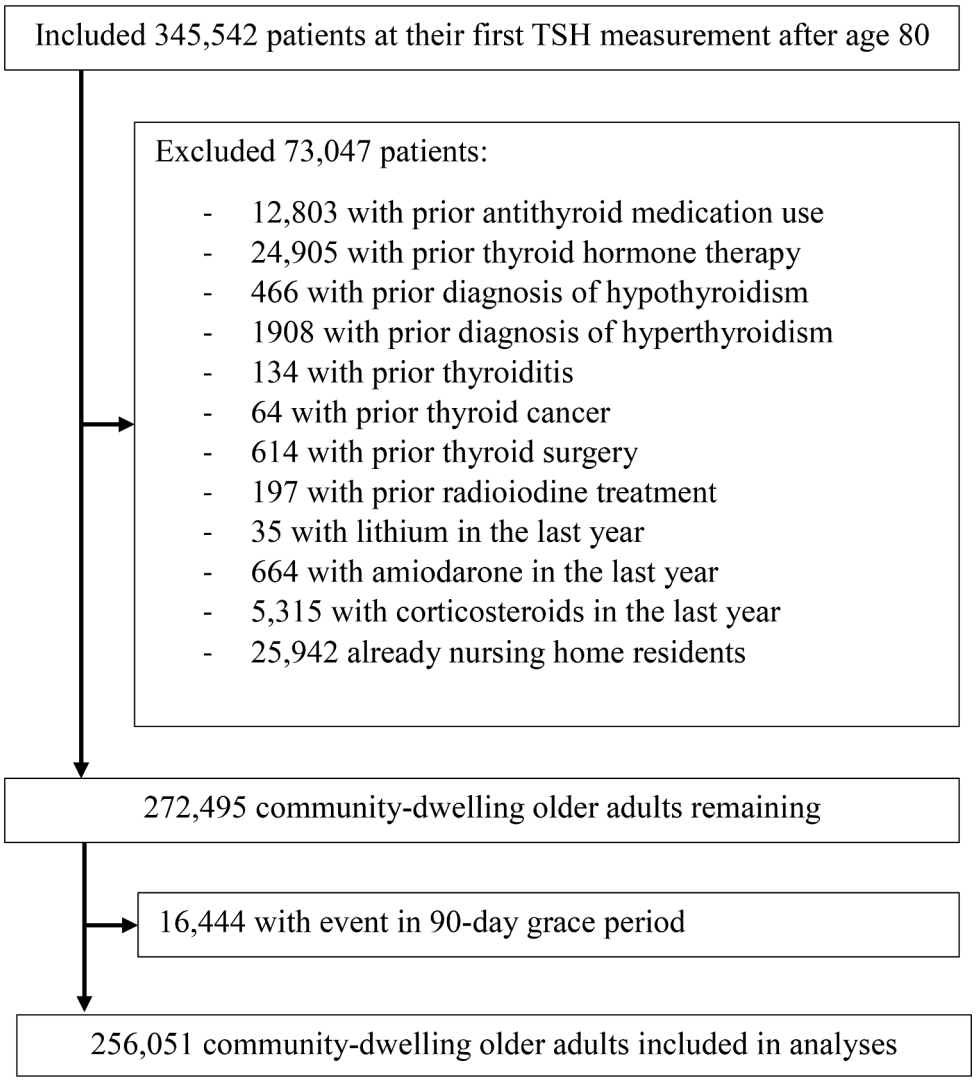

Fig. 1. Flowchart of study population selection process.

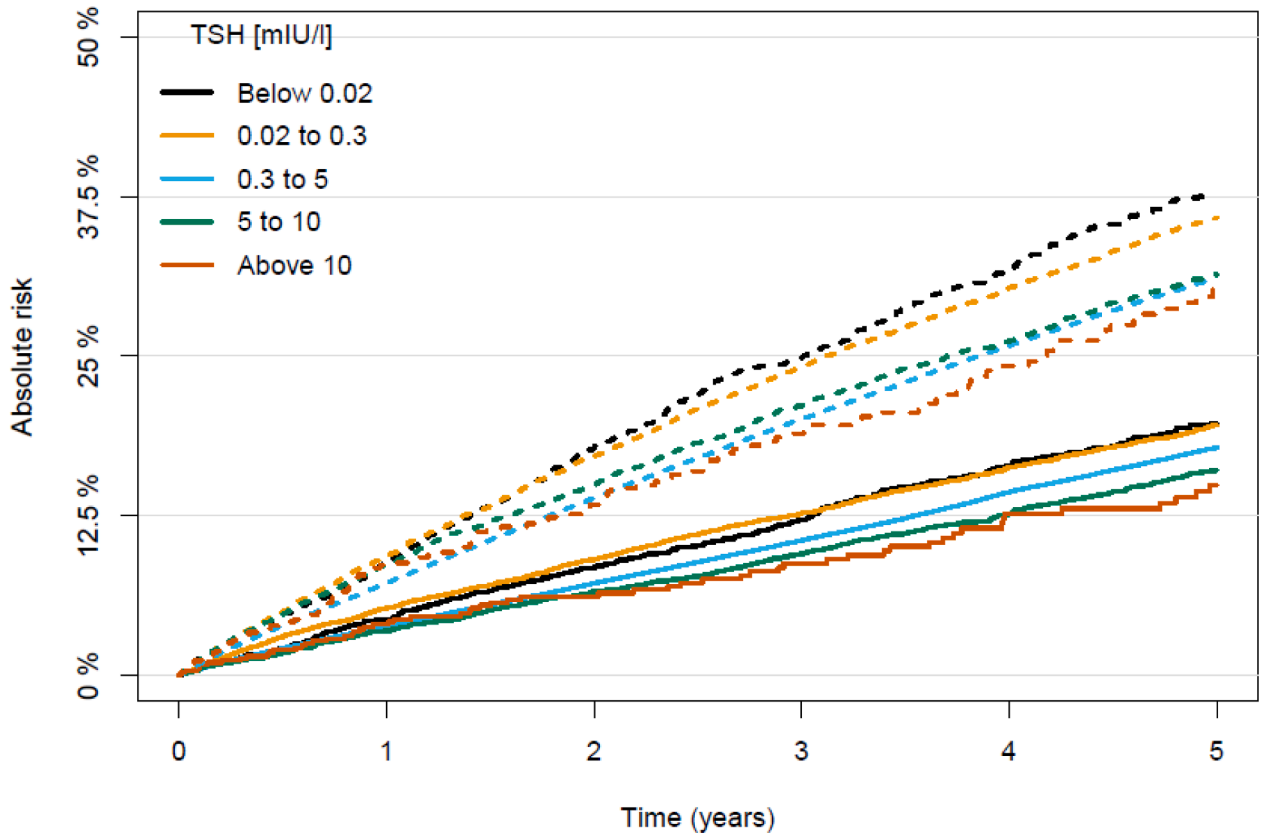

Fig. 2. Cumulative incidence of nursing home admission by thyroid function as evaluated by thyrotropin (TSH) in community dwelling older adults aged 80 years or over. Solid lines are nursing home admission, while dashed lines are death (competing risk).

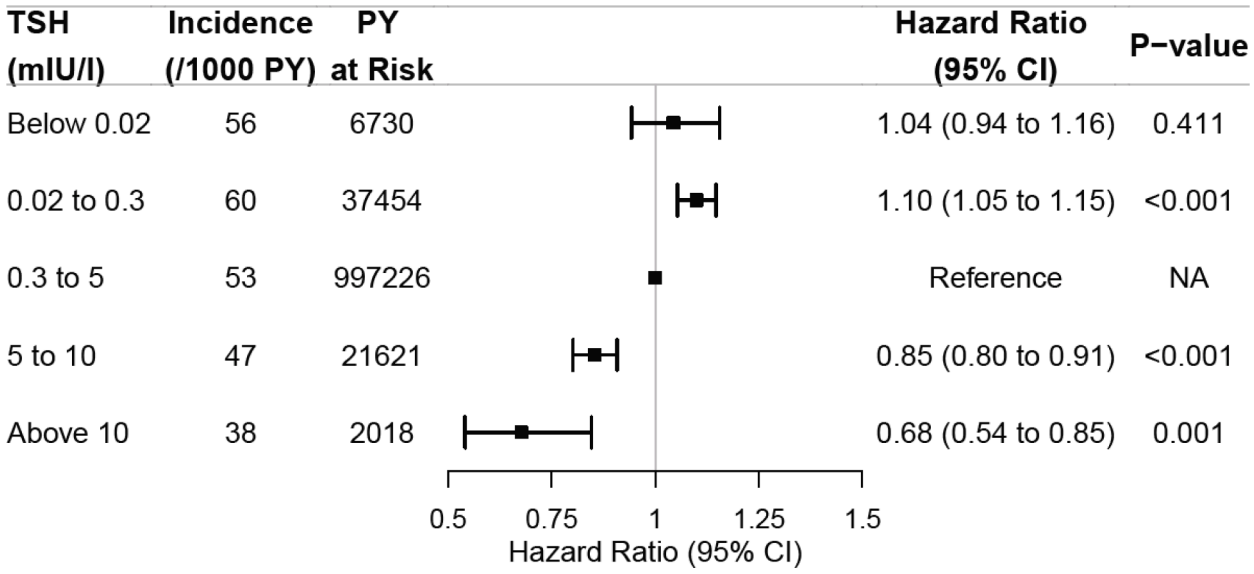

Fig. 3. Forest plot of the association between thyrotropin (TSH) and rate of nursing home admission.
Adjusted for age, sex, year of inclusion, ischemic heart disease, atrial fibrillation, heart failure, dementia, hypertension, diabetes, chronic kidney disease, history of cancer, and chronic obstructive pulmonary disease. PY, person years.

was a clear trend, with lower mortality hazards in subjects with TSH above 10 mIU/l to higher mortality hazards in subjects with low to suppressed TSH (Fig. 4). Accordingly, statistically significant associations with all-cause mortality were found for subjects with TSH between 0.02–0.3 mIU/l (HR: 1.16, 95% CI: 1.13 to 1.19, $P < 0.001$) and TSH < 0.02 mIU/l (HR: 1.14, 95% CI: 1.07 to 1.21, $P < 0.001$).

5.3. *Treatment for hypothyroidism*

The nested case control study exploring the association between treatment of high TSH and nursing home admission included 1510 cases and 7517 controls. There was a non-signifcant trend towards higher hazard of nursing home admission within the first 6 months of initating

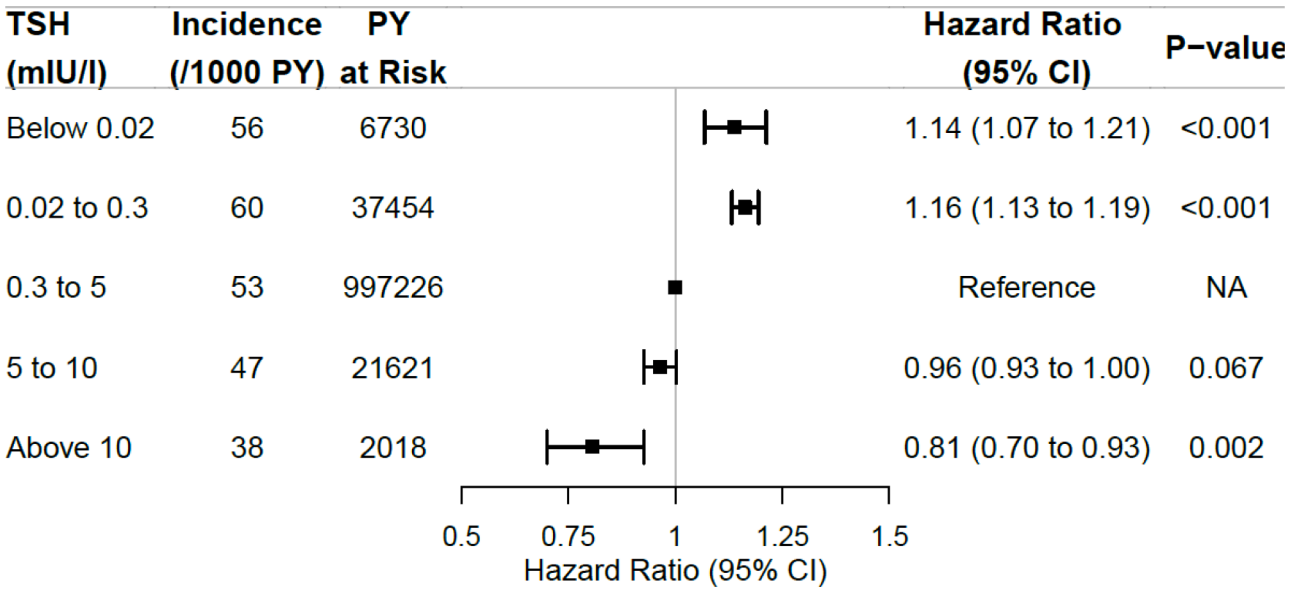

Fig. 4. Forest plot of the association between thyrotropin (TSH) and risk of all-cause mortality.
Adjusted for age, sex, year of inclusion, ischemic heart disease, atrial fibrillation, heart failure, dementia, hypertension, diabetes, chronic kidney disease, history of cancer, and chronic obstructive pulmonary disease.

treatment (HR: 1.39, 95% CI: 1.00–1.94, $P = 0.052$) compared to no treatment. This trend attenuated with greater time since treatment in a dose-response pattern.

A similar pattern was seen for the hazard of all-cause mortality. This analysis included 8129 cases and 14,691 controls. The greatest hazard was observed within the first 6 months of initiating treatment (HR: 1.80, 95% CI: 1.49–2.17, $P < 0.001$) compared to no treatment. A non-significant trend remained at 6–12 months (HR: 1.23, 95% CI: 0.98–1.53, $P = 0.072$) before leveling out after 12 months (HR: 1.04, 95% CI: 0.95–1.14, $P = 0.426$).

6. Sensitivity analysis

We performed three different sensitivity analyses. First, we retained analysis without the 90-day grace period as a sensitivity analysis. Second, we performed a sensitivity analysis including only participants with data provided from the GCPL. Third, in an analysis excluding all participant with abnormal TSH and missing peripheral hormones, we classified participants with abnormal TSH into classical disease categories (subclinical and overt) according to peripheral hormone level. Reference ranges used to define categories are shown in supplementary Table 2.

The overall results of the association between thyroid function and nursing home admission were similar to results of both the sensitivity analysis of patients from the GCPL with known assays (Supplementary Figure 2) and the sensitivity analysis without the 90-day grace period (Supplementary Figure 3).

The association between thyroid function and all-cause mortality in the sensitivity analysis of patients from the GCPL with known assays was similar to the primary results, except that TSH between 5 and 10 mIU/l was significantly associated with lower mortality hazard (Supplementary Figure 4). The sensitivity analysis without the 90-day grace period also yielded similar results to the primary analysis for TSH of 0.02–0.3 mIU/l and TSH below 0.02 but showed no association between higher TSH and all-cause mortality, in contrast to the primary analysis (Supplementary Figure 5).

The sensitivity analysis classifying patients into thyroid disease subgroups also showed comparable results to the primary analyses both for nursing home admission and for all-cause mortality. These analyses excluded 4806 patients (25.0% of all with abnormal TSH) with missing peripheral hormone measurement and 176 patients with ambiguous blood samples (0.9% of all with abnormal TSH).

7. Discussion

We investigated the association between thyroid function and nursing home admission as well as all-cause mortality in a large cohort of community dwelling adults aged 80 years or over, covering 75% of Denmark. We found that hypothyroidism/raised TSH was associated with a lower hazard of nursing home admission and to a smaller degree lower all-cause mortality. Conversely, hyperthyroidism/low TSH was associated with increased all-cause mortality while the impact on nursing home admission was less pronounced.

8. Nursing home admission

This is the first report of the association between thyroid function and hazard of nursing home admission. Previous studies examined the association using surrogate markers such as disability evaluated by activities of daily living (ADL) and findings were conflicting (Gussekloo et al., 2004; Pearce et al., 2016).

An individual patient data meta-analysis of five cohorts reported no association between thyroid function and functional decline at a 5-year follow-up (Du et al., 2021). Their study was based on unselected prospective cohorts. In contrast, we retrospectively included routine patient samples and employed strict inclusion criteria to obtain a cohort unaffected by thyroid-affecting conditions and medications. Further they included only 2000 participants at baseline and used two time points for analysis and did not report the available sample size for analysis at 5-years or differences in dropout even though disabled participants may be unable to participate in the re-evaluation at 5-years. In contrast, we included a 10-fold larger sample size and used a time to event approach, where loss to follow-up only occurred by treatment or emigration out of Denmark. Finally, we examined hazard of nursing home admission while they pooled standardized measure of ADL across different scales.

9. All-cause mortality

Our finding that low and suppressed TSH was associated with raised mortality in older adults is consistent with previous reports (Collet et al.,

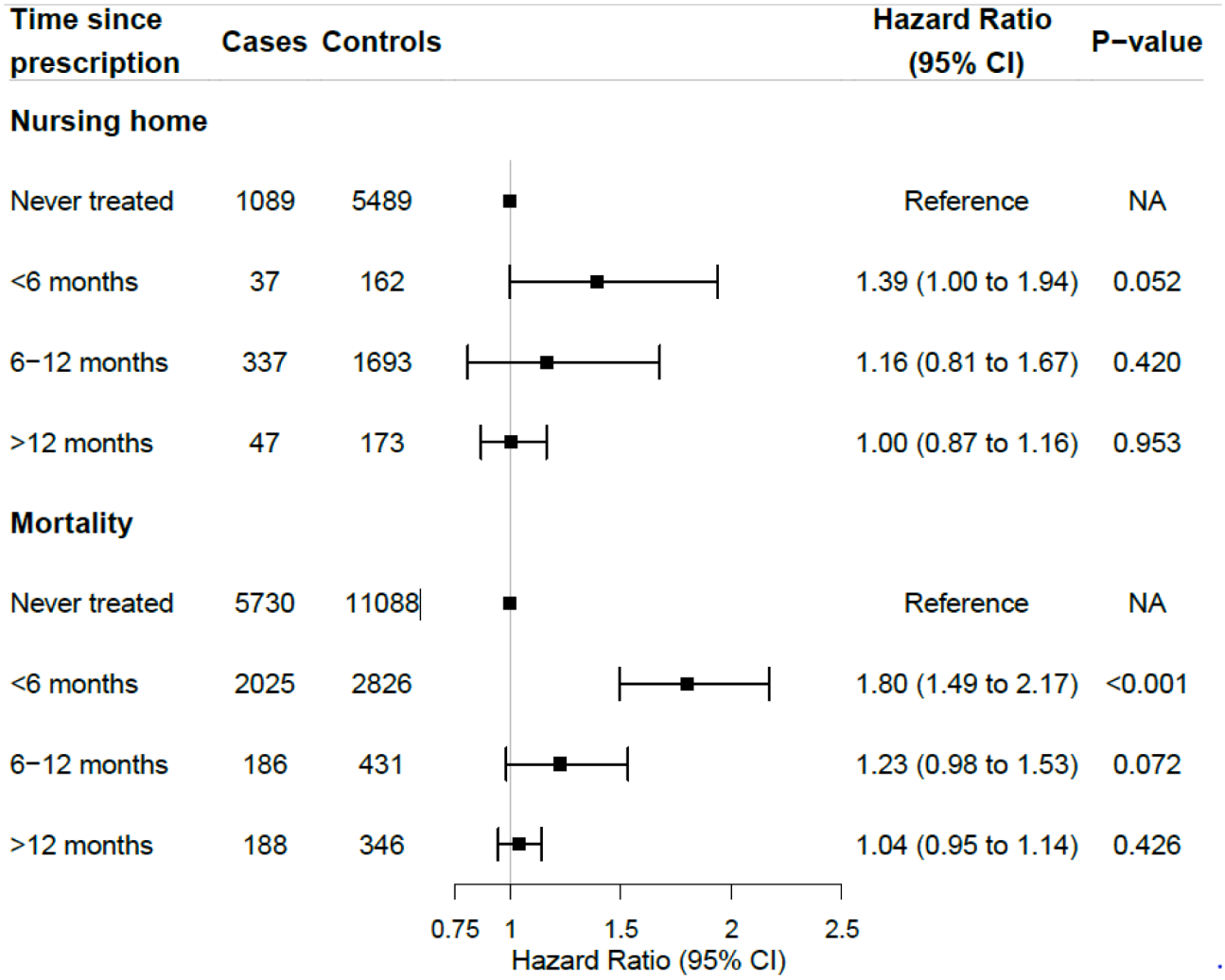

Fig. 5. Nested case control studies showing the association between time from first prescription of thyroid hormone treatment to event.
Matched by age and sex and adjusted for year of inclusion, ischemic heart disease, atrial fibrillation, heart failure, dementia, hypertension, diabetes, chronic kidney disease, history of cancer, and chronic obstructive pulmonary disease.

2012). Hyperthyroidism was associated with several adverse outcomes including atrial fibrillation, heart failure, and fractures (Blum et al., 2015; Gencer et al., 2012; Selmer et al., 2012) which may contribute to the greater all-cause mortality.

We saw slightly reduced all-cause mortality in those with raised TSH. These results are consistent with previous reports (Gussekloo et al., 2004; Jansen et al., 2015; Ogliari et al., 2017; Rozing et al., 2010; Toft, 2001). It may be speculated that the adverse effects of low and suppressed TSH extend into higher TSH as protective effects. Age and study design seem to be important for this association. Old age is a spectrum, and implications in the young-old and oldest-old may differ. The oldest-old may have more comorbidities and frailty, and it is plausible that slight hypothyroidism may be protective against the adverse effects seen in hyperthyroidism (Riis et al., 2022; Sgarbi & Ward, 2021). A large meta-analysis of 26 studies of adults aged over 60 found increased mortality rate with hypothyroidism (Tsai et al., 2020). However, only two studies focused on older adults aged 80 years or over, and this group had a trend towards lower mortality (relative risk 0.75, $P = 0.09$), consistent with our findings of lower mortality with a high TSH. Moreover, increased mortality was only found in retrospective studies. Our results may provide an explanation for this discrepancy, as only after the introduction a 90-grace period, we found an association with reduced hazard of all-cause mortality in patients with high TSH. This is consistent with confounding by the non-thyroidal illness syndrome (Effraimidis et al., 2021).

10. Treatment of hypothyroidism

Exploratory analysis of treatment of hypothyroidism showed no impact on either outcome past 12 months after treatment initiation. This is consistent with recent randomized controlled trials showing no effect on symptoms (Mooijaart et al., 2019; Stott et al., 2017). However, we found raised mortality and a trend towards increased nursing admissions early after initiation of thyroid hormone treatment. This is in line with the trend that lower TSH associates with mortality. The early effect may be due to the increased strain precipitating ischemic heart events and arrythmias and there is a need for larger randomized controlled trials on mortality and cardiovascular disease (Ruggeri et al., 2017).

11. Strengths and limitations

A strength of our study is the large sample size. We included routine measurements of thyroid function tests covering 75% of Denmark. Older adults have frequently routine blood samples taken and testing of thyroid function is often included. There is a risk of confounding by indication, but the above supports that selection bias should be lower in this age group. Based on the number of citizens in the areas in this period it is calculated that approximately 90% of the whole population over 80 had

a thyroid function test. This further supports our claim of limited risk of selection bias.

Another limitation is the lack of information on smoking habits. We adjusted analysis for a broad range of conditions related to smoking, but residual confounding could still be present. Finally, we employed strict inclusion criteria to reduce the risk of confounding, which on the other hand reduces generalizability to these patient groups. We believe that the balance in our analysis allows for valid interpretation of our data.

It may be speculated that prevalent cases of thyroid disease may have a shorter lifespan in young age and therefore older patients with raised TSH have a more favourable prognosis. However, we excluded patients previously diagnosed with or treated for thyroid dysfunction and we would also expect this to be ameliorated by adjustment for differences in exposure characteristics. Finally, this does not explain why there seems to be less treatment response in this age group (Stott et al., 2017). Therefore, we believe the different implications found with lower thyroid function found in the literature as well as our study are more likely a result of true age differences.

12. Clinical implications

Our results corroborate the notion that subclinical hypothyroidism is beneficial in old age and supports maintaining the independent living prioritised by older adults. Moreover, initiation of treatment of hypothyroidism may raise nursing home admissions and mortality. Hence, out results support that we should watch, wait, and not treat older adults until overt hypothyroidism with markedly elevated TSH develops. Conversely, while low TSH increased the risk of nursing home admission and death, it remains to be settled if treatment of low TSH is beneficial to older adults.

13. Conclusion

Hypothyroidism is associated with reduced hazard of nursing home admission and to a less extent all-cause mortality in community-dwelling adults over 80 years while hyperthyroidism was associated with increased all-cause mortality but not hazard of nursing home admission. Treatment of hypothyroidism may cause a transient rise in mortality and nursing home admissions. Further studies are warranted to evaluate the effect of treatment of hypothyroidism on disability and mortality in the oldest old.

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Impact statement

We confirm that this research is novel. This study is the first to report the association between thyroid function and nursing home admissions. Our results show that hypothyroidism may be associated with less disability and mortality in old age. Therefore, our results may impact future research of treatment of hypothyroidism in older people.

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CRediT authorship contribution statement

Johannes Riis: Formal analysis, Methodology, Visualization, Writing – original draft, Writing – review & editing. **Kristian Kragholm:** Conceptualization, Data curation, Methodology, Writing – review & editing. **Christian Torp-Pedersen:** Conceptualization, Data curation, Funding acquisition, Methodology, Resources, Software, Supervision, Writing – review & editing. **Stig Andersen:** Conceptualization, Funding acquisition, Methodology, Writing – review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.archger.2022.104806.

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