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# Chapter 8

## Thyroid status and renal function in older persons in the general population

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## Abstract

*Background:* Prevalence estimates of thyroid dysfunction and chronic kidney disease both increase with age. The aim of this study was to investigate the cross-sectional association between low thyroid function and renal function in subjects aged 85 years and to assess whether a low thyroid function at age 85 years is associated with an accelerated decline in renal function during follow up.

*Methods:* We included 558 participants from the Leiden 85-plus Study. At baseline (age 85), thyroid stimulating hormone (*TSH*), free thyroxine (*fT4*) and free triiodothyronine (*fT3*) levels were measured. Thyroid function groups were created using clinical cut-off values of *TSH* and *fT4*. Serum creatinine concentrations were determined at baseline and annually during a 5 year follow-up period. Estimated glomerular filtration rates (*eGFR*) were calculated by means of the MDRD equation.

*Results:* At baseline, subjects with higher levels of *TSH* and lower levels of *fT4* and *fT3* had lower renal function. Participants with hypothyroidism (mean 53.7 (2.0) mL/min/1.73m<sup>2</sup>) and subclinical hypothyroidism (55.7 (2.1) mL/min/1.73m<sup>2</sup>) had lower mean *eGFR* (*SE*) than participants with normal thyroid function (59.5 (0.7) mL/min/1.73m<sup>2</sup>); the highest *eGFR* was observed in participants with hyperthyroidism (*eGFR* (61.5 (3.1) mL/min/1.73m<sup>2</sup>) (*p*-for trend=0.004). There was no association between thyroid hormone levels at baseline and the change in renal function during follow-up.

*Conclusions:* Although low thyroid function was associated with lower renal function at age 85 years, an association between a low thyroid function and change in renal function over time was absent. Our findings question the causal relevance of the thyroid status for the deterioration of renal function in the oldest old.

## Introduction

Renal function declines with increasing age.<sup>1</sup> Up to 47 percent of individuals aged 70 years and over are estimated to suffer from some stage of Chronic Kidney Disease (CKD).<sup>2</sup> Throughout all age strata, CKD is associated with an increased risk of adverse cardiovascular outcomes, such as myocardial infarctions, heart failure and death.<sup>3,4</sup> In the general population, CKD is commonly caused by diabetes mellitus, and hypertension,<sup>5</sup> but treatment of these risk factors does not fully prevent the decline in renal function with advancing age. Therefore, identification of other risk factors for a decline in renal function, that are potentially amenable for treatment, is needed.

Alike CKD, overt and subclinical hypothyroidism are common disease entities in the general population, especially in older persons.<sup>6,7</sup> Up till 14 % of individuals aged  $\geq 80$  years are reported to have elevated serum thyroid stimulating hormone (TSH) levels.<sup>6</sup> In the general population, overt hypothyroidism and subclinical hypothyroidism are both associated with an increased cardiovascular risk,<sup>8,9</sup> which could be attributed to various cardiovascular effects of thyroid hormones.<sup>9</sup> A low thyroid hormone state has been associated with adverse blood lipid alterations,<sup>10</sup> endothelial dysfunction,<sup>11</sup> and accelerated atherosclerosis.<sup>12</sup>

Several small observational studies indicated a decline in renal function in patients with overt hypothyroidism as estimated by serum creatinine measurements<sup>13-15</sup> and labeled edetic acid.<sup>16</sup> These alterations attenuated or even reversed after thyroid hormone supplementation.<sup>13-15</sup> Two very recent reports additionally showed a negative effect of subclinical hypothyroidism on renal function over time in patients with pre-existing CKD.<sup>17,18</sup> Potential pathophysiological mechanisms connecting a low thyroid function to a decrease in renal function could pertain to a decrease in cardiac output, direct vasoactive effects, a reduction in the size of glomeruli, and promotion of arteriosclerosis as induced by low serum thyroid hormone concentrations.<sup>19</sup>

Although prevalence estimates of a low thyroid function and CKD both increase with age, it is unknown whether subclinical and overt hypothyroidism are also associated with a deterioration of renal function over time specifically in older persons. Therefore, the aim of this study was to investigate the association between low thyroid function and renal function specifically in an elderly population. For this purpose, we investigated the cross-sectional association between thyroid status and renal function in subjects 85 years and assessed whether a low thyroid hormone state at age 85 years associated with an accelerated decline in renal function over time. This is of special interest as negative effects of commonly appreciated risk factors in the general population,<sup>20,21</sup> including the impact of a low thyroid hormone state on mortality,<sup>7,22-24</sup> proved absent in the oldest old.

## Methods and material:

### *Study population*

The Leiden 85-plus Study is a population-based prospective follow-up study of 85-year-old inhabitants of Leiden, the Netherlands. The study protocol has been described in detail previously.<sup>21</sup> In short, between 1997 and 1999, all residents of Leiden, the Netherlands, celebrating their 85th birthday (belonging to the 1912-1914 birth cohort) were contacted and asked to participate. Out of the 705 individuals who were found eligible, 14 died before the recruitment phase and 92 refused participation leaving a total of 599 individuals to be enrolled in the study (response rate 87%).<sup>21</sup> Within one month after their 85th birthday, participants were visited at home. During these visits, participants underwent face-to-face interviews, performance tests were done and a venous blood sample was drawn. 37 participants refused blood sampling. In the present analyses, 558 participants were included with complete information on thyroid hormone status and renal function. Participants were visited annually until reaching the age of 90 years or death. At age 88, 376 individuals underwent a second blood withdrawal. The medical ethical committee of the Leiden University Medical Centre approved the study protocol, and informed consent was obtained from all participants.

### *Laboratory measurements*

Blood was withdrawn in a supine position and analyzed immediately. Plasma levels of TSH and free thyroxine (fT4) were measured in a fully automatic fashion using an Elecsys 2010 system (Hitachi, Tokyo, Japan). For TSH, the coefficients of variation (CV) ranged between 5% and 11%. For fT4, CVs varied between 5% and 8%. An electrochemiluminescence technique was applied (Boehringer, Mannheim, Germany). Plasma levels of free triiodothyronine (fT3) were determined by a microparticle enzyme immunoassay (Abbott Diagnostics, Abbott Park, Ill) for which CVs were between 3% and 8%.

The following thyroid hormone groups were created based on serum TSH and fT4 levels as widely accepted;<sup>25</sup> 1) Euthyroidism; TSH levels between 0.5 and 4.5 mIU/L. 2) overt hypothyroidism; TSH >4.5 mIU/L and fT4 <13 pmol/L, 3) subclinical hypothyroidism; TSH >4.5 mIU/L and fT4 between 13 and 23 pmol/L, 4) overt hyperthyroidism; TSH <0.5 mIU/L and fT4 >23 pmol/L and 5) subclinical hyperthyroidism; TSH levels <0.5 mIU/L and fT4 concentrations between 13 and 23 pmol/L. Since only two subjects had overt hyperthyroidism, groups 4 and 5 were merged into one category named “hyperthyroidism”. Three patients, two of whom with low TSH and low T4 levels and one with high TSH and high T4 levels, fell out of our classification. When new thyroid dysfunction was discovered (n=39) subjects were referred to their general practitioner for further work-up.<sup>22</sup>

Serum creatinine concentrations were measured according to the Jaffé method (Hitachi 747; Hitachi, Tokyo, Japan). For the primary analyses, glomerular filtrations rates were estimated using the four variable version of the Modification of Diet in Renal Disease Study (*MDRD*) formula<sup>26</sup> which has been validated in older adults.<sup>27</sup> Subjects were divided into three eGFR groups (<30, 30-60, >60 mL/min/1.73m<sup>2</sup>). For the purpose of sensitivity analyses, creatinine clearances were calculated using the Chronic Kidney Disease Epidemiology Collaboration (*CKD-EPI*)<sup>28</sup> and Cockcroft-Gault formulas.<sup>29</sup> Plasma C-reactive protein (*CRP*) levels were assessed by utilization of a Hitachi 747 automated analyzer at the day the sample was drawn.

Information on the presence of disease was obtained from general practitioners and nursing home physicians. The presence of cardiovascular disease was defined as a history of a cerebrovascular accident or transient ischemic attack, angina pectoris, myocardial infarction, peripheral vascular disease (including a history of arterial grafting, endarterectomy, and/or angioplasty), an electrocardiogram suggesting myocardial ischemia or past infarction, and a history of heart failure.<sup>30</sup> Diabetes mellitus (*DM*) was considered present when diagnosed by a primary care physician, when routine non-fasting glucose levels exceeded 11.0 mmol/L, or when an individual was being prescribed anti-diabetic medication. Past and/or currently active malignancies were grouped into one category. Also, a simple physical examination was performed which included an assessment of weight, height, and blood pressure. With an intervening period of two weeks, blood pressure was measured twice by using a mercury sphygmomanometer.<sup>31</sup> For every measurement, patients had rested for at least 5 minutes and performed no vigorous exercise in the preceding 30 minutes. Information on the use of thyroid medication (antithyroid medication and/or thyroxine supplementation) was obtained from pharmacy records.

### *Statistical analyses*

Baseline characteristics were presented as means with standard deviation (*SD*), medians plus interquartile ranges (*IQR*) or numbers with percentages (%) across thyroid hormone groups. Differences between thyroid hormone groups were tested by means of one-way ANOVA, Kruskal Wallis and Chi square tests, as appropriate.

Mean (standard error of the mean (*SE*) or 95% confidence interval (*95%CI*)) eGFR values within tertiles of thyroid hormone distributions or thyroid hormone groups at baseline were calculated using univariate and multivariate linear regression models. Univariate models (*Model 1*) comprised tertiles of the specific thyroid hormone distribution or the different thyroid hormone groups as independent variables. In multivariate models, sex, *DM*, smoking, the presence of cardiovascular disease (composite score  $\geq 1$ ), malignancies, and amiodarone usage were added as possible confounders (*Model 2*).

To examine the effects of the different thyroid hormone groups and thyroid hormone concentrations at baseline on change of renal function over time, linear mixed models were fitted. A model with fixed intercept and slope and unstructured covariance matrix was adopted because of its best fit as judged upon by the maximum likelihood estimate method and Akaike's information criterion. Mean annual changes per group were estimated by means of multivariate models including the baseline variables sex, DM, smoking, cardiovascular disease, malignancies, and amiodarone treatment as possible confounders. The effect of thyroid hormone status on the change in renal function over time was evaluated by implementation of an interaction term between thyroid hormone state and time.

As an alternative approach, regression lines were fitted on the repeated measurements for each individual separately. Then these betas were pooled within the different thyroid hormone strata (tertiles for each hormone) and groups (as earlier specified) and compared by means of a one-way ANOVA test. In addition, we compared the percentage of individuals developing stage 4 or 5 CKD ( $<30 \text{ mL/min/1.73m}^2$ ) during follow-up between the different thyroid function groups.

As sensitivity analyses, models were rerun 1) in three different baseline strata of renal function, 2) only in the 535 individuals not on drugs interfering with thyroid hormone measurements (thyroxine and/or antithyroid drugs), 3) specifically in those who lived to celebrate their 90th birthday ( $n=299$ ), and in order to exclude those with possible non-thyroidal illness 4) only in subjects having CRP levels  $< 5 \text{ mg/L}$  ( $n=317$ ). Also, creatinine clearances as estimated with the Cockcroft Gault and CKD-EPI formulas were used as outcome variables. Further, multivariable models were further adjusted for systolic blood pressure, C-reactive protein levels, BMI, and total cholesterol levels. Finally, we investigated the association between different thyroid hormone change patterns over a 3 year period (85-88 years of age) and progression of renal function in the years thereafter. For this purpose, we categorized patients into four categories: 1) Those having elevated TSH levels ( $>4.5 \text{ mIU/L}$ ) at age 85 and 88 (Persistent hypothyroid group,  $n=31$ ), 2) those having TSH levels between 0.5 and 4.5 mIU/L at both time points (Persistent euthyroid group,  $n=276$ ), 3) those persistently having levels  $< 0.5 \text{ mIU/L}$  (Persistent hyperthyroid group,  $n=12$ ) and 4) patients changing categories (Change group,  $n=53$ ).

In linear regression analyses and linear mixed models, betas with 95 percent confidence intervals (95%CI) not including 0 were considered statistically significant. For all other tests, a p-value smaller than 0.05 indicated statistical significance. All analyses were performed using SPSS 20 (IBM Inc., New York, USA). Figures were created using Prism 5.02 (Graphpad, 1992).

**Table 1.** Baseline characteristics of the study population according to thyroid status

|                                      | O<br>hypothyroidism<br>n=40 | SC<br>hypothyroidism<br>n=35 | Euthyroidism<br>n=451 | O and SC<br>hyperthyroidism<br>n=29 | p-value |
|--------------------------------------|-----------------------------|------------------------------|-----------------------|-------------------------------------|---------|
| General                              |                             |                              |                       |                                     |         |
| Men, n, % <sup>1</sup>               | 9 (22.5)                    | 7 (20.0)                     | 161 (35.7)            | 10 (34.5)                           | 0.104   |
| BMI, kg/m <sup>2</sup>               | 28.5 (4.8)                  | 28.2 (4.1)                   | 26.7 (4.5)            | 25.1 (4.3)                          | 0.040   |
| Smoker, n, % <sup>1</sup>            | 5 (12.5)                    | 5 (14.3)                     | 74 (16.4)             | 4 (13.8)                            | 0.888   |
| Malignancy, n, % <sup>1</sup>        | 6 (15.0)                    | 11 (31.4)                    | 76 (16.9)             | 5 (17.2)                            | 0.178   |
| Institutionalized, n, % <sup>1</sup> | 13 (32.5)                   | 2 (5.7)                      | 81 (18.0)             | 5 (17.2)                            | 0.027   |
| Cardiovascular profile               |                             |                              |                       |                                     |         |
| Previous CVD, n, % <sup>1,2</sup>    | 21 (52.5)                   | 23 (65.7)                    | 205 (45.5)            | 16 (55.2)                           | 0.090   |
| DM, n, % <sup>1</sup>                | 7 (17.5)                    | 7 (20.0)                     | 65 (14.4)             | 2 (6.9)                             | 0.483   |
| CRP, mg/L <sup>3</sup>               | 4.0 (2.0-8.0)               | 8.0 (3.0-11.0)               | 3.0 (1.0-7.0)         | 5.0 (1.0-10.0)                      | 0.007   |
| Thyroid profile                      |                             |                              |                       |                                     |         |
| TSH, mIU/L <sup>3</sup>              | 6.45 (5.57-8.27)            | 5.57 (5.05-6.66)             | 1.67 (1.18-2.34)      | 0.19 (0.01-0.37)                    | -       |
| fT4, pmol/L                          | 10.16 (1.24)                | 15.10 (1.41)                 | 14.58 (2.31)          | 17.70 (3.92)                        | -       |
| fT3, pmol/L                          | 3.20 (0.59)                 | 3.32 (0.64)                  | 3.39 (0.52)           | 3.65 (0.72)                         | -       |
| Medication usage                     |                             |                              |                       |                                     |         |
| Thyroid hormone, n(%) <sup>1</sup>   | 2 (5.0)                     | 6 (17.1)                     | 6 (1.3)               | 2 (6.9)                             | <0.001  |
| Antithyroid med, n, % <sup>1</sup>   | 1 (2.5)                     | 2 (5.7)                      | 0 (0.0)               | 1 (3.4)                             | <0.001  |

1. Categorical data are presented as numbers plus percentages and differences between groups were tested by means of a X<sup>2</sup>-square test.
2. CV disease comprised a composite score of a history of a myocardial infarction, angina pectoris, heart failure, peripheral arterial disease and/or cerebrovascular accident/transient ischemic attack. A score  $\geq 1$  indicated presence of CV disease.
3. Nonnormally distributed data are presented as Medians plus interquartile ranges, differences were tested by means of a Kruskal-Wallis test.

O: Overt. SC: Subclinical, CV: cardiovascular, DM: Diabetes Mellitus, CRP: C-reactive protein, TSH: thyroid stimulating hormone, fT4: free thyroxine, fT3: free triiodothyronine.

## Results

Of the total study population, 33.6 percent was male and 18.3 percent was institutionalized in a care home or a nursing home. 82 (14.8%) participants had diabetes mellitus, 52.2% (n=291) suffered from a history of cardiovascular disease, and 98 (17.6%) participants had a past or current malignancy. The mean (SD) eGFR, as calculated with the MDRD formula, was 59.0 (14.4) mL/min/1.73m<sup>2</sup> (CKD-EPI: 49.0 (13.4), Cockcroft-Gault: 45.4 (11.5) mL/min). In **Table 1**, baseline characteristics are compared between the different thyroid hormone groups. As compared to euthyroid subjects, those with overt and subclinical hypothyroidism were more frequently women and had more comorbidities. Also, they had higher BMI and CRP levels and were prescribed more frequently thyroxine as well as anti-thyroid medication.

**Table 2.** Baseline levels of renal function within tertiles of distributions of TSH and thyroid hormones

|                                       | Tertiles of distribution of thyroid hormones |                       |                       | p-for trend <sup>1</sup> |
|---------------------------------------|----------------------------------------------|-----------------------|-----------------------|--------------------------|
|                                       | Lower<br><b>TSH, mIU/L</b><br>0.01 – 1.38    | Middle<br>1.39 – 2.35 | Higher<br>2.35 – 33.0 |                          |
| n                                     | 186                                          | 188                   | 184                   |                          |
| Crude eGFR, mean (SE) <sup>2</sup>    | 60.1 (1.1)                                   | 60.3 (1.0)            | 56.6 (1.1)            | 0.021                    |
| Adjusted eGFR, mean (SE) <sup>3</sup> | 61.5 (2.8)                                   | 61.9 (2.8)            | 58.2 (2.7)            | 0.037                    |
| <b>fT3, pmol/L</b>                    |                                              |                       |                       |                          |
|                                       | 0.77 – 3.19                                  | 3.20 – 3.63           | 3.63 – 6.60           |                          |
| n                                     | 201                                          | 199                   | 144                   |                          |
| Crude eGFR, mean (SE) <sup>2</sup>    | 57.8 (1.0)                                   | 58.8 (1.0)            | 61.1 (1.2)            | <0.0001                  |
| Adjusted eGFR, mean (SE) <sup>3</sup> | 59.3 (2.8)                                   | 59.5 (2.7)            | 62.1 (2.8)            | 0.074                    |
| <b>fT4, pmol/L</b>                    |                                              |                       |                       |                          |
|                                       | 8.4 – 13.4                                   | 13.5 – 15.3           | 15.3 – 30.9           |                          |
| n                                     | 189                                          | 190                   | 174                   |                          |
| Crude eGFR, mean (SE) <sup>2</sup>    | 57.4 (1.0)                                   | 59.4 (1.0)            | 60.0 (1.1)            | 0.083                    |
| Adjusted eGFR, mean (SE) <sup>3</sup> | 57.4 (2.8)                                   | 60.2 (2.8)            | 61.5 (2.7)            | 0.005                    |

1. The p-for trend was calculated by means of regression analysis.

2. Crude means and SDs were calculated by means of regression analyses.

3. Adjusted means and SDs were calculated by means of multivariate regression analyses including sex, diabetes mellitus, smoking, cardiovascular disease, malignancies, and amiodarone usage as possible confounders.

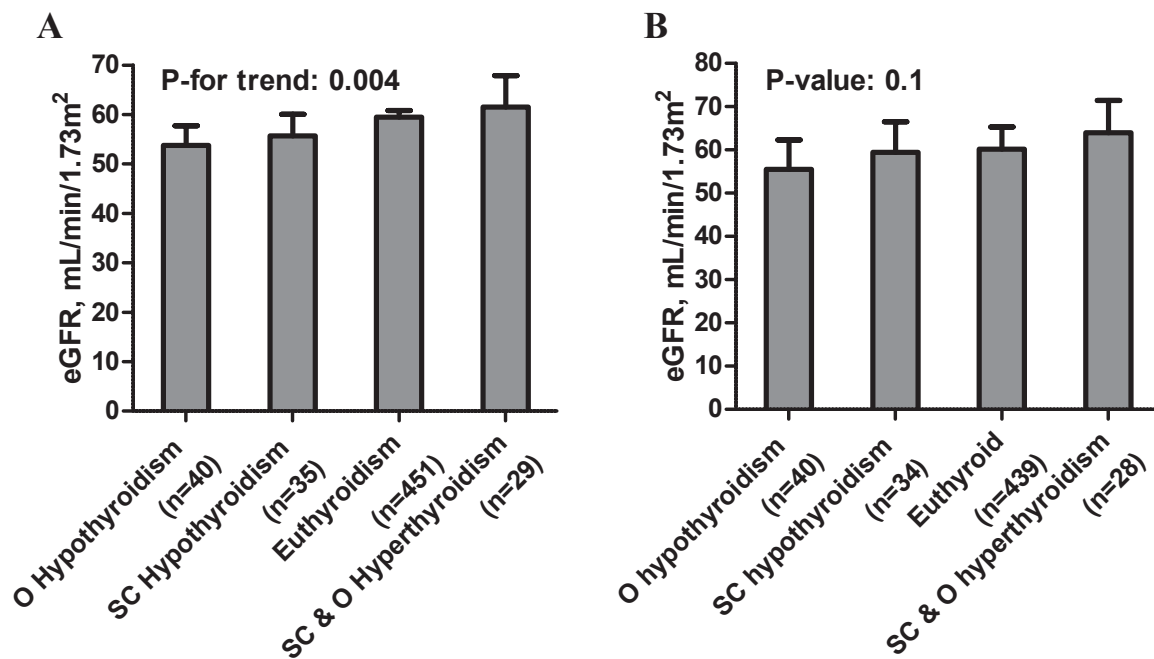
\* In these analyses, a maximum of 14 individuals did not provide data.

The median (IQR) TSH level was 1.82 (1.16-2.90) mIU/L. 451 (81.2%) participants were classified in the euthyroid group, and 40 (7.2%) and 35 (6.3%) of participants were classified as having hypothyroidism and subclinical hypothyroidism, respectively. 4.9 percent (n=27) had subclinical hyperthyroidism and 0.4 percent (n=2) suffered from overt hyperthyroidism (5.3 percent in total). Median creatinine (IQR) levels were 92 (81-107)  $\mu$ mol/L translating into a mean (SD) eGFR (MDRD) of 59.0 (14.4) mL/min/1.73m<sup>2</sup>. 305 participants had an eGFR <60 mL/min/1.73m<sup>2</sup> (CKD  $\geq$ 3) of whom 7 and 2 values fitting CKD stage 4 (15-30 mL/min/1.73m<sup>2</sup>) and 5 (<15 mL/min/1.73m<sup>2</sup>), respectively.

As apparent from **Figure 1A**, 85-year old participants with overt hypothyroidism (53.7 (2.0) mL/min/1.73m<sup>2</sup>) and participants with subclinical hypothyroidism (55.7 (2.1) mL/min/1.73m<sup>2</sup>) had a lower mean baseline eGFR (SE) than participants with normal thyroid function (59.5 (0.7) mL/min/1.73m<sup>2</sup>). The highest eGFR was observed in participants with hyperthyroidism (61.5 (3.1) mL/min/1.73m<sup>2</sup>). After adjustment for confounders (**Figure 1B**), a trend remained. In **Table 2**, mean (95% CI) eGFR values are presented across tertiles of distribution of the different thyroid hormones. The eGFR was lower in participants with higher TSH levels (p=0.021). eGFR values were lower within the lower fT3 tertiles (<0.0001) and, although not statistically significant, also lower in lower fT4 tertiles (p=0.083). After adjustment for possible confounding variables, associations were statistically significant for TSH (p=0.0037) and for fT4 (p=0.005).

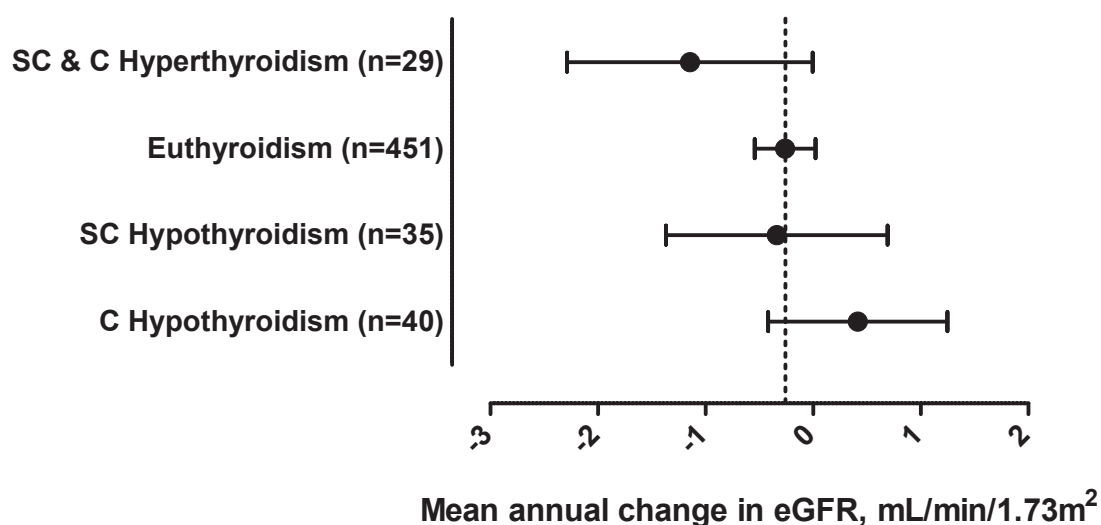
Throughout a median follow-up of 5 years, during which 259 individuals died, the eGFR declined on average (SE) with  $-0.25$  (SE  $0.13$ ,  $p=0.052$ ) mL/min/1.73m<sup>2</sup> per year. **Figure 2** shows the estimated adjusted mean (95%CI) annual changes in eGFR across thyroid function groups as obtained from linear mixed models. No significant differences were observed in the change in eGFR between thyroid function groups. In a second approach in which individual specific betas (slopes) were pooled within the different thyroid hormone groups (**Appendix 3**), similar results were found ( $p=0.149$ ). No association between baseline thyroid hormone concentrations as continuous variables and the change in eGFR over time was present. Also, the percentage of individuals developing new CKD stage 4 or 5 did not differ between the thyroid function groups ( $p=0.755$ , data not shown).

**Figure 1.** Mean crude (A) and adjusted (B) eGFR (mL/min/1.73 m<sup>2</sup>) across different thyroid hormone groups at baseline



Mean (95% CI) eGFR at baseline within the different thyroid hormone groups. The value for P for trend was calculated by means of polynomial trend analysis in a one-way ANOVA test. B, Mean adjusted eGFR (mL/min/1.73 m<sup>2</sup>) across different thyroid hormone groups at baseline. Mean (95% CI) eGFR at baseline within the different thyroid hormone groups was adjusted for sex, DM, smoking, the presence of cardiovascular disease (composite score 1), malignancies, and amiodarone usage. The value for P trend was calculated by means of linear regression analysis. O, overt; SC, subclinical.

In sensitivity analyses, subgroup analyses in three different baseline strata of renal function, solely in survivors reaching age 90 ( $n=299$ ), and in those with CRP levels below 5 mg/L yielded no different results. Results did not materially change with respect to the effects of basal thyroid hormone status on change in eGFR over time when renal function was estimated with CKD-EPI and Cockcroft Gault formulas (results not presented). Further adjustment for systolic blood pressure, C-reactive protein levels, BMI, and total cholesterol levels in multivariable models neither changed findings. In the 535 individuals not on drugs interfering with thyroid hormone measurements, results were not different as in total the population (**Appendix 4**). Finally, we did not observe an association between different thyroid hormone groups as defined upon two thyroid hormone measurements in time (85 and 88 years of age, see methods) and renal function at 88 years of age and change in renal function from that point on forward (results shown in **Figure 1 and 2 of Appendix 5**).



**Figure 2.** Mean annual change in eGFR (milliliters per minute per 1.73 m<sup>2</sup>) across different thyroid function groups. Mean (95% CI) annual change in eGFR per group was calculated by means of multivariate linear mixed models including sex, DM, smoking, cardiovascular disease, malignancies, and amiodarone usage as possible confounders. Negative values indicate a decline, whereas a positive value indicates an improvement in renal function over time. The mean annual changes in eGFR within the different thyroid function groups did not differ significantly from the euthyroid group (reference, dotted line). O, overt; SC, subclinical.

## Discussion

In this community based sample of the oldest old, positive cross-sectional associations between thyroid function and renal function were observed. Over time, thyroid function was not associated with change of renal function.

In our cross sectional analyses, a low thyroid status associated with lower eGFR values at baseline in univariate as well as multivariate models when compared to participants with euthyroidism and overt- and subclinical- hyperthyroidism. These findings align with cross-sectional observations from other large scaled community-based surveys.<sup>32,33</sup> To our knowledge, this is the first study to investigate the longitudinal association between thyroid hormone status and the change in renal function over time in the oldest old. We observed no longitudinal association as such. Although statistically non-significant, one may interpret the findings in **Figure 2** as a slight trend in which overt hypothyroidism conveys a protective and hyperthyroidism a harmful effect on the change in renal function over time. However, this explanation seems unlikely. Not only had those with overt hypothyroidism a lower, and those with overt/subclinical hyperthyroidism a higher eGFR at baseline, it is biologically less plausible that hypothyroidism is protective against a decline in renal function. We therefore interpret this trend through the concept of “regression to the mean”. In addition, analyses including the thyroid hormone measurements at 88 years of age further support the absence of an association between thyroid hormone status and (change of) renal function. Thus, our observations contrast with findings in younger individuals having overt hypothyroidism<sup>13,14</sup> and subclinical hypothyroidism<sup>17,18</sup> who experienced a faster decline in renal function which in turn seemed to be attenuated or reversed by thyroid hormone replacement therapy.<sup>13,18</sup>

It is of interest to speculate why the association between thyroid status and change of renal function over time is absent in the oldest old. As a result of selection due to survival, the oldest old may be least susceptible to the detrimental effects of common risk factors including a low thyroid status. Consequently, other pathophysiological mechanisms may be at play in this age category. This reasoning finds support in earlier studies in the oldest old indicating a reversal or disappearance of negative effects of traditional risk factors like hypertension and hypercholesterolemia<sup>20,34</sup> but also overt and subclinical hypothyroidism.<sup>22,23,35</sup> The association between subclinical hypothyroidism and risk for cardiovascular events seems to diminish specifically in the elderly<sup>22,23,25,35</sup> It has been suggested that a low thyroid function in the elderly represents a physiological downregulation of the HPT-axis, possibly benefitting life expectancy.<sup>36</sup> A possible explanation lies in a slower metabolic rate which related to an increased survival in several species.<sup>37</sup> In a recent study in families of nonagenarian siblings, a lower family mortality score was found to be associated with lower thyroid function in the offspring, leading the authors to speculate that low thyroid function may be an inheritable trait.<sup>38</sup> This would imply that a low thyroid function could already be of protective effect in specific subgroup of younger individuals. Throughout all of these explanations however, our findings question the causal relation between low thyroid function and decline in renal function in the oldest old, and as a result, question the benefits of thyroid hormone replacement in old age.

Notably, the positive cross-sectional association in our study between thyroid function and renal function could also be explained through the concept of reverse causality. Severe CKD commonly induces a hypothyroid state which exists in the absence of primary HPT-axis dysfunction.<sup>39</sup> Presence of this low thyroid state in states of disease, commonly referred to as non-thyroidal illness or low-T3 syndrome, associates with substantially increased mortality rates.<sup>40,41</sup> Consistently, a previous analysis in the Leiden 85 plus Study showed that low fT3 levels were associated with an increased mortality risk.<sup>22</sup> This finding did however not withstand multivariate adjustment and was contradicted by another study in which this association appeared absent.<sup>23</sup>

As TSH levels in non-thyroidal illness typically descend or remain within range, the finding of an increased prevalence of elevated TSH levels in the oldest old 6 does not fit this hypothesis. When we excluded those with CRP levels below 5 mg/L, cross-sectional associations between thyroid function and renal function remained present, pleading against non-thyroidal illness as an explanation for our results.

A strength of the present study is its population-based design with inclusion of the oldest old. As there were no exclusion criteria, the Leiden 85-plus Study is a representation of the very oldest in the general population. For the interpretation of our results, some general limitations have to be discussed. First, as thyroid status could possibly influence plasma creatinine levels via muscle metabolism and volume status, the eGFR may not be a good approximation of renal function in this association.<sup>42</sup> Nevertheless, overt hypothyroidism was also linked to a reduced eGFR as measured by labeled edetic acid.<sup>16</sup> In addition, sensitivity analyses using CKD-EPI and Cockcroft Gault formulas yielded similar results. Secondly, as subjects in whom new thyroid dysfunction was discovered were referred to their general practitioner, the possible initiation of treatment could have masked a possible effect. As our results did not change when analyses were repeated solely in those not on thyroid hormone therapy, this effect is unlikely of great importance. Lastly, bias due to competing events (death), and selection on basis of survival at age 85 could theoretically both have masked a true association.

In conclusion, in older persons in the general population, overt and subclinical hypothyroidism are associated with lower renal function at baseline but not with an additional decline in renal function over time. Ultimately, our findings suggest an absence of a causal relation between low thyroid function and decline in renal function in the oldest old. Further studies are warranted to disentangle the association between thyroid status and renal function throughout different age groups and whether thyroid hormone replacement therapy impacts positively on renal function in those with low thyroid function.

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