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# Thyroid Status and Death Risk in U.S. Veterans With Chronic Kidney Disease

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## Abstract

**Objective—**Given that non-dialysis dependent chronic kidney disease (NDD-CKD) patients have a disproportionately higher prevalence of hypothyroidism compared to their non-CKD counterparts, we sought to determine the association between thyroid status, defined by serum thyrotropin (TSH) levels, and mortality among a national cohort of NDD-CKD patients.

**Patients and Methods—**Among 227,422 US veterans with Stage 3 NDD-CKD with ≥1 TSH measurement(s) during 10/1/2004-9/30/12, we first examined the association of thyroid status, defined by TSH categories of <0.5, 0.5-5.0 (euthyroidism), and >5.0mIU/L, with all-cause mortality. We then evaluated six granular TSH categories: <0.1, 0.1-<0.5, 0.5-<3.0, 3.0-5.0, >5.0-10.0, >10.0mIU/L. We concurrently examined thyroid status, thyroid-modulating therapy, and mortality in sensitivity analyses.

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**Results—**In expanded case-mix Cox analyses, compared to euthyroidism, baseline and time-dependent TSH levels >5.0mIU/L were associated with higher mortality (adjusted HRs [aHRs] [95%CI] 1.19 [1.15-1.24] and 1.23 [1.19-1.28], respectively), as were baseline and time-dependent TSH <0.5mIU/L (aHRs [95%CI] 1.18 [1.15-1.22] and 1.41 [1.37-1.45]). Granular examination of thyroid status showed that incrementally higher TSH ≥3.0mIU/L were associated with increasingly higher mortality in baseline and time-dependent analyses, and TSH categories <0.5mIU/L were associated with higher mortality (reference: 0.5-<3.0mIU/L) in baseline analyses. In time-dependent analyses, untreated and undertreated hypothyroidism and untreated hyperthyroidism were associated with higher mortality (reference: spontaneous euthyroidism), whereas hypothyroidism treated-to-target showed lower mortality.

**Conclusion—**Among US veterans with NDD-CKD, high-normal TSH (≥3.0mIU/L) and lower TSH (<0.5mIU/L) levels were associated with higher death risk. Interventional studies identifying the target TSH range associated with the greatest survival in NDD-CKD patients are warranted.

### Keywords

Thyroid; thyrotropin; hypothyroidism; mortality; chronic kidney disease

## Introduction

Thyroid dysfunction is a highly prevalent yet under-recognized endocrine complication affecting a large proportion of chronic kidney disease (CKD) patients.[1,2] Several large population-based studies show that hypothyroidism is increasingly more common with incrementally impaired kidney function.[3-7] Data from 14,623 participants in the Third National Health and Nutrition Examination Survey has shown that the prevalence of hypothyroidism was 5.4%, 10.9%, 20.4%, 23.0%, and 23.1% among those with estimated glomerular filtration rates (eGFRs) of ≥90, 60-89, 45-59, 30-44, and <30ml/min/1.73m$^2$, respectively.[5] More recently, among a large national cohort of 461,607 US veterans with Stage 3-5 CKD, for every 10ml/min/1.73m$^2$ decrement in eGFR, there was an 18% higher likelihood of hypothyroidism.[6] While there are comparatively fewer reports in end-stage renal disease (ESRD) patients, a similarly high prevalence (~22%) of hypothyroidism has been observed in large dialysis cohorts.[8,9]

In the general population, adverse cardiovascular sequelae may result from untreated hypothyroidism (e.g., altered cardiac structure and function, endothelial dysfunction, dyslipidemia, accelerated atherosclerosis, electrophysiologic changes[10-13]) as well as with hyperthyroidism (e.g., atrial fibrillation, heart failure, coronary ischemia[12,14]). Hence, this high burden of thyroid dysfunction may have an important bearing upon the survival of kidney disease patients, who suffer from disproportionately high cardiovascular death risk (~40% of deaths[15,16]). Indeed, a growing body of evidence shows that hypothyroidism, defined by elevated serum thyrotropin (TSH) levels as the most sensitive and specific clinical goal standard of thyroid function assessment,[17-19] is associated with higher mortality in some,[8,9,20,21] but not all,[22] studies of the dialysis population. Recent data have also corroborated a link between hyperthyroidism and sudden cardiac death among hemodialysis patients from the *Die Deutsche Diabetes Dialyse Studie* (4D Trial),[22] and with all-cause mortality in a national peritoneal dialysis cohort.[9] However, little is known about the

association between thyroid status and mortality risk in CKD patients who are non-dialysis dependent (NDD).

To address this knowledge gap, we conducted a study examining the relationship between thyroid status and mortality risk among a large longitudinal cohort of US veterans with Stage 3 CKD and repeated measures of serum TSH over time. We hypothesized that both higher and lower TSH levels were independently associated with higher mortality risk in this nationally representative NDD-CKD cohort. Based on prior studies of thyroid status and mortality in the dialysis population,[8,20] we were also specifically interested in examining the TSH threshold of ≥3.0mIU/L as the level above which higher mortality is observed in NDD-CKD patients.

## Methods

### Source Cohort

We conducted a historical cohort study using data from the *"Racial and Cardiovascular Risk Anomalies in CKD" (RCAV)* study, constructed to examine US veterans with incident CKD who underwent care within the Veterans Affairs (VA) healthcare system over the period of October 1, 2004 to September 30, 2012.[23-26] Patients were included provided that they underwent at least one TSH measure anytime during the study period; had the requisite covariates needed to calculate eGFR (e.g., age, race, serum creatinine) within one year of study entry (i.e., date of the baseline TSH); and had Stage 3 CKD (eGFR 30-<60ml/min/1.73m$^2$) at study entry. Patients were excluded if they were receiving dialysis at the time of study entry; had an improbable TSH level (i.e., 0mIU/L); or had an implausible follow-up time value. The study was approved by the Institutional Review Committees of the Memphis and Tibor Rubin VA Medical Centers.

### Exposure Ascertainment

The exposure of interest was thyroid status defined by serum TSH concentration (irrespective of treatment status). In primary analyses, we examined thyroid status categorized as TSH levels of >5.0, 0.5-5.0, and <0.5mIU/L (based on thresholds used in the general population for ascertainment of hypothyroidism, euthyroidism, and hyperthyroidism, respectively).[8,9,17] In secondary analyses, we examined thyroid status using more granular categorizations of TSH, defined according to the usual TSH ranges for these designations: overt-hypothyroid (>10.0mIU/L), subclinical-hypothyroid (>5.0-10.0mIU/L), high-normal (3.0-5.0mIU/L), low- normal (0.5-<3.0mIU/L), subclinical-hyperthyroid (0.1-<0.5mIU/L), and overt-hyperthyroid (<0.1mIU/L) ranges.[8,9,20] We were specifically interested in the TSH threshold of ≥3.0mIU/L as the level above which higher mortality may be observed.[8,20] We also examined TSH as a continuous predictor of mortality using restricted cubic spline analyses with knots defined at the 33$^{rd}$ and 66$^{th}$ percentiles of observed TSH values.

We first examined the association between *baseline thyroid status* and all-cause mortality in order to ascertain *long-term* associations of thyroid status with death risk.[27] As underlying illness may influence serum TSH levels in the absence of true thyroid functional disease while also increasing patients' risk of death, we conducted two types of sensitivity analyses

of baseline thyroid status and mortality risk: (1) analyses which included a 30-day lag period between the date of baseline TSH measurement and start of follow-up time to minimize bias from reverse causation,[20] and (2) analyses which examined the association of incident hypothyroidism and incident hyperthyroidism (defined as those who had a baseline TSH level that was within reference range [0.5-5.0mIU/L] and had second TSH level was >5.0mIU/L and <0.5mIU/L, respectively) with mortality.

We then examined the association between *time-dependent thyroid status* and all-cause mortality, in which thyroid status was time-updated with repeated TSH measures in order to ascertain *short-term* associations of thyroid status with death risk, and to account for changes in thyroid status over time.[27] The median (IQR) and minimum-maximum number of TSH measurements contributed by each patient was 4 (2, 6) and 1-54, respectively.

To determine the impact of thyroid-modulating therapy on the association of thyroid status with mortality, we compared death risk across the following categories that concurrently considered patients' TSH levels and medication status: hypothyroid overtreated (*TSH <0.5mIU/L, on thyroid hormone replacement*), hypothyroid untreated (*TSH >5.0mIU/L, not on thyroid hormone replacement*), hypothyroid undertreated (*TSH >5.0mIU/L, on thyroid hormone replacement*), hypothyroid treated-to-target (*TSH 0.5-5.0mIU/L, on thyroid hormone replacement*), spontaneously euthyroid (*TSH 0.5-5.0mIU/L, not on thyroid hormone replacement or anti-thyroid medication*), hyperthyroid undertreated (*TSH <0.5mIU/L, on anti-thyroid medication*), hyperthyroid untreated (*TSH <0.5mIU/L, not on anti-thyroid medication*), and hyperthyroid overtreated (*TSH >5.0mIU/L, on anti-thyroid medication*). Serum TSH data were obtained from the Decision Support System National Data Extracts (DSS-NDE) Laboratory Results file.[28] Medication data were obtained from VA pharmacy dispensation records.[29]

## Outcome Ascertainment

Our outcome of interest was all-cause mortality. Patients were followed for outcomes starting the day after TSH measurement. Patients were censored for kidney transplantation, loss to follow-up, or the last date of available follow-up data (July 26, 2013), whichever occurred first. All-cause mortality data, censoring events, and associated dates were obtained from VA Vital Status File, which has been observed to have a sensitivity and specificity of 98.3% and 99.8%, respectively, in comparison to the National Death Index.[30]

## Socio-demographic, Comorbidity, Medication, and Laboratory Covariates

Patients' baseline socio-demographic information (age, sex, race, ethnicity) was obtained from the VA Corporate Data Warehouse and from Medicare through the VA-Medicare data merge project[31] as previously described.[23-26] Information about comorbidities was extracted from the VA Inpatient and Outpatient Medical SAS datasets using ICD-9 diagnostic and procedure codes and Current Procedural Terminology codes.[32] Charlson Comorbidity Index (CCI) scores were estimated using the Deyo modification for administrative datasets without including kidney disease.[33] Body mass index data were obtained from the VA Vital Status file. Laboratory data except serum creatinine were obtained from the DSS-NDE Laboratory Results files.[28] VA Corporate Data Warehouse LabChem data files were used to extract

serum creatinine data.[34] Using serum creatinine and demographic data, eGFR was calculated using the Chronic Kidney Disease Epidemiology Collaboration equation.[35]

## Statistical Analyses

We estimated the association between thyroid status and mortality using Cox proportional hazard models with five hierarchical levels of covariate adjustment. In time- dependent analyses, all laboratory data were examined as time-dependent covariates:

1. Unadjusted model: Included serum TSH level as the primary exposure of interest;
2. Case-mix model: Adjusted for age, sex, race, and ethnicity;
3. Expanded case-mix model: Adjusted for covariates in the case-mix model, as well as diabetes, congestive heart failure (CHF), cardiovascular disease (CVD), hypertension, hyperlipidemia, and CCI score;
4. Expanded case-mix+laboratory model, also known as adjustment for malnutrition- inflammation-cachexia syndrome (MICS) covariates: Adjusted for covariates in the expanded case-mix model, as well as eGFR, serum albumin, hemoglobin, cholesterol, triglycerides, and low-density lipoprotein (LDL);
5. Expanded case-mix+laboratory+thyroid medication model: Adjusted for covariates in the expanded case-mix+laboratory model, as well as thyroid hormone supplementation and anti-thyroid medication use.

We *a priori* defined the expanded case-mix adjusted model as our preferred model, which included core socio-demographic measures and other confounders of the association between thyroid status and mortality. While there were no missing data for covariates in the case-mix and expanded case-mix models (e.g., age, sex, race, ethnicity, comorbidities), there were varying degrees of missing data for laboratory variables including albumin (17.3%), hemoglobin (15.4%), triglycerides (13.7%), cholesterol (13.6%), and LDL (18.9%; proportions shown represent missing baseline data). Hence, further adjustment for potential confounders in expanded case-mix+laboratory and expanded case-mix+laboratory+thyroid medication models (which have the potential for inherent selection bias due to missing data) were conducted as sensitivity analyses. In these analyses, missing data were handled using multiple imputation.

To address differential quality of care as a potential confounder of thyroid status—mortality associations, we conducted a series of sensitivity analyses that incrementally adjusted for proxies of provider attentiveness/adherence with health care recommendations and patient medical compliance, in addition to covariates in the expanded case-mix+laboratory+ thyroid medication model: (1) Angiotensin converting enzyme inhibitor (ACE-i), angiotensin receptor blocker (ARB), or statin prescription within one year of study entry, (2) receipt of influenza vaccination within one year of study entry, or (3) patient's history of non-compliance with medical treatment ascertained by ICD-9 code V15.81.

We additionally conducted subgroup analyses of thyroid status (categorized as TSH levels >5.0, 0.5-5.0 [euthyroid], and <0.5mIU/L) 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 SAS version 9.4 (SAS Institute Inc., Cary, NC), Stata version 14 (Stata Corporation, College Station, TX), and SigmaPlot Version 12.5 (Systat Software, San Jose, CA).

## Results

### Study Population

Among 227,426 patients who met eligibility criteria (eFigure 1), 6.4%, 90.0%, and 3.4% of patients had baseline TSH levels of >5.0, 0.5-5.0 (euthyroid), and <0.5mIU/L, respectively. The mean ± SD, median (IQR), and minimum-maximum of observed baseline TSH values were 2.7 ± 6.7, 1.9 (1.2, 2.8), and 0.001-531.5mIU/L, respectively. Compared to patients whose baseline TSH levels were <0.5mIU/L or in the euthyroid range, those with TSH levels >5.0mIU/L were older, more likely to be non-Hispanic White, and less likely to be non-Hispanic Black; were more likely to have cardiovascular disease and less likely to have hypertension; were more likely to have higher total cholesterol and triglyceride levels; and were less likely to be prescribed an ACE-i or ARB within one year of study entry (Table 1). Compared to patients who were euthyroid at baseline, those who were hyperthyroid and hypothyroid were also more likely to have CHF and less likely to have hyperlipidemia. Baseline characteristics of patients categorized by finer gradations of TSH are shown in eTable 1.

**Thyroid Status and Mortality—**Patients contributed a total of 1,134,837 patient-years of follow-up during which time 67,706 all-cause deaths occurred. Median (IQR) at-risk time was 65 (38, 83) months. In analyses of baseline thyroid status adjusted for expanded case-mix covariates, TSH levels >5.0 and <0.5mIU/L were each associated with higher mortality risk (reference: euthyroidism): adjusted HRs (aHRs) (95%CI) 1.19 (1.15-1.24) and 1.18 (1.15-1.22), respectively (Figure 1A and eTable 2). These associations were mildly attenuated after further adjustment for expanded case- mix+laboratory and expanded case-mix+laboratory+thyroid medication covariates, but remained statistically significant. Similarly, in analyses of time-dependent thyroid status, TSH levels >5.0 and <0.5mIU/L were each associated with higher mortality risk across all levels of adjustment (Figure 1B and eTable 2).

In sensitivity analyses of baseline TSH that included a 30-day lag period, we observed a robust association of TSH levels >5.0 and <0.5mIU/L with higher mortality risk in expanded case-mix models (reference: euthyroidism): aHRs (95%CI) 1.17 (1.13-1.22) and 1.17 (1.14-1.21), respectively (eFigure 2A and eTable 3). In a subcohort of patients who had a baseline TSH in euthyroid range and a subsequent TSH measurement (N=161,802), we identified 6,027 and 3,445 patients who had incident hypothyroidism and hyperthyroidism, respectively. Sensitivity analyses showed that incident hypothyroidism and incident hyperthyroidism were each associated with higher mortality risk in expanded case-mix models (reference: euthyroidism): aHRs (95%CI) 1.27 (1.20-1.35) and 1.22 (1.16-1.27), respectively (eTable 4).

**Granular Thyrotropin Levels and Mortality—**A continuum of TSH increase and reduction from the reference range is recognized, with early or subclinical disease defined by an abnormal TSH with a reference range serum free thyroxine (FT4) measurement, which were not available for our study. In analyses that more granularly examined baseline TSH levels, we found that TSH categories ≥3.0mIU/L were associated with incrementally higher death risk in expanded case-mix models (reference: low- normal TSH): aHRs (95%CI) 1.04 (1.02-1.06), 1.15 (1.11-1.18), and 1.38 (1.31-1.46) for TSH levels in the upper-normal, subclinical-hypothyroid range, and overt-hypothyroid range, respectively (eFigure 3A and eTable 5). These patterns of association persisted in analyses adjusted for expanded case-mix+laboratory and expanded case-mix+laboratory+thyroid medication covariates. We also observed that TSH categories <0.5mIU/L were associated with higher mortality risk in expanded case-mix analyses: aHRs (95%CI) 1.21 (1.16-1.26) and 1.13 (1.02-1.25) for TSH levels in the subclinical-hyperthyroid and overt-hyperthyroid range. Associations between subclinical-hyperthyroid range TSH levels and mortality persisted in expanded case-mix+laboratory and expanded case-mix+laboratory+thyroid medication analyses. Similar associations were observed in analyses of baseline TSH that included a 30-day lag period (eFigure 2B and eTable 3).

In analyses of time-dependent TSH levels adjusted for expanded case-mix covariates, we analogously observed that TSH categories ≥3.0mIU/L were associated with increasingly higher mortality (reference: low-normal TSH): aHRs (95%CI) 1.05 (1.03-1.07), 1.34 (1.30-1.38), and 1.87 (1.76-1.99) for TSH levels in the upper-normal, subclinical-hypothyroid range, and overt- hypothyroid range, respectively (eFigure 3B and eTable 5). Associations remained significant in expanded case-mix+laboratory and expanded case-mix +laboratory+thyroid medication adjusted analyses. We similarly observed that TSH levels in the subclinical-hyperthyroid and overt-hyperthyroid range were associated with higher mortality: aHRs (95%CI) 1.27 (1.22-1.32) and 1.13 (1.02-1.25), respectively. Associations between subclinical-hyperthyroid and overt- hyperthyroid range TSH levels and mortality persisted in expanded case-mix+laboratory+thyroid medication analyses (eFigure 3B and eTable 5).

In sensitivity analyses of baseline and time-dependent TSH as continuous predictors of mortality using restricted cubic splines adjusted for expanded case-mix covariates, we observed a U-shaped association between TSH level and mortality, with a nadir of risk observed at TSH levels ~1.7-2.1mIU/L (Figure 2).

**Adjustment for Quality of Care Indicators—**To account differential quality of care as a potential confounder of thyroid status— mortality associations, in sensitivity analyses we also examined several models that incrementally adjusted for proxies of provider attentiveness/adherence with health care recommendations and patient medical compliance, in addition to expanded case-mix+ laboratory+thyroid medication covariates. Similar to expanded case-mix+laboratory+thyroid medication models, we observed that baseline and time-dependent TSH levels >5.0 and <0.5mIU/L were each associated with higher mortality risk in analyses that incrementally adjusted for ACEi/ARB or statin use, receipt of the influenza vaccination, and history of noncompliance (eTable 6).

Following incremental adjustment for these quality of care indicators, we also found that associations of baseline TSH levels in the upper-normal, subclinical-hypothyroid, overt-hypothyroid, and subclinical hyperthyroid ranges with mortality risk remained robust (eTable 7). Following incremental adjustment for ACEi/ARB or statin use, receipt of the influenza vaccination, and history of noncompliance, time-dependent TSH levels in the upper-normal, subclinical-hypothyroid, overt-hypothyroid, and subclinical hyperthyroid ranges, as well as in the overt hyperthyroid range, were associated with higher mortality risk, similar to expanded case-mix+laboratory+thyroid medication covariates.

**Thyroid Status and Mortality Across Clinically Relevant Subgroups—**We also examined the association between thyroid status (categorized as TSH >5.0, 0.5- 5.0 [euthyroidism], and <0.5mIU/L; reference: euthyroidism) and mortality across clinically relevant subgroups. In baseline analyses adjusted for expanded case-mix covariates, we observed that hypothyroidism was associated with higher mortality across all subgroups except those who were female, and that hyperthyroidism was associated with higher mortality across all subgroups (Figure 3A and eTable 8). Interaction tests demonstrated that differences in estimates of the thyroid function—mortality association across subcategories were statistically significant for subgroups of underlying cardiovascular disease and body mass index (BMI) (*p-interactions=.03* and *.05*, respectively; Figure 3A). In these analyses, we observed that point estimates of the hypothyroidism—mortality association were stronger among those without vs. with underlying cardiovascular disease and higher (≥25kg/$m^2$) vs. lower BMI (<25kg/$m^2$), and that stronger point estimates of the hyperthyroidism—mortality association were also observed among those with higher vs. lower BMI.

In time-dependent analyses, we similarly observed that hypothyroidism was associated with higher mortality across all subgroups except those who were female, and that hyperthyroidism was associated with higher mortality across all subgroups (Figure 3B and eTable 9). Interaction tests demonstrated that differences in estimates of the thyroid function — mortality association across subcategories were statistically significant for subgroups of age, race, underlying CHF, and BMI *(p-interactions=<.001, <.001, .05*, and *.04*, respectively; Figure 3B), with stronger point estimates of hypothyroidism—mortality among those of younger (<60 years) vs. older (≥60 years) age, Black vs. non-Black race, with vs. without CHF, and higher vs. lower BMI, while stronger point estimates of the hyperthyroidism—mortality association were observed among those of younger vs. older age, non-Black vs. Black race, with vs. without CHF, and higher vs. lower BMI.

**Thyroid Status, Medication Use, and Mortality—**In the overall cohort, 6.0% and <0.1% of patients were prescribed thyroid hormone supplementation or anti-thyroid medication at the time of study entry. In baseline analyses adjusted for expanded case-mix covariates, we observed that presumed untreated and undertreated hypothyroidism as well as untreated hyperthyroidism were associated with higher mortality risk (reference: spontaneous euthyroidism): aHRs (95% CI) 1.20 (1.16-1.24), 1.13 (1.07-1.20), and 1.23 (1.18-1.28), respectively (Figures 4A–B and eTable 10). In time- dependent analyses, the same patterns of association were observed. In addition, hypothyroidism treated-to-target

TSH range was associated with lower mortality risk (aHR [95%CI] 0.88 [0.85-0.91]) (Figures 4C–D and eTable 10).

## Discussion

To our knowledge, this is the first study that has examined the association between thyroid status defined by repeated measures of serum TSH with mortality in NDD-CKD patients. Among a large national cohort of US veterans with Stage 3 CKD, granular examination of thyroid status showed that TSH levels in the high-normal (TSH ≥3.0mIU/L) and hyperthyroid ranges (TSH <0.5mIU/L) were independently associated with higher mortality risk. These associations persisted across multiple secondary and sensitivity analyses that considered baseline and time-dependent (i.e., repeated) TSH measures (as a proxy of long-term and short-term associations, respectively); incrementally adjusted for potential confounders of the thyroid status—mortality associations across multivariable models, including quality of care indicators (e.g., ACEi/ARB or statin use, receipt of the influenza vaccination, history of noncompliance); and examined multiple clinically relevant subgroups. In sensitivity analyses that identified cases of incident thyroid disease, we also observed that TSH levels in the hypothyroid and hyperthyroid range were each associated with higher mortality risk.

Our study also adds new knowledge to the field regarding the impact of thyroid- modulating therapy upon the survival of kidney disease patients. While United States Renal Data System data show that levothyroxine is one of the most commonly prescribed medications among NDD-CKD and ESRD Medicare Part D beneficiaries,[36] there have been a paucity of studies examining the efficacy and safety of thyroid hormone replacement therapy in these populations. In a study of 2,715 dialysis patients whose TSH levels and medication status were concurrently examined at study entry, we found patients who were presumed to be hypothyroid treated-to-target had similar mortality vs. patients who were spontaneously euthyroid, whereas those with undertreated or untreated hypothyroidism had higher mortality risk.[20] While these limited data suggest benefit, thyroid hormone supplementation is a therapy that carries risk, given its 1) narrow toxic-to-therapeutic window,[37] 2) augmentation of protein catabolism and protein-energy wasting[38] (i.e., one of the strongest death predictors in advanced CKD patients[39]), and 3) potential to precipitate adverse cardiovascular sequelae (e.g., atrial fibrillation, angina) with overtreatment.[18,40] Using the national VA database with exceptional capture of prescription dispensation data over time,[29] in both baseline and time-dependent analyses we found that untreated and undertreated hypothyroidism and untreated hyperthyroidism were each associated with higher mortality risk compared to spontaneous euthyroidism, whereas hypothyroidism treated-to-target (i.e., TSH 0.5-5.0mIU/L based on general population thresholds[17]) had similar to slightly lower mortality risk. In time-dependent analyses, there also appeared to be a trend between overtreated hypothyroidism and lower mortality risk, although only marginally decreased. While mild medication-induced thyrotoxicosis may be tolerated in the short-term in particular patient groups (i.e., younger patients), further studies are needed to determine the long- term safety and effectiveness of thyroid-modulating therapy and specific TSH treatment targets.

As another noteworthy finding, our categorical analyses showed that incrementally higher TSH levels even in the high-normal range (TSH ≥3.0mIU/L) were associated with increasingly higher mortality risk. Several other studies have similarly shown that TSH levels exceeding 3.0mIU/L are associated with higher mortality in dialysis patients.[8,20] Even in the general population, there remains considerable controversy regarding the optimal upper limit of the target TSH range. While some experts recommend a therapeutic TSH upper limit of 2.5-3.0mIU/L,[19,41,42] others favor using upper TSH laboratory reference range values (~5.0mIU/L).[43,44] Given the potential risks of under- and overtreatment, rigorous prospective studies are warranted determine the optimal TSH target range in the CKD and ESRD populations.

While thyroid dysfunction was linked with higher death risk across almost all subgroups, it bears mention that stronger hypothyroidism—mortality associations were particularly observed among subgroups of younger vs. older age, Black vs. non-Black race, and those with vs. without underlying CHF, corroborating emerging data in the general population.[45] As some experts advise that the “normal” range of may differ according to age and race/ethnicity,[46] future studies are needed to more precisely define the ideal TSH thresholds among these CKD subgroups. Indeed, the increase in the upper reference for serum TSH with age may be especially relevant in the older NDD-CKD population, as most now recommend targeting a higher TSH for the elderly general population on levothyroxine therapy.[44] Furthermore, prior studies in the general population have suggested that those with CHF may have lower reserve with which to tolerate hemodynamic, volume, and electrophysiologic changes associated with hypothyroidism. Hence, NDD-CKD patients with structural heart disease may be particularly vulnerable to the ill effects of hypothyroidism, and future studies are needed to determine the specific mechanistic pathways linking thyroid perturbations and death in this population.

The strengths of our study include its examination of a large national cohort of NDD- CKD patients with comprehensive availability of detailed patient-level information, including longitudinal laboratory and prescription data; a stable study population to examine the long-term and short-term associations of thyroid status, thyroid-modulating therapy, and outcomes; and reduced confounding by differential health care access. Several limitations of our study should be acknowledged. First, the indications for TSH testing in this cohort, a requirement for inclusion in the study, are unknown. However, this inclusion criterion was required of all patients irrespective of underlying thyroid status and thus should not impair the study’s internal validity. Furthermore, that the vast majority of our source population (82.3% of >3.5million patients) underwent TSH testing provides further reassurance regarding the study’s external validity. Second, the categories of thyroid status are generally classified based on serum TSH and FT4 measurements. Given the sparsity of concurrent FT4 and free triiodothyronine (T3) measurements and their unclear reliability in advanced CKD (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),[1,2,47-49] we elected to define thyroid status based on TSH levels only. Although some aberrations of TSH have been described in the context of CKD,[50,51] 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 critically illness states[1,2,52]), and serum TSH has been strongly associated with outcomes in our previous studies of dialysis patients,.[8,9,20,21] Additionally, we observed persistent associations between TSH alterations and mortality in sensitivity analyses that incorporated a 30- day lag period and restricted analyses to incident cases of thyroid disease, hence excluding patients who died immediately after TSH measurement to minimize risk of observing a reverse- causal association (i.e., severe illness may lead to TSH alterations as well as heightened mortality risk). Third, as our analyses included patients who were both incident (i.e., treatment- naïve) and prevalent (i.e., existing) users of thyroid hormone supplementation and anti-thyroid medications, we cannot exclude potential bias towards a protective effect of thyroid-modulating therapy (i.e., patients receiving treatment at study entry may have been healthier than those who stopped or died using treatment prior to study entry due to adverse effects).[53] Fourth, given the retrospective nature of the study, we are not able to determine whether differential quality of care by providers or non-compliance with medical treatment may be a potential confounder of aberrant thyroid status and death risk. However, it should be noted that we observed robust thyroid status—mortality associations following incremental adjustment for proxies of quality of care. Lastly, as with all observational studies, we cannot exclude the possibility of residual confounding, and our findings do not confirm a causal relationship between thyroid status, thyroid modulating therapy, and mortality risk.

## Conclusion

In conclusion, our study has found that higher TSH levels even in the high-normal range (≥3.0mIU/L) and lower TSH levels <0.5mIU/L were independently associated with higher mortality risk in a national cohort of NDD-CKD patients. We also observed that untreated and undertreated hypothyroidism and hyperthyroidism were associated with higher mortality compared with spontaneous euthyroidism, whereas hypothyroidism treated-to-target was associated with similar to slightly improved survival. At this time, rigorous prospective studies are needed to determine the precise optimal TSH range in NDD-CKD patients, and whether treatment to these targets ameliorates mortality risk in this population.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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## List of Abbreviations

| | |
|---|---|
| **4D Trial** | *Die Deutsche Diabetes Dialyse Studie* (4D Trial) |
| **ACEi** | angiotensin converting enzyme inhibitor |
| **ARB** | angiotensin receptor blocker |
| **BMI** | body mass index |
| **CCI** | Charlson Comorbidity Index |
| **CHF** | congestive heart failure |
| **CKD** | chronic kidney disease |
| **CVD** | cerebrovascular disease |
| **DSS-NDE** | Decision Support System National Data Extracts |
| **eGFR** | estimated glomerular filtration rate |
| **ESRD** | end-stage renal disease |
| **FT4** | free thyroxine |
| **LDL** | low-density lipoprotein |
| **MICS** | malnutrition-inflammation-cachexia syndrome |
| **NDD-CKD** | non-dialysis dependent chronic kidney disease |
| **RCAV** | *Racial and Cardiovascular Risk Anomalies in Chronic Kidney Disease* |
| **TSH** | thyrotropin |
| **T3** | triiodothyronine |
| **VA** | Veterans Affairs |

## References

1. Rhee CM. The interaction between thyroid and kidney disease: an overview of the evidence. Curr Opin Endocrinol Diabetes Obes. 2016; 23(5):407–415. [PubMed: 27428519]
2. Rhee CM, Brent GA, Kovesdy CP, et al. Thyroid functional disease: an under-recognized cardiovascular risk factor in kidney disease patients. Nephrol Dial Transplant. 2015; 30(5):724–737. [PubMed: 24574542]
3. Carrero JJ, Qureshi AR, Axelsson J, et al. Clinical and biochemical implications of low thyroid hormone levels (total and free forms) in euthyroid patients with chronic kidney disease. J Intern Med. 2007; 262(6):690–701. [PubMed: 17908160]
4. Chonchol M, Lippi G, Salvagno G, Zoppini G, Muggeo M, Targher G. Prevalence of subclinical hypothyroidism in patients with chronic kidney disease. Clin J Am Soc Nephrol. 2008; 3(5):1296–1300. [PubMed: 18550654]
5. Lo JC, Chertow GM, Go AS, Hsu CY. Increased prevalence of subclinical and clinical hypothyroidism in persons with chronic kidney disease. Kidney Int. 2005; 67(3):1047–1052. [PubMed: 15698444]

6. Rhee CM, Kalantar-Zadeh K, Streja E, et al. The relationship between thyroid function and estimated glomerular filtration rate in patients with chronic kidney disease. Nephrol Dial Transplant. 2015; 30(2):282–287. [PubMed: 25246335]
7. Targher G, Chonchol M, Zoppini G, et al. Prevalence of thyroid autoimmunity and subclinical hypothyroidism in persons with chronic kidney disease not requiring chronic dialysis. Clin Chem Lab Med. 2009; 47(11):1367–1371. [PubMed: 19769543]
8. Rhee CM, Kim S, Gillen DL, et al. Association of thyroid functional disease with mortality in a national cohort of incident hemodialysis patients. J Clin Endocrinol Metab. 2015; 100(4):1386–1395. [PubMed: 25632971]
9. Rhee CM, Ravel VA, Streja E, et al. Thyroid Functional Disease and Mortality in a National Peritoneal Dialysis Cohort. J Clin Endocrinol Metab. 2016; 101(11):4054–4061. [PubMed: 27525529]
10. Hak AE, Pols HA, Visser TJ, Drexhage HA, Hofman A, Witteman JC. Subclinical hypothyroidism is an independent risk factor for atherosclerosis and myocardial infarction in elderly women: the Rotterdam Study. Ann Intern Med. 2000; 132(4):270–278. [PubMed: 10681281]
11. Klein I, Danzi S. Thyroid disease and the heart. Circulation. 2007; 116(15):1725–1735. [PubMed: 17923583]
12. Klein I, Ojamaa K. Thyroid hormone and the cardiovascular system. N Engl J Med. 2001; 344(7): 501–509. [PubMed: 11172193]
13. Taddei S, Caraccio N, Virdis A, et al. Impaired endothelium-dependent vasodilatation in subclinical hypothyroidism: beneficial effect of levothyroxine therapy. J Clin Endocrinol Metab. 2003; 88(8):3731–3737. [PubMed: 12915662]
14. Gencer B, Collet TH, Virgini V, et al. Subclinical thyroid dysfunction and the risk of heart failure events: an individual participant data analysis from 6 prospective cohorts. Circulation. 2012; 126(9):1040–1049. [PubMed: 22821943]
15. US Renal Data SystemUSRDS 2016 Annual Data Report: Atlas of End-Stage Renal Disease in the United States Bethesda, MD: 2016
16. Saran R, Li Y, Robinson B, et al. US Renal Data System 2015 Annual Data Report: Epidemiology of Kidney Disease in the United States. Am J Kidney Dis. 2016; 67(3 Suppl 1):Svii, S1–305.
17. Ladenson PW. Diagnosis of Hypothyroidism In: Braverman LE, Cooper DS, eds Werner and Ingbar's The Thyroid 10th. Philadelphia, PA: Lippincott Williams and Wilkins; 2013 606611
18. Jonklaas J. Treatment of Hypothyroidism In Braverman LE, Cooper DS, eds Werner and Ingbar's The Thyroid 10th. Philadelphia, PA: Lippincott Williams and Wilkins; 2013 611628
19. Baloch Z, Carayon P, Conte-Devolx B, et al. Laboratory medicine practice guidelines. Laboratory support for the diagnosis and monitoring of thyroid disease. Thyroid. 2003; 13(1):3–126. [PubMed: 12625976]
20. Rhee CM, Alexander EK, Bhan I, Brunelli SM. Hypothyroidism and Mortality among Dialysis Patients. Clin J Am Soc Nephrol. 2013; 8(4):593–601. [PubMed: 23258793]
21. Rhee CM, You AS, Nguyen DV, et al. Thyroid Status and Mortality in a Prospective Hemodialysis Cohort. J Clin Endocrinol Metab. 2017; 102(5):1568–1577. [PubMed: 28324018]
22. Drechsler C, Schneider A, Gutjahr-Lengsfeld L, et al. Thyroid function, cardiovascular events, and mortality in diabetic hemodialysis patients. Am J Kidney Dis. 2014; 63(6):988–996. [PubMed: 24315768]
23. Kovesdy CP, Norris KC, Boulware LE, et al. Association of Race With Mortality and Cardiovascular Events in a Large Cohort of US Veterans. Circulation. 2015; 132(16):1538–1548. [PubMed: 26384521]
24. Lu JL, Molnar MZ, Naseer A, Mikkelsen MK, Kalantar-Zadeh K, Kovesdy CP. Association of age and BMI with kidney function and mortality: a cohort study. Lancet Diabetes Endocrinol. 2015; 3(9):704–714. [PubMed: 26235959]
25. Molnar MZ, Kalantar-Zadeh K, Lott EH, et al. Angiotensin-converting enzyme inhibitor, angiotensin receptor blocker use, and mortality in patients with chronic kidney disease. J Am Coll Cardiol. 2014; 63(7):650–658. [PubMed: 24269363]

26. Novak M, Mucsi I, Rhee CM, et al. Increased Risk of Incident Chronic Kidney Disease, Cardiovascular Disease, and Mortality in Patients With Diabetes With Comorbid Depression. Diabetes Care. 2016; 39(11):1940–1947. [PubMed: 27311494]
27. Dekker FW, de Mutsert R, van Dijk PC, Zoccali C, Jager KJ. Survival analysis: time- dependent effects and time-varying risk factors. Kidney Int. 2008; 74(8):994–997. [PubMed: 18633346]
28. US Department of Veterans Affairs; Health Services Research and Development Service; VA Information Resource CenterVIReC Research User Guide: VHA Decision Support System Clinical National Data Extracts 2nd. Hines, IL: VA Information Resource Center; 2009
29. US Department of Veterans Affairs; Health Services Research and Development Service; VA Information Resource CenterVIReC Research User Guide: VHA Pharmacy Prescription Data 2nd. Hines, IL: VA Information Resource Center; 2008
30. Sohn MW, Arnold N, Maynard C, Hynes DM. Accuracy and completeness of mortality data in the Department of Veterans Affairs. Popul Health Metr. 2006; 4:2. [PubMed: 16606453]
31. Stroupe KT, Tarlov E, Zhang Q, Haywood T, Owens A, Hynes DM. Use of Medicare and DOD data for improving VA race data quality. J Rehabil Res Dev. 2010; 47(8):781–795. [PubMed: 21110252]
32. US Department of Veterans Affairs; Health Services Research and Development Service; VA Information Resource CenterVIReC Research User Guide: VHA Medical SAS Datasets FY2006-2007 Hines, IL: VA Information Resource Center; 2007
33. Deyo RA, Cherkin DC, Ciol MA. Adapting a clinical comorbidity index for use with ICD-9-CM administrative databases. J Clin Epidemiol. 1992; 45(6):613–619. [PubMed: 1607900]
34. US Department of Veterans Affairs; Health Services Research and Development Service; VA Information Resource CenterVIReC Resource Guide: VA Corporate Data Warehouse Hines, IL: VA Information Resource Center; 2012
35. Levey AS, Stevens LA, Schmid CH, et al. A new equation to estimate glomerular filtration rate. Ann Intern Med. 2009; 150(9):604–612. [PubMed: 19414839]
36. US Renal Data SystemUSRDS 2012 Annual Data Report: Atlas of End-Stage Renal Disease in the United States Bethesda, MD: 2012
37. Wartofsky L. Levothyroxine: therapeutic use and regulatory issues related to bioequivalence. Expert Opin Pharmacother. 2002; 3(6):727–732. [PubMed: 12036412]
38. Lim VS. Thyroid function in patients with chronic renal failure. Am J Kidney Dis. 2001; 38(4 Suppl 1):S80–84. [PubMed: 11576928]
39. Kalantar-Zadeh K, Rhee C, Sim JJ, Stenvinkel P, Anker SD, Kovesdy CP. Why cachexia kills: examining the causality of poor outcomes in wasting conditions. J Cachexia Sarcopenia Muscle. 2013; 4(2):89–94. [PubMed: 23749718]
40. Sawin CT, Geller A, Wolf PA, et al. Low serum thyrotropin concentrations as a risk factor for atrial fibrillation in older persons. N Engl J Med. 1994; 331(19):1249–1252. [PubMed: 7935681]
41. Baskin HJ, Cobin RH, Duick DS, et al. American Association of Clinical Endocrinologists medical guidelines for clinical practice for the evaluation and treatment of hyperthyroidism and hypothyroidism. Endocr Pract. 2002; 8(6):457–469.
42. Wartofsky L, Dickey RA. The evidence for a narrower thyrotropin reference range is compelling. J Clin Endocrinol Metab. 2005; 90(9):5483–5488. [PubMed: 16148345]
43. Garber JR, Cobin RH, Gharib H, et al. Clinical practice guidelines for hypothyroidism in adults: cosponsored by the American Association of Clinical Endocrinologists and the American Thyroid Association. Thyroid. 2012; 22(12):1200–1235. [PubMed: 22954017]
44. Jonklaas J, Bianco AC, Bauer AJ, et al. Guidelines for the treatment of hypothyroidism: prepared by the american thyroid association task force on thyroid hormone replacement. Thyroid. 2014; 24(12):1670–1751. [PubMed: 25266247]
45. Rhee CM, Curhan GC, Alexander EK, Bhan I, Brunelli SM. Subclinical hypothyroidism and survival: the effects of heart failure and race. J Clin Endocrinol Metab. 2013; 98(6):2326–2336. [PubMed: 23720788]
46. Surks MI, Boucai L. Age- and race-based serum thyrotropin reference limits. J Clin Endocrinol Metab. 2010; 95(2):496–502. [PubMed: 19965925]

47. Soldin OP. Measuring serum thyroid-stimulating hormone, thyroid hormones, thyroid- directed antibodies, and transport proteins. In: Braverman LE, , Cooper DS, editorsWerner and Ingbar's The Thyroid 10th. Philadelphia, PA: Lippincott Williams and Wilkins; 2013 279297

48. Kaptein EM. Thyroid hormone metabolism and thyroid diseases in chronic renal failure. Endocr Rev. 1996; 17(1):45–63. [PubMed: 8641223]

49. Langton JE, Brent GA. Nonthyroidal illness syndrome: evaluation of thyroid function in sick patients. Endocrinol Metab Clin North Am. 2002; 31(1):159–172. [PubMed: 12055987]

50. Carrero JJ, , Stenvinkel P, , Lindholm B. Endocrine Aspects of Chronic Kidney Disease. In: Taal MW, Chertow GM, Marsden PA, Skorecki K, Yu AS, , Brenner BM, editorsTaal: Brenner and Rector's The Kidney 9th. Philadelphia, PA: Elsevier Saunders; 2012 21222137

51. Kaptein EM, LoPresti JS, Kaptein MJ. Is an isolated TSH elevation in chronic nonthyroidal illness "subclinical hypothyroidism"? J Clin Endocrinol Metab. 2014; 99(11):4015–4026. [PubMed: 25166720]

52. Wiersinga WM, , Van den Berghe G. Nonthyroidal Illness Syndrome. In: Braverman LE, , Cooper DS, editorsWerner and Ingbar's The Thyroid 10th. Philadelphia, PA: Lippincott Williams and Wilkins; 2013 203216

53. Ray WA. Evaluating medication effects outside of clinical trials: new-user designs. Am J Epidemiol. 2003; 158(9):915–920. [PubMed: 14585769]

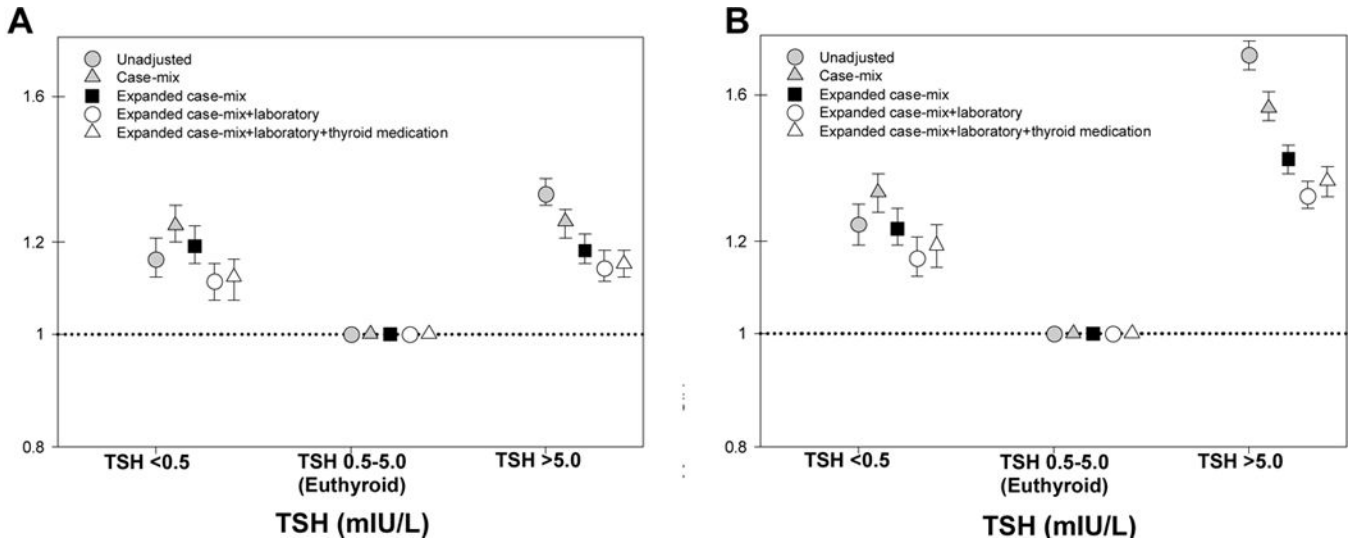


**Figure 1. Association between baseline (Panel A) and time-dependent (Panel B) thyroid status and all-cause mortality**

Unadjusted model included serum TSH level. Case-mix model adjusted for covariates in the unadjusted model, as well as age, sex, race, and ethnicity. Expanded case-mix model adjusted for covariates in the case-mix model, as well as diabetes, congestive heart failure, cardiovascular disease, hypertension, hyperlipidemia, and Charlson Comorbidity Index. Expanded case-mix+laboratory model adjusted for covariates in the expanded case-mix model, as well as estimated glomerular filtration rate, serum albumin, hemoglobin, cholesterol, triglycerides, low-density lipoprotein. Expanded case-mix+laboratory+thyroid medication model adjusted for covariates in the expanded case-mix+laboratory model, as well as thyroid hormone supplementation and anti-thyroid medication use.

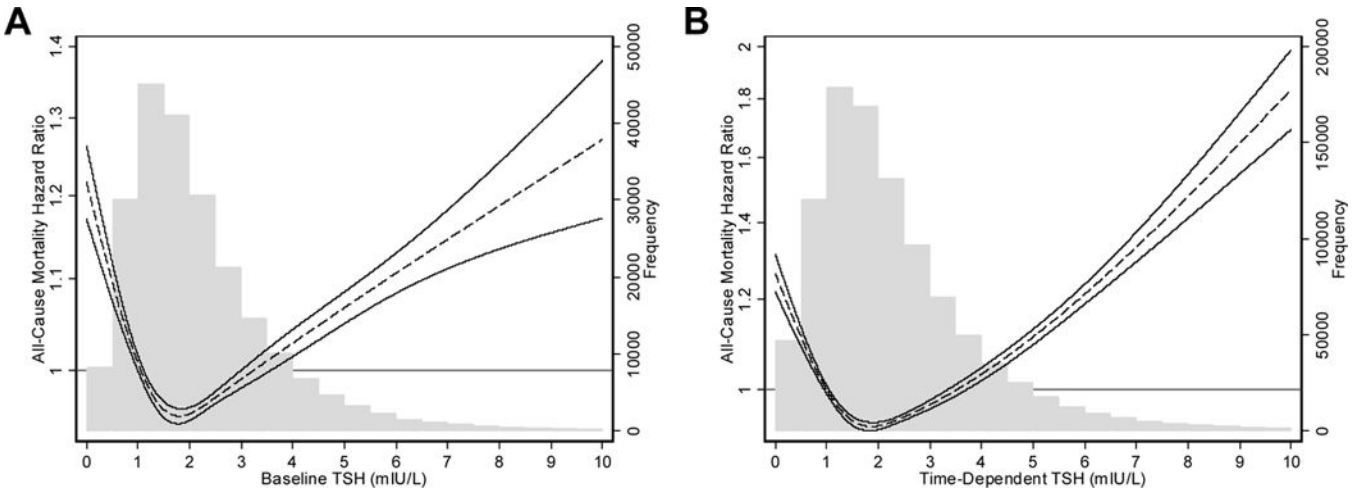


**Figure 2. Association between continuous baseline (Panel A) and time-dependent (Panel B) thyrotropin (TSH) and all-cause mortality**

Figures present hazard ratios (short-dashed line) and 95%CI's (solid lines) for TSH analyzed as a spline with knots at the 33rd and 66th percentiles of observed values (TSH levels 1.4mIU/L and 2.4mIU/L, respectively). A histogram of observed TSH values and a hazard reference ratio of 1 (dashed line) is overlaid. Analyses shown are expanded case-mix adjusted models, which included serum TSH level, age, sex, race, ethnicity, diabetes, congestive heart failure, cardiovascular disease, hypertension, hyperlipidemia, and Charlson Comorbidity Index.

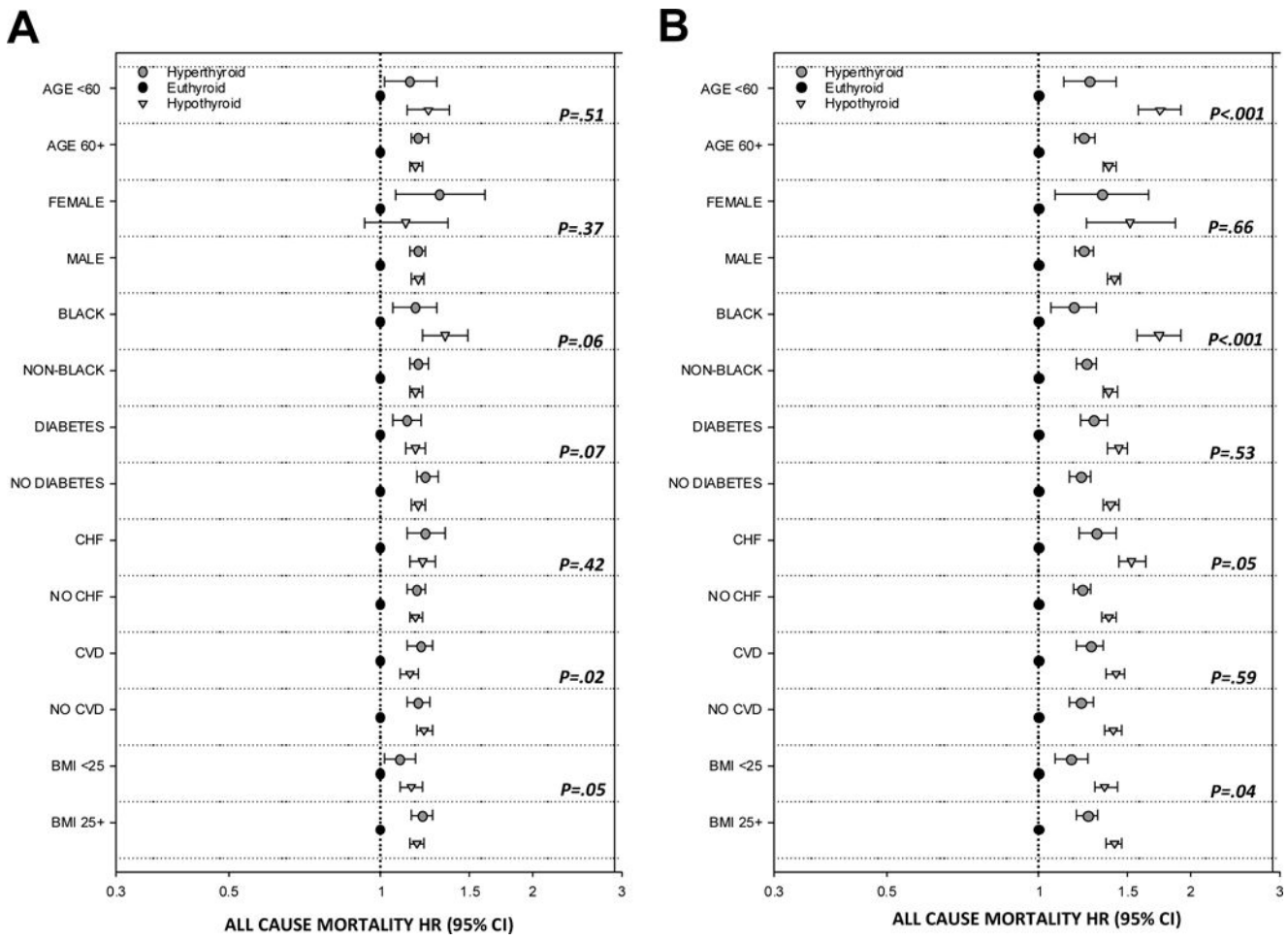


**Figure 3. Baseline (Panel A) and time-dependent (Panel B) thyroid status and all-cause mortality across clinically relevant subgroups**

*P*-values for interaction tests presented. Analyses shown are expanded case-mix adjusted models, which included serum TSH level, age, sex, race, ethnicity, diabetes, congestive heart failure, cardiovascular disease, hypertension, hyperlipidemia, and Charlson Comorbidity Index. Abbreviations: eGFR, estimated glomerular filtration rate; CHF, congestive heart failure; CVD, cardiovascular disease; BMI, body mass index.

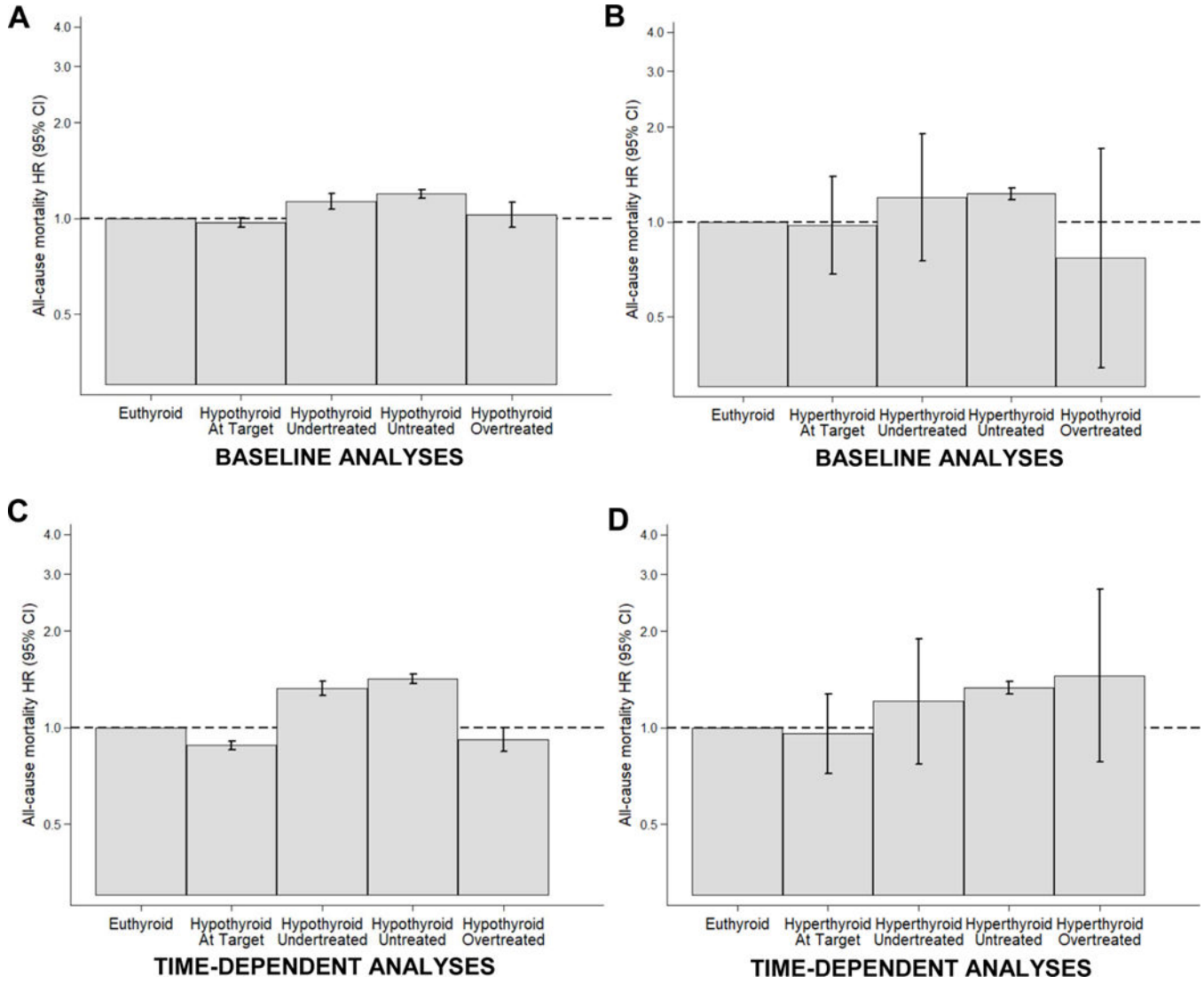


**Figure 4. Baseline (Panels A and B) and time-dependent (Panels C and D) thyroid status, thyroid medications, and all-cause mortality**

Analyses shown are expanded case-mix adjusted models, which included serum TSH level, age, sex, race, ethnicity, diabetes, congestive heart failure, cardiovascular disease, hypertension, hyperlipidemia, and Charlson Comorbidity Index.

**Table 1**

Baseline characteristics according to thyroid status defined by thyrotropin (TSH).

| | TSH (mIU/L) | | | | |
|---|---|---|---|---|---|
| | **Overall (N=227,426)** | **<0.5 (N=7,807)** | **0.5-5.0 (N=205,166)** | **>5.0 (14,453)** | ***P*** |
| Age, years (mean ± SD) | 71 ± 10 | 70 ± 11 | 71 ± 10 | 73 ± 11 | *<.001* |
| Female (%) | 3 | 6 | 3 | 4 | *<.001* |
| **Race/ethnicity (%)** | | | | | |
| Non-Hispanic White | 84 | 78 | 84 | 88 | *<.001* |
| Non-Hispanic Black | 12 | 19 | 12 | 7 | |
| Hispanic | 2 | 2 | 2 | 3 | |
| Other | 2 | 2 | 2 | 2 | |
| Body mass index (kg/m$^2$) | 29.3 ± 5.8 | 28.8 ± 5.7 | 29.4 ± 5.7 | 29.0 ± 6.0 | *<.001* |
| **Comorbidities** | | | | | |
| Diabetes (%) | 37 | 36 | 37 | 36 | *<.001* |
| Congestive heart failure (%) | 11 | 13 | 11 | 14 | *<.001* |
| Cardiovascular disease (%) | 36 | 35 | 36 | 39 | *<.001* |
| Cerebrovascular disease (%) | 9 | 9 | 9 | 9 | *.70* |
| Hypertension (%) | 80 | 80 | 81 | 75 | *<.001* |
| Hyperlipidemia (%) | 70 | 64 | 70 | 65 | *<.001* |
| Charlson comorbidity index (median [IQR]) | 1 (1, 3) | 2 (1, 3) | 1 (1, 3) | 2 (1, 3) | *<.001* |
| **Laboratory Values (mean ± SD or median [IQR])** | | | | | |
| eGFR (ml/min/1.73m$^2$) | 53 ± 6 | 52 ± 7 | 53 ± 6 | 52 ± 7 | *<.001* |
| Serum albumin (mg/dl) | 4.0 (3.8, 4.3) | 4.0 (3.7, 4.2) | 4.0 (3.8, 4.3) | 4.0 (3.7, 4.3) | *<.001* |

| | TSH (mIU/L) | | | | |
|---|---|---|---|---|---|
| | **Overall (N=227,426)** | **<0.5 (N=7,807)** | **0.5-5.0 (N=205,166)** | **>5.0 (14,453)** | ***P*** |
| Hemoglobin (g/dl) | 14.0 (12.9, 15.1) | 13.8 (12.5, 14.9) | 14.1 (12.9, 15.1) | 13.8 (12.5, 14.9) | *<.001* |
| Total cholesterol (mg/dl) | 165 (142, 193) | 163 (140, 190) | 165 (142, 193) | 167 (141, 197) | *<.001* |
| Triglycerides (mg/dl) | 128 (89, 188) | 121 (84, 177) | 128 (89, 187) | 134 (92, 201) | *<.001* |
| LDL (mg/dl) | 93 (74, 117) | 92 (73, 115) | 93 (74, 117) | 93 (73, 119) | *<.001* |
| **Medications (%)** | | | | | |
| Thyroid hormone supplement | 6 | 17 | 4 | 20 | *<.001* |
| Anti-thyroid medication | <1 | <1 | <1 | <1 | *<.001* |
| ACE-inhibitor and/or ARB | 40 | 41 | 40 | 35 | *<.001* |
| Statin | 22 | 20 | 22 | 21 | *<.001* |
| **Quality of Care Indicators (%)** | | | | | |
| Receipt of influenza vaccine within one year of study entry | 27 | 27 | 27 | 26 | *.003* |
| History of non-compliance with medical treatment[b] | 3 | 3 | 3 | 3 | *.77* |

[a] Abbreviations: eGFR, estimated glomerular filtration rate; ACE-inhibitor, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker.

[b] Ascertained by ICD-9 code (V15.81).