**Thyroid-related hormones and hypertension incidence in middle aged and older Hispanic/Latino adults: The HCHS/SOL Study**

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**Abstract**

**Background**: Thyroid-related hormones act to regulate metabolic pathways and blood pressure (BP). However, the relationship of thyroid stimulating hormone (TSH), peripheral thyroid hormones, and the role of the hypothalamic-pituitary-thyroid axis on hypertension development is not fully understood. We assessed sex-specific associations of thyroid-related hormones with BP and hypertension in Hispanic/Latino adults followed for 6 years.

**Methods**: We studied 1,789 adults, aged 45-74, free of diabetes at baseline from a subcohort of the Hispanic Community Health Study/Study of Latinos. We assessed TSH, free-thyroxine (FT4), triiodothyronine (T3), and various indicators of thyroid axis. Using multivariable linear and Poisson regression adjusted for survey design and confounding variables, we estimated *a priori* sex-specific associations of thyroid-related hormones with change in BP and hypertension development.

**Results**: In men and women, TSH and TSH/FT4 ratio were associated with change in diastolic-BP and T3 with change in pulse-pressure and the development of hypertension from prehypertension. . In men, 1-SD increase in TSH (Incident-Rate-Ratio(IRR)=1.42; 95%CI: 1.15,1.75) and TSH/FT4 ratio (IRR=1.20; 95%CI: 1.07,1.35) were positively associated with the development of hypertension from prehypertension while TSH/FT4 ratio (IRR=0.85; 95%CI: 0.72,1.00) was protective in women. We observed sex-specific differences in associations of T3/FT4 ratio, and indices of pituitary sensitivity to thyroid hormones with change in pulse-pressure and hypertension development.

**Conclusion**: Thyroid-related hormones are associated with sex-specific changes in BP and hypertension among Hispanic/Latino adults consistent with selected studies conducted in other populations. Mechanisms underlying associations of pituitary sensitivity to thyroid hormones with BP and hypertension development warrant further study.

**Keywords**: Triiodothyronine; Thyrotropin; Prehypertension; Thyroxine; Hypertension; Hispanic/Latino

**Introduction**

Hypertension or high blood pressure (BP) is a primary risk factor for kidney, neurological, and cardiovascular disease (CVD).[[1]](#endnote-2),[[2]](#endnote-3) Elevated systolic (SBP) and diastolic blood pressure (DBP), as well as pulse pressure (SBP minus DBP) are linked to pathologic cardiac remodeling, atherosclerosis, and increased risk of CVD.2,[[3]](#endnote-4),[[4]](#endnote-5) The incidence of hypertension has increased globally and in the United States (US) and varies by sex in Hispanic/Latino heritage groups.[[5]](#endnote-6),[[6]](#endnote-7) Hypertension treatment and control rates are also lower in Hispanic/Latino vs non-Hispanic white adults.[[7]](#endnote-8),[[8]](#endnote-9),[[9]](#endnote-10) A variety of mechanisms have been postulated for the development of hypertension from prehypertensive and normotensive states, many of which have implications for prevention and treatment.8,9 Prior studies have demonstrated sex-specific differences in both thyroid axis regulation[[10]](#endnote-11),[[11]](#endnote-12) and hypertension which is linked to cardiometabolic risk factors, disorders, complications and genetic susceptibility.[[12]](#endnote-13),[[13]](#endnote-14),[[14]](#endnote-15),[[15]](#endnote-16)

Other studies have suggested that endocrine systems, including thyroid hormones, are key to the development of hypertension and BP regulation.8,9,[[16]](#endnote-17) Thyroid function is controlled through complex feedback of the hypothalamus-pituitary-thyroid (HPT) axis which comprises thyroid stimulating hormone (TSH), and peripheral thyroid hormones – thyroxine (T4) and triiodothyronine (T3). The HPT axis is regulated by negative feedback loops that regulate levels of TSH and circulating thyroid hormones.[[17]](#endnote-18),[[18]](#endnote-19) Local mechanisms involving conversion of T4 to T3 through deiodination and transport of T4 and biologically active T3 to target tissues.17,18 Various measures have been utilized in prior studies to evaluate thyroid axis regulation using indices of pituitary sensitivity to thyroid hormones and ratios which simultaneously assess interdependent hormones and investigate complex hormonal interactions. [[19]](#endnote-20),[[20]](#endnote-21),[[21]](#endnote-22),[[22]](#endnote-23),[[23]](#endnote-24) Sex-specific differences in thyroid hormone regulation,18 including higher prevalence of thyroid disease and thyroid autoimmunity in women, have also been demonstrated.[[24]](#endnote-25),[[25]](#endnote-26)

Thyroid dysfunction, in turn, has been linked to elevated BP through alterations in cardiovascular hemodynamics, increased heart rate and peripheral vascular resistance, and dysregulation of the renin-angiotensin-aldosterone system (RAAS).[[26]](#endnote-27) Prior studies have demonstrated positive associations of hypothyroidism with DBP and hyperthyroidism with SBP.[[27]](#endnote-28),[[28]](#endnote-29) Findings from previous studies, however, have reported mixed associations of thyroid-related hormones within the reference range with BP and hypertension. Positive and null associations of TSH, T3 and T4, have been demonstrated with hypertension and BP.[[29]](#endnote-30),[[30]](#endnote-31),[[31]](#endnote-32),[[32]](#endnote-33),[[33]](#endnote-34),[[34]](#endnote-35),[[35]](#endnote-36),[[36]](#endnote-37),[[37]](#endnote-38),[[38]](#endnote-39),[[39]](#endnote-40),[[40]](#endnote-41),[[41]](#endnote-42),[[42]](#endnote-43) A few studies have also reported sex-specific 29,[[43]](#endnote-44),[[44]](#endnote-45),[[45]](#endnote-46) and positive associations of pituitary sensitivity to thyroid hormones with BP and hypertension.[[46]](#endnote-47),[[47]](#endnote-48) Differences in thyroid profile were demonstrated by race-ethnicity in a representative sample of US adults using the National Health and Nutrition Examination Survey (NHANES).[[48]](#endnote-49),[[49]](#endnote-50) Higher total T4 and prevalence of hyperthyroidism, and lower TSH and prevalence of hypothyroidism were reported among Mexican Americans compared to Non-Hispanic whites.48,49 In our sample of heterogenous Hispanic/Latino adults, thyroid hormone levels varied by Hispanic/Latino background.[[50]](#endnote-51) The present study is unique in evaluating associations of thyroid-related hormones with BP and hypertension in a heterogenous Hispanic/Latino population. In addition, the majority of prior studies were cross-sectional in design and may be impacted by reverse causality with existing hypertension altering thyroid homeostasis. To the best of our knowledge, sex-specific differences and the influence of thyroid axis regulation, including indices of pituitary sensitivity to thyroid hormones on the stages of hypertension development and BP change have not been explored in longitudinal investigations.

The Hispanic Community Health Study/Study of Latinos (HCHS/SOL) is the largest longitudinal cohort of US Hispanic/Latino adults and was designed to assess the prevalence and development of chronic diseases and to distinguish between protective or harmful factors that influence the health of Hispanic/Latino adults.[[51]](#endnote-52) The current ancillary study is nested within the HCHS/SOL cohort with the addition of sex and thyroid-related hormones, which were not initially assessed in the HCHS/SOL cohort baseline examination (V1).[[52]](#endnote-53) We evaluated *a priori* sex-specific associations of thyroid-related hormones with stages of hypertension development and BP change in Hispanic/Latino adults after 6 years of follow-up. Stratification by sex was conducted *a priori* based on biological evidence of sex-specific differences in thyroid axis and BP regulation, and hypertension development. We expanded previously reported sex-specific associations and explored the relationship of thyroid axis regulation with BP change and hypertension development.

**Methods**

**Study population**

Our study analyzed a subsample of the HCHS/SOL from the ancillary study “Persistent Organic Pollutants, Endogenous Hormones, and Diabetes in Latinos.” A full description of the HCHS/SOL study methods and details of the database has been described elsewhere.51 Briefly, HCHS/SOL is a multicenter community-based cohort study that recruited 16,145 Hispanic/Latino individuals from four US urban areas (Bronx, New York (NY); Miami, Florida (FL); Chicago, Illinois (IL); and San Diego, California (CA)) through a multi-stage complex survey sampling design. Baseline examination conducted between 2008 – 2011 collected information on socio-demographic characteristics, lifestyle and clinical factors, and medical history of participants. The first re-examination with an average follow-up of 6 years occurred between 2014 – 2017 and collected information on sociodemographic characteristics, repeat lifestyle and clinical factors, and medical history. Informed consent and Institutional Review Board approval was obtained at each field center, the coordinating center and the central laboratory of the HCHS/SOL study.

Details of the ancillary study has been previously described.52 The ancillary study selected 2,350 participants ages 45-74 years returning for the first 6-year follow-up reexamination (V2) with stratification conducted based on sex and glucose levels at V1, and progression to diabetes at V2 from prediabetes at V1 as described in our previous paper. The exclusion criteria for the ancillary study included: participants who did not provide consent, had diabetes at V1, had no lipid measurements at V1, or were < 45 or > 74 years.50,52 We excluded peri/pre-menopausal women (n=363) focusing on high-risk postmenopausal women to provide a clearer understanding of the pathways influencing the development of hypertension within this high-risk group and to limit the confounding effect of estrogen secretion on thyroid hormone measures.15,[[53]](#endnote-54) We also excluded participants based on use of medications related to hormones and BP dysregulation (n=191; Table S1)[[54]](#endnote-55) resulting in a study population of 1,789 adults (1,073 men and 716 postmenopausal women) ages 45-74 years. Our analysis assessing stages in the development of hypertension further excluded hypertensive individuals at V1 resulting in a study population of 798 adults (484 men and 314 postmenopausal women; (Table S1)).54

**Hypertension and blood pressure measures**

A team of trained HCHS/SOL study staff collected information on blood pressure and BP medication use at V1 and V2. A trained technician measured BP after a 5-minute rest period using an OMRON HEM-907 XL automated sphygmomanometer (Omron Healthcare, Inc., Lake Forest, IL). Three BP measurements were taken on the right arm of seated participants using a cuff which was sized to the upper right arm circumference.5,6 Blood pressure measurements were spaced one minute apart and the average SBP (mmHg), and DBP (mmHg) were obtained. Our primary outcome, hypertension, was defined using the American College of Cardiology/American Heart Association (ACC/AHA) guidelines.9 Participants were classified into three states namely normotension (SBP <120 mmHg and DBP <80 mmHg), elevated blood pressure or prehypertension (SBP ≥120 and ≤129 mmHg and DBP <80 mmHg) and hypertension (SBP ≥130 mmHg or DBP >80 mmHg or self-reported use of hypertension medication). The secondary outcomes for our study included the following BP measures: SBP, DBP and pulse pressure defined as SBP (mmHg) minus DBP (mmHg). When applicable, our secondary analysis of BP measures adjusted for BP medication use to account for the size of potential treatment effect attributed to medication use. To accomplish this, for participants who reported BP medication use, including multiple drugs, we added a constant value of 10 mmHg and 5 mmHg to observed SBP and DBP measures, respectively.[[55]](#endnote-56),[[56]](#endnote-57) We also conducted a sensitivity analysis of BP measures excluding individuals who reported BP medication use.

**Thyroid-related hormones**

Our study examined three thyroid-related hormones, namely TSH, free T4 (FT4), and T3, collected at V1 in men and postmenopausal women. Details of the laboratory assays, limits of detection, and inter-assay coefficients of variation for individual thyroid-related hormones have been previously described.50 Briefly, we analyzed stored serum samples for thyroid-related hormones using a Roche COBAS 6000 chemistry analyzer (Roche Diagnostics, Indianapolis, Indiana). Various methods have been utilized in prior studies to examine thyroid axis regulation.19,20,21,22 First, ratios of hormones are used with the aim of simultaneously assessing interdependent hormones and investigating complex hormonal interactions.[[57]](#endnote-58) Our study examined pituitary response to thyroid hormone feedback and deiodination using ratios of TSH to FT4 and TSH to T3, and T3/FT4 ratio, respectively. Higher levels of T3 to FT4 are consistent with greater deiodination while higher TSH to FT4 and TSH to T3 ratios are consistent with decreased pituitary (TSH) response to thyroid hormones.21

Second, we assessed additional indicators of pituitary sensitivity to thyroid hormones using four indices: Thyrotroph T4 Resistance Index (TT4RI), TSH Index (TSHI), Thyroid Feedback Quantile-based Index (TFQI), and Parametric Thyroid Feedback Quantile-based Index (PTFQI). Details and methods to calculate these indices have been described in previous studies.19,20 Briefly, TSHI was developed to examine the FT4-TSH feedback relationship under the assumption that changes in TSH were mainly due to changes in FT4. TSHI is calculated as Ln TSH (mIU/L) + 0.1345 \* FT4 (pmol/L) while TT4RI is calculated as FT4 (pmol/L) \* TSH (mIU/L). Higher levels of TSHI and TT4RI suggest lower pituitary sensitivity to thyroid hormones. TFQI and PTFQI were developed to minimize the effects of outlier values, with the PTFQI allowing for adjustment for population differences. These indices rank FT4 and TSH and convert them to quantiles between 0 and 1 accounting for sampling weights. TFQI was calculated using the cumulative distribution function (cdf) as cdf FT4-(1-cdf TSH), while PTFI was calculated using the standard normal cdf (Ф) as Ф ((FT4 – μ FT4) / σ FT4) - (1 - Ф ((Ln TSH – μ Ln TSH) / σ Ln TSH)), where μ = corresponding mean for TSH and FT4 in men and women, σ = corresponding standard deviation for TSH and FT4 in men and women. For these indices, higher values indicate reduced pituitary (TSH) sensitivity to thyroid hormones. Specifically, a negative index indicates higher inhibition, or higher sensitivity of the pituitary to FT4, and a positive index indicates lower inhibition, or lower sensitivity to FT4.19,20

For comparison to prior studies which examined associations of thyroid-related hormones with hypertension and BP in euthyroid individuals, we conducted a sub-analysis among euthyroid individuals. Individuals were classified as euthyroid if they were not taking thyroid medications and all thyroid-related hormone levels were in the normal range for the laboratory based upon the following criteria: T3 levels between 60-181 ng/dL, TSH levels between 0.27-4.2 mIU/L and FT4 levels between 0.93-1.70 ng/dL. The study population for the euthyroid analyses was comprised of 912 men and 610 postmenopausal women for the analysis of change in BP measures, while the analysis assessing stages in the development of hypertension excluded euthyroid individuals who were hypertensive at V1 and comprised 407 men and 268 postmenopausal women.

**Covariates**

Using a directed acyclic graph and information from prior literature, we identified several potential confounders (Figure S1).54 At V1, study participants reported their age in years, sex (men, women), Hispanic/Latino background (Dominican, Central American, Cuban, Mexican, Puerto Rican, South American, or more than one background), educational attainment (categorized as less than high school diploma, high school diploma/General Education Development Diploma (GED) or greater than high school diploma or GED), alcohol use (categorized as no current use (never or former alcohol users); low level use (<7 drinks/week in women or <14 drinks/week in men); or high level use (7+ drinks/week in women or 14+ drinks/week in men), smoking status (categorized as never, former, or current smoker), physical activity levels based on the WHO Global Physical Activity Questionnaire (categorized as low, moderate, or high physical activity levels)[[58]](#endnote-59), diet quality per the Alternative Healthy Eating Index score 2010 (AHEI-2010; range from 0 to 110, with higher scores indicating healthier eating habits)[[59]](#endnote-60) and family history of hypertension (categorized as yes or no and derived from whether father, mother or sibling had been diagnosed with hypertension). HCHS/SOL study recruitment sites (Bronx, NY; Chicago, IL; Miami, FL; and San Diego, CA) were recorded based on the location of examination.

Following a standard protocol, trained study personnel collected information on anthropometric measurements, namely weight (kilograms), height (centimeters), hip circumference (centimeters) and waist circumference (centimeters). Waist-to-hip ratio was calculated as waist circumference (cm) divided by hip circumference (cm) while body mass index (BMI) was calculated as weight (kg) divided by height (m2). We examined the change in BMI and waist-to-hip ratio measurements assessed as BMI at V2 minus BMI at V1 and waist-to-hip ratio at V2 minus waist-to-hip ratio at V1, respectively. Participants also reported proxy measures of acculturation including nativity and years of residence in the US, and language spoken at home. Acculturation score from the Multi-Ethnic Study of Atherosclerosis (MESA) was derived by summing scores from these measures of acculturation (range from 0-5 with 0 indicating least acculturation and 5 indicating highest acculturation).[[60]](#endnote-61) Trained study staff also recorded participants’ self-reported medication use which included lipid lowering medication, and nonsteroidal anti-inflammatory drugs (NSAIDs).

We also included information on participants’ prediabetes status (categorized as prediabetic or normoglycemic), biomarker measures of high sensitivity C-reactive protein (hsCRP; mg/L), total lipids (mg/dL) estimated as (2.27 \* total cholesterol (mg/dL) + triglycerides (mg/dL) + 62.31),[[61]](#endnote-62) sleep apnea syndrome (defined as apnea/hypopnea index [3% desaturation] ≥ 15),[[62]](#endnote-63) and chronic kidney disease (defined based on estimated glomerular filtration rate: normal - GFR ≥90 mL/min/1.73m2, mild - GFR 60-90 mL/min/1.73m2, moderate - GFR 30-<60 mL/min/1.73m2, severe - GFR 15-<30 mL/min/1.73m2, and end-stage - GFR <15 mL/min/1.73m2).[[63]](#endnote-64)

**Statistical analyses**

Our analyses accounted for selection into the ancillary study and the complex survey design of the HCHS/SOL study by including sampling weights and accounting for cluster sampling and stratification. Due to missing information on hormone concentrations, BP measures, and covariates (Table S1),54 we examined whether variables with missing data were related to other covariates in our dataset and employed multiple imputation methodology using the STATA MICE procedure (version 17.0)[[64]](#endnote-65) to handle missing data. Details of the multiple imputation analysis have been previously described.50 Our analysis was examined *a priori* by sex using the subpopulation command in STATA. For the descriptive analyses, we accounted for complex survey design and sampling weights for the ancillary study and assessed means (95% confidence intervals) for continuous variables and frequencies (percentages) for categorical variables, and we compared differences using t-tests and X2 tests for continuous and categorical variables, respectively. We performed Z-score standardization of continuous hormones using the corresponding sample mean and standard deviation of hormone measures from the HCHS/SOL ancillary study and present findings as a one standard deviation (1-SD) increase in hormone concentration.

We used Poisson regression models to assess incidence of hypertension incorporating an offset for time elapsed between V1 and V2. Among individuals free of hypertension at V1, we examined associations of baseline thyroid-related hormones with the development of hypertension from normotension and prehypertension at V1 and the development of prehypertension from normotension at V1 and present incidence rate ratios (IRR: 95% CI). Using linear regression models, we examined associations of baseline thyroid-related hormones with change in BP measures between V1 and V2. Furthermore, we assessed non-linear dose-response associations using quartiles of thyroid-related hormones.

Multivariable models adjusted for age, Hispanic/Latino background, HCHS/SOL study recruitment center, acculturation score-MESA, educational attainment, family history of hypertension, NSAIDs, lipid lowering medication use, physical activity level, alcohol consumption, smoking status, AHEI-2010, BMI, waist-to-hip ratio, change in BMI and waist-to-hip ratio, total lipids, hsCRP, prediabetes, sleep apnea, and chronic kidney disease. Models assessing associations of thyroid-related hormones with change in BP measures additionally adjusted for baseline BP measures and the follow-up time between V1 and V2. We also conducted additional analysis to evaluate interaction by sex using Wald tests which assessed the inclusion of sex and cross-product terms (hormone\*sex) to linear and Poisson models. Overall, findings from Wald tests supported inclusion of sex and cross product terms (hormone\*sex) to linear regression models in line with *a priori* sex stratification while Wald tests for Poisson models demonstrated mixed findings (results not shown). All statistical analyses were carried out using STATA (version 17.0, StataCorp, College Station, TX).

**Results**

**Descriptive analyses**

Our analyses included 1,789 adults among whom 716 were postmenopausal women and 1,073 were men. At V1, we observed similar prevalence of hypertension (58% and 59%) and prehypertension (15% and 16%) in men and postmenopausal women. Compared to men, women were older (59.3 years and 55.5 years), less active, had a higher proportion of obesity, were never smokers, were never drinkers, and used more BP medication (Table 1). TSH levels (1.78 mIU/L and 1.63 mIU/L) were higher in women compared to men while T3 (128.7 ng/dL and 123.4 ng/dL) and FT4 (1.16 ng/dL and 1.13 ng/dL) levels were higher in men compared to women (Table 1). Thyroid-related hormone levels were not significantly different by hypertension status at V1 in either men or postmenopausal women (Table S2).54

**Multivariable analyses**

**Association of thyroid-related hormones with change in blood pressure and development of hypertension in postmenopausal women**

In postmenopausal women, a one-unit increase in the ratio of TSH to FT4 (β=0.04 mmHg, 95% CI: 0.01,0.06) and a 1-SD increase in TSH (β=1.68 mmHg, 95% CI: 0.52,2.83) were positively associated with change in DBP, while a 1-SD increase in T3 (β=1.13 mmHg, 95% CI: 0.13,2.13) was positively associated with change in pulse pressure. Conversely, the ratio of TSH to T3, TSHI, and TT4RI were inversely associated with change in pulse pressure (Table 2). The ratio of T3 to FT4 was associated with developing prehypertension from normotension (IRR=1.03, 95% CI: 1.00, 1.05) and hypertension from prehypertension (IRR=1.01, 95% CI: 1.00, 1.02), while a 1-SD increase in T3 (IRR=1.55, 95% CI: 1.13, 2.12) was significantly associated with developing hypertension from prehypertension (Table 3). In contrast, the ratio of TSH to FT4 (IRR=0.85, 95% CI: 0.72, 1.00) and TSH to T3 (IRR=0.65, 95% CI: 0.46, 0.94) were significantly associated with decreased risk of developing hypertension from prehypertension while PTFQI and TFQI were associated with decreased risk of developing prehypertension from normotension (Table 3). We did not observe significant non-linear associations of thyroid-related hormones with change in BP measures among postmenopausal women in quartile models (Table S3).54 FT4 and T3, however, demonstrated non-linear associations with the development of prehypertension from normotension (p for trend=0.027) and hypertension from prehypertension (p for trend=0.023), respectively (Figure 1 and Table S4).54

**Association of thyroid-related hormones with change in blood pressure and development of hypertension in men**

In men, a one-unit increase in the ratio of TSH to FT4 (β=0.30 mmHg, 95% CI: 0.05,0.54) and a 1-SD increase in TSH (β=2.87 mmHg, 95% CI: 0.06,5.69) were also positively associated with change in DBP while a 1-SD increase in T3 (β=1.30 mmHg, 95% CI: 0.28,2.32) was positively associated with change in pulse pressure. In addition, a 1-SD increase in TSH (IRR=1.42, 95% CI: 1.15, 1.75), T3 (IRR=1.17, 95% CI: 1.00, 1.37), and in contrast to the findings in postmenopausal women, a one-unit increase in the ratio of TSH to FT4 (IRR=1.20, 95% CI: 1.07, 1.35) and TSH to T3 (IRR=1.20, 95% CI: 1.07, 1.35) were significantly associated with developing hypertension from prehypertension (Table 4). PTFQI, TSHI and TT4RI were also significantly associated with developing hypertension from prehypertension (Table 4). In quartile models, T3 demonstrated non-linear associations with change in pulse pressure (p for trend=0.005) and the development of hypertension from prehypertension (p for trend=0.007), respectively (Figure 1 and Tables S3 and S5).54

**Euthyroid analyses**

In both linear (Table S6)54 and quartile models (p for trend=0.014; Table S7),54 T3 demonstrated significant associations with change in pulse pressure in euthyroid men. A 1-SD increase in T3 was associated with change in pulse pressure in euthyroid men (β=1.32 mmHg, 95% CI: 0.04,2.60; Table S6),54 while in euthyroid postmenopausal women, a 1-SD increase in T3 was associated with change in SBP (β=3.33 mmHg, 95% CI: 1.29,5.36), change in DBP (β=1.38 mmHg, 95% CI: 0.23,2.54), change in pulse pressure (β=2.03 mmHg, 95% CI: 0.58,3.48; Table S6),54 and the development of hypertension from prehypertension (IRR=1.44, 95% CI: 1.04, 2.00; Table S8).54 In addition, the ratio of TSH to T3 was inversely associated with change in SBP, and T3/FT4 ratio was positively associated with change in pulse pressure, while TSH, TSHI, TT4RI, TSH/T3, ratio and TSH/FT4 ratio were inversely associated with change in pulse pressure in euthyroid postmenopausal women (Table S6).54

**Sensitivity analyses**

Our sensitivity analyses assessing associations of thyroid-related hormones with change in BP measures excluding individuals who reported BP medication use did not demonstrate substantial differences compared to the analysis accounting for potential treatment effect attributable to BP medication use (results not shown).

**Discussion**

We examined associations of thyroid-related hormones with the development of hypertension and BP change in a heterogenous Hispanic/Latino population. In both men and postmenopausal women, increased TSH and ratio of TSH to FT4 (consistent with decreased pituitary response to thyroid hormone feedback) were positively associated with change in DBP, while T3 was positively associated with change in pulse pressure and the development of hypertension from prehypertension. TSH was associated with the development of hypertension from prehypertension in men, while FT4 demonstrated significant non-linear associations with the development of prehypertension in postmenopausal women.

In postmenopausal women but not men, the ratio of T3 to FT4, consistent with greater deiodination, was associated with the development of prehypertension and hypertension. Likewise, increased ratio of TSH to T3, TSHI and TT4RI, consistent with decreased pituitary sensitivity or response to thyroid hormones were associated with change in pulse pressure in postmenopausal women but not men. Differences between men and postmenopausal women in relationships of indices related to sensitivity of the pituitary to thyroid hormones were also seen with stages in the development of hypertension. The ratios of TSH to FT4 and TSH to T3 were inversely associated with the development of hypertension in women, but positively associated in men, consistent with increased sensitivity of the pituitary in women and decreased sensitivity in men. Similarly, increased PTFQI, TSHI, and TT4RI were positively associated with the development of hypertension in men; while PTFQI and TFQI were inversely associated with the development of prehypertension in women also consistent with increased sensitivity of the pituitary in women at the earlier stages in the development of hypertension.

In general, we observed fewer significant associations in the analyses of euthyroid individuals compared to those of the overall cohort, with the relationships of TSH and TSH/FT4 ratio with DBP in men and postmenopausal women and T3, TSH, and TSH/FT4 ratio with the development of hypertension in men becoming non-significant, although the inverse associations of TSH and TSH/FT4 ratio with pulse pressure became significant in women. These findings suggest that thyroid hormone levels outside of the normal reference range may be more important in BP regulation than variation within the normal reference range in this population.

The present study provides new insights on the associations of thyroid-related hormones with the development of hypertension in a heterogenous Hispanic/Latino population using updated ACC/AHA guidelines. We extended previous studies and have addressed questions related to sex-specific associations in the complex interplay of thyroid-related hormones and measures of pituitary sensitivity to thyroid hormones with BP change and stages in the development of hypertension. Our results with T3 are consistent with the majority of studies conducted in other populations. Similar to our study, T3 was positively associated with hypertension and BP within and outside the reference range in studies conducted in United States, European and Chinese populations.34,35,36,37 Jamal et al, however, reported associations of FT3 with pulse rate in both men and women, while FT4 but not T3 was associated with pulse pressure in their sample of Chinese adults.44 Our findings of increased pulse pressure with T3 in both men and postmenopausal women warrants additional investigation given that pulse pressure is a marker of arterial stiffness and increased risk of CVD.[[65]](#endnote-66),[[66]](#endnote-67) In prior studies, sex-specific43,44,45 and mixed associations were demonstrated for TSH with hypertension and BP in euthyroid individuals, the general population,individuals with essential hypertension and primary hyperaldosteronism and individuals without thyroid cysts.29,30,31,32,33,42,[[67]](#endnote-68),[[68]](#endnote-69) While we found significant non-linear inverse associations of FT4 with development of prehypertension from normotension in postmenopausal women, some studies conducted in European and Chinese adults have demonstrated positive associations of FT4 with hypertension and BP but were cross-sectional in nature.44,45

The mixed findings from previous studies suggest that thyroid-related hormones may not sufficiently explain the relationship between the thyroid axis and BP regulation. To the best of our knowledge, this is the first study examining longitudinal associations of indicators of pituitary sensitivity to thyroid hormones with BP change and stages in the development of hypertension. While we found positive associations of TSH/FT4 ratio with change in DBP in men and postmenopausal women, associations of indices of pituitary sensitivity to thyroid hormones with the development of hypertension differed for men and postmenopausal women. We observed inverse associations in women and positive associations in men, consistent with increased sensitivity in women and decreased sensitivity in men. In postmenopausal women but not men, we also observed associations with prehypertension suggesting that other mechanisms may be involved early in the disease process.

Both TFQI and PTFQI measures account for outlier values in the presence of thyroid dysfunction and have been linked to diabetes, metabolic disease, and dyslipidemia in multiple investigations.20,22,47 Only a few cross-sectional studies have explored relationships between indices of pituitary sensitivity to thyroid hormones with BP and hypertension. Consistent with our findings in men, studies conducted in Iran and Chinese adults demonstrated positive associations of TFQI, PTFQI, TSHI, and TT4RI with hypertension.46,47 Positive cross-sectional associations were reported for indices of pituitary sensitivity to thyroid hormones with BP but the analysis by Yang et al. was not stratified by sex.34 In addition, some studies have shown associations of hypothyroidism with DBP,[[69]](#endnote-70),[[70]](#endnote-71),[[71]](#endnote-72),[[72]](#endnote-73) particularly in women[[73]](#endnote-74) while hyperthyroidism was associated with SBP.28 The present study could not examine associations of thyroid-related hormones with isolated systolic and diastolic hypertension because of limited sample size. Nevertheless, future longitudinal studies are important to further examine these relationships especially as they relate to indices of pituitary sensitivity to thyroid hormones.

The mechanisms through which thyroid-related hormones are linked to the development of hypertension are complex and may occur through cardiometabolic effects such as hyperlipidemia, endothelial dysfunction, changes in vascular resistance, renal hemodynamics, and sodium homeostasis.[[74]](#endnote-75),[[75]](#endnote-76),[[76]](#endnote-77) Thyroid dysfunction characterized by higher TSH and T3 and lower T4 are related to obesity, insulin resistance, and increased dysregulation of the HPT axis.[[77]](#endnote-78) Glucose dysregulation, in turn, has also been related to hypertension.8,9,47 Thyroid dysfunction observed in hypothyroidism impacts BP regulation through decreased production of nitric oxide, endothelial dysfunction, and impaired relaxation of vascular smooth muscle.[[78]](#endnote-79) Hyperthyroidism is linked to hypertension through immune system and RAAS pathway impairments, increased peripheral vascular resistance, heart rate and cardiac output, and reduced systemic vascular resistance.26,28

In our study, the ratio of T3 to FT4, which indicates increased deiodinase enzyme activity, was positively associated with the development of hypertension and prehypertension in postmenopausal women but not men. The relevance of deiodination is supported by a previous study which demonstrated associations of type 2 iodothyronine deiodinase gene polymorphisms with hypertension in euthyroid individuals.[[79]](#endnote-80) Sex-specific differences in the activity of the HPT axis and thyroid function regulation are not fully understood but may be related to the influence of sex steroid hormones and the activity of leptin, deiodinases, and thyrotropin releasing hormone which differentially impact basal conditions, stress responses, and energy homeostasis in men and women.[[80]](#endnote-81) Future longitudinal studies examining relationships between thyroid-related hormones and BP regulation in premenopausal women are also critical to further delineate effects mediated by sex steroids.

The present study has considerable strengths. Our analysis is novel in examining prospective associations of thyroid-related hormones and indicators of deiodination and pituitary sensitivity to thyroid hormones with the development of hypertension and BP change. We assessed associations of hormones with longitudinal change in various BP measures and stages in the development of hypertension after an average follow-up of 6 years. Our study carefully classified menopause status using endogenous hormone levels and clinical data and excluded individuals using medications related to hormones. We applied multiple imputation methodology to prevent loss of information and maintained a robust sample size with adequate statistical power to detect observed effects. Finally, we included a wide range of covariates as potential confounders to better account for the complex multifactorial disease etiology of hypertension.

Our study is also subject to some limitations. First, multiple comparisons were not accounted for since these were prespecified hypotheses; however, the number of comparisons presents the possibility of false positive findings highlighting the need to replicate these findings in other studies.[[81]](#endnote-82) Second, we included a limited number of thyroid-related hormones and utilized only baseline measurement of hormones. Hence, our findings may not be reflective of an individual’s hormone concentrations across time. Third, we excluded participants based on medication use influencing thyroid hormones at V1 and evaluated associations among euthyroid individuals in a sub-analysis. We measured thyroid-related hormones only at V1. We do not expect a large number will start thyroid medication between V1 and V2, although we do not have a way to assess the impact of those who do initiate thyroid therapy.. Fourth, hypertension was not the primary endpoint of our ancillary study where Hispanic/Latino adults free of diabetes at V1 were selected based on prediabetes status (normoglycemia or prediabetes) to assess associations of persistent organic pollutants exposure and endogenous hormones with the development of diabetes. However, our previous study did not find substantial differences in demographic characteristics for the ancillary vs full HCHS/SOL cohort.50 We also adjusted the present analysis for prediabetes status to account for potential selection bias. Fifth, our analysis of incident hypertension and the sub-analysis in euthyroid individuals may be limited in sample size. However, we found some significant and robust associations that make our findings noteworthy. Sixth, lifestyle covariates, some medication use, and measures of socio-economic status were assessed by self-report and are subject to potential recall bias. Seventh, our results may not be generalizable to non-Hispanic populations..

**Conclusions**

In an adult Hispanic/Latino population, we observed positive associations of TSH and TSH/FT4 ratio with change in DBP and T3 with change in pulse pressure in both men and postmenopausal women. Overall, T3 was associated with the development of hypertension but not prehypertension in men and postmenopausal women, while TSH was associated with the development of hypertension in men suggesting that these hormones are operative at a later stage in hypertension development. We observed sex-specific differences in the association of T3/FT4 ratio and various indicators of pituitary sensitivity to thyroid hormones with pulse pressure, a marker of arterial stiffness, and with the development of hypertension and prehypertension. In the present study, FT4 demonstrated non-linear associations with the development of prehypertension from normotension only in postmenopausal women. Sex-specific differences observed in the present study warrants additional investigation in future longitudinal studies.

**Table legends**

Table 1. Sociodemographic characteristics of Hispanic/Latino men and postmenopausal women at baseline examination

Table 2. Multivariable linear regression models for associations of endogenous thyroid-related hormones with change in blood pressure measures among Hispanic/Latino men and postmenopausal women

Table 3. Multivariable Poisson regression models for prospective associations of endogenous thyroid-related hormones with incident prehypertension and hypertension among postmenopausal Hispanic/Latino women; N=314

Table 4. Multivariable Poisson regression models for prospective associations of endogenous thyroid-related hormones with incident prehypertension and hypertension among Hispanic/Latino men; N=484

Figure legends

Figure 1. Significant non-linear associations of endogenous thyroid-related hormones in quartiles with change in blood pressure, incident prehypertension and hypertension among Hispanic/Latino men and postmenopausal women

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