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Impact of Thyroid Status on Incident CKD and CKD Progression in a Nationally Representative Cohort

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Abstract

Background: Experimental data suggest hypothyroidism engenders chronic kidney disease (CKD) due to alterations in kidney structure and function, while epidemiologic studies of the hypothyroidism—CKD association have shown mixed findings. We sought to examine the relationship between thyroid status with the development and/or progression of CKD in a large national cohort.

Methods: We investigated the association of incident thyroid status with the composite endpoint of incident CKD or CKD progression among patients from the OptumLabs® Data Warehouse, which contains de-identified retrospective administrative claims data, including medical claims and eligibility information from a large national US health insurance plan, as well as electronic health record data from a nationwide network of provider groups. We examined patients with ≥2 serum thyrotropin (TSH) measurements over 1/1/2007-12/31/2018, in which their first TSH was within reference range and their second TSH was used to ascertain incident thyroid status,

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defined as hypothyroidism, euthyroidism, and hyperthyroidism (>5.0, 0.5–5.0, and <0.5mIU/L, respectively). We then examined seven granular TSH exposure groups, as well as continuous TSH levels using splines.

Results: Among 4,152,830 patients who met eligibility criteria, those with hypothyroidism and hyperthyroidism each had higher risk of incident CKD or CKD progression in expanded case-mix Cox models (ref: euthyroidism): adjusted HRs (aHRs) (95%CIs) 1.37 (1.34, 1.40) and 1.42 (1.39, 1.45), respectively. Incrementally higher TSH levels in the high-normal, subclinical, overt, and severe overt hypothyroid ranges (≥3.0–5.0, >5.0–10.0, >10.0–20.0, and >20.0mIU/L, respectively) were associated with increasingly higher risk of the composite endpoint (ref: TSH 0.5-<3.0mIU/L): aHRs (95%CIs) 1.10 (1.09, 1.11), 1.37 (1.34, 1.40), 1.70 (1.59, 1.83), and 1.70 (1.50, 1.93), respectively. Incrementally lower TSH levels in the subclinical and overt hyperthyroid ranges (<5.0 and <0.1mIU/L, respectively) were also associated with the composite endpoint: aHRs (95% CIs) 1.44 (1.41, 1.47) and 1.48 (1.39, 1.59), respectively. Spline analyses confirmed a U-shaped association between lower and higher TSH levels with the composite endpoint.

Conclusion: Among a nationally representative cohort, TSH levels in the high-normal (≥3.0 mIU/L) and lower (<0.5 mIU/L) ranges were associated with incident CKD or CKD progression. Further studies are needed to determine whether correction of thyroid status ameliorates CKD risk.

Keywords

Thyroid status; hypothyroidism; hyperthyroidism; thyrotropin; chronic kidney disease

Introduction

While thyroid dysfunction is common in the broader US population (i.e., ~20 million US adults estimated to be affected[1]), there has been growing recognition that there is a substantially higher prevalence of this endocrine derangement in chronic kidney disease (CKD) patients vs. their non-CKD counterparts.[2–4] For example, data from the National Health and Nutrition Examination Survey (NHANES) have demonstrated an increasingly higher prevalence of hypothyroidism with incrementally impaired kidney function (i.e., 5%, 11%, 20%, and 23% of participants with estimated glomerular filtration rates [eGFRs] ≥90, 60–89, 45–59, and <45ml/min/1.73m^2, respectively).[5] Additionally, a large national study of 461,607 US Veterans with stages 3–5 CKD has shown that incrementally lower eGFR levels are associated with an increasingly higher risk of hypothyroidism (i.e., each 10ml/min/1.73m^2 decrement in eGFR associated with an 18% higher risk of hypothyroidism),[6] which has been further corroborated by multiple US and international cohorts.[7–13]

Although the mechanistic link between thyroid and kidney disease is not wholly understood, experimental and clinical data suggest that hypothyroidism deleteriously affects kidney structure (i.e., due to decreased kidney-to-body weight ratio, truncated tubular mass, glomerular basement membrane changes[14–20]) and function (i.e., due to decreased cardiac output, impaired intra-renal hemodynamics, alterations in renin-angiotensin-aldosterone activity, increased tubulo-glomerular feedback[21–26]) via multiple pathways. Furthermore, multiple cross-sectional cohorts have demonstrated potent associations of hypothyroidism with kidney dysfunction,[5–8, 10, 11, 13, 27, 28] whereas sparse longitudinal studies have shown

conflicting findings.[9, 12, 27, 28] Given the high burden of thyroid dysfunction among US adults, there is compelling need to investigate the role of thyroid status as a risk factor for CKD and its progression over time using rigorous epidemiologic approaches.

Thus, to address these knowledge gaps, we sought to examine the impact of thyroid dysfunction upon incident CKD or CKD progression in a large national cohort of US adults from the OptumLabs® Data Warehouse.[29, 30] Given the availability of detailed longitudinal patient-level data, including laboratory result information, in this cohort, we ascertained incident thyroid status, defined by serum thyrotropin (TSH) levels as the most sensitive and specific biochemical marker of thyroid function,[2–4, 31] with the risk of developing de novo CKD and its progression over time.

Methods

Source Population

We conducted a historical cohort study using data from the OptumLabs® Data Warehouse,[29, 30] which contains de-identified retrospective administrative claims data, including medical claims and eligibility information from a large national US health insurance plan, as well as electronic health record data from a nationwide network of provider groups. This data source was comprised of a geographically diverse sample of the US population with comprehensive capture of longitudinal data on patients' socio-demographics, diagnostic and procedural codes, laboratory test results, and clinical events.

Patients were included provided that they 1) underwent at least two or more serum TSH measurements within a two-year exposure-window over 1/1/2007 to 12/31/2018, in which the first (baseline) TSH was within reference range (in order to ascertain incident thyroid functional disease), 2) were age 18 years old or older at the time of study entry (defined as the time of the baseline TSH measurement), 3) had at least one or more eGFR values that was >15ml/min/1.73m^2 within one-year preceding the baseline TSH measurement (defined as the baseline eGFR), 4) had at least one or more eGFR measurements after the second TSH measurement (designated as the index TSH), and 5) had both medical and pharmacy coverage as well as a minimum period of continuous enrollment of one-year following the baseline (first) TSH measurement and a minimum period of continuous enrollment of one-day after the index (second) TSH for claims data only. Patients were excluded if at study entry they had 7) evidence of a prior diagnosis of hypo- or hyperthyroidism ascertained by diagnostic/procedural codes, 8) use of thyroid hormone supplementation or anti-thyroid medication, 9) prior radioactive iodine or surgical thyroid ablation, 10) end-stage renal disease (ESRD) with receipt of dialysis or kidney transplantation prior to the index TSH measurement, 11) an eGFR value of <15ml/min/1.73m^2 between the first and second TSH measurements, or 12) an implausible follow-up period.

Criteria 1 and 7 through 9 were implemented to ensure consideration of incident thyroid functional disease, and criterion 1's requirement for at least two or more consecutive TSH levels within a two-year exposure window was to ensure sufficient continuity of care within the national health insurance plan and/or network of provider groups during which thyroid status could be reliably captured in the aforementioned Primary Study Cohort (designated

as “Cohort A: Two-Year Cohort”). We also designated a Secondary Cohort in which we limited the exposure window for two consecutive TSH measurements to one-year (“Cohort B: One-Year Cohort”), in order to reduce the possibility of outside TSH measurements that may not have been captured by the national health insurance plan or provider group network. This study was deemed IRB exempt due to the use of de-identified data.

Exposure Ascertainment

Our exposure of interest was incident thyroid status defined by two consecutive serum TSH levels. In order to ascertain incident thyroid status, all patients were required to have a baseline (first) TSH level within reference range (TSH 0.5-5.0mIU/L), and exposure status was designated according to the index (second) TSH level.

In primary analyses, exposure groups were categorized as 1) hypothyroid (TSH >5.0mIU/L), 2) euthyroid (TSH 0.5-5.0mIU/L), and 3) hyperthyroid (TSH <0.5mIU/L) TSH ranges.[31–33] In secondary analyses, incident thyroid status was defined using more granular TSH categorizations, namely 1) severe overt hypothyroid (>20.0mIU/L), 2) overt hypothyroid (>10.0-20.0mIU/L), 3) subclinical hypothyroid (>5.0-10.0mIU/L), 4) high-normal TSH (3.0-5.0mIU/L), 5) low-normal TSH (0.5-<3.0mIU/L), 6) subclinical hyperthyroid (0.1-<0.5mIU/L), and 7) overt hyperthyroid (<0.1mIU/L) TSH ranges. In sensitivity analyses, we also examined TSH as restricted cubic splines with knots at the 10^{th}, 50^{th}, and 90^{th} percentiles of observed TSH values in order to flexibly examine TSH as a continuous predictor of incident CKD or CKD progression.

Outcome Ascertainment

Our primary outcome of interest was time to the composite endpoint of 1) incident CKD or 2) CKD progression. Incident CKD was defined as two consecutive eGFR levels <60ml/min/1.73m^2 separated by ≥90 days following the baseline eGFR measurement, and with a decline of ≥25% from the baseline eGFR level based on definitions from Kidney Disease Improving Global Outcomes [KDIGO] guidelines.[34] CKD progression was defined as a ≥30% decline in eGFR level within three-years of the baseline eGFR measurement, which has been proposed by the Food and Drug Administration and National Kidney Foundation as an acceptable surrogate endpoint in CKD trials.[35] The eGFR levels were calculated from serum creatinine measurements and socio-demographic data using the Chronic Kidney Disease Epidemiology Collaboration equation.[36] At-risk time began the day after the index TSH measurement. Patients were censored for death, kidney transplantation, loss to follow-up, or the last date of available follow-up data (6/1/2019), whichever occurred first.

Socio-demographic, Comorbidity, Medication, and Laboratory Data

Data were used to determine patients’ baseline socio-demographic information (e.g., age, sex, race/ethnicity), comorbid conditions (ascertained from International Classification of Diseases, Ninth and Tenth Revision, Clinical Modification diagnostic and procedural codes and Current Procedural Terminology codes), laboratory data, and medications. Charlson Comorbidity Index (CCI) scores were estimated using the Deyo modification for administrative datasets without including kidney disease.[37]

Statistical Analysis

Baseline characteristics between exposure groups were compared using chi-squared, analysis of variance, and Kruskal-Wallis tests according to data type. We examined associations between incident thyroid status and the composite outcome of incident CKD or CKD progression using Cox proportional hazard models. Cox models were conducted using four incremental levels of covariate adjustment:

1. Unadjusted model: Included serum TSH level as the primary exposure of interest;
2. Case-mix adjusted model: Adjusted for covariates in the unadjusted model, as well as age, sex, and race/ethnicity;
3. Expanded case-mix adjusted model: Adjusted for covariates in the case-mix model, as well as CCI score, diabetes, coronary artery disease (CAD), congestive heart failure (CHF), atrial fibrillation, hyperlipidemia, and hypertension; and
4. Expanded case-mix+laboratory adjusted model: Adjusted for covariates in the case-mix model, as well as body mass index (BMI), smoking status, serum albumin, hemoglobin, serum bicarbonate, and cholesterol levels.

In the abovementioned models, comorbidity and laboratory covariates were extracted using the most proximate value up to one-year on or prior to the index TSH date. We *a priori* defined the expanded case-mix model as our preferred model, which included core socio-demographic measures and other key confounders of the association between hypothyroidism and CKD outcomes. Due to the greater proportion of missing BMI and laboratory covariates, designated the expanded case-mix+laboratory model as an exploratory model, which included confounders as well as potential causal pathway intermediates of the hypothyroidism–CKD association.

Missing covariate data were addressed with multiple imputation methods using ten imputed datasets. In the Primary Cohort (Cohort A), there were no missing values for covariates except for BMI (41%), serum albumin (18%), hemoglobin (30%), serum bicarbonate (26%), and cholesterol (20%). We additionally conducted subgroup analyses of thyroid status across clinically relevant categories of socio-demographics, comorbidity status, and laboratory measures. Proportional hazards assumptions were confirmed by graphical analysis. Analyses and figures were generated using Stata version 13.1 (Stata Corporation, College Station, TX, USA).

Results

Study Cohort

In the primary cohort, there were 4,152,830 patients who met eligibility criteria (Supplemental Figure 1), among whom the mean±SD age of the cohort was 55±16 years; 59% were women; and 75% were non-Hispanic White, 10% were non-Hispanic Black, 8% were Hispanic, 3% were Asian, and 4% were of Other/Unknown race/ethnicity. Based on index TSH levels, 87,484 (2.1%), 3,976,767 (95.8%), and 88,559 (2.1%) of patients had hypothyroid, euthyroid, and hyperthyroid TSH ranges, respectively (Table 1), and

the minimum-maximum range of TSH values was 0.001-57.5mIU/L. Upon examining finer TSH gradations, 1709 (<0.1%), 5101 (0.1%), 80,674 (1.9%), 533,476 (12.6%), 3,443,320 (82.9%), 80,291 (1.9%), and 8268 (<0.1%) of patients had index TSH levels in the severe overt hypothyroid, overt hypothyroid, subclinical hypothyroid, high-normal, low-normal TSH, subclinical hyperthyroid, and overt hyperthyroid TSH ranges, respectively (Supplementary Table 1).

Baseline characteristics of the Primary Cohort are shown in Table 1. Compared to euthyroid patients, patients with hypothyroid TSH ranges tended to be older; were more likely to be female; were more likely to be non-Hispanic White and were less likely to be non-Hispanic Black; were more likely to have CAD, CHF, and atrial fibrillation; and were less likely to have hyperlipidemia. In contrast, patients with hyperthyroid TSH ranges tended to be younger; were more likely to be female; were less likely to be non-Hispanic White and were more likely to be non-Hispanic Black; were more likely to have CHF; were less likely to have hyperlipidemia; and were more likely to be smokers. A similar pattern of findings was observed for the baseline characteristics of the Secondary Cohort (Supplementary Table 2). Baseline characteristics stratified according to finer gradations of incident thyroid status for the Primary and Secondary Cohorts are shown in Supplementary Tables 1 and 3, respectively.

Incident Thyroid Status and Risk of Incident CKD or CKD Progression

In the Primary Cohort, patients contributed a total of 17,316,304 patient-years of follow-up time, during which 306,768 incident CKD or CKD progression events occurred (crude event rate 18 events per 1000 person-years follow-up). Median (IQR) at-risk time was 3.8 (2.0, 6.1) years. In primary analyses, compared with patients who were euthyroid, those with hypothyroid-range TSH levels had higher risk of the composite endpoint of incident CKD or CKD progression in unadjusted, case-mix, expanded case-mix, and expanded case-mix+laboratory adjusted Cox models: HRs (95% CIs) 1.81 (1.78, 1.85), 1.45 (1.42, 1.48), 1.37 (1.34, 1.40), and 1.25 (1.23, 1.28), respectively (Figure 1A and Supplementary Table 4). Conversely, patients with hyperthyroid-range TSH levels also had higher risk of the composite endpoint in unadjusted, case-mix, expanded case-mix, and expanded case-mix+laboratory Cox models (reference: euthyroid patients): HRs (95% CIs) 1.53 (1.50, 1.56), 1.54 (1.51, 1.57), 1.42 (1.39, 1.45), and 1.23 (1.20, 1.25), respectively.

We also examined the relationship between the incident thyroid status and risk of incident CKD or CKD progression in the Secondary Cohort, a subcohort of 2,227,965 patients from the Primary Cohort whose exposure window for two consecutive TSH measurements was limited to one-year. In the Secondary Cohort, patients contributed a total of 9,015,423 patient-years of follow-up time, during which 195,874 incident CKD or CKD progression events occurred (crude event rate 22 events per 1000 person-years follow-up), and median (IQR) at-risk time was 3.6 (1.7, 6.0) years. Similar to the Primary Cohort, compared to euthyroid patients, those with hypothyroid-range TSH levels had higher risk of the composite endpoint in unadjusted, case-mix, expanded case-mix, and expanded case-mix+laboratory Cox models: HRs (95% CIs) 1.74 (1.70, 1.78), 1.43 (1.40, 1.46), 1.36 (1.33, 1.39), and 1.24 (1.21, 1.27), respectively (Figure 1B and Supplementary Table

4). In addition, patients with hyperthyroid-range TSH levels had higher risk of incident CKD or CKD progression in unadjusted, case-mix, expanded case-mix, and expanded case-mix+laboratory Cox models (reference: euthyroid patients): HRs (95% CIs) 1.43 (1.39, 1.46), 1.46 (1.42, 1.49), 1.37 (1.34, 1.41), and 1.20 (1.17, 1.23), respectively.

Granular Serum Thyrotropin Categorizations and Risk of Incident CKD or CKD Progression

In secondary analyses examining finer gradations of incident thyroid status in the Primary Cohort, incrementally higher TSH levels were associated with increasingly higher risk of the composite endpoint in expanded case-mix models (reference: low-normal TSH 0.5-<3.0mIU/L): HRs (95% CIs) 1.10 (1.09, 1.11), 1.37 (1.34, 1.40), 1.70 (1.599, 1.83), and 1.70 (1.50, 1.93) for high-normal, subclinical, overt, and severe overt hypothyroid-range TSH levels, respectively (Figure 2A and Supplementary Table 5). This pattern of findings was robust with incremental adjustment for expanded case-mix+laboratory covariates. Conversely, there was a graded association between incrementally lower TSH levels were associated with increasingly higher risk of incident CKD or CKD progression in expanded case-mix analyses of the Primary Cohort (reference: low-normal TSH 0.5-<3.0mIU/L): HRs (95% CIs) 1.44 (1.41, 1.47) and 1.48 (1.39, 1.59) for subclinical and overt hyperthyroid TSH ranges, respectively. These associations remained statistically significant with further adjustment for expanded case-mix+laboratory covariates.

In analyses of the Secondary Cohort, we observed a similar relationship between higher and lower TSH categories with the composite endpoints. In expanded case-mix analyses, TSH levels ≥3.0mIU/L were associated with higher risk of incident CKD or CKD progression (reference: low-normal TSH 0.5-<3.0mIU/L): HRs (95% CIs) 1.11 (1.10, 1.12), 1.37 (1.33, 1.40), 1.65 (1.51, 1.79), and 1.56 (1.34, 1.82) for TSH levels in the high-normal, subclinical, overt, and severe overt hypothyroid ranges, respectively (Figure 2A and Supplementary Table 5). Similar to the Primary Cohort, TSH levels <0.5mIU/L were also associated with higher risk of incident CKD or CKD progression (reference: low-normal TSH 0.5-<3.0mIU/L): HRs (95% CIs) 1.40 (1.37, 1.44) and 1.35 (1.25, 1.47) for subclinical and overt hyperthyroid TSH ranges, respectively. These associations were robust with further adjustment for expanded case-mix+laboratory covariates.

Restricted Cubic Spline Analyses of Continuous Serum Thyrotropin Levels

In sensitivity analyses examining serum TSH levels as a continuous predictor of the composite endpoint using restricted cubic splines in the Primary Cohort, we observed that there was a U-shaped relationship between higher and lower TSH levels and incident CKD or CKD progression, with a nadir of risk observed at TSH levels ~1.0-2.9mIU/L in expanded case-mix models (Figure 3A). A similar pattern of findings was observed in restricted cubic analyses of the Secondary Cohort adjusted for expanded case-mix covariates (Figure 3B).

Thyroid Status and Incident CKD or CKD Progression Across Clinically Relevant Subgroups

We also examined the association of incident thyroid status with risk of the composite endpoint across clinically relevant subgroups. In expanded case-mix analyses of the Primary Cohort, we observed that both hypothyroidism and hyperthyroidism were each associated

with higher risk of incident CKD or CKD progression across all subgroups (Figure 4A and Supplementary Table 6). Interaction tests demonstrated that the differences in the estimates of the thyroid status—incident CKD/CKD progression associations were statistically significant for subgroups of age, sex, race/ethnicity, CCI score, diabetes, CAD, CHF, atrial fibrillation, hyperlipidemia, hypertension, BMI, serum albumin, hemoglobin, bicarbonate, and cholesterol levels (all p-interaction values <0.001; Supplementary Table 6). In these analyses, we observed that point estimates of the hypothyroidism—incident CKD/CKD progression association were stronger among those who were younger (<55 years), male, and non-Hispanic Black; without underlying hyperlipidemia or hypertension; and with lower serum albumin (<4g/dL), bicarbonate (<24mEq/L), and cholesterol (<200mg/dL) levels. Additionally, we observed that stronger point estimates of the hyperthyroidism—incident CKD/CKD progression association were observed among those who were younger, male, non-Hispanic White, and Hispanic; with lower CCI scores (≤2); without underlying diabetes, CAD, CHF, atrial fibrillation, hyperlipidemia, hypertension, and smoking status; with lower BMI (<30kg/m^2); with higher serum albumin (≥4g/dL) and hemoglobin (≥12g/dL) levels; and with lower serum bicarbonate (<24mEq/L) levels. A similar pattern of findings was observed in analyses of the Secondary Cohort (Figure 4B and Supplementary Table 6).

Discussion

To our knowledge, this is the first study that has examined the relationship between incident thyroid status ascertained by serum TSH levels with the risk of developing de novo CKD or CKD progression. In this large nationally representative cohort of US adults with detailed longitudinal laboratory data, granular examination of thyroid status showed that TSH levels in the high-normal (≥3.0mIU/L) and hyperthyroid range (<0.5mIU/L) were each independently associated with heightened risk of incident CKD or CKD progression over time. These associations persisted across multiple secondary and sensitivity analyses that incrementally adjusted for potential confounders of the thyroid status—CKD association across multivariable models, including socio-demographics comorbidities, body mass index, smoking status, and laboratory covariates, and considered clinically relevant subgroups.

To date there has been ongoing debate as to whether hypothyroidism is a novel modifiable risk factor for kidney dysfunction. Whereas multiple cross-sectional studies from US and international cohorts have demonstrated a link between hypothyroidism and kidney dysfunction,[5–8, 10, 11, 13, 27, 28] longitudinal data have been limited with mixed findings.[9, 12, 27, 28] For example, while cross-sectional analyses from the Atherosclerosis Risk in Communities (ARIC)[28] and Leiden 85-Plus[27] studies showed that hypothyroidism was linked with lower eGFR, longitudinal data from these cohorts did not confirm a significant association between baseline thyroid status with incident CKD nor eGFR decline. In contrast, longitudinal studies from the Kangbuk Samsung Health Study[12] and the Taipei Databank for Public Health Analysis[9] have shown that elevated serum TSH levels are associated with new-onset CKD. Yet it bears mention that inference from these studies are limited by their non-consideration of incident thyroid status or TSH levels outside of the reference range; utilization of non-orthodox definitions for incident CKD; or restriction to elder adults only.[9, 12, 27, 28]

Our study also adds new knowledge to the field by showing that there is a U-shaped relationship of both lower and higher levels of thyroid function (defined by elevated and depressed serum TSH levels, respectively) with risk of incident CKD and CKD progression over time. Whereas several of the abovementioned studies have reported a linear relationship between increasingly lower levels of thyroid function with incrementally worse eGFR levels,[7, 27, 28] our study is the first to demonstrate that both hypo- and hyperthyroidism are risk factors for de novo CKD or CKD progression. As potential mechanisms for hypothyroidism and CKD, experimental models and clinical studies have shown that low thyroid function adversely affects kidney structure and function in both development and adulthood via multiple pathways. In animal models, hypothyroidism has been shown to confer 1) decreased kidney size-to-body weight ratio,[16, 20] 2) truncated tubular mass,[14, 17, 19] and 3) altered glomerular basement membrane architecture (i.e., reduced volume and area, mesangial matrix expansion, and increased glomerular capillary permeability).[15, 18, 38] Hypothyroidism may also lead to kidney dysfunction through multiple mechanisms, including 1) decreased cardiac output ensuing from systolic and diastolic dysfunction, decreased inotropy and chronotropy, and reduced blood volume,[23, 24] 2) intra-renal vasoconstriction due to reduced vasodilator (nitric oxide, adrenomedullin) synthesis and activity,[22, 24] 3) decreased renin-angiotensin-aldosterone production and activity leading to impaired autoregulation of renal perfusion,[21, 22, 25, 26] and 4) altered chloride channel expression with increased distal tubular Cl-delivery, renal afferent arteriole vasoconstriction, and lower GFR (increased tubulo-glomerular feedback).[22, 25] Animal studies have also demonstrated that hypothyroidism results in lower single nephron GFR, renal plasma flow, and glomerular transcapillary hydrostatic pressure,[15, 39] and human case series have confirmed that hypothyroidism results in reversible plasma flow reductions and decreased GFR as measured by creatinine-based estimating equations and gold-standard isotopic scans.[22, 25, 40, 41] Conversely, there is biological plausibility that hyperthyroidism may contribute to impaired kidney function vis-à-vis its effects on the heart (i.e., atrial fibrillation, high-output cardiac failure).[23, 42] Further studies are needed to investigate the pathways by which thyroid dysfunction engenders kidney disease. Future research is also needed to determine whether treatment of hypothyroid and hyperthyroid patients with thyroid-modulating pharmacotherapies mitigates kidney dysfunction in those at-risk for or with underlying CKD, which may motivate broader screening in this population.

Another noteworthy finding was our observation that higher TSH levels even in the high-normal range are independently associated with higher risk of incident CKD or CKD progression over time. A growing body of data have shown that mildly depressed thyroid function (i.e., manifested as high-normal TSH levels exceeding ~2.5-3.0mIU/L) is associated with cardiovascular disease (i.e., endothelial dysfunction,[43] coronary artery calcification[44]) and worse survival in advanced CKD[32] and end-stage renal disease patients.[33, 45] Given their high burden of underlying cardiovascular disease,[46] it has been postulated that CKD patients may have lower reserve with which to tolerate hemodynamic changes associated with mild thyroid perturbations, with subsequent implications on kidney function.[2–4] Further research is needed to determine the precise TSH targets conferring optimal health in the CKD population.

The strengths of our study include its examination of a large nationally representative contemporary cohort of US adults with extended follow-up; detailed availability of longitudinal data on socio-demographics, comorbidities, laboratory results, and clinical events; rigorous ascertainment of incident thyroid status; and utilization of established definitions of incident CKD and CKD progression. However, several limitations of our study bear mention. First, inclusion in the study required that patients had two or more TSH measurements. While the indications for TSH testing in this study cohort are unknown, this requirement applied equally to patients irrespective of thyroid function and should not impair the study's internal validity. Second, given the sparsity of free thyroxine (FT4) and free triiodothyronine measurements and their unclear accuracy in kidney disease[2–4] (i.e., peripheral conversion of T4- to-T3 is sensitive to non-thyroidal illness; routinely used FT4 assays are dependent upon protein-hormone binding, and the presence of uremic toxins that interfere with protein-hormone binding may lead to spurious levels[47–52]), we stratified patients according to TSH ranges that typically reflect the spectrum of overt to subclinical thyroid disease.[31–33] Although some aberrations of TSH have been described in the context of CKD, it remains a more robust metric of thyroid status particularly in the setting of underlying illness (i.e., TSH levels typically remain normal in mild-moderate non-thyroidal illness, and become suppressed only in severe critical illness states).[53] Lastly, as with all observational studies, we cannot exclude the possibility of residual confounding.

In conclusion, our study found that both higher TSH levels in the high-normal (≥3.0mIU/L) and hyperthyroid (<0.5mIU/L) range are associated with higher risk of incident CKD or CKD progression in a nationally representative cohort of US adults. Given the substantial burden of kidney disease in the US population and the high prevalence of thyroid dysfunction in those with CKD, there is compelling need for further research identifying the specific pathways by which thyroid dysfunction contributes to kidney disease, the impact of thyroid-modulating pharmacotherapies on mitigating kidney dysfunction, and the exact TSH targets associated with optimal kidney health in those at-risk for or with underlying CKD.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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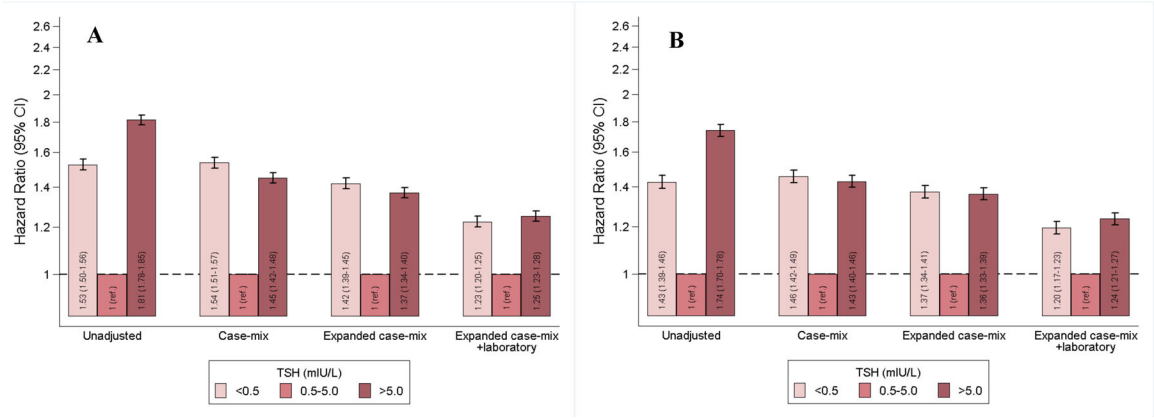

Figure 1. Associations of incident thyroid status with risk of incident chronic kidney disease (CKD) and CKD progression in the Primary Cohort (Panel A) and Secondary Cohort (Panel B).
Abbrev.: TSH, thyrotropin.

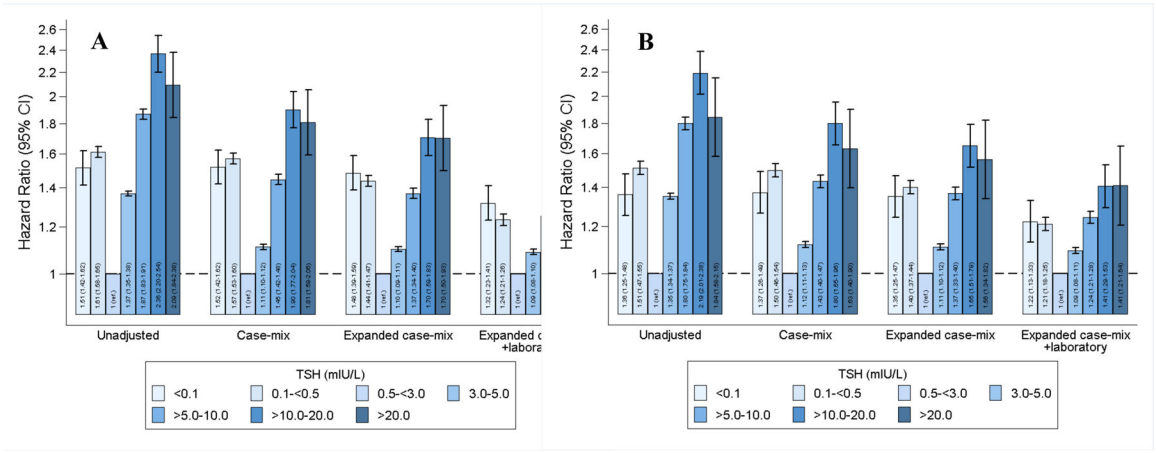

Figure 2. Associations of granular serum thyrotropin categorizations with risk of incident chronic kidney disease (CKD) and CKD progression in the Primary Cohort (Panel A) and Secondary Cohort (Panel B).

Abbrev.: TSH, thyrotropin.

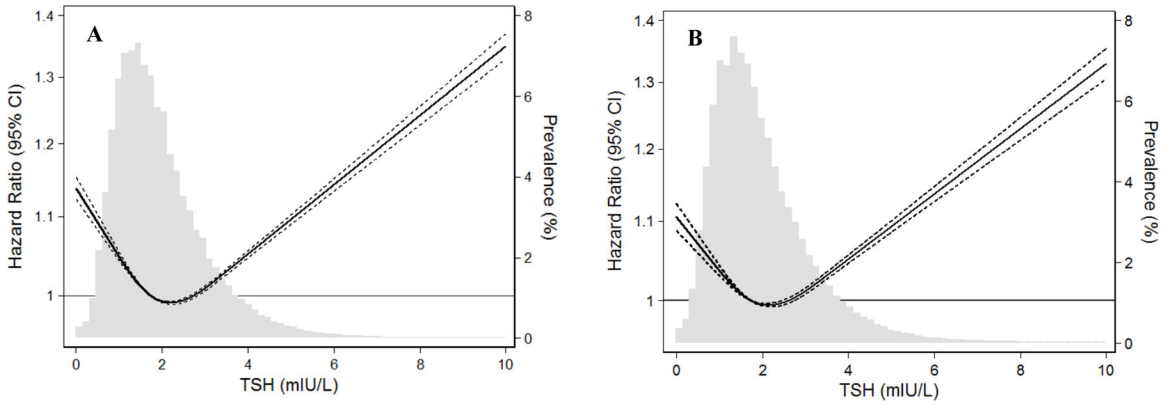

Figure 3. Restricted cubic spline analysis of continuous serum thyrotropin levels with risk of incident chronic kidney disease (CKD) and CKD progression in the Primary Cohort (Panel A) and Secondary Cohort (Panel B).

Abbrev.: TSH, thyrotropin.

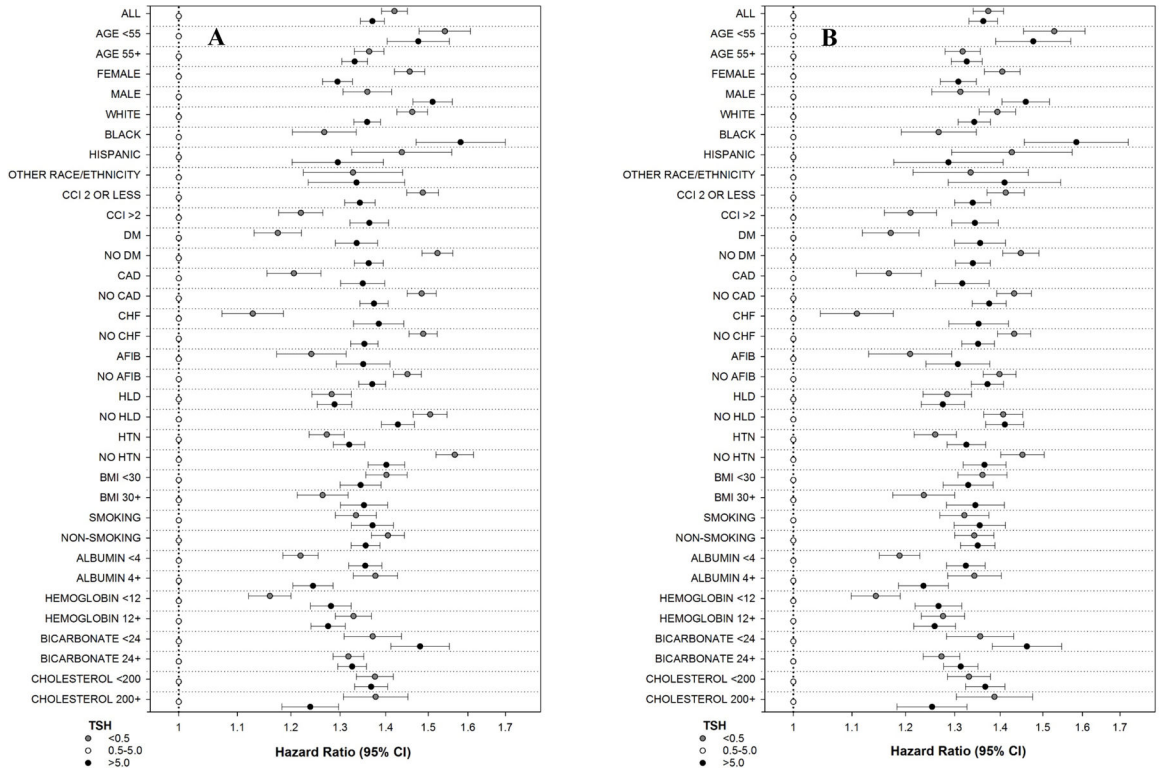

Figure 4. Subgroup analyses of incident thyroid status with risk of incident chronic kidney disease (CKD) and CKD progression in the Primary Cohort (Panel A) and Secondary Cohort (Panel B).

Abbrev.: CCI, Charlson Comorbidity Index; DM, diabetes; CAD, coronary artery disease; CHF, congestive heart failure; AFIB, atrial fibrillation; HLD, hyperlipidemia; HTN, hypertension; BMI, body mass index; TSH, thyrotropin.

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Table 1.

Baseline characteristics of the Primary Cohort stratified by incident thyroid status.

	Serum Thyrotropin (TSH) Categories (mIU/L)				
	Overall	**Hyperthyroid <0.5mIU/L**	**Euthyroid 0.5-5.0mIU/L**	**Hypothyroid >5.0mIU/L**	**p-value**
N of patients, %	4,152,830	88,559 (2.1)	3,976,787 (95.8)	87,484 (2.1)	-
Age (years), mean±SD	55±16	54±17	55±16	60±17	<0.001
Female, %	59	65	59	62	<0.001
Race, %					<0.001
Non-Hispanic White	75	68	75	79	
Non-Hispanic Black	10	17	10	6	
Hispanic	8	7	8	8	
Asian	3	3	3	3	
Unknown/Missing	4	5	4	5	
CCI, median (IQR)	0 (0, 2)	1 (0, 2)	0 (0, 2)	1 (0, 2)	<0.001
Comorbidities, %					
Diabetes	19	19	19	20	<0.001
Coronary artery disease	13	14	13	18	<0.001
Congestive heart failure	6	8	5	11	<0.001
Atrial fibrillation	6	7	5	11	<0.001
Hyperlipidemia	45	36	46	43	<0.001
Hypertension	46	44	46	46	<0.001
Smoking	29	39	29	29	<0.001
Body composition					
BMI (kg/m^2), mean ± SD	29.9±7.2	28.9±7.1	29.9±7.2	30.0±7.5	<0.001
Laboratory results, median (IQR)					
Serum albumin (g/dL)	4.2 (3.9, 4.4)	4.0 (3.7, 4.3)	4.2 (3.9, 4.5)	4.1 (3.7, 4.4)	<0.001
Hemoglobin (g/dL)	13.7 (12.7, 14.7)	13.2 (12.0, 14.3)	13.7 (12.7, 14.7)	13.3 (12.0, 14.3)	<0.001
Bicarbonate (mEq/L)	27 (25, 29)	26 (24, 28.5)	27 (25, 29)	27 (25, 29)	<0.001
Cholesterol (mg/dL)	183 (157, 210)	176 (150, 204)	183 (157, 210)	181 (153, 211)	<0.001

Abbrev.: CCI, Charlson Comorbidity Index; BMI, body mass index.