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ORIGINAL ARTICLE

Low thyroid function is not associated with an accelerated deterioration in renal function

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ABSTRACT

Background. Chronic kidney disease (CKD) is frequently accompanied by thyroid hormone dysfunction. It is currently unclear whether these alterations are the cause or consequence of CKD. This study aimed at studying the effect of thyroid hormone alterations on renal function in cross-sectional and longitudinal analyses in individuals from all adult age groups.

Methods. Individual participant data (IPD) from 16 independent cohorts having measured thyroid stimulating hormone, free thyroxine levels and creatinine levels were included. Thyroid

hormone status was defined using clinical cut-off values. Estimated glomerular filtration rates (eGFR) were calculated by means of the four-variable Modification of Diet in Renal Disease (MDRD) formula. For this IPD meta-analysis, eGFR at baseline and eGFR change during follow-up were computed by fitting linear regression models and linear mixed models in each cohort separately. Effect estimates were pooled using random effects models.

Results. A total of 72 856 individuals from 16 different cohorts were included. At baseline, individuals with overt hypothyroidism ($n = 704$) and subclinical hypothyroidism ($n = 3356$) had a average (95% confidence interval) −4.07 (−6.37 to −1.78) and −2.40 (−3.78 to −1.02) mL/min/1.73 m^2 lower eGFR as compared with euthyroid subjects ($n = 66\ 542$). In (subclinical) hyperthyroid subjects ($n = 2254$), average eGFR was 3.01 (1.50–4.52) mL/min/1.73 m^2 higher. During 329 713 patient years of follow-up, eGFR did not decline more rapidly in individuals with low thyroid function compared with individuals with normal thyroid function.

Conclusions. Low thyroid function is not associated with a deterioration of renal function. The cross-sectional association may be explained by renal dysfunction causing thyroid hormone alterations.

Keywords: chronic renal failure, CKD, creatinine clearance, epidemiology, thyroid function

INTRODUCTION

The prevalence of chronic kidney disease (CKD) is globally increasing, reaching endemic levels [1]. Since this growth is accompanied by a substantial increase in cardiovascular morbidity and mortality [2, 3], prevention of CKD and its secondary complications are of increasing importance. To date, however, aggressive management of known risk factors such as blood pressure, albuminuria and glucose control has not resulted in a clear reduction of this trend. These observations stress the need for further studies on other risk factors being amenable for treatment.

In cross-sectional studies, lower renal function is accompanied by reductions in free thyroxine (fT4) and triiodothyronine (T3) and an elevation in serum thyroid stimulating hormone (TSH) levels [4–6]. This finding can be interpreted in two ways: first, CKD (similar to other chronic illnesses) induces a systemic lowering of the hypothalamic–pituitary–thyroid (HPT) axis, known as 'non-thyroidal illness' [7]. Alternatively, primary hypothyroidism could be the cause of a reduction in renal function. Indeed, studies in patients with severe primary hypothyroidism show a consistent reduction in renal function, which resolves after initiation of thyroid hormone supplementation [8, 9].

Although large-scale observational studies show clear associations between subclinical hypothyroidism and an increased risk for heart failure [10], coronary heart disease and mortality [11] findings are not consistent with the association between subclinical hypothyroidism and lower renal function [12–14]. In an observational study in patients with CKD Stages 2–4 and subclinical hypothyroidism, subjects not being prescribed thyroid hormone treatment showed a more rapid decline of renal function as compared with patients who received thyroid hormone supplementation [12, 13]. However, no association between thyroid hormone status and a decline in renal function was observed in a population-based study of the oldest old [14].

In light of these conflicting findings, this study sets out to evaluate the association between thyroid hormone status and renal function cross-sectionally and longitudinally by performing an individual patient data (IPD) meta-analyses on data from 16 independent cohorts participating in the Thyroid Studies Collaboration.

MATERIALS AND METHODS

Data from 16 different cohorts (four from the Netherlands, three from Italy, two from USA, two from Japan (and partly Brazil), and one from Germany, Norway, Belgium, Australia and Ireland), providing measures of thyroid and renal function were used for our analyses [11]. Nine of these cohorts [15–23] were also included in an earlier study evaluating the association between thyroid function and cardiovascular mortality [11]. Details of these cohorts have been described previously. In addition to these nine cohorts, seven cohorts [24–30] with data on thyroid and renal function were added to the collaboration. Six out of these seven cohorts were population-based studies; two comprising individuals from all age categories [27, 30], two having included those with an average age ∼70 years [28, 29] and two other studies included specifically the oldest [25, 26]. The seventh study was comprised of patients with chronic heart failure [24].

Thyroid function

Thyroid function tests were measured at baseline in each cohort. We used common definitions to define thyroid hormone groups by using cohort-specific cut-off values which are summarized in Supplementary data, Appendix S1: (i) overt hypothyroidism was defined as elevated TSH levels in combination with reduced fT4 levels; (ii) subclinical hypothyroidism was defined as an elevated serum TSH level with a normal fT4 concentration; (iii) subjects were categorized in the euthyroid group when having TSH levels within the specific reference range; and (iv) those with lowered TSH levels with or without elevated fT4 levels were categorized as (subclinically) hyperthyroid. Subjects with subclinical hyperthyroidism and overt hyperthyroidism were combined because of low numbers in each group.

Renal function

Creatinine levels were measured according to each cohort's protocol. Differences exist in their methodology; five cohorts utilized colorimetric assessments [15–17, 22, 25], five cohorts utilized the traditional Jaffé method [19, 21, 26, 27, 29] and the newer enzymatic method was applied in four cohorts [20, 23, 28, 30]. In the Bari cohort [24], creatinine levels were measured with both the Jaffé and colorimetric method. In the Nord-Trøndelag Health (HUNT) study [18], the baseline examination (HUNT2) was performed using the Jaffé method and subsequently adjusted by means of a validated calibration formula [31]. The alkaline picrate methodology was used for the follow-up examination (HUNT3) .

Estimated glomerular filtrations rate (eGFR) was assessed by means of the four-variable Modification of Diet in Renal Disease (MDRD) formula [32]. For sensitivity analyses, eGFR was calculated on basis of the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula [33]. The MDRD formula was used as primary outcome instead of the CKD-EPI because not all creatinine measurements were based on traceable isotope dilution mass spectrometry [34].

Statistical analyses

Baseline characteristics for each cohort are presented as means with SDs or numbers with percentages (%), as appropriate. To analyse the association between thyroid hormone status and renal function, a two-stage IPD meta-analysis was used as previously specified [11]. First, effect estimates were calculated at a cohort level. Thereafter, they were pooled at a meta-analysis level.

For the cross-sectional associations between thyroid hormone status and renal function, linear regression analyses were fitted. Thyroid hormone groups were entered as categorical variables with the euthyroid group serving as the reference. Effect estimates (betas) represented the difference in eGFR (mL/min/1.73 m^2) at baseline for the specific thyroid hormone group with respect to the euthyroid group. The same concept was applied to TSH and fT4 groups, again those with normal levels serving as the reference category. TSH and fT4 were also entered as continuous variables in which effect estimates illustrated an increase in eGFR per 1 mIU/L and per 1 pmol/L increase in serum TSH and fT4 levels, respectively.

For the longitudinal analyses, examining the association between thyroid hormone status at baseline and the change in renal function over time, linear mixed models were fitted in each cohort separately. Because of the large variability in the number and timing of measurement points within cohorts and between cohorts, we chose to adopt random effects models. An average change in eGFR (mL/min/1.73 m^2/year) for each cohort was calculated and presented in a figure. Slopes were not pooled because of large heterogeneity in effect estimates and participant characteristics. As for the linear regression analyses, thyroid hormone groups were entered as categorical variables. In addition, an interaction term of thyroid hormone group and time was included to allow for dependence of the slope on thyroid hormone status. Effect estimates obtained from these models indicated the additional change in eGFR per year as compared with the change in the euthyroid group. All models were adjusted for age, sex, cardiovascular disease and when available, for thyroid hormone supplementation and/or anti-thyroid medication. In sensitivity analyses, models were rerun also adjusting for diabetes mellitus, if available.

Outcomes obtained from linear regression analyses (cross-sectionally) and from linear mixed models (longitudinally) were pooled by means of random effects models assuming the variance model as proposed by DerSimonian and Laird [35]. Sensitivity analyses were performed by rerunning all previous models in subgroups of sex and age. Another sensitivity analysis was performed excluding the HUNT study because creatinine measurements at baseline and follow-up were performed with different assays. The same was done for the Health, Aging and Body Composition (Health ABC) study. Also, sensitivity analyses were done by excluding all cohorts with positive changes in eGFR over time [22, 26, 27, 29]. To further examine the potential of selection/publication bias, funnel plots were created. Bubble plots were created plotting the effect size against mortality rates in each cohort.

For differences, a 95% confidence interval (CI) not including zero was considered to indicate statistical significance. For all other tests, a P-value <0.05 was adopted as cut-off. Stata 12.1 (StataCorp LP, Texas, USA) was used to perform all analyses. Figures were created using Stata and Prism 5.02 (GraphPad Software Inc., La Jolla, CA, USA; 1992).

RESULTS

This study included data from 16 cohorts, comprising a total of 72 856 individuals of whom 704 were hypothyroid, 3356 subclinically hypothyroid, 66 542 euthyroid and 2254 (subclinically) hyperthyroid. Baseline characteristics of the different cohorts are presented in Table 1. As illustrated, the average age at baseline ranged from 49 to 85 years and the proportion of individuals with pre-existing cardiovascular disease from 1.9% to 100%. Within the different cohorts, 0–9.9% of subjects were prescribed thyroid hormone replacement therapy and 0–4.7% used antithyroid medication. Usage of thyroid hormone supplementation was more common in the subclinical hypothyroid and hypothyroid groups, whereas more individuals in the hyperthyroid group used antithyroid medication (Supplementary data, Appendix S2).

Cross-sectional analyses

In Figure 1, the average eGFR per cohort is shown with mean (SD) values ranging from 59.0 (14.4) mL/min/1.73 m^2 in the Leiden 85-plus study to 102.6 (26.7) mL/min/1.73 m^2 in Radiation Effects Research Foundation (RERF). Figure 2 details forest plots presenting the differences in eGFR at baseline between the hypothyroid, subclinical hypothyroid and subclinical hyperthyroid group versus euthyroid group for each cohort separately. Pooled estimates show that eGFR was on average −4.07 (95% CI: −6.37 to −1.78) mL/min/1.73 m^2 lower in the hypothyroid and −2.40 (−3.78 to −1.02) mL/min/1.73 m^2 lower in the subclinical hypothyroid group as compared with the euthyroid group. Conversely, average eGFR was 3.01 (1.50–4.52) mL/min/1.73 m^2 higher in (subclinical) hyperthyroid subjects.

Longitudinal analyses

Of the 16 cohorts, 13 contributed a total of 113,670 measurements during 329 713 patient-years of follow-up. Figure 3 depicts adjusted average annual changes in eGFR (mL/min/1.73 m^2/year) per cohort, showing a range in annual change from −1.43 (0.06) to +8.98 (1.05) mL/min/1.73 m^2/year. Figure 4 demonstrates the pooled differences in eGFR change per year within the different thyroid hormone groups as compared with the euthyroid group. The change in eGFR was 0.35 (0.07–0.64) mL/min/1.73 m^2 per year higher in the overt hypothyroid compared with the euthyroid group. No significant differences in eGFR change over time were noted in the other thyroid hormone groups as compared with euthyroid subjects.

Table 1. Baseline characteristics of the different cohorts

Cohort	Country	Total no. of participants/ mean years of follow-up per individual/no. of serum measurements per individual	Percentage of men	Average age (SD), years	Part with CVD (%)	Part with hypo/subcl hypo/(subcl) hyper (%)	Part using thyroxine/anti-thyroid medication at baseline (%)
CHS [15]	USA	3112/6.7/4	40.0	72.6 (5.6)	1.9	1.2/15.9/0.4	0/0
Health ABC study [16]	USA	2776/4.5/3	48.9	74.7 (2.9)	30.3	0.9/4.5/0.4	9.9/0
EPIC study [17]	UK	9869	43.5	59.0 (9.2)	4.6	1.8/5.6/4.5	na
Bari study [24]	Italy	338/2.4/3	76.9	64.3 (13.0)	100	0/12.1/3.3	5.0/1.8
HUNT study [18]	Norway	33927/11.2/2	31.4	58.6 (13.4)	10.6	0.6/4.1/1.7	5.0/0.2
BELFRAIL study [25]	Belgium	542/1.7/2	37.3	84.8 (0.4)	58.7	3.9/2.2/4.0	9.7/0.0
Leiden 85-plus study [19]	The Netherlands	558/3.9/6	33.9	85	48.6	7.2/6.1/5.3	2.9/0.7
Pisa study [20]	Italy	2260	65.3	65.8 (13.0)	98.5	0.1/5.2/6.3	0
PROSPER study [26]	The Netherlands	5794/0.3/2	48.3	75.3 (3.3)	43.9	0.6/3.7/3.4	4.4/0.1
SHIP study [27]	Germany	4236/9.3/3	49.2	49.7 (16.3)	6.1	0.3/2.8/8.5	6.3[a]
Busselton Health study [22]	Australia	832/13.0/2	46.8	52.8 (10.3)	5.8	0.9/4.9/3.7	1.1/0.0
Japanese-Brazilian Thyroid study [20]	Japan/Brazil	1110	46.8	56.5 (12.5)	14.1	1.0/8.9/11.2	0/0
RERF [23]	Japan	1730/7.5/7	32.9	69.0 (8.8)	na	3.9/6.6/3.2	3.8/0.2
Rotterdam study [28]	The Netherlands	1875/4.7/2	38.3	68.8 (7.5)	27.8	2.0/3.1/6.7	2.5
InCHIANTI [29]	Italy	1209/8.9/4	43.5	69.0 (0.4)	12.4	0.8/2.7/10.2	2.1/0.7
PREVEND [30]	The Netherlands	2688/3.4/6	48.4	48.5 (12.6)	9.1	1.0/1.5/2.7	na

[a]Combined thyroid supplementation/antithyroid medication.

CHS, Cardiovascular Health Study; EPIC, European Prospective Investigation into Cancer and Nutrition Study; SHIP, Study of Health in Pomerania; InCHIANTI, Invecchiare in Chianti; PREVEND, Prevention of Renal and Vascular End-Stage Disease; na, not available; subcl, subclinical; hypo, hypothyroidism.

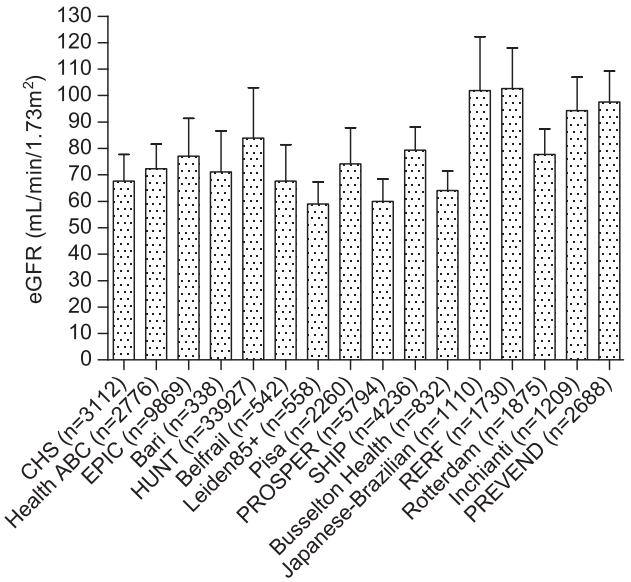

FIGURE 1: Mean (SD) eGFR (mL/min/1.73 m^2) at baseline in the different cohorts.

All analyses were repeated cross-sectionally and longitudinally in subgroups of sex (Supplementary data, Appendices S3 and S5) and age (<50, 50–65, 65–80 and >80 years) (Supplementary data, Appendices S4 and S6) rendering no differences in results. When models were adjusted for diabetes mellitus, results were not substantially different (Supplementary data, Appendices S7 and S8). Using the CKD-EPI formula instead of the four-variable MDRD formula, findings were comparable (data not shown). When pooling was repeated excluding the HUNT and Health ABC studies, similar results were found. The same held for the analyses excluding cohorts with positive changes in eGFR over time. Finally, analyses were repeated in individuals not using thyroid hormone supplementation or antithyroid medication, with no effect on the findings (data not shown).

To examine the possibility of selection bias as a consequence of death, study-specific effect estimates were regressed on mortality incidence rates for each study, showing no statistically significant association (data not shown). Finally, a funnel plot did not show evidence of publication bias (data not shown).

DISCUSSION

In this IPD meta-analysis comprising data from 72 856 individuals out of 16 independent cohorts, we found a positive cross-sectional association between thyroid function and renal function in which those with low thyroid function had lower eGFR values as compared with euthyroid and (subclinical) hyperthyroid subjects. During follow-up, low thyroid function was not associated with an additional decline in renal function as compared with the euthyroid group.

The presence of a cross-sectional association between low thyroid function and renal dysfunction aligns with findings in several previous cohorts [14, 36, 37], two of which were also included in this meta-analysis [14, 36]. Also compatible with our previous report, low thyroid function did not associate with an additional decline in renal function versus a euthyroid state [14]. Rather, we observed a relative increase in renal function in subjects with overt hypothyroidism as compared with individuals with thyroid hormone concentrations within the reference range. Three potential clarifications should be considered: first, whereas those with hypothyroidism have a lower eGFR at baseline, the observation of an increase in eGFR values over time relative to the euthyroid group may be explained by the concept of 'regression to the mean'. Regression to the mean implies that when a variable has extreme values at a certain measurement, a second measurement will tend, by chance, to show a value closer to the true mean. In case of an extremely high value, the second measurement tends to be lower and vice versa, in case of

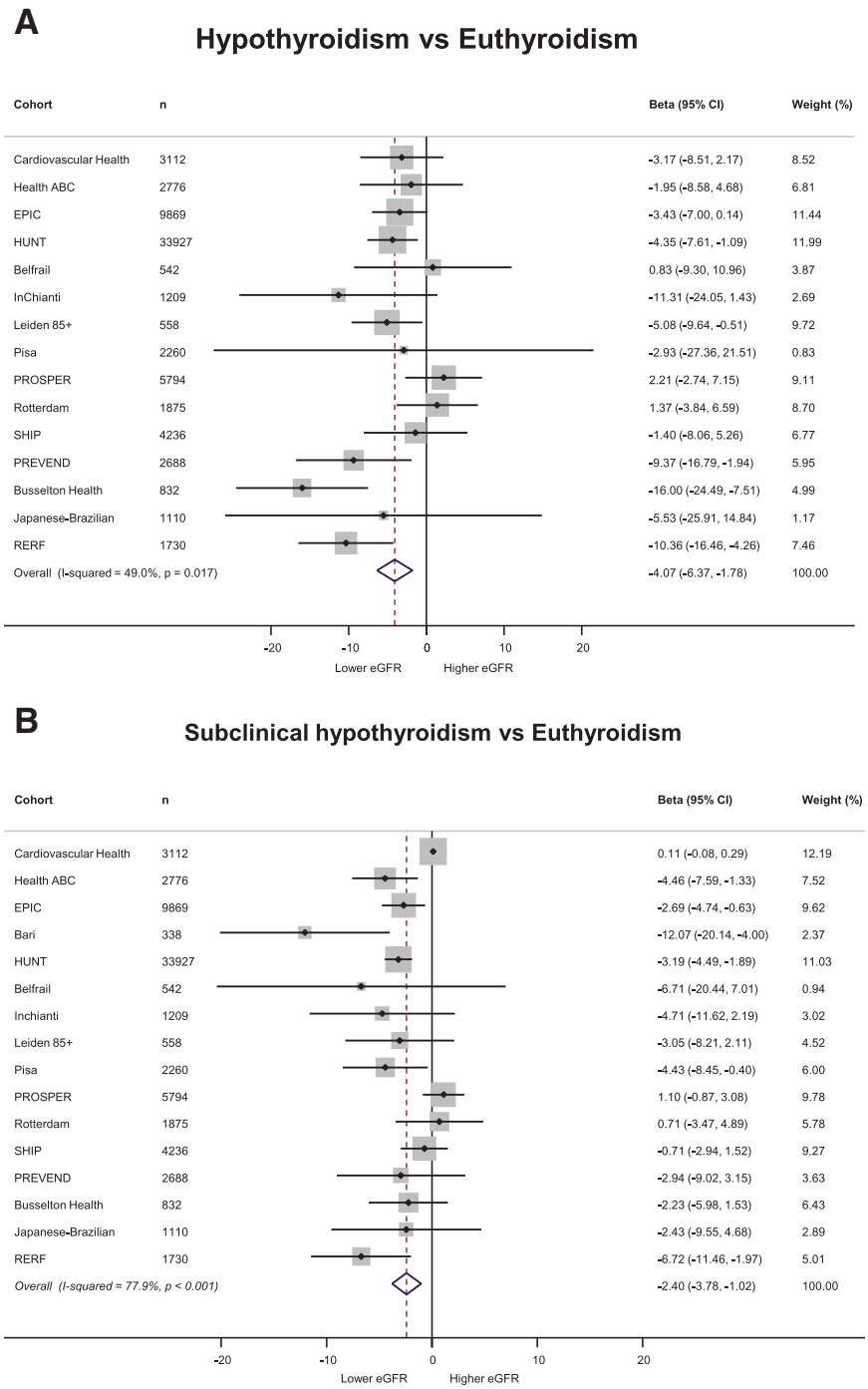

FIGURE 2: Forest plots providing the pooled differences in eGFR (mL/min/1.73 m^2) at baseline in each thyroid group as compared with the euthyroid group.

an extremely low value, the second measurement will tend to portrait a higher value. Secondly, as overt hypothyroidism is generally considered an indication for thyroid hormone supplementation, the relative rise in eGFR over time could be the resultant of treatment rather than due to hypothyroidism itself. Yet, sensitivity analyses excluding subjects on thyroid medication did not reveal differential findings. Nevertheless, changes in thyroid status and medication during follow-up could have translated into different outcomes. Finally, patients with hypothyroidism could be more inactive resulting in a lower muscle mass, thereby lowering creatinine levels.

We did not observe a difference in eGFR change over time in the subclinical hypothyroid group as compared with euthyroid subjects. Because subclinical hypothyroidism is not a strict indication for thyroid hormone supplementation, thyroid hormone supplementation likely did not play an interfering role. Results of a previous non-randomized study suggest that thyroxine supplementation preserves renal function over time in patients with CKD Stages 2–4 [12]. Findings from that study are, however, hampered by several limitations. First, in the absence of a randomized design and/or appropriate adjustment,

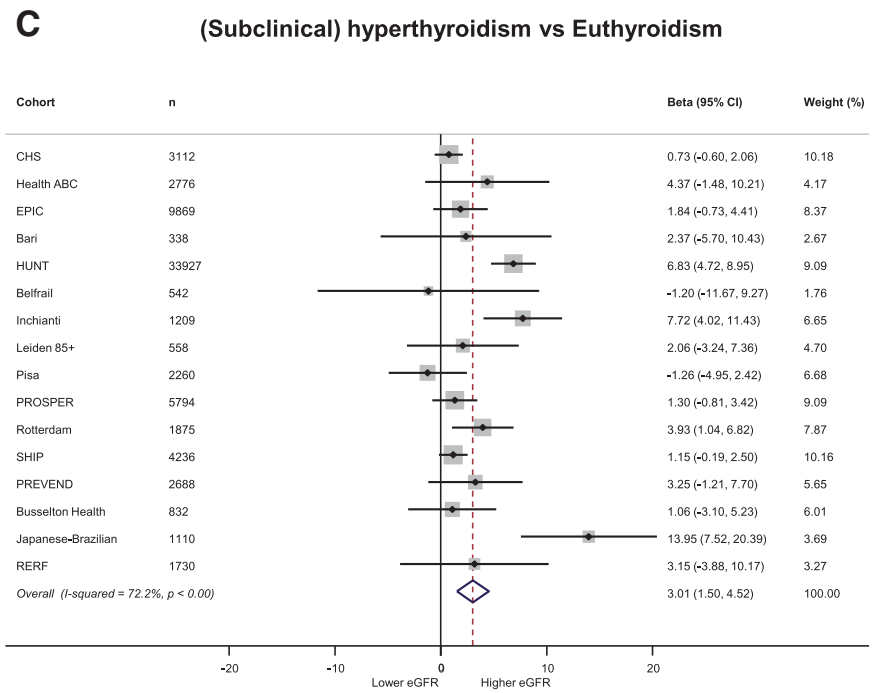

FIGURE 2: Continued.

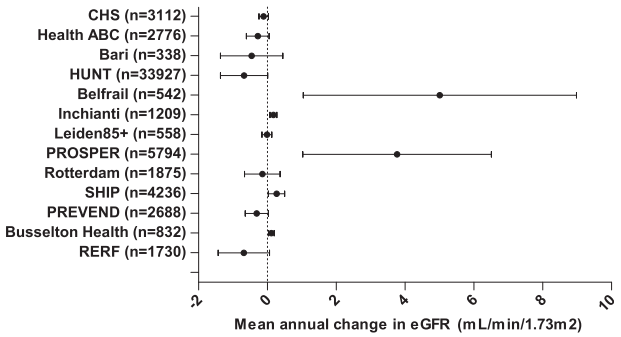

FIGURE 3: Mean (SD) changes in eGFR (mL/min/1.73 m^2/year) in the different cohorts.

confounding by indication may have imposed systematic error. Patient characteristics and physician preferences likely influenced the decision to initiate treatment. The non-treatment group indeed seemed overall less healthy than the treatment group. Secondly, 49 out of 358 individuals were excluded from the analyses because of a follow-up duration <12 months. This loss to follow-up may have been dependent on treatment status and outcome, and as a result, have introduced selection bias. Therefore, in addition to previous literature, current findings do not support a causal relationship between subclinical hypothyroidism and a decline in renal function over time.

It is of interest to speculate why eGFR increased over time in cohorts with an average higher age [25, 26]. One of the explanations may be that those individuals with more rapid declines in renal function died sooner. Alternatively, as muscle metabolism and habitus change in old age, conventional equations for assessing eGFR are poorly validated in elderly individuals [38]. Nevertheless, in the Leiden 85-plus study, comprising individuals in similar age categories as PROSPER (Prospective Study of Pravastatin in the Elderly at Risk) and BELFRAIL (the Belgian cohort of the Very Elderly), average annual change in eGFR was considerably lower. When repeating our analyses excluding cohorts with positive changes in eGFR, results did not change, leading us to believe that this paradoxical increase in eGFR would not have translated into bias. Given the absence of a longitudinal association, the concept of reversed causation (CKD causing thyroid hormone abnormalities) may explain the observed cross-sectional association between low thyroid and renal function in our study. CKD, and especially end-stage renal disease, is frequently accompanied by abnormal TSH, low triiodothyronine (fT3) and fT4 levels fitting the spectrum of so-called 'non-thyroidal illness' [39]. In the absence of primary disease in the HPT axis, its pathogenesis is multifactorial and occurs at multiple levels including peripheral deiodinase-dependent conversion defects and central alterations in thyroid hormone signalling [40]. It could be speculated that deiodinase defects in early phases prevail over central mechanisms, leading to a compensatory increase in TSH secretion. Further studies on this hypothesis could include (free) T3 measurements to study effects of deiodinase subtypes.

To our knowledge, this is the first IPD meta-analysis studying the association between thyroid hormone status and renal function. Findings from our study are strengthened by the large population size, its global representativeness and availability of IPD, making it possible to standardize definitions, statistical models and outcomes. Several limitations need to be discussed. First, methodology of creatinine measurements was not similar across studies. Since differences in renal function were calculated between groups and individuals on a study level, this cannot have resulted in systematic error. For some studies, different assays were used between

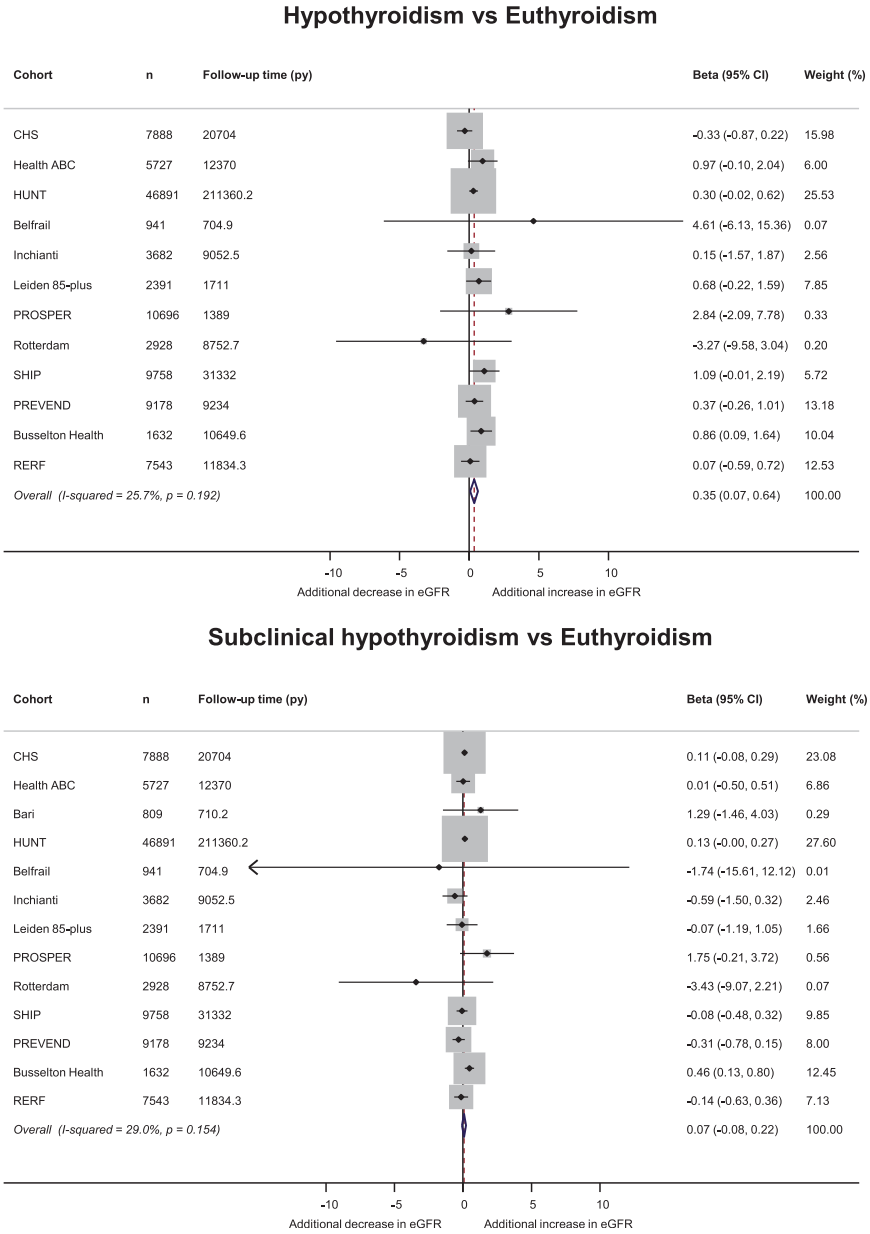

FIGURE 4: Forest plots providing the pooled additional changes in eGFR (mL/min/1.73 m^2/year) per year in each thyroid group as compared with the euthyroid group. n = number of observations.

the visits in the longitudinal analyses, which may have resulted in dilution of the results to the null. For example, in the HUNT study and Health ABC, different assays were used at baseline and during follow-up. However, sensitivity analyses excluding results from the HUNT study and Health ABC did not change our findings. Also, eGFR is an approximation of renal function. Determining measured GFR would benefit classification of individuals in their outcome. Nevertheless, estimation equations have been shown to be accurate for following changes in GFR over time [41]. Secondly, our study was not specifically designed to study the impact of overt hypothyroidism on renal function. Only a minority of individuals in our study had TSH levels >20 mIU/L. Also, thyroid hormone usage was more prevalent in the hypothyroid and subclinically hypothyroid groups and could have prevented its downstream effects on renal function. However, adjustment for thyroid medication revealed no differences in findings suggests that overt hypothyroidism is not associated with an additional decline in renal function over time. Potential confounding effects of other drugs such as amiodarone, glucocorticoids and lithium could not be determined because these parameters were not available in most cohorts. Since relatively few individuals in the general population use these medications, effects on parameters are likely small. Finally, censoring due to events of death could have caused selection bias. Meta-regression analyses did, however, not reveal an association between the proportion of mortality and the effect estimate in the studies included. Also, estimation equations have been shown to be accurate for assessing GFR slopes over time and its determinants [42, 43], which supports the legitimacy of studying thyroid dysfunction as a risk factor for changes in renal function in these cohorts.

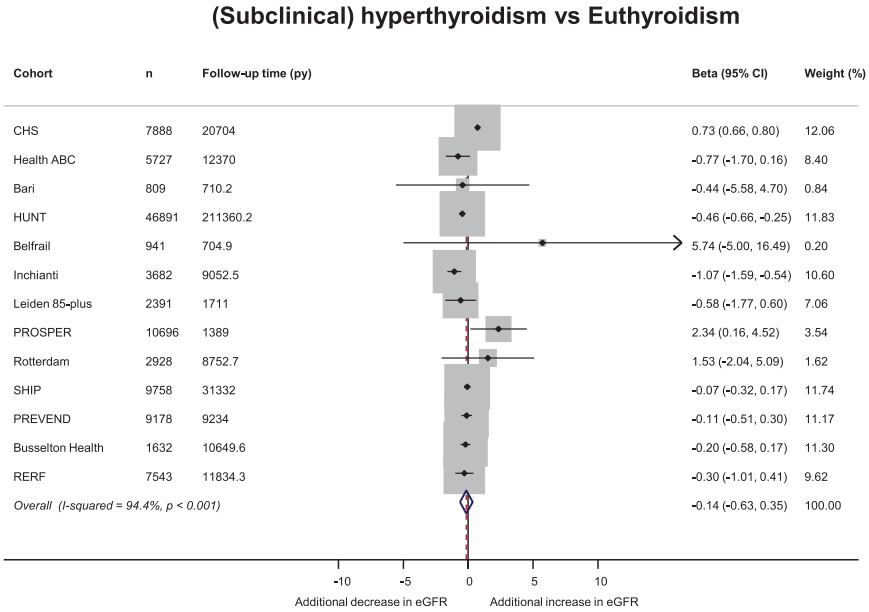

FIGURE 4: Continued.

Overall, we found that, cross-sectionally, low thyroid function was associated with lower eGFR values as compared with euthyroid subjects. During follow-up, subjects with low thyroid function did not have a more pronounced decline in renal function over time than euthyroid subjects. We conclude that low thyroid function, and especially subclinical hypothyroidism, is not associated with deterioration in renal function and speculate that cross-sectional findings may be explained by renal dysfunction causing thyroid hormone alterations. Further studies should shed light on the link between thyroid and renal function and possible differences among causes of thyroid disease.

SUPPLEMENTARY DATA

Supplementary data are available at ndt online.

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CONFLICT OF INTEREST STATEMENT

The sponsor had no role in the design and conduct of the study; in the collection, analysis and interpretation of the data; or in the preparation, review or approval of the manuscript. The authors have no conflicts to report.

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Uric acid is not associated with diabetic nephropathy and other complications in type 1 diabetes

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ABSTRACT

Background. To examine the association between plasma uric acid (UA) and the presence of diabetic complications including diabetic nephropathy and cardiovascular risk factors in patients with type 1 diabetes.

Methods. This study, which is cross-sectional in design, included 676 Caucasian type 1 diabetes patients from the Steno Diabetes Center Copenhagen. Participants with UA within the three lowest sex-specific quartiles were compared with participants with levels in the highest quartile. Unadjusted and adjusted linear regression analyses were applied. Adjustment included sex, age, diabetes duration, body mass index, high-density lipoprotein cholesterol, smoking, haemoglobin A1c, 24-h pulse pressure, urinary albumin excretion rate (UAER), estimated glomerular filtration rate (eGFR) and treatment with renin–angiotensin–aldosterone system blockers.

Results. Of the 676 patients, 372 (55%) were male, mean ± SD age was 55 ± 13 years and eGFR was 82 ± 26 mL/min/1.73 m^2. The median UA was 0.30 (interquartile range 0.23–0.37) mmol/L. UA in the upper sex-specific quartile was associated with lower eGFR, higher UAER and carotid–femoral pulse wave velocity and lower 24 h and daytime diastolic blood pressure (BP) in unadjusted analyses ($P < 0.001$). Moreover, UA in the upper sex-specific quartile was associated with higher nighttime systolic BP and the presence of cardiovascular disease in unadjusted analyses ($P \leq 0.01$), but significance was lost after adjustment ($P \geq 0.17$). UA was higher across the retinopathy groups [nil ($n = 142$), simplex ($n = 277$), proliferative ($n = 229$) and blind ($n = 19$)] in unadjusted analyses ($P < 0.0001$), but not after adjustment ($P = 0.12$). Patients with an accelerated decline in eGFR (≥3 mL/min/year) had significantly higher UA at baseline ($P = 0.006$) compared with slow decliners (<3 mL/min/year), but significance was lost after adjustment ($P = 0.10$).

Conclusions. In type 1 diabetes patients, higher UA was associated with lower kidney function and other diabetic complications. The association between higher UA and lower eGFR and lower diastolic BP was independent of traditional risk factors.

Keywords: coronary artery, diabetes mellitus, diabetic kidney disease, disease uric acid, GFR

INTRODUCTION

The complex pathogenesis of diabetic complications is not fully understood [1, 2] and so far many risk factors have been proposed. One of these is uric acid (UA). Elevated levels of UA have been proposed as a risk factor for chronic kidney disease (CKD), hypertension and cardiovascular disease in people with as well as without diabetes [3–7].

In the clinical setting, the majority of observational studies have shown that higher UA is associated with the incidence and development of CKD in patients with type 1 diabetes independent of other risk factors [5, 6, 8–10]. Prospective data from the Second Joslin Kidney Study showed that higher UA is one of the strongest risk factors for early loss of renal function (measured by