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Subclinical Hypothyroidism and Survival: The Effects of Heart Failure and Race

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Context: Studies examining the association between subclinical hypothyroidism and mortality have yielded conflicting results. Emerging data suggest these associations may depend upon underlying congestive heart failure (CHF) and/or race, but this has not been empirically determined.

Objective: Our objective was to examine the association between subclinical hypothyroidism and hypothyroidism overall with mortality according to pre-existing CHF and race.

Design and Participants: We examined the associations of subclinical hypothyroidism (TSH higher than assay upper limit of normal; total T_4 within reference) and hypothyroidism overall (TSH higher than assay upper limit of normal; total T_4 below lower limit of normal or within reference) with all-cause mortality among Third National Health and Nutrition Examination Survey participants stratified by CHF and race using multivariable Cox models. To confirm whether differences between strata were statistically significant, we tested for interaction on the basis of CHF (separately) and race by likelihood ratio testing.

Results: There were 14 130 (95.0%) euthyroid controls and 749 (5.0%) participants with hypothyroidism, 691 (4.6%) of whom had subclinical disease. Subclinical hypothyroidism vs euthyroidism was associated with greater mortality in those with CHF but not in those without: adjusted hazard ratios (HRs) (95% confidence intervals [CIs]) = 1.44 (1.01–2.06) and 0.97 (0.85–1.11), respectively (*P* interaction = .03). Similar findings were observed for hypothyroidism overall. Hypothyroidism overall vs euthyroidism was associated with greater mortality in Black participants (HR = 1.44 [95% CI = 1.03–2.03]) but not in non-Blacks (HR = 0.95 [95% CI = 0.83–1.08]) (*P* interaction = .03).

Conclusion: Among participants with CHF, subclinical hypothyroidism and hypothyroidism overall are associated with greater death risk. Additional studies are needed to confirm findings and explore possible mechanisms for the differential hypothyroidism-mortality association across race. **(*J Clin Endocrinol Metab* 98: 2326–2336, 2013)**

Hypothyroidism is a highly prevalent condition (>9.5 million people in the United States) (1) with pervasive effects on virtually every organ system (ie, hematologic, neuropsychiatric, reproductive, and cardiovascular) (2). Most hypothyroidism is subclinical disease (1), and there is considerable controversy as to whether subclinical

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Abbreviations: ACE, angiotensin-converting enzyme; ACR, albumin to creatinine ratio; aHR, adjusted hazard ratio; BMI, body mass index; CHD, coronary heart disease; CHF, congestive heart failure; CI, confidence interval; eGFR, estimated glomerular filtration rate; LLN, lower limit of normal; MI, myocardial infarction; NDI, National Death Index; NHANES III, Third National Health and Nutrition Examination Survey; TT_4; total T_4 ULN, upper limit of normal.

hypothyroidism negatively impacts survival (3, 4). Previous studies evaluating the associations between subclinical hypothyroidism and mortality have yielded conflicting results, likely due to the heterogeneity of patient populations within and across studies (4–17).

Emerging data suggest these associations may be dependent upon underlying cardiovascular risk. Whereas studies in populations with high underlying cardiovascular risk (eg, patients at high risk for or who had recent cardiac events) have observed that subclinical hypothyroidism is associated with greater all-cause and cardiovascular mortality (9, 11, 12), this has not been observed in lower-risk groups (5–8, 14, 16). In a previous meta-analysis, the association between subclinical hypothyroidism and mortality did not differ among patients with and without underlying cardiovascular disease (18), whereas in a subsequent meta-analysis, pre-existing congestive heart failure (CHF) was observed to modify the association between subclinical hypothyroidism and CHF events (19). Given hypothyroidism's impact on cardiac contractility, systemic vascular resistance, electrophysiologic irritability, and atherosclerosis (20, 21), it has been speculated that subclinical hypothyroidism might predispose to death from cardiac causes. It is plausible that subpopulations with CHF may be predisposed to cardiac morbidity and mortality associated with subclinical hypothyroidism, owing to underlying distortions in ventricular architecture that confer heightened susceptibility to hypothyroid-related perturbations (22).

Thyrotropin (commonly referred to as thyroid stimulating hormone; TSH) is considered the most sensitive and specific biochemical metric of thyroid function (23). In subclinical hypothyroidism, serum TSH is elevated in the context of normal thyroxine (T_4) levels. Notably, previous studies have also shown that median TSH levels are lower in Blacks than among persons of other races (1, 24–27), perhaps owing to a different physiological set point (28). Therefore, it is plausible that the hypothalamic-pituitary-thyroid axis may be intrinsically different in Blacks vs non-Blacks. There have been conflicting results in regard to the differential association between subclinical hypothyroidism and outcomes across racial groups in the aforementioned meta-analyses. Whereas there appeared to be greater risk of coronary heart disease (CHD) events in Whites compared with Blacks (18), modification by race was not observed for CHF events, CHD mortality, or all-cause mortality (18, 19). Given the low representation of Blacks, analyses may have been underpowered to detect interaction by race.

We hypothesized that the association between subclinical hypothyroidism and mortality differs according to CHF and race. We conducted the following study to examine whether the association between 1) subclinical hypothyroidism and 2) hypothyroidism overall with mortality is modified by concomitant CHF and race using a large, nationally representative sample of the U.S. adult population from the Third National Health and Nutrition Examination Survey (NHANES III) with detailed laboratory data and extended follow-up over which to observe outcomes.

Subjects and Methods

Source cohort

We conducted a retrospective cohort study using data from the NHANES III, a survey executed by the National Center for Health Statistics (NCHS) from 1998 to 1994 to provide national estimates of the health and nutritional status of U.S. children and adults. The survey employed a complex, multistage, stratified, clustered sampling design in which children, elderly, Black, and Mexican-American participants were oversampled to enable precise estimation within these subgroups (29). At the time of enrollment, participants' self-reported sociodemographics, comorbid conditions, and medications were assessed; blood and urine samples were collected for measurement of serum TSH, total T_4 (TT_4), creatinine, and urine albumin and creatinine (details below). The NHANES III study protocol was approved by the NCHS Institutional Review Board, and all participants gave their informed written consent before participation. The current study was deemed exempt by the Partners Healthcare Institutional Review Board.

We included NHANES III participants ages ≥18 years old at enrollment, who had baseline serum TSH, TT_4, and creatinine measurements and had available follow-up data (n = 15 467). From these, we excluded participants with secondary hypothyroidism (TSH < lower limit of normal [LLN] and TT_4 < LLN) (30) due to sparse representation (n = 2). Given that the comparison of interest was between primary hypothyroidism (subclinical and overall) vs euthyroidism with mortality within strata of CHF and race, we excluded participants with primary hyperthyroidism (TSH < LLN; n = 560), secondary hyperthyroidism (TSH > upper limit of normal [ULN] and TT_4 > ULN; n = 8) (30), and missing data on CHF status (n = 18); race was not missing for any patients. The final analytical cohort contained 14 879 participants. Within the NHANES III, race and comorbidity status (including CHF) were self-identified by participants.

Laboratory measures

TSH was measured with a chemiluminescence immunometric assay (Nichols Institute Diagnostics, San Juan Capistrano, California), and TT_4 was measured with an RIA (Roche Molecular Biochemicals, Indianapolis, Indiana). The normal reference ranges for TSH and TT_4 were 0.39 to 4.6 mIU/L and 4.5 to 13.2 μg/dL, respectively (1, 31). Spot urine albumin was measured by solid-phase fluorescent immunoassay, and spot urine and serum creatinine were measured by the Jaffe rate reaction (31). Microalbuminuria and macroalbuminuria were defined as an albumin to creatinine ratio (ACR) of 30 to 299 mg/g and ≥300 mg/g, respectively (32). Serum creatinine measurements were calibrated to the Cleveland Clinic laboratory by subtracting 0.23

mg/dL as previously described (33). Estimated glomerular filtration rate (eGFR) was calculated using the Chronic Kidney Disease Epidemiology Collaboration equation (eGFR = $141 \times \min[\mathrm{Scr}/\kappa, 1]^{\alpha} \times \max[\mathrm{Scr}/\kappa, 1]^{-1.209} \times 0.993^{\mathrm{Age}} \times 1.018$ [if female] $\times 1.159$ [if Black]; Scr is serum creatinine, $\kappa = 0.7$ for females and 0.9 for males, $\alpha = -0.329$ for females and -0.411 for males, min indicates the minimum of Scr/κ or 1, and max indicates the maximum of Scr/κ or 1) (34).

Exposure ascertainment

In co-primary analyses, we sought to examine how mortality was associated with hypothyroidism overall and with subclinical hypothyroidism. In the former analyses, participants with TSH higher than ULN were considered hypothyroid, and participants with TSH within the reference range were considered euthyroid. In the latter analyses, hypothyroid participants were parsed into subclinical and overt disease on the basis of their TT_4 levels (subclinical is within reference range; overt is below LLN) (30). Given that TT_4 levels may not be concordant with unbound, biologically active free T_4 levels (35), secondary analyses were also conducted in which subclinical and overt hypothyroidism were defined by severity of TSH derangement (subclinical is ≤10 mIU/L; overt is >10 mIU/L); this cutoff was selected based on the TSH threshold at which treatment of subclinical hypothyroidism is often recommended based on published guidelines (36).

Outcome ascertainment

The primary outcome of interest was all-cause mortality. Mortality data were available through December 31, 2006, and were ascertained through linkage of NHANES III to death certificate data from the National Death Index (NDI). The NDI is a central computerized index of annually updated death record information compiled from data submitted by state vital statistics offices to the NCHS. The NDI is considered the gold standard for death ascertainment for epidemiologic research, because it has been shown to provide superior coverage of deaths compared with other sources (37). Participants were considered at risk the day after baseline TSH and TT_4 measurements until death or end of follow-up. Secondary analyses considered death from cardiovascular causes; this was ascribed on the basis of International Statistical Classification of Diseases, Injuries, and Causes of Death codes, 10th revision codes (Supplemental Table 1, published on The Endocrine Society's Journals Online web site at http://jcem.endojournals.org) (38, 39). Cause-of-death information was available for 98.8% of the source cohort.

Statistical analyses

Baseline characteristics between exposure groups were compared using 2-sample *t* tests, Wilcoxon rank sum tests, and χ^2 tests as dictated by data type. Analogous methods were used to estimate associations between exposure and mortality in all analyses. Unadjusted associations between exposure and mortality were estimated using Kaplan-Meier plots, log-rank testing, and unadjusted Cox proportional hazards models. Multivariable Cox proportional hazards models were adjusted for potential confounders of the exposure-mortality association based on published data that included age, sex, categories of race/ethnicity (non-Hispanic Black and non-Hispanic White referred to as Black and White, respectively, in this report; Mexican-American; and other race/ethnicity), diabetes, active smoking status, hypertension, hypercholesterolemia, previous stroke, previous myocardial infarction (MI), pre-existing CHF, body mass index (BMI), ACR (categorized as <30, 30–299, or ≥300 mg/g or missing), and eGFR (categorized as <60 or ≥60 mL/min/1.73 m^2). Sensitivity analyses were also conducted in which 1) multivariable Cox models were additionally adjusted for cardiovascular medications (amiodarone, angiotensin-converting enzyme [ACE] inhibitors, β-blockers, dihydropyridine and nondihydropyridine calcium channel blockers, digoxin, thiazide and loop diuretics, statins, niacin, gemfibrozil, and long-acting nitrates) and 2) participants on baseline thyroid supplementation (n = 260) and thyroid-suppressive therapy (n = 3) were excluded. The proportional hazards assumption was confirmed graphically and through Schoenfeld residual testing.

Stratum-specific estimates were estimated within subgroups defined by race, pre-existing CHF, and pre-existing atherosclerotic disease (previous MI or stroke). Statistical significance of effect modification was assessed by likelihood ratio testing comparing models with and without the corresponding 2-way factor-by-exposure cross-product terms (eg, CHF × subclinical hypothyroidism). An interaction *P* value of <.05 was considered statistically significant. Analyses were performed using Stata MP version 10.1 (StataCorp, College Station, Texas).

Results

Cohort description

The overall study cohort consisted of 14 879 participants, 14 130 (95.0%) of whom were euthyroid and 749 (5.0%) of whom had hypothyroidism overall; among the latter, 691 had subclinical hypothyroidism (representing 4.6% of the total cohort and 92.3% of participants with hypothyroidism overall). Compared with euthyroidism, participants with subclinical hypothyroidism tended to be older, female, and White; had higher prevalence of low eGFR, diabetes, micro- and macroalbuminuria, CHF, hypertension, hypercholesterolemia, previous stroke, previous MI, higher BMI, and exogenous thyroid hormone use; and had a lower prevalence of smoking (Table 1). Similar patterns of association were observed when comparing patients with hypothyroidism overall with euthyroidism (Table 1) and when comparing subclinical hypothyroidism as defined by TSH levels with euthyroidism (Supplemental Table 2).

Subclinical hypothyroidism and mortality according to pre-existing CHF

Within the overall cohort, participants contributed a total of 199 299 patient-years of at-risk time during which 3337 all-cause deaths (1477 cardiovascular deaths) were observed. Median time at risk was 14.3 years. In the overall cohort, a significant association between subclinical hypothyroidism and hypothyroidism overall with all-cause mortality was not observed: adjusted hazard ratios (aHRs) = 1.04 (with 95% confidence interval [CI] of 0.91–1.18) and 1.02 (95% CI, 0.90–1.15), respectively.

Table 1. Comparison of Baseline Characteristics Between Thyroid Functional Status Categorizations[a]

	Euthyroid (n = 14 130)	Hypothyroid Overall (n = 749)	Subclinical Hypothyroid (n = 691)
TSH, mIU/L			
Median	1.49	6.5	6.30
IQR	1.00–2.10	5.30–9.80	5.3–8.72
Min--Max	0.39–4.60	4.65–382	4.65–83.0
Age, y	45.4 ± 19.2	59.3 ± 19.1	59.2 ± 19.2
		$P < .001$	$P < .001$
Female sex, %	52.4	64.4	63.8
		$P < .001$	$P < .001$
Race, %			
White	40.1	57.7	57.5
Black	28.1	11.4	11.3
Mexican-American	27.6	27.1	27.4
Other	4.1	3.9	3.9
		$P < .001$	$P < .001$
Diabetes, %			
Yes	7.5	11.0	10.6
No	92.4	88.9	89.3
Don't know/blank	0.1	0.1	0.1
		$P = .002$	$P = .01$
Active smoking, %	26.1%	15.4%	15.3%
		$P < .001$	$P < .001$
eGFR (mL/min/1.73m^2), %			
≥60	93.9%	79.6%	80.2%
30–59	5.7%	18.4%	17.8%
<30	0.4%	2.0%	2.0%
		$P < .001$	$P < .001$
ACR (mg/g), %			
<30	87.1	78.4	77.9
30–299	8.9	13.8	14.2
≥300	1.9	3.1	2.9
Missing	2.1	4.8	5.1
		$P < .001$	$P < .001$
CHF, %			
Yes	2.9	7.9	7.8
No	97.1	92.1	92.2
		$P < .001$	$P < .001$
Hypertension, %			
Yes	25.4	35.4	35.6
No	73.8	64.1	64.0
Don't know/blank	0.9	0.5	0.4
		$P < .001$	$P < .001$
Hypercholesterolemia, %			
Yes	16.5	27.0	26.6
No	33.0	36.5	36.2
Don't know/blank	50.6	36.6	37.2
		$P < .001$	$P < .001$
Previous stroke, %			
Yes	2.4	5.2	5.5
No	97.6	94.8	94.5
Don't know/blank	0.0	0.0	0.0
		$P < .001$	$P < .001$
Previous MI, %			
Yes	3.7	9.4	8.8
No	95.2	89.3	89.7
Don't know/blank	1.2	1.3	1.5
		$P < .001$	$P < .001$
BMI (kg/m^2), %			
<18.5	2.2	1.5	1.6
18.5–24.9	38.3	33.0	33.6
25–29.9	34.4	35.5	35.2

(*Continued*)

Table 1. Continued

	Euthyroid (n = 14 130)	Hypothyroid Overall (n = 749)	Subclinical Hypothyroid (n = 691)
30–34.9	16.1	16.3	16.6
35–39.9	5.7	8.8	8.1
≥40	3.3	4.9	4.9
		$P < .001$	$P = .005$
Exogenous thyroid hormone use, %	1.3	10.4	9.7
		$P < .001$	$P < .001$

Abbreviations: IQR, interquartile range; Max, maximum; Min, minimum.

[a] Data are presented as mean ± SD or proportions unless otherwise indicated. Significance testing was performed separately for hypothyroid overall vs euthyroid and subclinical hypothyroid vs euthyroid by 2-sample *t* test, Wilcoxon rank sum test, or χ^2 test. Thyroid functional status was categorized as euthyroid (TSH within reference range), hypothyroid overall (TSH higher than ULN), and subclinical hypothyroid (TSH higher than ULN and TT_4 within reference range).

In the primary analyses, pre-existing CHF modified the association between subclinical hypothyroidism (*P* interaction = .03) and hypothyroidism overall (*P* interaction = .01) with all-cause mortality. Subclinical hypothyroidism was significantly associated with greater all-cause mortality compared with euthyroidism in those with CHF (aHR = 1.44 [95% CI, 1.01–2.06]) but not in those without CHF (aHR = 0.97 [95% CI, 0.85–1.11]) (Figure 1A). Similarly, hypothyroidism overall was significantly associated with greater all-cause mortality compared with euthyroidism in those with CHF (aHR = 1.47 [95% CI, 1.05–2.05]) but not in those without CHF (aHR = 0.95 [95% CI, 0.83–1.09]) (Figure 1B). In sensitivity analyses adjusted for cardiovascular medications, results were qualitatively similar (Table 2). After exclusion of participants using baseline thyroid medications, associations between subclinical hypothyroidism and hypothyroidism overall with mortality in participants with pre-existing CHF were even more potent (Table 2).

A similar pattern of results was observed in secondary analyses of subclinical hypothyroidism defined by TSH levels only. Subclinical hypothyroidism was significantly associated with greater all-cause mortality compared with euthyroidism in those with CHF (aHR = 1.77 [95% CI, 1.19–2.64]) but not in those without CHF (aHR = 0.97 [95% CI, 0.84–1.12]) (*P* interaction = .01; Supplemental Figure 1). In sensitivity analyses adjusted for cardiovascular medications, results were qualitatively similar (Table 2). After exclusion of participants using baseline thyroid medications, the association between subclinical hypothyroidism with mortality in participants with pre-existing CHF was even more potent (Table 2).

Hypothyroidism overall and mortality according to race

Race modified the association between hypothyroidism overall with all-cause mortality (*P* interaction = .03). Hypothyroidism overall was significantly associated with greater all-cause mortality compared with euthyroidism in Black participants (aHR = 1.44 [95% CI, 1.03–2.03) but not in those who were non-Black (aHR = 0.95 [95% CI, 0.83–1.08) (Figure 2B). In sensitivity analyses adjusted for cardiovascular medications, results were qualitatively similar (Table 2). After exclusion of participants using baseline thyroid medications, the association between hypothyroidism overall with mortality in Black participants was even more potent (Table 2).

In stratified analyses, subclinical hypothyroidism was associated with greater all-cause mortality compared with euthyroidism in Black participants (HR 1.51 [95% CI, 1.05–2.17) but not in other races (HR = 0.96 [95% CI, 0.84–1.10]); however, tests of interaction (*P* interaction = .07) did not reach statistical significance (Figure 2A). In sensitivity analyses adjusted for cardiovascular medications, results were qualitatively similar (Table 2). After exclusion of participants using baseline thyroid medications, tests of interaction for race were statistically significant (*P* interaction = .005) (Table 2).

Similarly, in stratified analyses, subclinical hypothyroidism defined by TSH levels trended toward greater all-cause mortality only among Black participants (aHR = 1.48 [95% CI, 0.96–2.28]), but not in those of other races (aHR = 0.98 [95% CI, 0.85–1.14]); however, estimates and tests for interaction did not reach statistical significance (*P* interaction = .08; Supplemental Figure 2). In sensitivity analyses adjusted for cardiovascular medications, results were qualitatively similar. After exclusion of participants using baseline thyroid medications, tests of interaction for race were statistically significant (*P* interaction = .03) (Table 2).

Subclinical hypothyroidism and mortality considering both pre-existing CHF and race

The concurrent effects of race and CHF on the association between subclinical hypothyroidism and hypothy-

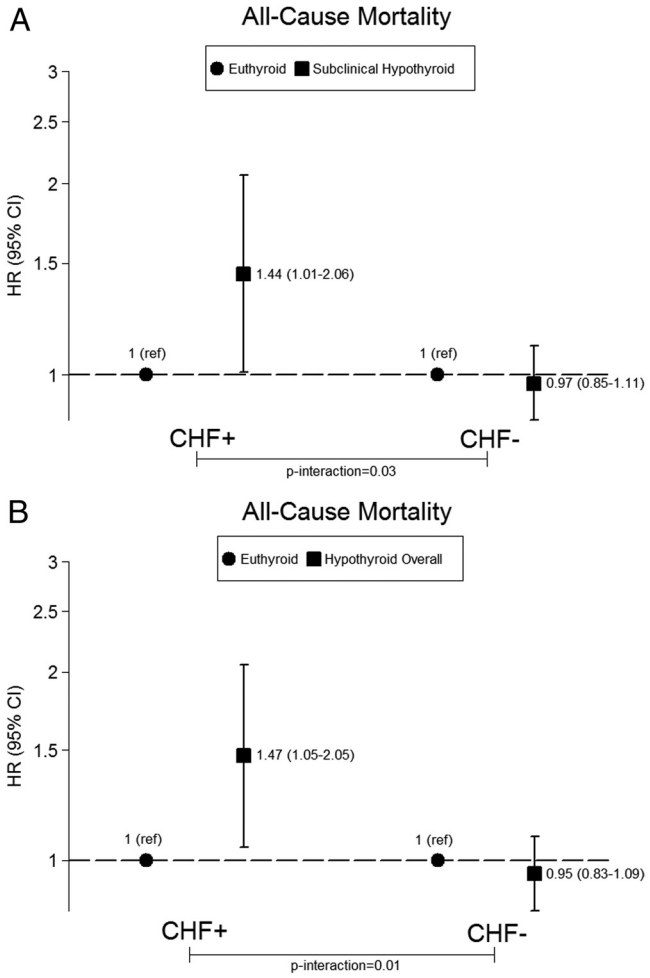

Figure 1. Comparison of the association between subclinical hypothyroidism (TSH higher than ULN; TT_4 within reference range) (A) and hypothyroidism overall (TSH higher than ULN) (B) vs euthyroidism (TSH within reference range) with all-cause mortality, stratified by pre-existing CHF status. Analyses were adjusted for age, sex, race/ethnicity, diabetes, smoking, hypertension, hypercholesterolemia, previous stroke, previous MI, BMI, ACR, and eGFR (specification for each as per Table 1). Statistical significance of effect modification was assessed by likelihood ratio testing.

roidism overall with all-cause mortality were considered (Table 3). Among participants without CHF, race modified the association between subclinical hypothyroidism and mortality: aHR (95% CI) was 1.43 (0.96–2.14) among Blacks and 0.89 (0.77–1.03) among non-Blacks (*P* interaction = .002). Similarly, among participants with CHF, race modified the association between subclinical hypothyroidism and mortality; aHR (95% CI) was 2.68 (0.84–8.61) among Blacks and 1.36 (0.92–2.02) among non-Blacks (*P* interaction = .03).

Among participants without CHF, race modified the association between hypothyroidism overall and all-cause mortality; aHR (95% CI) was 1.55 (1.06–2.27) among Blacks and 0.87 (0.75–1.00) among non-Blacks (*P* interaction = .005). In contrast, among participants with CHF, hypothyroidism overall was associated with elevated risk that did not differ according to race (*P* interaction = .7).

When cardiovascular mortality was considered (Table 4), race modified the association between subclinical hypothyroidism and mortality among participants without CHF (*P* interaction = .01) but not among participants with CHF (*P* interaction > 0.9). Similarly, race modified the association between hypothyroidism overall and mortality among participants without CHF (*P* interaction = .004) but not among participants with CHF (*P* interaction = .4).

Subclinical hypothyroidism and mortality according to pre-existing atherosclerotic disease

In stratified analyses, subclinical hypothyroidism was associated greater all-cause mortality compared with euthyroidism in participants with atherosclerotic disease (aHR = 1.34 [95% CI, 1.04–1.74]) but not in those without (aHR = 0.91 [95% CI, 0.73–1.14]); however, tests of interaction did not reach statistical significance (*P* interaction = .2). Subclinical hypothyroidism defined by TSH levels was also associated with greater all-cause mortality compared with euthyroidism in participants with atherosclerotic disease but not in those without (aHR = 1.32 [95% CI, 1.00–1.75] and 0.96 [95% CI, 0.82–1.13], respectively); however, tests of interaction did not reach statistical significance (*P* interaction = .2). Similarly, hypothyroidism overall was associated with greater all-cause mortality compared with euthyroidism in participants with atherosclerotic disease but not in those without (aHR = 1.30 [95% CI, 1.02–1.66] and 0.93 [95% CI, 0.81–1.08]); however, tests of interaction did not reach statistical significance (*P* interaction = .08).

Discussion

In this large, nationally representative sample of U.S. adults, we observed that pre-existing CHF was an important modifier of the association between subclinical hypothyroidism and hypothyroidism overall with mortality. Subclinical hypothyroidism and hypothyroidism overall were each associated with greater all-cause mortality in those with CHF, but not in those without. Additionally, race modified the association between hypothyroidism overall with mortality; hypothyroidism overall was associated with greater all-cause mortality in Blacks but not in other races. These findings were robust across multiple secondary analyses as well as sensitivity analyses that adjusted for cardiovascular medications and excluded participants on baseline thyroid medications. When race and CHF were considered concurrently, we observed that sub-

Table 2. Stratified Analyses of the Association Between Subclinical Hypothyroidism and Hypothyroidism Overall With All-Cause Mortality

		HR (95% CI)		
	n	Multivariable Adjusted[a]	Multivariable + Cardiovascular Medication Adjusted[b]	Exclusion of Thyroid Medication Use[c]
Subclinical hypothyroidism (TSH/TT_4-based definition) vs euthyroidism				
Overall cohort	14 879	1.04 (0.91–1.18)	1.04 (0.91–1.18)	1.08 (0.94–1.23)
Pre-existing CHF				
Yes	470	1.44 (1.01–2.06)	1.47 (1.02–2.12)	1.49 (1.02–2.16)
No	14,409	0.97 (0.85–1.11)	0.97 (0.85–1.12)	1.01 (0.88–1.17)
P for interaction		.03	.04	.03
Race				
Black	4061	1.51 (1.05–2.17)	1.47 (1.02–2.12)	1.54 (1.06–2.25)
Non-Black	10 818	0.96 (0.84–1.10)	0.96 (0.84–1.10)	1.00 (0.87–1.15)
P for interaction		.07	.07	.005
Subclinical hypothyroidism (TSH-based definition) vs euthyroidism				
Overall cohort	14,879	1.05 (0.91–1.20)	1.05 (0.91–1.20)	1.07 (0.93–1.24)
Pre-existing CHF				
Yes	470	1.77 (1.19–2.64)	1.82 (1.22–2.72)	1.80 (1.19–2.72)
No	14 409	0.97 (0.84–1.12)	0.97 (0.83–1.12)	1.00 (0.85–1.16)
P for interaction		.01	.02	.03
Race				
Black	4061	1.48 (0.96–2.28)	1.44 (0.94–2.23)	1.53 (0.99–2.35)
Non-Black	10 818	0.98 (0.85–1.14)	0.97 (0.89–1.13)	1.00 (0.86–1.17)
P for interaction		.08	.08	.03
Hypothyroidism overall vs euthyroidism				
Overall cohort	14 879	1.02 (0.90–1.15)	1.02 (0.90–1.15)	1.06 (0.93–1.20)
Pre-existing CHF				
Yes	470	1.47 (1.05–2.05)	1.50 (1.07–2.11)	1.53 (1.06–2.20)
No	14 409	0.95 (0.83–1.09)	0.95 (0.84–1.09)	0.99 (0.86–1.14)
P for interaction		.01	.01	.01
Race				
Black	4061	1.44 (1.03–2.03)	1.41 (0.99–1.99)	1.66 (1.15–2.37)
Non-Black	10 818	0.95 (0.83–1.08)	0.95 (0.83–1.08)	0.97 (0.85–1.12)
P for interaction		.03	.03	.01

[a] Adjusted for age, sex, race (omitted from models stratified on race), diabetes, smoking, hypertension, hypercholesterolemia, previous stroke, previous MI, pre-existing CHF (omitted from models stratified on CHF), BMI, ACR, and eGFR.

[b] Adjusted for all covariates in multivariable-adjusted model as well as amiodarone, ACE inhibitors, β-blockers, calcium channel blockers (dihydropyridine and nondihydropyridine), digoxin, thiazide and loop diuretics, antihyperlipidemics (statins, niacin, and gemfibrozil), and long-acting nitrates.

[c] Participants on baseline thyroid supplementation and suppressive therapy excluded; adjusted for all covariates in multivariable-adjusted model.

clinical hypothyroidism and hypothyroidism overall were associated with greater mortality in the context of Black race, CHF, or both.

There has been ongoing debate as to whether subclinical hypothyroidism, considered to be a milder form of hypothyroidism, adversely impacts survival (3, 4). There is plausible reason to suspect that subclinical hypothyroidism is causally associated with greater mortality risk. Previous data have suggested that subclinical hypothyroidism is associated with ischemic heart disease (13), CHF (14), accelerated coronary atherogenesis (40), and cardiac conduction abnormalities (41) that may predispose to malignant ventricular arrhythmias. Nonetheless, previous studies that directly examined the associations of subclinical hypothyroidism with all-cause and cardiovascular mortality have yielded mixed results (4–8, 10–17). Studies in patients of average underlying cardiovascular risk have tended to be negative (5–8, 14, 16), whereas those in patients at high cardiovascular risk have tended to be positive (9, 11, 12). Two meta-analyses have sought to examine this issue more systematically. The first, by Gencer et al (19), indicated that subclinical hypothyroidism was associated with a greater risk of heart failure events among patients with pre-existing CHF but not among those without. The directionality of the association was similar to that seen in this study; however, interaction tests did not reach statistical significance, and the study did not consider survival as an outcome. The second, by Rodondi et al (18), examined for but did not detect a differential association of subclinical hypothyroidism with CHD events and mortality among patients who did and did not have any form of pre-existing cardiovascular

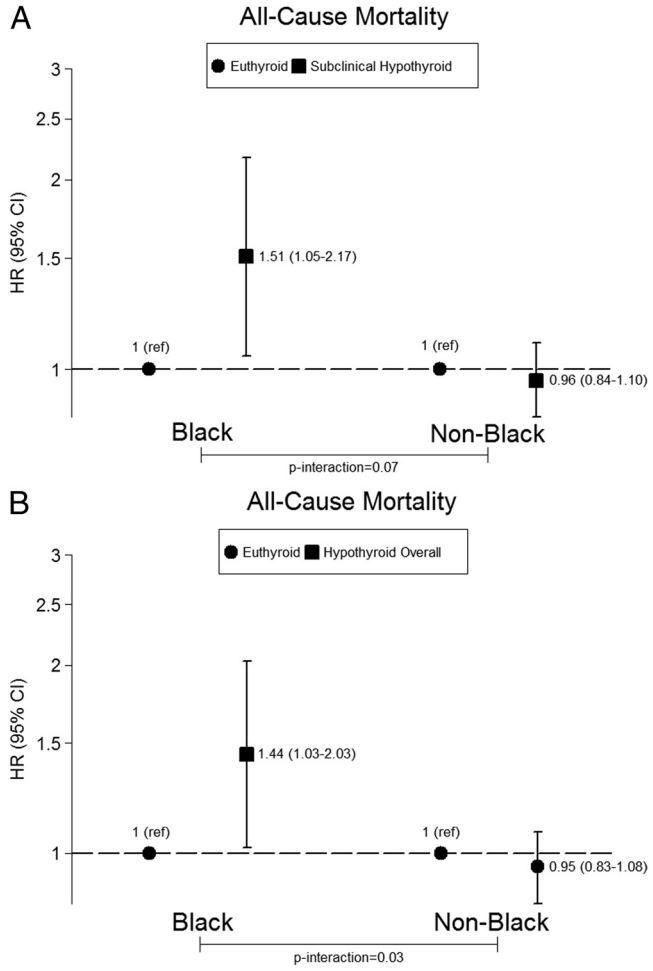

Figure 2. Comparison of the association between subclinical hypothyroidism (TSH higher than ULN; TT_4 within reference range) (A) and hypothyroidism overall (TSH higher than ULN) (B) vs euthyroidism (TSH within reference range) with all-cause mortality, stratified by race (Black vs non-Black). Analyses were adjusted for age, sex, diabetes, smoking, hypertension, hypercholesterolemia, previous stroke, previous MI, pre-existing CHF, BMI, ACR, and eGFR (specification for each as per Table 1). Statistical significance of effect modification was assessed by likelihood ratio testing.

disease. One possibility is that subclinical hypothyroidism poses unique risk among patients with CHF, possibly related to consequent alterations in neurohormonal activation, ventricular remodeling, cardiac contractility, and vascular tone, but not those with other forms of cardiovascular disease. Therefore, when CHF is subsumed into a broader category of heart disease, other types of which do not interact with subclinical hypothyroidism, effect modification by heart failure is diluted and not observed.

To our knowledge, ours is the first study to observe that CHF modifies the association between subclinical hypothyroidism and hypothyroidism overall with all-cause mortality among nonhospitalized patients. In the overall cohort, we did not observe significant associations between either subclinical hypothyroidism or hypothyroidism overall with mortality. However, in stratified analyses, both were associated with greater death risk in those with CHF but not in those without. It is possible that the pooled (nonstratified) analysis masked important subgroup effects. Given that most NHANES III participants did not have pre-existing CHF, analyses of the population as a whole may have been dominated by effects among those without CHF. Given the compensatory alterations in neurohormonal activation, ventricular remodeling, cardiac contractility, and vascular tone required to maintain cardiac output in structural heart disease (22), it is plausible that participants with pre-existing CHF may have a lower reserve with which to tolerate the acute hemodynamic, volume, and electrophysiologic changes associated with subclinical hypothyroidism, with subsequent implications on mortality.

This is also the first study to observe that Blacks have a greater mortality risk related to hypothyroidism compared with other races. For reasons not yet fully elucidated, epidemiologic studies have shown that Blacks have a lower median TSH and distribution compared with Whites (24–27); thus, definitions of hypothyroidism using standard TSH reference ranges indicate that Blacks have a lower prevalence of hypothyroidism. It has been suggested that there may be misclassification of thyroid functional disease among Blacks on this basis and that race-based reference ranges should be considered (28, 42). Two of the aforementioned meta-analyses comparing the association between subclinical hypothyroidism and outcomes across racial groups have shown conflicting results (18, 19). Rodondi et al (18) found that subclinical hypothyroidism was associated with increased CHD events in Whites but not among Blacks; neither meta-analysis observed effect modification by race for CHF events or mortality (18, 19). In contrast, we observed that hypothyroidism was associated with greater mortality among Blacks but not among non-Blacks, which was consistent across multiple sensitivity analyses. The larger representation of Blacks in our cohort compared with previous studies may have provided greater power to detect interaction by race. Additional studies are needed to confirm this finding and to explore potential genetic, biologic, socioeconomic, and psychosocial factors that may explain differential racial susceptibility.

Our study has several strengths, including its large sample size, large representation of Black participants, extended follow-up period, comprehensive availability of thyroid functional test data, and robustness of findings across analytical strategies. However, several limitations of our study bear mention. First, thyroid functional disease categorizations were based on one-time measure-

Table 3. Associations Between Subclinical Hypothyroidism and Hypothyroidism Overall With All-Cause Mortality Within Strata Defined by CHF Status and Race[a]

	Subclinical Hypothyroidism (TSH/TT_4-Based Definition)			Hypothyroidism Overall		
	HR (95% CI)		*P* Interaction for CHF	HR (95% CI)		*P* Interaction for CHF
	CHF Present	CHF Absent		CHF Present	CHF Absent	
Black	2.68 (0.84–8.61)	1.43 (0.96–2.14)	.03	1.61 (0.58–4.50)	1.55 (1.06–2.27)	.4
Non-Black	1.36 (0.92–2.02)	0.89 (0.77–1.03)	<.001	1.50 (1.03–2.18)	0.87 (0.75–1.00)	.001
P interaction for race	.03	.002		.7	.005	

[a] Reference for each cell is euthyroidism (HR = 1; not shown); estimates are adjusted for age, sex, diabetes, active smoking status, hypertension, hypercholesterolemia, previous stroke, previous MI, BMI, eGFR, and ACR by Cox proportional hazards regression. For Black with CHF present, n = 113; Black with CHF absent, n = 3948; Non-Black with CHF present, n = 357; and Non-Black with CHF absent, n = 10 461.

ments of TSH with or without TT_4 and were therefore subject to misclassification. In healthy ambulatory patients, TSH is typically maintained in a narrow range over time (ie, variation of 0.5 mIU/L when measured monthly over a 1-year period) (43, 44). Nonetheless, we cannot exclude the possibility that, in some patients studied here, TSH deviated from its normal set point on the basis of nonthyroidal illness. Most commonly, TSH falls in response to systemic illness; resultant bias should therefore favor patients with higher TSH levels and would render conservative the observed association between hypothyroidism and death. However, because TSH was not measured longitudinally, we cannot exclude the possibility that there was misclassification bias in the opposite direction. Second, direct thyroid hormone measurements in NHANES III used TT_4 levels in lieu of free T_4 levels, with the former measurements subject to thyroid functional status misclassification on the basis of differential levels of thyroid-binding globulin or differential T_4 protein binding (35). Thus, we employed two definitions of subclinical hypothyroidism (based on concurrent TSH/TT_4 levels vs TSH levels only) that yielded essentially the same findings. Third, CHF status was self-identified as opposed to using objective measurements (ie, echocardiography), which may have identified a subset with more severe disease. It is also possible that self-report of CHF status may have resulted in misclassification of disease, such that participants with other types of cardiovascular disease (ie, atherosclerosis) may have identified themselves as having CHF. Lastly, as with all observational studies, we cannot exclude the possibility of residual confounding.

In conclusion, our findings demonstrated that subclinical hypothyroidism, as well as hypothyroidism overall, are associated with a greater risk of mortality in subpopulations with pre-existing CHF and of Black race. These findings bear particular relevance given the high prevalence of hypothyroidism and CHF and the racial/ethnic diversity of the U.S. population. At this stage, additional studies are needed to confirm findings; to elaborate underlying genetic, biologic, and environmental determinants of hypothyroidism and its associated complications across racial/ethnic groups; and to examine the differential therapeutic effectiveness and safety of thyroid hormone supplementation for subclinical hypothyroidism and hypothyroidism overall vis-à-vis effects on survival according to race/ethnicity and underlying cardiovascular risk.

Table 4. Associations Between Subclinical Hypothyroidism and Hypothyroidism Overall With Cardiovascular Mortality Within Strata Defined by CHF Status and Race[a]

	Subclinical Hypothyroidism (TSH/TT_4-Based Definition)			Hypothyroidism Overall		
	HR (95% CI)		*P* Interaction for CHF	HR (95% CI)		*P* Interaction for CHF
	CHF Present	CHF Absent		CHF present	CHF Absent	
Black	2.03 (0.35–11.68)	1.98 (1.14–3.44)	.09	1.25 (0.23–6.68)	2.06 (1.20–3.51)	.05
Non-Black	1.39 (0.87–2.23)	0.87 (0.70–1.07)	.01	1.53 (0.98–2.40)	0.86 (0.70–1.06)	.01
P interaction for race	>.9	.01		.4	.004	

[a] Reference for each cell is euthyroidism (HR = 1; not shown); estimates are adjusted for age, sex, diabetes, active smoking status, hypertension, hypercholesterolemia, previous stroke, previous MI, BMI, eGFR, and ACR by Cox proportional hazards regression. For Black with CHF present, n = 113; Black with CHF absent, n = 3948; Non-Black with CHF present, n = 357; and Non-Black with CHF absent, n = 10 461.

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