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Association between hypothyroidism and chronic kidney disease observed among an adult population 55 years and older

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Abstract

Hypothyroidism and chronic kidney disease (CKD) are highly prevalent conditions with a potential mechanistic link. We sought to determine whether hypothyroidism is associated with CKD among a large diverse community-based cohort.

A cross-sectional study was performed (January 1, 1990–December 31, 2017) within a large integrated health system. Individuals age ≥55 years of age with outpatient measurements of thyroid stimulating hormone (TSH) and ≥2 serum creatinine values were included. Hypothyroidism was defined as TSH >4 mIU/L and/or receipt of thyroid hormone replacement and further categorized as hypothyroid status: TSH >4 mcIU/mL and attenuated-hypothyroid status: TSH <4 mcIU/mL with receipt of thyroid hormone replacement. Euthyroidism was defined as TSH <4 mIU/L and no thyroid hormone replacement. Our primary measure was CKD defined as an estimated glomerular filtration rate (eGFR) <45 mL/min/1.73 m^2. Multivariable logistic regression adjusting for age, sex, race, and comorbidities was used to estimate odds ratios (OR) for CKD by thyroid status.

Among 378,101 individuals, 114,872 (30.4%) had hypothyroidism among whom 31,242 and 83,630 had hypothyroid and attenuated-hypothyroid statuses, respectively. Individuals with hypothyroidism had a CKD OR (95%CI) of 1.25 (1.21–1.29) compared with those with euthyroidism. Granular examination of thyroid statuses showed that hypothyroid and attenuated-hypothyroid statuses had CKD ORs (95% CI) of 1.59 (1.52–1.66) and 1.12 (1.08–1.16), respectively. A similar relationship was observed in analyses that defined CKD as an eGFR <60 L/min/1.73 m^2.

Among individuals 55 years and older, we observed that those with hypothyroidism were more likely to have CKD. A stronger association was found among patients of hypothyroid status compared with attenuated-hypothyroid status suggesting a dose dependent relationship.

Abbreviations: CKD = chronic kidney disease, eGFR = estimated glomerular filtration rate, EHR = electronic health records, KPSC = Kaiser Permanente Southern California, OR = odds ratio, RAAS = renin angiotensin aldosterone system, TSH = thyroid-stimulating hormone.

Keywords: chronic kidney disease, epidemiology, hypothyroidism

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1. Introduction

Chronic kidney disease (CKD) is a highly prevalent condition with numerous health consequences including heightened risk for cardiovascular disease, infections, impaired physical function, and death.[1–3] Approximately 15% of the adult population have CKD, among whom there is a 2-fold higher risk of death and a 1.5-fold higher risk of hospitalization compared with their non-CKD counterparts, even after accounting for differences in socio-demographic characteristics.[1,2] While hypertension and diabetes are well known risk factors, identifying new mechanistic links or risk factors for CKD may impact management strategies.

Thyroid function has been suggested to have a relationship with kidney function and CKD.[4–12] It has been hypothesized that hypothyroidism may lead to altered kidney function via effects on cardiac output, intra-renal hemodynamics, and renin angiotensin aldosterone system (RAAS), as well as structural changes including decreased kidney-to-body weight ratio, truncated tubular mass, and altered glomerular architecture.[13] Patients with CKD have been observed to have a higher prevalence of hypothyroidism.[4–7] Conversely, hypothyroidism has also been suggested to be a risk factor for depressed kidney function.[8–12] Overall, these clinical observations have been limited to select populations.

If hypothyroidism has a mechanistic link to CKD, it may have important clinical implications for the CKD population. Hypothyroidism is not only highly prevalent, but also easily diagnosed and treatable.[14,15] At the same time, there are no uniform screening guidelines for hypothyroidism, particularly in the CKD population.[15–18] In this study, we used electronic health records (EHR) from a large, diverse population of adults age 55 years and older to determine whether hypothyroidism was associated with CKD.

2. Methods

2.1. Source cohort

We performed a cross-sectional study of members within Kaiser Permanente Southern California (KPSC) in the period January 1, 1990 and December 31, 2017.[19] KPSC is an integrated health system providing comprehensive care to over 4.6 million members at 15 medical centers and >200 satellite clinics throughout Southern California. The patient population is racially/ethnically and socio-economically diverse, reflecting the general population of Southern California.[20,21] All KPSC members have similar benefits and access to healthcare services, clinic visits, procedures, and copays for medications. Healthcare encounters are tracked using an EHR from which all study information was extracted. All data for this study were collected as part of routine clinical encounters in which healthcare providers determined the need for laboratory measurements, procedures, and medications. The study protocol was reviewed and approved by the KPSC Institutional Review Board (No. 10758) and was deemed exempt from informed consent.

2.2. Study population

Individuals ≥55 years of age with outpatient measurements of serum TSH and 2 serum creatinine values were included in the study population (Fig. 1). Only outpatient measurements were chosen to minimize risk of misclassification of thyroid status during acute illnesses (i.e., non-thyroidal illness) and to minimize capturing acute kidney injury. Exclusion criteria included individuals with hyperthyroidism, end stage renal disease on renal replacement therapy, polycystic kidney disease, glomerulonephritis, rheumatologic or autoimmune diseases, or prior renal transplant.

2.3. Study covariates

Information on demographics (including age, sex, and race/ethnicity), comorbidities (diabetes mellitus, hypertension, end stage renal disease on renal replacement therapy, polycystic kidney disease, glomerulonephritis, rheumatologic or autoimmune diseases, or renal transplant), laboratory results (thyroid-stimulating hormone [TSH], creatinine, estimated glomerular filtration rate [eGFR], hemoglobin A1c), and medication usage (anti-thyroid medications, thyroid hormone replacement medications, anti-hyperglycemic medications) were extracted. eGFR was calculated by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation.[22] All disease conditions were identified using International Classification of Diseases (ICD) diagnosis codes unless otherwise specified. Diabetes was defined as having at least 1 hemoglobin A1c result ≥6.5% or at least 1 dispensation of anti-hyperglycemic medication (including any insulin and/or oral anti-hyperglycemic agents) within 6 months of the index TSH date. Hypertension was defined as
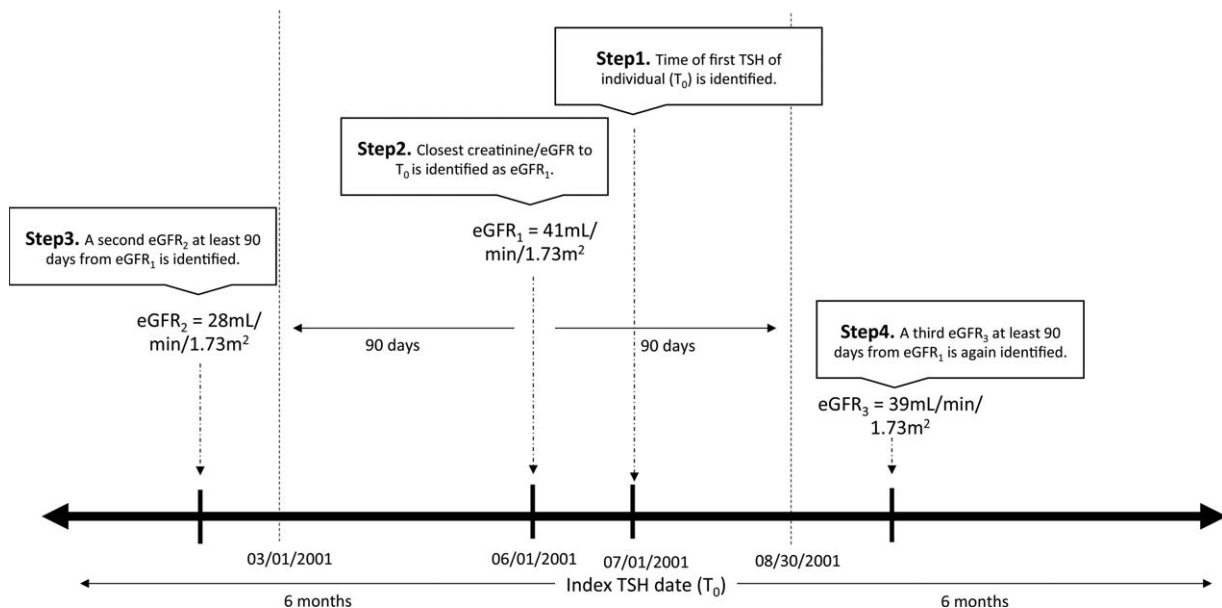

Figure 1. Example of identifying corresponding creatinine and eGFRs to index TSH date (T_0). Starting from T_0, July 1, 2001 in this individual's example, a query for the corresponding (most proximate) creatinine/eGFR within 6 months is performed, yielding $eGFR_1$. A query for a second eGFR that is at least 90 days apart (outside the dotted lines) from $eGFR_1$ but still within the 6 months time frame of T_0 is performed, yielding $eGFR_2$. Given that $eGFR_2$ is of a different CKD class when compared with $eGFR_1$, a query for a third (subsequent) eGFR that satisfies the above criteria is performed, yielding $eGFR_3$. The average of the $eGFR_1$ and $eGFR_3$, in this case, 40 mL/min/1.73 m², is taken and entered as the corresponding eGFR for this individual. CKD = chronic kidney disease, eGFR = estimated glomerular filtration rate, TSH = thyroid-stimulating hormone.

at least 2 ICD codes regardless of encounter setting within 6 months of the index TSH date.[23] All medications were identified using Generic Product Identifier (GPI) codes. Information on pharmacy fills was retrieved from the KPSC pharmacy analytic database.

2.4. Exposure ascertainment

Thyroid status was categorized based on TSH values and thyroid hormone replacement and anti-thyroid medication use. TSH was measured using chemiluminescent microparticle immunoassay by Abbot Architect assays. The reference range of 0.35 to 4.00 mIU/L for normal was set based on the manufacturer, Abbot Diagnostic studies in conjunction with Southern California Permanente Medical Group Endocrinology Committee Review.[15,24] We adopted the upper and lower limits of this range as our cut-off. If there were multiple TSH measurements during the study window, the first TSH value was used and was considered the index TSH date.

Hyperthyroidism was defined as use of anti-thyroid medication (methimazole and/or propylthiouracil) and/or TSH level below the lower limit of normal (TSH <0.35 mIU/L). These patients were excluded in the study as noted above. The study population was categorized into hypothyroid and euthyroid individuals based on thyroid function. Hypothyroidism was defined as an elevated level of TSH (>4.00 mIU/L) and/or receipt of thyroid hormone replacement (levothyroxine sodium, thyroid, thyroid strong, bovine thyroid, pork thyroid, liothyronine sodium, and liotrix). Hypothyroidism was further classified into those with a hypothyroid status and those with an attenuated-hypothyroid status. Hypothyroid status was defined as a TSH >4 mIU/L regardless of thyroid hormone replacement while attenuated-hypothyroid status was defined as a TSH <4 mIUl/L and on thyroid hormone replacement. Individuals were considered to be on a medication if it was dispensed within 6 months of the index TSH date.

2.5. Main measures

Our primary measure was CKD defined as an eGFR <45 mL/min/1.73 m^2. Our secondary measure was CKD defined as eGFR <60 mL/min/1.73 m^2. Using the index TSH date, a query for corresponding creatinine values within 6 months of the index TSH date was performed. The most proximate creatinine to the index TSH date was used. Once this creatinine value was identified and its respective eGFR was calculated, a second creatinine and eGFR value at least 90 days apart from the initial eGFR but within the same 6-month window (to index TSH date) was obtained. If the second eGFR was within the same CKD stage as defined by Kidney Disease Improving Global Outcomes (KDIGO), the average of the 2 eGFRs was taken.[25] If the second eGFR identified was of a distinct CKD stage, a query for a third (subsequent) creatinine and its respective eGFR within the same timeframe criteria was performed until at least 2 eGFR values fell in the same CKD stage. An average of the 2 eGFRs (from the 2 queries matching in CKD stage) was used to report the eGFR for each individual (Fig. 1).

2.6. Statistical analysis

Prevalence of CKD by thyroid status were determined and compared along with demographics, comorbidities, and laboratory values. Chi-squared test was used for comparison of categorical variables, and the 2 sample Wilcoxon rank-sum test was used for continuous variables. Age and eGFR were reported as means and standard deviations. Sex, race/ethnicity, presence of diabetes, hypertension, and thyroid medication use were reported as an absolute number and percentage. The number and percentage of individuals within each thyroid status were classified into different CKD stages as defined by KDIGO.[25]

Multivariable logistic regression analysis was performed to estimate CKD odds ratio (OR) by thyroid status using euthyroid individuals as reference. Sequential adjustment based on baseline demographics including age, sex, and race/ethnicity, followed by comorbidities of diabetes and hypertension were performed. All statistical analyses were conducted using SAS statistical software (version 9.2, SAS Institute Cary, NC).

3. Results

3.1. Study population

A total of 441,485 individuals who had outpatient serum TSH and creatinine measurements were identified. After 63,384 individuals were excluded based on exclusion criteria, a total of 378,101 individuals were included in our study population. (Fig. 2) Among this cohort, 114,872 (30.4%) individuals had hypothyroidism with 31,242 (27.2%) who had hypothyroid status and 83,630 (72.8%) who had attenuated-hypothyroid status (Fig. 1). The mean (±SD) age of the cohort was 67 (±9) years and 57% of patients were women. Whites, blacks, Hispanics, and Asian/Pacific Islanders comprised 58%, 10%, 21%, and 10% of the cohort, respectively. The mean (±SD) eGFR was 76 (±18) mL/min/1.73 m^2. The cohort was comprised of 13% with diabetes and 47.0% with hypertension (Table 1).

3.2. Prevalence of CKD by thyroid status

Among individuals with hypothyroidism, a total of 8271 (7.2%) had CKD (defined as an eGFR <45 mL/min/1.73 m^2) compared with 12,868 (4.9%) with euthyroidism (P <.001) (Table 1). Within the hypothyroidism population, CKD was present in 2937 (9.4%) individuals with hypothyroid status compared with 5334 (6.4%) with attenuated hypothyroid status.

Using eGFR <60 mL/min/1.73 m^2 to define CKD, a total 26,467 (23.0%) individuals with hypothyroidism had CKD compared with 44,929 (17.1%) with euthyroidism (P <.001). (Table 1). Within the hypothyroidism population, 8574 (27.4%) hypothyroid status individuals had CKD compared with 17,893 (21.4%) with attenuated hypothyroid status.

3.3. Regressions analysis for thyroid status and CKD

The crude OR (95% CI) for CKD (defined as eGFR <45 mL/min/1.73 m^2) was 1.51 (1.47–1.55) for individuals with hypothyroidism compared with those with euthyroidism. Compared with euthyroid individuals, the crude ORs (95% CI) for CKD were 2.02 (1.94–2.11) and 1.33 (1.28–1.37) for hypothyroid and attenuated-hypothyroid status, respectively. The fully adjusted CKD OR (95% CI) was 1.25 (1.21–1.29) for individuals with hypothyroidism compared with euthyroidism. The adjusted CKD ORs (95% CI) were 1.59 (1.52–1.66) and 1.12 (1.08–1.16) for individuals with hypothyroid and attenuated-hypothyroid status, respectively (Table 2).
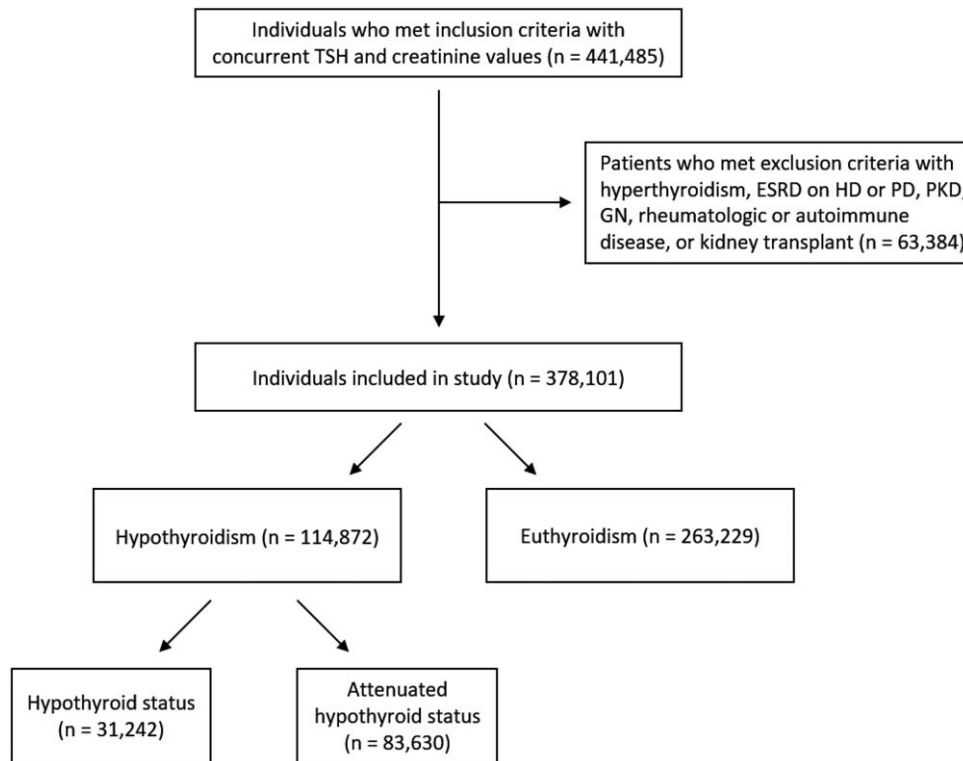
Figure 2. Study population. A total of 441,485 individuals who had outpatient serum TSH and creatinine measurements were identified. After 63,384 patients were excluded based on exclusion criteria, 378,101 individuals were included in our study population. Among this cohort, 114,872 (30.4%) individuals had hypothyroidism, among whom 31,242 (27.2%) had hypothyroid status and 83,630 (72.8%) had attenuated-hypothyroid status. TSH = thyroid-stimulating hormone.

Using eGFR <60 mL/min/1.73 m² to define CKD, the adjusted OR (95% CI) for CKD was 1.25 (1.23–1.28) among individuals with hypothyroidism. Among hypothyroid and attenuated-hypothyroid status individuals, the adjusted ORs (95% CI) for CKD were 1.58 (1.53–1.63) and 1.14 (1.12–1.17) respectively (Table 2).

4. Discussion

In this study of 378,101 individuals age 55 years and older with serum TSH and serum creatinine measurements, we observed a higher prevalence of CKD among individuals with hypothyroidism compared with those with euthyroidism. Individuals with

Table 1
Study cohort characteristics by thyroid status.

	Overall	Hypothyroid	Euthyroid	P-value
N (column %)	378,101	114,872	263,229	
eGFR, mean (SD)	75.6 (17.9)	73.0 (18.1)	76.7 (17.7)	<.001
N by CKD stage (%)				<.001
eGFR 45–<60 (Stage 3a)	50,257 (13.3%)	18,196 (15.8%)	32,061 (12.2%)	
eGFR 30–<45 (Stage 3b)	17,682 (5.6%)	6833 (6.0%)	10,849 (4.1%)	
eGFR 15–<30 (Stage 4)	3,167 (0.8%)	1318 (1.2%)	1849 (0.7%)	
eGFR <15 (Stage 5)	290 (0.1%)	120 (0.1%)	170 (0.1%)	
Age, mean (SD)	67.0 (8.9)	68.2 (9.3)	66.5 (8.7)	<.001
Female (%)	214,099 (56.6%)	64,361 (56.0%)	149,738 (56.9%)	<.001
Race (%)				<.001
White	220,227 (58.3%)	72,667 (63.3%)	147,560 (56.1%)	
Black	39,028 (10.3%)	8779 (7.6%)	30,249 (11.5%)	
Hispanic	79,307 (21.0%)	23,892 (20.8%)	55,415 (21.1%)	
API	36,942 (9.8%)	8,805 (7.7%)	28,137 (10.7%)	
Other	2597 (0.7%)	729 (0.6%)	1868 (0.7%)	
Diabetes (%)	47,602 (12.6%)	13,531 (11.8%)	34,071 (12.9%)	<.001
Hypertension (%)	177,529 (47.0%)	54,737 (47.7%)	122,792 (46.7%)	<.001
Thyroid hormone replacement use	102,973	102,973	0	—

CKD = chronic kidney disease, eGFR = estimated glomerular filtration rate.

Table 2

Odds ratio of CKD across each thyroid status.

Thyroid Status	Crude OR (95% CI)	Adjusted OR (95% CI)*	Adjusted OR (95% CI)†
CKD as defined by eGFR <45 mL/min/1.73 m²			
Hypothyroidism	1.51 (1.47–1.55)	1.25 (1.22–1.29)	1.25 (1.21–1.29)
Hypothyroid status	2.02 (1.94–2.11)	1.56 (1.49–1.63)	1.59 (1.52–1.66)
Attenuated hypothyroid status			
	1.33 (1.28–1.37)	1.13 (1.10–1.17)	1.12 (1.08–1.16)
Euthyroidism	Reference	Reference	Reference
CKD as defined by eGFR <60 mL/min/1.73 m²			
Hypothyroidism	1.46 (1.43–1.48)	1.26 (1.23,1.28)	1.25 (1.23–1.28)
Hypothyroid status	1.84 (1.79–1.89)	1.55 (1.50–1.59)	1.58 (1.53–1.63)
Attenuated hypothyroid status			
	1.32 (1.30–1.35)	1.16 (1.13–1.18)	1.14 (1.12–1.17)
Euthyroidism	Reference	Reference	Reference

CKD = chronic kidney disease, eGFR = estimated glomerular filtration rate, OR = odds ratio.

* Adjusted for demographics including age, sex, and race.

† Additionally adjusted for hypertension and diabetes.

hypothyroidism were 25% more likely to have CKD compared with those who were euthyroid. Upon examining more granular categories of hypothyroidism, we also found that there was a stronger association with CKD by thyroid status. Specifically, individuals with a hypothyroid status and an attenuated-hypothyroid status had 60% and 10% more likelihood for CKD compared with those with euthyroidism. Our findings from a real-world clinical setting of a large diverse population in the United States suggest a potential dose dependent relationship between thyroid status and CKD.

There has been increasing recognition of an interplay between thyroid status and kidney function.[4–12] A study of National Health and Nutrition Examination Survey (NHANES) III participants found that those with incrementally lower GFR had an increasingly higher prevalence of hypothyroidism.[6] These findings were corroborated in a study of the national Veterans Affairs (VA) population demonstrating an inverse relationship between lower eGFR and higher risk of hypothyroidism.[7] A prior study from Norway observed that lower thyroid function in clinically-normal ranges was associated with reduced eGFR.[8] Subsequent studies have shown that hypothyroidism even in the mild "subclinical" range is associated with decreased kidney function in other non-US populations.[11,12] However, interpretation of these data are limited by their non-consideration of a broader spectrum of thyroid function; restricted generalizability based on the size, race/ethnicity, or comorbidity status (i.e., diabetics only) of these study populations; and the sparse examination of potential confounders of thyroid status and kidney function.[8–12]

Hypothyroidism has been shown to cause changes in kidney structure and function in both development and adulthood. For example, animal models have shown that hypothyroidism leads to decreased kidney-to-body weight ratio, truncated tubular mass, changes in glomerular structure, decreased single nephron GFR, low renal plasma flow, and lower glomerular transcapillary hydrostatic pressure.[26–30] Case series have further shown hypothyroid patients have reduced renal plasma flow and GFR measured by creatinine-based estimating equations and gold-standard isotopic scans.[31–33] It has also been theorized that hypothyroidism leads to kidney dysfunction due to impaired systolic and diastolic function leading to reduced cardiac output, decreased vasodilator synthesis and activity leading to changes in

intra-renal hemodynamics, altered RAAS, and increased tubulo-glomerular feedback.[13,34–38]

Diagnosis of hypothyroidism is simple, and its treatment is cost-effective and safe.[15] Yet, there are inconsistent recommendations with respect to the screening for hypothyroidism. At this time, the United States Preventive Service Task Force (USPSTF) does not recommend screening of hypothyroidism among asymptomatic non-pregnant adults.[16,17] The American Academy of Family Physicians also support the USPSTF recommendations.[18] In contrast, the American Thyroid Association (ATA) and the American Association of Clinical Endocrinologists (AACE) recommends that screening for hypothyroidism should be considered in patients age over 60, and that "aggressive case finding" should be considered in those at increased risk for hypothyroidism.[15] Furthermore, the American College of Cardiology and American Heart Association recommends thyroid function screening tests in patients with newly diagnosed heart failure, which may pertain to a large proportion of CKD patients.[39,40] Our study adds to the growing literature of the relationship between thyroid status and kidney function and may support screening of certain populations such as those with CKD. Given our findings, the attenuation of hypothyroid status or treatment of hypothyroidism may potentially impact renal function and CKD risk.

Our study has several potential limitations that may confound the interpretation of our findings. First, the cross-sectional design limits our ability to draw conclusions regarding the directionality between hypothyroidism and CKD. Our findings may be affected by selection bias in which individuals with a higher pre-test probability of thyroid and kidney dysfunction were more likely to undergo laboratory testing by their providers. Second, we used eGFR as our sole criteria for ascertaining CKD due to the lack of reliable information on other kidney disease markers (i.e., albuminuria, proteinuria). Third, our study was limited to those ages 55 and older, and thus we cannot generalize our findings to younger patients. Finally, thyroid status was designated based on a single TSH value without a free T4 value and a further confirmation of elevated TSH. TSH may be prone to fluctuations and/or individuals may have had transient hypothyroid states which may not be clinically relevant. Confirmation of hypothyroidism with additional thyroid function testing would be important to avoid potential overtreatment.

Despite these limitations, our study is one of the largest diverse populations within a real-world clinical environment examining the association between thyroid disease and CKD. Although our study population is of older age, CKD is disproportionately greater among older individuals, and the relevance of our findings likely remain largely significant and may even support the ATA/AACE recommendations for aggressive case finding among those age over 60 years of age.[15] In addition, while unable to take into account markers of kidney damage (i.e., albuminuria, proteinuria), we utilized a rigorous approach in ascertaining cases of CKD which only examined outpatient measurements and required at least 2 eGFR values separated by at least 90 days. Most importantly, our granular distinction of those with hypothyroid versus attenuated-hypothyroid status among those with hypothyroidism allowed us to identify a dose dependent relationship between thyroid status and CKD.

In conclusion, we observed that CKD was associated with hypothyroidism among individuals from a large diverse real-world population. Our findings also suggested a dose dependent relationship as those with hypothyroid status more than treated/attenuated hypothyroid patients had a stronger association with CKD. Future and more definitive studies are needed to examine whether correction of confirmed hypothyroidism with thyroid hormone replacement may ultimately improve kidney outcomes.

Author contributions

Acquisition, analysis or interpretation of data: Bonnie H. Li, Cheng-Wei Huang, Connie M. Rhee, John J. Sim.
Administrative, technical, or material support: Steven J. Jacobsen.
Critical revision of the manuscript for important intellectual content: Steven J. Jacobsen, Kristi Reynolds, Bonnie H. Li.
Data analysis: Bonnie H. Li.
Drafting of the manuscript: Cheng-Wei Huang, John J. Sim, Connie M. Rhee.
Statistical analysis: Bonnie H. Li.
Study concept and design: Cheng-Wei Huang, John J. Sim, Connie M. Rhee.
Study supervision: John J. Sim, Connie M. Rhee.
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