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Thyroid Hormones and Diabetes in Euthyroid Hispanic/Latino Adults of Diverse Backgrounds: HCHS/SOL

Victoria Persky,[1] Chibuzor Abasilim,[1] Konstantina Tsintsifas,[1] Tessa Day,[1] Robert M. Sargis,[2] Martha Daviglus,[3] Jianwen Cai,[4] Sally Freels,[1] Robert Kaplan,[5,6] Carmen R. Isasi,[5] Amber Pirzada,[3] Michelle L. Meyer,[7] Gregory A. Talavera,[8] Bharat Thyagarajan,[9] Shivani Agarwal,[10] Noel Chavez,[11] Arielle Grieco,[1] and Mary E. Turyk[1]

[1]Division of Epidemiology and Biostatistics, School of Public Health, University of Illinois Chicago, Chicago, IL 60612, USA
[2]Division of Endocrinology, Diabetes, and Metabolism, Department of Medicine, University of Illinois Chicago and Medical Service, Jesse Brown VA Medical Center, Chicago, IL 60612, USA
[3]Institute for Minority Health Research, University of Illinois Chicago, Chicago, IL 60612, USA
[4]Department of Biostatistics, University of North Carolina at Chapel Hill, Chapel Hill, NC 27599, USA
[5]Department of Epidemiology and Population Health, Albert Einstein College of Medicine, Bronx, NY 10461, USA
[6]Public Health Sciences Division, Fred Hutchinson Cancer Center, Seattle, WA 98109, USA
[7]Department of Emergency Medicine, University of North Carolina at Chapel Hill, Chapel Hill, NC 27599, USA
[8]Department of Psychology, San Diego State University, San Diego, CA 92182, USA
[9]Department of Laboratory Medicine and Pathology, University of Minnesota, Minneapolis, MN 55415, USA
[10]Fleischer Institute for Diabetes and Metabolism, Albert Einstein College of Medicine, Montefiore Medical Center, Bronx, NY 10461, USA
[11]Division of Community Health Sciences, University of Illinois Chicago, Chicago, IL 60612, USA

Correspondence: Victoria Persky, MD, Division of Epidemiology and Biostatistics, School of Public Health, University of Illinois Chicago, 1603 Taylor St, Chicago, IL 60612, USA. Email: vwpersky@uic.edu.

Abstract

Context: Previous studies have demonstrated associations of endogenous thyroid hormones with diabetes; less is known about stages of diabetes development at which they are operative, mechanisms of associations, and the role of the hypothalamic-pituitary-thyroid axis.

Objective: This study examined associations of thyroid hormones with incident prediabetes and diabetes and with changes in glycemic traits in the Hispanic Community Health Study/Study of Latinos (HCHS/SOL), the largest cohort of Hispanic/Latino adults with diverse backgrounds in the United States.

Methods: The study includes 592 postmenopausal euthyroid women and 868 euthyroid men aged 45 to 74 years without diabetes at baseline participating in the Hispanic Community Health Study/Study of Latinos (HCHS/SOL). Baseline hormones included thyrotropin (TSH), free thyroxine (FT4), total triiodothyronine (T3), and indices calculated from thyroid hormones evaluating pituitary sensitivity to thyroid hormone. Transitions to diabetes and prediabetes, and changes in glycemic traits determined at the 6-year follow-up visit, were examined using multivariable Poisson and linear regressions.

Results: Among women, T3 (incident rate ratio [IRR] = 1.65; 95% CI, 1.22-2.24; $P = .001$) and TSH (IRR = 2.09; 95% CI, 1.01-4.33; $P = .047$) were positively, while FT4 (IRR = 0.59; 95% CI, 0.39-0.88; $P = .011$) was inversely, associated with transition from prediabetes to diabetes. Among men, the T3/FT4 ratio was positively associated with transition from normoglycemia to prediabetes but not from prediabetes to diabetes. Indices measuring sensitivity of the pituitary to thyroid hormone suggested increased sensitivity in men who transitioned from prediabetes to diabetes.

Conclusion: Positive associations in women of T3 and TSH and inverse associations of FT4, as well as inverse associations of thyroid indices in men with transition from prediabetes to diabetes, but not from normoglycemia to diabetes, suggest decreased pituitary sensitivity to thyroid hormones in women and increased sensitivity in men later in the development of diabetes.

Key Words: thyoid, hormones, diabetes, prediabetes

Abbreviations: BMI, body mass index; BP, blood pressure; CRP, C-reactive protein; CV, coefficient of variation; FPG, fasting plasma glucose; FT4, free thyroxine; HbA_{1c}, glycated hemoglobin A_{1c}; HCHS/SOL, Hispanic Community Health Study/Study of Latinos; HDL, high-density lipoprotein; HOMA-B, Homeostasis Model Assessment Index of β-Cell Function; HOMA-IR, Homeostasis Model Assessment Index of Insulin Resistance; HPT, hypothalamic-pituitary-thyroid; hsCRP, high-sensitivity C-reactive protein; IRR, incident rate ratio; MESA, Multi-Ethnic Study of Atherosclerosis; OGTT, oral glucose tolerance test; PTFQI, Parametric Thyroid Feedback Quantile-based Index; T2D, type 2 diabetes; T3, total triiodothyronine; TFQI, Thyroid Feedback Quantile-based Index; TSH, thyrotropin; TSHI, TSH Index; TT4RI, Thyrotroph T4 Resistance Index; WHR, waist-to-hip ratio.

Currently, 37.1 million adults or 14.7% of the US adult population have diabetes, most of which is type 2 diabetes (T2D); an additional 38.0% have prediabetes and are at heightened risk of developing T2D [1]. Diabetes prevalence rates among Hispanic/Latinos adults are among the highest in the United States with 15.5% of Hispanic individuals, 17.4% of Black individuals, and 13.6% of White individuals having the disease [1]. Among subgroups of adult Hispanic/Latinos, Mexican

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and Puerto Rican groups have the highest rates of diagnosed diabetes. The development of prediabetes and T2D occurs over several decades, first involving insulin resistance in peripheral tissues, including muscle, adipose, and liver, followed by pancreatic β-cell failure and loss of insulin secretory capacity in the context of increased insulin demand [2]. Thus, multiple factors contribute to diabetes pathogenesis, including genetic susceptibility, disruptions in glucose transporter type 4 (GLUT4) responsible for insulin-dependent glucose uptake into muscle cells, adipose tissue inflammation, defects in lipid and energy metabolism, mitochondrial dysfunction, and oxidative stress.

One of the factors contributing to diabetes is thyroid dysregulation. Previous studies have shown that both hypothyroidism and hyperthyroidism are associated with diabetes [3], with evidence that race/ethnicity may in turn affect thyroid homeostasis. A previous study from the National Health and Nutrition Examination Survey (NHANES) III noted that thyrotropin (TSH) levels in Mexican Americans were higher than those in Black individuals [4]. In the diverse Hispanic cohort serving as the basis for this investigation, TSH levels were lower only in Hispanic men of more than one heritage (vs Mexican men), while free thyroxine (FT4) levels were higher in Cuban men (vs Mexican men) and Puerto Rican women (vs Mexican women). Total triiodothyronine (T3) was lower in men of Mexican than in those of Cuban, multiheritage, and Central American ethnicity, while in women, T3 was lower in those of Mexican compared with those of not only Cuban and Central American, but also of Dominican and Puerto Rican ethnicity [5].

Specific mechanisms for effects of alterations in thyroid hormones on diabetes have not been delineated, nor has the impact of thyroid dysregulation on the stages of diabetes development or the levels at which thyroid hormones might be operative. The effects of thyroid hormones on muscle and hepatic glucose uptake are also unclear. Previous literature suggests that decreased muscle glucose uptake is primarily represented by postload glucose, while impaired suppression of hepatic glucose release is primarily represented by fasting glucose, while also contributing to postload glucose [6]. In addition, the complex effects of the hypothalamic-pituitary-thyroid (HPT) axis on glucose homeostasis are poorly understood. Recently, several indices have been developed to measure the sensitivity of the pituitary to changes in peripheral thyroid hormones and applied in cross-sectional studies to investigate relationships between the biology of the thyroid axis and prediabetes/diabetes [7-9]. Application of these indices in longitudinal studies with measures of glycemic traits, as well as prediabetes and diabetes, has been lacking. Finally, most previous studies have been cross-sectional, leaving open the possibility of reverse causality, with existing diabetes altering thyroid homeostasis. This study addresses these gaps in the literature by examining associations of thyroid hormones with incident prediabetes and diabetes and with changes in glycemic traits in the Hispanic Community Health Study/Study of Latinos (HCHS/SOL), the largest cohort of Hispanic/Latino adults with diverse backgrounds in the United States at high risk for diabetes.

Materials and Methods

The HCHS/SOL, a prospective cohort of 16 415 Hispanic/Latino adults with high rates of diabetes, offers a unique opportunity to examine effects of thyroid hormones on diabetes and prediabetes in a large diverse prospective cohort with substantial variation in the prevalence of the disease. Details of the HCHS/SOL study have been described elsewhere [10-12]. After institutional research committees approved the investigation and consent was obtained from participants, 16 415 Hispanic/Latino adults aged 18 to 74 years were recruited from San Diego, California; Bronx, New York; Miami, Florida; and Chicago, Illinois, from March 2008 through June 2011. Recruitment was based on a 2-stage probability sampling of households, with stratified random selection of census blocks followed by stratified random selection of households, oversampling of blocks with higher concentrations of Hispanic individuals, households with Hispanic/Latino surnames, and people aged 45 to 74 years. Sampling weights were then generated to reflect the probabilities of selection at each stage. Participants included individuals of Mexican, Puerto Rican, Cuban, Dominican, Central American, and South American backgrounds.

Baseline examination (visit 1) included questionnaire data on demographic factors; education; income; acculturation; years of residence in the United States; language preference; physical activity; weight at age 21, 45, and 65; weight change in the last year; smoking and medical history; medication use; reproductive and breast feeding history; two 24-hour dietary recalls; dietary frequency; blood pressure; height; weight; waist-to-hip ratio (WHR); and fasting serum and plasma samples, with measurements that included total, low-density lipoprotein, and high-density lipoprotein (HDL) cholesterol, triglycerides, fasting glucose, 2-hour postload glucose in the subset of participants with normal fasting glucose without a diabetes diagnosis and with intact stomach and intestine, insulin, glycated hemoglobin A_{1c} (HbA_{1c}), and high-sensitivity C-reactive protein (hsCRP). From 2014 to 2017, the study implemented on average a 6-year follow-up (visit 2), which included repeat lifestyle and medical history, height, weight, WHR, dietary history, lipids, fasting glucose and insulin, postload glucose, and HbA_{1c}. Prior to the baseline (visit 1) and follow-up (visit 2) visit, participants were instructed to refrain from physical activity and smoking, and fast for at least 8 hours with allowances for water and essential medication.

The Persistent Organic Pollutants, Endogenous Hormones and Diabetes in Latinos Ancillary Study selected participants ages 45 to 74 years at baseline from the HCHS/SOL study using a case-cohort study design. To select the random sample, participants were stratified by baseline glucose measurements (1176 with prediabetes at baseline and 1174 with normal baseline glucose measurements), approximately equally divided between men and women ages 45 to 74 years (1148 men and 1202 women), and with only 1 participant per household within each sex and blood glucose subgroup. Participants who transitioned from prediabetes to diabetes during the follow-up period were oversampled to ensure that approximately half of those with prediabetes had transitioned to diabetes. Of the 2343 HCHS/SOL ancillary study participants with hormone measurements available, 868 euthyroid men and 592 euthyroid women were included in the final analysis after exclusions summarized in Fig. 1 and Supplementary Table S1 [13].

Hormone Measurements

Serum samples for thyroid hormone measurements were collected at the baseline (visit 1) HCHS/SOL examination visit. All hormones were measured using a Roche COBAS 6000 chemistry analyzer (Roche Diagnostics). TSH was measured

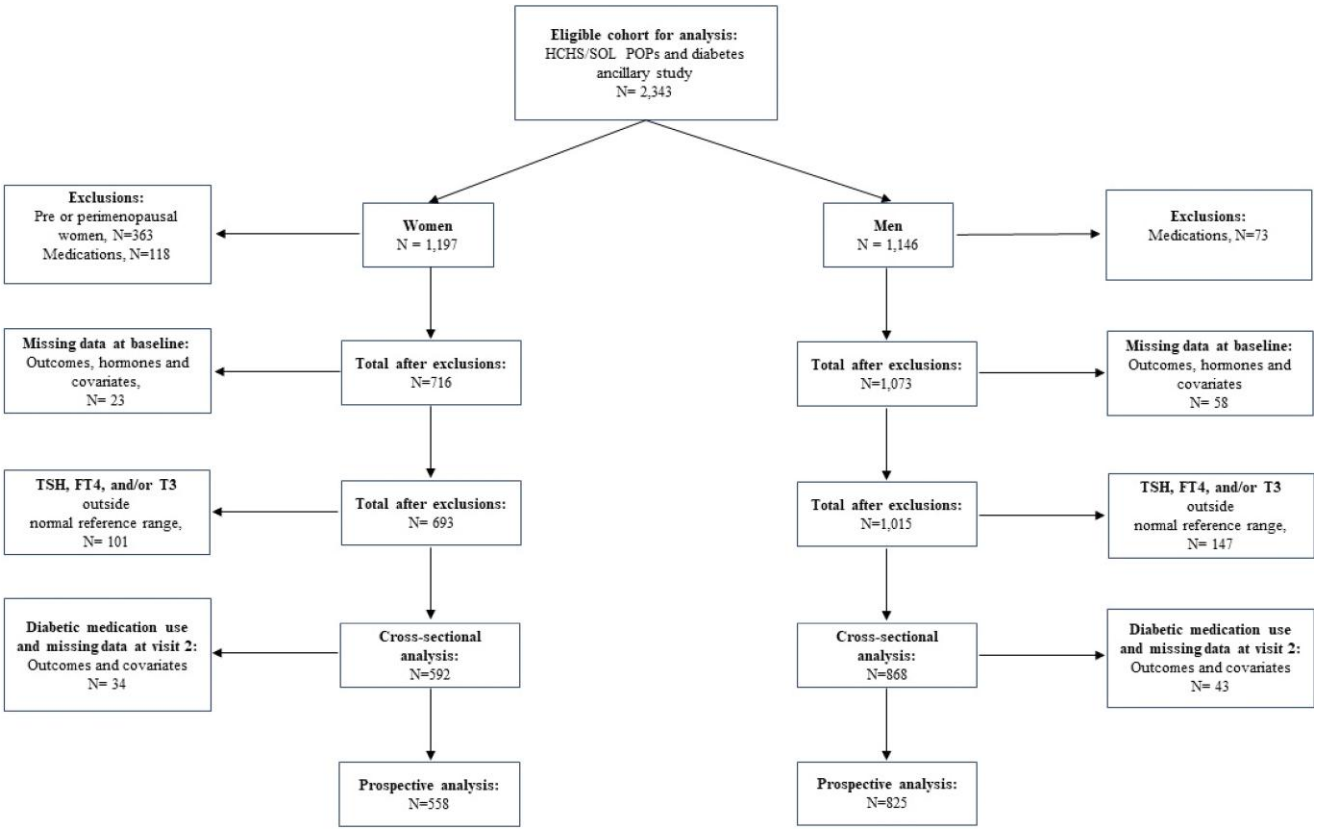

Figure 1. Study selection[a].

[a]More details regarding the exclusions can be found in Supplementary Table S1 (S1).

using a TSH reagent/sandwich immunoassay method/electrochemiluminescence (catalog No. 11731459122, RRID: AB_2756377, Roche Diagnostics). This method has been standardized against the second International Reference Preparation (IRP) World Health Organization Reference Standard 80/558. Interassay coefficients of variation (CVs) were 2.1% at 1.596 mIU/L and 2.9% at 9.037 mIU/L. FT4 was measured using a FT4 reagent/competitive immunoassay/electrochemiluminescence (catalog No. 06437281160, RRID:AB_2924686, Roche Diagnostics). This method has been standardized by isotope dilution gas chromatography–mass spectrometry. Interassay CVs were 2.5% at 1.16 ng/dL and 2.6% at 2.64 ng/dL. Total T3 was measured using a T3 reagent/competitive immunoassay/electrochemiluminescence (catalog No. 11731360122, RRID:AB_2827369, Roche Diagnostics). This method has been standardized against reference standards by weighing T3 into analyte-free human serum matrix. Interassay CVs were 6.0% at 152.4 ng/dL and 7.2% at 353.00 ng/dL. All hormone assays were Food and Drug Administration approved and independently assessed with external proficiency testing materials. All assays were performed by the Advanced Research & Diagnostics Laboratory at the University of Minnesota, which is a Clinical Laboratory Improvement Amendments and College of American Pathologists–certified laboratory.

We defined euthyroid as having TSH, FT4, and T3 levels in the normal reference range by the laboratory that performed the measurements without utilization of thyroid medications. For TSH, normal reference ranges were 0.27 to 4.20 mIU/L; for FT4, normal reference ranges were 0.93 to 1.70 ng/dL; and for T3 the normal reference range was 60 to 170 ng/dL.

Outcome Assessment

All participants had fasting plasma glucose (FPG) and HbA_{1c} measured. FPG was measured in EDTA plasma using a hexokinase enzymatic method (Roche Diagnostics) on a Roche Modular P chemistry analyzer (Roche Diagnostics). HbA_{1c} was measured in EDTA whole blood using a Tosch G7 automated high-performance liquid chromatography analyzer (Tosch Bioscience Inc). Insulin was measured in serum using a commercial enzyme-linked immunosorbent assay (Mercodia AB).

Following the initial fasting blood draw, all participants who did not report taking antihyperglycemic medications, previous diagnosis with diabetes, and/or who had an FPG of less than 150 mg/dL underwent a standard 75-g 2-hour oral glucose tolerance test (OGTT), and 2-hour plasma glucose was measured. Homeostasis Model Assessment Index of Insulin Resistance (HOMA-IR) was calculated as the product of fasting glucose (mg/dL) and fasting insulin (mU/L) divided by 405, while Homeostasis Model Assessment Index of β-Cell Function (HOMA-B) was calculated as the product of fasting insulin (mU/L) and 360 divided by fasting glucose (mg/dL) minus 63. We defined prediabetes at baseline examination among participants if they met one of the following criteria: (1) laboratory tests outside the diabetic range (fasting time >8 hours and FPG = 100-125 mg/dL [5.6-6.9 mmol/L]; or 2-hour postload OGTT = 140-199 mg/dL [7.8-11.0 mmol/L];

or HbA_{1c} = 5.7%-6.4%), and (2) no self-reported diabetes or diabetes medication use. Normoglycemia was defined as (1) fasting time greater than 8 hours and FPG less than 100 mg/dL (5.6 mmol/L) and 2-hour postload glucose less than 140 mg/dL (7.8 mmol/L); and HbA_{1c} less than 5.7%, and (2) no self-reported diabetes or diabetes medication use.

Diabetes at study visit 2 was classified by HCHS/SOL as meeting one of the following criteria: (1) impaired fasting glucose (fasting time >8 hours and FPG ≥ 126 mg/dL [7.0 mmol/L] or fasting time ≤8 hours and fasting glucose ≥200 mg/dL [11.1 mmol/L]); or (2) impaired glucose tolerance (2-hour postload OGTT ≥ 200 mg/dL [11.1 mmol/L]), or (3) impaired HbA_{1c} (HbA_{1c} ≥ 6.5%) or (4) self-reported diabetes (American Diabetes Association guidelines plus self-reported diabetes) [14]. Furthermore, for the prospective analysis, we examined progression from normoglycemia to prediabetes, as well as to diabetes and from prediabetes to diabetes at study visit 2. We also examined continuous change scores for the following glycemic measures: HbA_{1c}, fasting glucose, postload glucose, fasting insulin, HOMA-B, and HOMA-IR. Change scores were calculated as the difference in glycemic measurement between study visit 2 and baseline examination.

Covariates

Covariates have been described in detail in a previous publication [15]. They included age, sex, HCHS/SOL recruitment center, educational attainment, Hispanic/Latino heritage (Dominican, Central American, Cuban, Mexican, Puerto Rican, South American, more than one other heritage), smoking status, annual household income, health insurance, alcohol consumption, physical activity level based on the World Health Organization Global Physical Activity Questionnaire [16], diet quality score per the Alternative Healthy Eating Index (AHEI)-2010 [17], family history of diabetes, and history of gestational diabetes only among female participants [15]. Anthropometric measurements of weight (kilograms), height (centimeters), hip (centimeters), and waist circumference (centimeters) were performed by trained study staff following a standard protocol. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared, while WHR was calculated as waist circumference in centimeters divided by hip measurement in centimeters. For the longitudinal analysis assessing continuous change scores in glycemic measures in absolute levels, we examined change in BMI and WHR measurements (visit 2—baseline). Acculturation score—Multi-Ethnic Study of Atherosclerosis (MESA) [18] (range, 0-5 with 0 indicating least acculturation and 5 indicating most acculturation) was defined by summing scores from proxy measures of acculturation—nativity and years of residence in the United States, and primary language spoken at home.

Participants' self-reported medication use was recorded by trained study staff at baseline examination. Three blood pressure (BP) measurements were taken on the right arm by a trained technician and the average systolic BP (mm Hg) and diastolic BP (mm Hg) were obtained. Hypertension was defined as average systolic BP greater than or equal to 140 mm Hg or average diastolic BP greater than or equal to 90 mm Hg or self-reported use of antihypertensive medication. Among women, menopause status was determined by a series of steps that included participant's age, history of bilateral oophorectomy, menstruation status, and pituitary hormones. Furthermore, measurements of lipid metabolism and inflammation at baseline examination namely hsCRP (mg/L), total cholesterol (mg/dL), triglycerides (mg/dL), HDL cholesterol (mg/dL), and low-density lipoprotein cholesterol (mg/dL) were included as covariates.

Statistical Analyses

Our analysis accounted for the complex sampling design (stratification, clustering, and unequal probability of selection) used to select participants for the HCHS/SOL, with an additional adjustment to the sampling weights to account for the sampling design of this ancillary study cohort. Statistical analyses were conducted using complex survey procedures in SAS 9.4 (SAS Institute Inc) and STATA (version 17.0, StataCorp). Due to skewed data, glycemic measures, namely fasting insulin, HOMA-B, HOMA-IR, insulin post OGTT, and glucose post OGTT, were natural log (ln)-transformed among male and female participants.

For descriptive analyses, means (95% CI) for continuous data and frequencies (percentages) for categorical data were assessed. Differences between groups were evaluated using t tests for continuous data and χ^2 tests for categorical data. SAS domain statements were used to correctly specify subpopulations in all subgroup analyses. For the descriptive analyses, we present findings for overall tests and pairwise contrasts across Hispanic/Latino background groups, MESA nativity subscore, cigarette smoking group, and recruitment center, although when overall tests were not statistically significant, pairwise contrasts should be interpreted with caution. Pearson correlation coefficients were used to examine correlations between hormones. Both the cross-sectional and longitudinal analyses were stratified by sex a priori. We standardized hormone measurements for our analyses using the corresponding sample mean and SD of the hormone measure from the current HCHS/SOL ancillary study. Cross-sectional associations of thyroid hormones with continuous glycemic measures were modeled using multivariable linear regression, while associations of thyroid hormones with prediabetes status were modeled using multivariable logistic regression. Longitudinal associations of thyroid hormones with diabetes incidence and progression were modeled using Poisson regression while associations with change scores for continuous glycemic measures were modeled using multivariable linear regression.

Covariates were evaluated as potential confounders by constructing nested models. For the cross-sectional analyses, level 1 models adjusted for age, BMI, WHR, acculturation score—MESA, HCHS/SOL study site, Hispanic/Latino ethnicity, educational attainment, statin medication use, family history of diabetes, and gestational diabetes (women only). Level 2 models adjusted for covariates in level 1 plus lifestyle factors such as cigarette use, alcohol use, AHEI, and physical activity. Level 3 models adjusted for covariates in level 2 plus hypertension, high triglycerides (≥200 mg/dL), and low HDL (<40 mg/dL), while level 4 models adjusted for covariates in level 3 plus CRP. Moreover, for the longitudinal analysis examining change scores in glycemic measures: Level 1 models additionally adjusted for baseline levels of each glycemic measure, follow-up time between visit 1 and 2, prediabetes status at baseline, and antidiabetic medication use at follow-up, while level 2 models additionally adjusted for change in BMI and WHR measurements. Other covariate adjustments for levels

1 through 4 in the longitudinal analysis were consistent with the cross-sectional analysis. Finally, before proceeding to higher level models, we examined model fit using R-Square and AIC for linear and logistic regression models, respectively. Using level 1 models, we examined model fit for associations of untransformed and ln-transformed hormones with (1) prediabetes and (2) untransformed and ln-transformed glycemic measures. We also determined whether BMI and WHR were independent predictors in both cross-sectional and longitudinal analyses by exploring change in estimates of hormone concentrations adjusted for BMI alone, WHR alone, and both BMI and WHR included in the model. We found no difference in estimates of interest across these alternative approaches and included both BMI and WHR in subsequent level 2 to 4 models. Overall results did not substantially vary among the different level models. Therefore, for simplicity, only level 4 model results are presented in the tables.

For the longitudinal analysis, to identify groups at higher risk, we examined potential effect modification of thyroid hormones with age and baseline obesity by including a product term (thyroid hormone × effect modifier) in level 4 models. Product terms with a P value less than .05 were considered statistically significant, and models were subsequently stratified by significant effect modifiers as follows: baseline BMI greater than or equal to vs less than the median (27.9 for men; 29.1 for women), and age greater than or equal to the median vs less than the median (52 years and 56 years for men and women, respectively).

Using Poisson regression models stratified by sex and adjusted for age and BMI at baseline examination, we conducted secondary analyses examining the relationships between thyroid hormones and transition from prediabetes to diabetes using 3 different phenotypes of prediabetes (impaired fasting glucose only, impaired glucose tolerance only, and either impaired fasting glucose or impaired glucose tolerance). Only fasting glucose prediabetes was defined by elevated fasting plasma glucose (100-125 mg/dL) with postload glucose normal at baseline (<140 mg/dL) and only impaired postload glucose was defined as (140-199 mg/dL) with fasting glucose normal at baseline (<100 mg/dL). In addition, we examined associations of thyroid hormones with incidence of diabetes in the combined cohort of those with normoglycemia and prediabetes at baseline. Likewise, we examined transition from normoglycemia to prediabetes defined only by elevated FPG, only elevated postload glucose, and both elevated FPG and postload glucose. For this subgroup analysis, we used multinomial logistic regression models because of limitations of Poisson regression with nominal outcomes, to examine associations adjusting for age and BMI at baseline examination and time elapsed between visit 1 and visit 2.

Finally, we explored the HPT axis using sensitivity indices previously described [7-9, 19]. TSH/FT4 is a rough index of the HPT axis. More recent indices have been developed to examine the axis further. The TSH Index (TSHI) was originally developed to examine the FT4-TSH feedback relationship within the traditional reference ranges, with β coefficients chosen under the assumption that changes in TSH were mainly due to changes in FT4 [19]. TSHI is calculated as Ln TSH (mIU/L) + 0.1345 × FT4 (pmol/L). A similar index is the Thyrotroph T4 Resistance Index (TT4RI) calculated as FT4 (pmol/L) × TSH (mIU/L). Higher levels of TSHI and TT4RI suggest lower pituitary sensitivity to thyroid hormones. The Thyroid Feedback Quantile-based Index (TFQI) and the Parametric Thyroid Feedback Quantile-based Index (PTFQI) were subsequently developed to minimize the effects of outlier values, with the PTFQI allowing for adjustment for population differences [8]. 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 (Φ) as $\Phi((FT4 - \mu FT4)/\sigma FT4) - (1 - \Phi((Ln TSH - \mu Ln TSH)/\sigma Ln TSH))$, where μ = the corresponding mean for TSH and FT4 in men and women, and σ = the corresponding SD for TSH and FT4 in men and women. PTFQI and TFQI range between −1 and 1, where the negative index indicates higher inhibition by FT4, or higher sensitivity than expected, and a positive index indicates lower inhibition, or lower sensitivity to FT4. In the last several years these indices have been used to examine relationships of pituitary sensitivity with diabetes and metabolic syndrome in NHANES [8], with diabetes and hypertension in Tehran [7], and with prediabetes in China [9].

Results

Hormones were measured in a total of 1197 women and 1146 men. Exclusions are summarized in Fig. 1 and Supplementary Table S1 [13], with criteria not mutually exclusive. Among women, the largest number of exclusions were those who were premenopausal or perimenopausal (n = 363), followed by those using sex steroids (n = 41) or thyroid hormones (n = 90). The largest exclusions for men were for 5-α reductase inhibitors (n = 31) followed by use of thyroid medications (n = 21). In addition, 23 women and 58 men were excluded because of missing data. Finally, 101 women and 147 men had levels of TSH, FT4, and/or T3 outside the clinically normal range, leaving 868 euthyroid men and 592 euthyroid women in the final analysis.

Demographic and lifestyle differences at baseline by sex and prediabetes status are presented in Table 1 and Supplementary Tables S2 and S3 [13]. Men and women with prediabetes were both somewhat older than those without prediabetes (60.6 years vs 58.2 years; $P = .09$ for women; 56.4 years vs 54.1 years; $P = .008$ for men). Similarly, the percentage who were obese (BMI ≥30) was significantly higher in those who were prediabetic (50.5% vs 26.2%; $P = .003$ for women: 34.1% vs 20.0%; $P = .004$ for men). Men, but not women, with prediabetes were also more likely to have hypertension (39.6% vs 29.2%; $P = .031$). There were no statistically significant differences in prediabetes status among either men or women with regard to physical activity, alcohol use, family history of diabetes, recruitment center, or education (see Table 1 and Supplementary Tables S2 and S3 [13]).

Correlations

Correlations among the thyroid hormones were small, with Pearson correlation coefficients of TSH with T3 (−0.04) and FT4 (−0.18), respectively, in women and T3 (−0.03) and FT4 (−0.10), respectively, in men (Supplementary Table S4 [13]).

Prospective Analyses

Women

Among postmenopausal women in this study, T3 (incident rate ratio [IRR] = 1.65; 95% CI, 1.22-2.24; $P = .001$) and the ratio of T3/FT4 were positively associated (IRR = 1.03; 95% CI, 1.01-1.04; $P = .0001$), while FT4 was inversely associated

Table 1. Demographic characteristics of euthyroid postmenopausal women and men by baseline diabetes status

	Women			Men		
	Prediabetes N = 329	Normoglycemic N = 263		Prediabetes N = 421	Normoglycemic N = 447	
	n (%) or Mean (95% CI)	n (%) or Mean (95% CI)	*P*	n (%) or Mean (95% CI)	n (%) or Mean (95% CI)	*P*
Age						
Age in y	60.60 (58.29-62.91)	58.16 (56.59-59.74)	.087	56.40 (55.16-57.63)	54.10 (52.86-55.33)	.008
Age 45-54	114 (24.9)	117 (34.7)	.236	224 (44.2)	289 (60.2)	.011
Age 55-64	171 (40.5)	119 (41.0)		143 (34.4)	124 (25.6)	
Age 65+	44 (34.6)	27 (24.3)		54 (21.4)	34 (14.2)	
Hispanic/Latino background[a]						
Dominican	40 (10.7)	32 (10.4)	.936	42 (9.9)	36 (7.2)	.173
Central American	43 (6.5)	19 (4.8)	.515	31 (4.9)	43 (10.4)	.181
Cuban	39 (26.4)	44 (30.2)	.798	101 (32.5)	81 (25.0)	.117
Mexican (ref)	120 (30.5)	99 (30.8)	Ref	146 (30.4)	170 (35.0)	Ref
Puerto Rican	66 (19.2)	42 (15.0)	.540	68 (13.4)	63 (14.0)	.771
South American	17 (3.6)	20 (5.1)	.516	24 (3.9)	45 (5.7)	.508
More than one/Other heritage	4 (3.0)	7 (3.7)	.804	9 (5.0)	9 (2.7)	.256
County of birth						
Foreign	251 (76.0)	209 (82.8)	.242	341 (83.0)	350 (78.3)	.238
United States (excluding territories)	78 (24.0)	54 (17.2)		80 (17.0)	97 (21.7)	
Nativity subscore (MESA)[b]						
Non-US born and YRSUS < 10	62 (17.1)	51 (24.3)	.017	85 (23.2)	89 (19.8)	.011
Non-US born and YRSUS 10-19	60 (16.5)	43 (16.2)	.071	88 (24.0)	74 (16.3)	.006
Non-US born and YRSUS ≥20	181 (55.6)	149 (55.3)	.055	212 (45.7)	222 (49.1)	.052
US born (ref)	26 (10.8)	20 (4.1)	Ref	36 (7.1)	62 (14.9)	Ref
Language preference						
Spanish	291 (91.2)	231 (86.1)	.255	366 (87.1)	365 (80.5)	.090
English	38 (8.8)	32 (13.9)		55 (12.9)	82 (19.5)	
Educational attainment						
Less than high school	165 (41.3)	107 (36.9)	.393	163 (39.2)	143 (29.9)	.198
High school diploma/GED	55 (13.7)	57 (21.1)		106 (20.3)	117 (23.3)	
Greater than high school diploma or GED	109 (45.0)	99 (42.0)		152 (40.5)	187 (46.8)	
BMI						
Under/normal weight (BMI < 25)	38 (13.9)	63 (28.7)	.003	67 (21.1)	114 (29.7)	.004
Overweight (25 ≤ BMI < 30)	116 (35.7)	110 (45.1)		187 (44.8)	230 (50.3)	
Obese (BMI ≥ 30)	175 (50.5)	90 (26.2)		167 (34.1)	103 (20.0)	
Physical activity level						
High	11 (3.1)	19 (5.9)	.434	77 (16.8)	79 (14.1)	.447
Moderate	137 (44.0)	116 (47.6)		197 (44.8)	214 (49.5)	
Low	181 (52.9)	128 (46.4)		147 (38.3)	154 (36.5)	
History of gestational diabetes						
No	322 (99.4)	261 (99.7)	.476			
Yes	7 (0.6)	2 (0.3)				
Hypertension (BP ≥ 140/90 or medication use)						
No	195 (57.2)	182 (60.4)	.705	244 (60.4)	332 (70.8)	.031
Yes	134 (42.8)	81 (39.6)		177 (39.6)	115 (29.2)	
Cigarette use[c]						
Never (ref)	219 (67.3)	170 (68.8)	Ref	162 (36.1)	196 (47.1)	Ref
Former	67 (16.7)	51 (16.4)	.907	147 (37.2)	151 (29.9)	.038
Current	43 (15.9)	42 (14.8)	.798	112 (26.7)	100 (23.0)	.095

(*continued*)

Table 1. Continued

	Women			Men		
	Prediabetes	**Normoglycemic**		**Prediabetes**	**Normoglycemic**	
	N = 329	**N = 263**		**N = 421**	**N = 447**	
	n (%) or Mean (95% CI)	**n (%) or Mean (95% CI)**	***P***	**n (%) or Mean (95% CI)**	**n (%) or Mean (95% CI)**	***P***
Alcohol use[d]						
None	195 (64.5)	169 (64.3)	.903	168 (45.8)	179 (44.8)	.887
Low	129 (34.4)	88 (34.2)		223 (48.2)	231 (48.2)	
High	5 (1.1)	6 (1.5)		30 (6.1)	37 (7.0)	
Family history of diabetes						
No	155 (51.0)	150 (59.5)	.290	224 (57.7)	289 (63.7)	.255
Yes	174 (49.0)	113 (40.5)		197 (42.3)	158 (36.3)	
Statin medication use						
No	276 (88.5)	229 (87.8)	.864	385 (89.8)	414 (91.9)	.502
Yes	53 (11.5)	34 (12.2)		36 (10.2)	33 (8.1)	
Recruitment center[e]						
Bronx	89 (28.2)	65 (31.3)	.978	98 (27.8)	84 (24.6)	.271
Chicago (ref)	77 (10.1)	51 (11.3)	Ref	97 (12.7)	132 (15.6)	Ref
Miami	70 (35.6)	71 (38.6)	.934	137 (38.9)	123 (33.5)	.138
San Diego	93 (26.2)	76 (18.7)	.236	89 (20.6)	108 (26.3)	.878
Acculturation score—MESA[f]	1.9 (1.66-2.13)	1.77 (1.47-2.07)	.506	1.64 (1.46-1.82)	2.07 (1.87-2.27)	.001

Abbreviations: BMI, body mass index; BP, blood pressure; MESA, Multi-Ethnic Study of Atherosclerosis; Ref, reference; YRSUS, years lived in the United States.
[a]*P* value for overall test for Hispanic/Latino background: women (*P* = .9526), men (*P* = .8896).
[b]*P* value for overall test for MESA Nativity Subscore: women (*P* = .1088), men (*P* = .0137).
[c]*P* value for overall test for cigarette smoking: women (*P* = .8032), men (*P* = .0661).
[d]No alcohol use defined as never or former users, low use defined as fewer than 7 drinks/week for women and fewer than 14 drinks/week for men, high level use defined as at least 7 drinks/week for women and at least 14 drinks/week for men.
[e]*P* value for overall test for recruitment center: women (*P* = .3418), men (*P* = .4541).
[f]MESA acculturation score is a summary score based on nativity, language spoken at home, and years of residence in the United States, and ranges from 0 to 5 in 0.5 increments. 0 indicates lowest level of acculturation, 5 the highest.

(IRR = 0.59; 95% CI, 0.39-0.88; *P* = .011) with transition from prediabetes to diabetes, but not from normoglycemia to prediabetes (Table 2). TSH (IRR = 2.09; 95% CI, 1.01-4.33; *P* = .047) and the ratio of TSH/FT4 (IRR = 1.37; 95% CI, 1.06-1.77; *P* = .016) were also positively associated only with transition from prediabetes to diabetes. T3 and the ratio of T3/FT4 were positively associated with change in fasting glucose, but not with changes in other glycemic measures (see Tables 2-4).

Men

Among men, the ratio of T3/FT4 was positively associated with transition from normoglycemia to prediabetes (IRR = 1.01; 95% CI, 1.00-1.01; *P* = .041) and with change in HOMA-B (Tables 4 and 5).

Associations of baseline thyroid hormones with incidence of diabetes in the combined cohort of baseline normoglycemic and prediabetes were similar to the results in participants with prediabetes at baseline (not shown in the tables).

Application of Indices of Pituitary Sensitivity to Peripheral Thyroid Hormones

Women

In women, there were no associations of any of the indices of pituitary thyroid hormone sensitivity with transition from either normoglycemia to prediabetes or from prediabetes to diabetes; nor were there any associations with any glucose homeostasis change measures (see Tables 2-4).

Men

In men, there were inverse associations of TSHI (IRR = 0.79; 95% CI, 0.64-0.96; *P* = .019), TFQI (IRR = 0.82; 95% CI, 0.69-0.98; *P* = .025), and PTFQI (IRR = 0.57; 95% CI, 0.35-0.93; *P* = .025) with both the transition from prediabetes to diabetes and, along with TT4RI, with change in HOMA-B, but not with transition from normoglycemia to prediabetes. There were no associations of any of the indices with any changes in measures of glucose homeostasis (Tables 3-5).

Effect Modification Prospective Stratified Analysis:

Body mass index

The results for interactions of BMI with thyroid hormones on measures of glucose homeostasis in women showed positive associations of TSH and TSH/FT4 with progression from normoglycemia to prediabetes only in those with BMI below the median (Supplementary Table S5 [13]). There were no other statistically significant interactions with BMI for either men or women (see Supplementary Tables S5 and S6 [13]).

Table 2. Association between hormones and diabetes progression at visit 2 among euthyroid women

	Normoglycemic at baseline→ Prediabetes at follow-up N = 134/257		Normoglycemic at baseline→ Prediabetes or diabetes at follow-up N = 140/263		Prediabetic at baseline→ Diabetes at follow-up N = 165/329	
	IRR (95% CI)	***P***	**IRR (95% CI)**	***P***	**IRR (95% CI)**	***P***
TSH	1.05 (0.63-1.75)	.852	1.07 (0.64-1.78)	.805	2.09 (1.01-4.33)	.047
T3	1.07 (0.89-1.28)	.469	1.09 (0.91-1.30)	.358	1.65 (1.22-2.24)	.001
FT4	0.85 (0.62-1.16)	.299	0.86 (0.64-1.16)	.326	0.59 (0.39-0.88)	.011
T3/FT4 ratio	1.01 (1.00-1.02)	.133	1.01 (1.00-1.01)	.098	1.03 (1.01-1.04)	.0001
TSH/FT4 ratio	1.05 (0.88-1.26)	.589	1.06 (0.88-1.26)	.550	1.37 (1.06-1.77)	.016
TSH/T3 ratio[a]	1.05 (0.80-1.38)	.733	1.05 (0.80-1.38)	.727	1.18 (0.76-1.82)	.465
PTFQI	0.79 (0.39-1.61)	.513	0.82 (0.41-1.65)	.569	0.90 (0.36-2.24)	.816
TFQI	0.91 (0.75-1.09)	.307	0.92 (0.76, 1.10)	.344	0.99 (0.78-1.26)	.958
TSHI	1.00 (0.82-1.22)	.997	1.01 (0.83-1.23)	.929	1.07 (0.80-1.44)	.63
TT4RI	0.97 (0.73-1.28)	.813	0.98 (0.74-1.29)	.859	1.20 (0.78-1.86)	.412

Model adjusted for age, BMI, waist-to-hip ratio, Hispanic background, acculturation score—MESA, recruitment site, education, statin medication use, family history of diabetes, gestational diabetes, cigarette use, alcohol use, physical activity, hypertension, high triglycerides, low HDL, and CRP.
Individual continuous hormone concentrations and hormone indices were standardized using the following SD: Women—TSH, 0.86 mIU/L; T3, 18.8 ng/dL; FT4, 0.13 ng/dL; PTFQI, 0.25; TFQI, 0.33; TSHI, 0.51; TT4RI, 12.6; Men—TSH, 0.81 mIU/L; T3, 18.6 ng/dL; FT4, 0.14 ng/dL; PTFQI, 0.34; TFQI, 0.35; TSHI, 0.52; TT4RI, 12.5. Hormone ratios are not standardized.
Abbreviations: BMI, body mass index; CRP, C-reactive protein; MESA, Multi-Ethnic Study of Atherosclerosis; FT4, free thyroxine; HDL, high-density lipoprotein; IRR, incident rate ratio; PTFQI, Parametric Thyroid Feedback Quantile-based Index; T3, total triiodothyronine; TFQI, Thyroid Feedback Quantile-based Index; TSH, thyrotropin; TSHI, TSH Index; TT4RI, Thyrotroph T4 Resistance Index.
[a]Natural log-transformed.

Age

In women, T3 was positively associated with transition from normoglycemia to prediabetes and was positively related to change in HbA_{1c} only in those below the median age, and FT4 was inversely related to fasting glucose only in those above the median age (see Supplementary Table S5 [13]). In men, the ratio of T3/FT4 was positively associated with progression from prediabetes to diabetes, change in fasting insulin, fasting glucose, and HOMA-IR, while FT4, TFQI, and PTFQI were inversely associated with postload glucose in those below the median age (see Supplementary Tables S5 and S6 [13]).

Separation of Effects on Fasting vs Postload Glucose

In an effort to identify possible mechanisms of hormonal action on the development of diabetes and prediabetes, we defined prediabetes as elevated fasting glucose with normal postload glucose or as elevated postload glucose with normal fasting glucose (Supplementary Tables S7 and S8 [13]).

Women

Among women, T3 (IRR = 1.79; 95% CI, 0.99-3.22; $P = .054$) and the ratio of T3/FT4 (IRR = 1.02; 95% CI, 1.00-1.05; $P = .033$) were positively associated with transition from prediabetes to diabetes when prediabetes was defined by postload, but not when it was defined by fasting glucose. The only significant association with the transition from normoglycemia to prediabetes was with one of the pituitary sensitivity indices, TT4RI, which was inversely associated with transition from normal to prediabetes only when defined by postload glucose.

Men

Among men, FT4 was inversely associated with transition from prediabetes to diabetes when prediabetes was defined by both fasting (IRR = 0.65; 95% CI, 0.43-0.99; $P = .048$) or postload (IRR = 0.55; 95% CI, 0.30-1.01; $P = .057$) glucose.

Cross-Sectional Analyses

Cross-sectional results are presented in Supplementary Tables S9 and S10 [13]. Among women, TSH, TSH/T3, and TSH/FT4 were inversely associated with prediabetes and postload glucose, while TSH/T3 was also inversely associated with almost all other measures of glucose homeostasis. T3 and the ratio of T3/FT4 were positively associated with changes in fasting glucose, fasting insulin, HOMA-B, HOMA-IR, and postload insulin. Among men, TSH, TSH/T3, and FT4 were inversely associated with prediabetes, while the ratio of T3/FT4 was positively associated with prediabetes and postload insulin; FT4 was also inversely associated with fasting insulin, HOMA-B and HOMA-IR; both T3 and T3/FT4 were also positively associated with fasting insulin, HOMA-B, and HOMA-IR. Indices of pituitary sensitivity to thyroid hormones were inversely associated with prediabetes and selected measures of glucose homeostasis in men and women.

Summaries of the cross-sectional and prospective findings are presented in Figs. 2 and 3.

Discussion

In women, but not in men, T3, T3/FT4, TSH, and TSH/FT4 were positively associated, while FT4 was inversely associated, with the transition from prediabetes to diabetes. There were no associations of thyroid hormones with conversion from normoglycemia to prediabetes, nor were there prospective associations of T3 or FT4 with changes in steady-state measures of insulin resistance (HOMA-IR), all of which

Table 3. Association of hormones with prospective change in continuous glucose outcomes among euthyroid men and women

	HbA_{1c} change score[a]		Fasting glucose change score[b]		Postload glucose change score[c,d]	
Women	β (95% CI)[e]	*P*	β (95% CI)[e]	*P*	β (95% CI)[e]	*P*
TSH	0.026 (−0.007 to 0.059)	.125	0.460 (−0.557 to 1.478)	.374	−0.348 (−4.127 to 3.432)	.856
T3	−0.006 (−0.033 to 0.021)	.688	1.532 (0.530 to 2.534)	.003	0.768 (−2.491 to 4.027)	.643
FT4	−0.020 (−0.044 to 0.004)	.099	−0.515 (−1.332 to 0.302)	.216	−1.649 (−4.938 to 1.639)	.324
T3/FT4 ratio	0.001 (−0.001 to 0.002)	.342	0.090 (0.038 to 0.141)	.001	0.073 (−0.098 to 0.245)	.400
TSH/FT4 ratio	0.039 (−0.006 to 0.083)	.087	0.691 (−0.622 to 2.004)	.301	0.265 (−4.434 to 4.964)	.912
TSH/T3 ratio[f]	0.036 (−0.019 to 0.090)	.199	−0.337 (−2.118 to 1.445)	.711	−1.477 (−8.673 to 5.718)	.687
PTFQI	−0.019 (−0.102 to 0.063)	.643	−0.578 (−3.889 to 2.733)	.732	−6.156 (−19.839 to 7.528)	.377
TFQI	−0.007 (−0.029 to 0.015)	.528	−0.175 (−1.041 to 0.692)	.692	−1.742 (−5.276 to 1.792)	.333
TSHI	0.005 (−0.025 to 0.035)	.724	0.019 (−1.042 to 1.079)	.973	−1.831 (−6.618 to 2.956)	.453
TT4RI	0.031 (−0.018 to 0.079)	.213	0.516 (−1.125 to 2.156)	.537	−1.790 (−8.001 to 4.421)	.572
Men						
TSH	−0.003 (−0.044 to 0.037)	.873	−0.629 (−1.921 to 0.662)	.339	−0.943 (−6.024 to 4.137)	.715
T3	0.0004 (−0.0565 to 0.0573)	.989	0.255 (−1.859 to 2.368)	.813	0.932 (−3.642 to 5.507)	.689
FT4	−0.009 (−0.053 to 0.034)	.671	0.647 (−0.984 to 2.278)	.436	−2.928 (−7.417 to 1.561)	.200
T3/FT4 ratio	0.00005 (−0.00245 to 0.00255)	.970	−0.021 (−0.121 to 0.078)	.671	0.124 (−0.130 to 0.379)	.338
TSH/FT4 ratio	−0.004 (−0.061 to 0.052)	.876	−1.094 (−2.873 to 0.686)	.228	−0.071 (−6.667 to 6.525)	.983
TSH/T3 ratio[f]	−0.007 (−0.083 to 0.070)	.866	−1.815 (−4.274 to 0.645)	.148	−4.550 (−13.629 to 4.529)	.325
PTFQI	−0.035 (−0.159 to 0.089)	.577	−0.399 (−5.150 to 4.351)	.869	−10.135 (−24.558 to 4.288)	.168
TFQI	−0.011 (−0.055 to 0.033)	.609	−0.144 (−1.848 to 1.561)	.868	−3.489 (−8.611 to 1.633)	.181
TSHI	−0.010 (−0.058 to 0.038)	.695	−0.597 (−2.287 to 1.093)	.488	−4.083 (−10.035 to 1.869)	.178
TT4RI	−0.009 (−0.086 to 0.067)	.808	−0.801 (−3.287 to 1.685)	.527	−3.485 (−13.165 to 6.194)	.480

Model adjusted for baseline diabetes status, time between visits, diabetes medication at follow-up, age, BMI, waist-to-hip ratio, acculturation score, recruitment site, Hispanic background, education, statin use, family history of diabetes, gestational diabetes (women only), cigarette use, alcohol use, physical activity, BMI change (V1 – V2), waist-to-hip ratio change (V1 – V2), hypertension, high triglycerides, low HDL, and CRP.
Individual continuous hormone concentrations and hormone indices were standardized using the following SD: women: TSH, 0.86 mIU/L; T3, 18.8 ng/dL; FT4, 0.13 ng/dL; PTFQI, 0.25; TFQI, 0.33; TSHI, 0.51; TT4RI, 12.6; men: TSH, 0.81 mIU/L; T3, 18.6 ng/dL; FT4, 0.14 ng/dL; PTFQI, 0.34; TFQI, 0.35; TSHI, 0.52; TT4RI, 12.5. Hormone ratios are not standardized.
Abbreviations: BMI, body mass index; CRP, C-reactive protein; FT4, free thyroxine; HbA_{1c}, glycated hemoglobin A_{1c}; HDL, high-density lipoprotein; PTFQI, Parametric Thyroid Feedback Quantile-based Index; T3, total triiodothyronine; TFQI, Thyroid Feedback Quantile-based Index; TSH, thyrotropin; TSHI, TSH Index; TT4RI, Thyrotroph T4 Resistance Index; V, visit.
[a]Adjusted for baseline HbA_{1c}.
[b]Adjusted for baseline fasting glucose.
[c]Adjusted for baseline post load glucose.
[d]Women N = 439, men N = 714.
[e]β Estimate interpreted as the change in glycemic measure per SD increase in hormone concentration.
[f]Natural log-transformed.

suggest effects of thyroid hormones in women occur later in disease development.

In women, the positive associations of T3, TSH and TSH/FT4 with transition from prediabetes to diabetes suggest decreased pituitary sensitivity, while in men indices of pituitary thyroid hormone sensitivity suggest increased pituitary sensitivity associated with the transition from prediabetes to diabetes. The findings in women are consistent with, while the findings in men are in contrast with, 2 previous studies adjusting for but not stratifying by sex, suggesting that lower pituitary thyroid hormone sensitivity increases diabetes risk [7, 8]. The findings in men are consistent with another study of prediabetes, also adjusting for but not stratifying by sex [9]. To the best of our knowledge, this is the first longitudinal study and the first study of sex differences that examines associations of thyroid sensitivity indices with the development of diabetes.

It is possible that among postmenopausal women sensitivity to T4 is not the relevant parameter, but that T3 (or demand for T3) is the key indicator. An additional possibility is that increased physiological demand for T3 underlies these relationships (as this could explain the associations with T3 and T3/FT4 ratio directly, while the TSH and higher TSH/FT4 ratios could also signal a shift to increased T3 demand secondary to metabolic tissue resistance). In contrast with the aforementioned findings, among men the T3/FT4 ratio was positively associated with transition from normoglycemia to prediabetes, suggesting possible effects earlier in the development of diabetes related to deiodinase activity.

There are few previous longitudinal studies of euthyroid individuals with which to compare these results. Jun et al [20] found that change in TSH, but not baseline TSH, in euthyroid adults was positively associated with incidence of diabetes. In a separate paper, the authors mention that the results were the same in men and women with change in TSH positively associated, while changes in T3 and FT4 were negatively associated, with diabetes risk [21]. Chaker et al [22] found that TSH was positively associated and FT4 was inversely associated with progression of diabetes from prediabetes, consistent with our findings. They noted that there was no effect modification by sex. Similarly, higher TSH levels were associated

Table 4. Association of hormones with prospective change in continuous insulin outcomes among euthyroid men and women

	Fasting insulin change score[a]		HOMA-B change score[b]		HOMA-IR change score[c]	
Women	β (95% CI)[d]	*P*	β (95% CI)[d]	*P*	β (95% CI)[d]	*P*
TSH	0.682 (−0.415 to 1.779)	.222	1.848 (−6.356 to 10.052)	.658	0.257 (−0.116 to 0.631)	.176
T3	0.600 (−0.806 to 2.005)	.402	−0.409 (−9.749 to 8.932)	.931	0.238 (−0.188 to 0.665)	.273
FT4	−0.468 (−1.525 to 0.589)	.384	1.408 (−7.217 to 10.032)	.748	−0.176 (−0.521 to 0.168)	.315
T3/FT4 ratio	0.046 (−0.013 to 0.105)	.125	−0.084 (−0.478 to 0.310)	.676	0.018 (−0.001 to 0.038)	.067
TSH/FT4 ratio	0.995 (−0.614 to 2.604)	.225	2.171 (−9.423 to 13.766)	.713	0.380 (−0.166 to 0.925)	.172
TSH/T3 ratio[e]	0.937 (−1.366 to 3.239)	.425	5.495 (−11.191 to 22.182)	.518	0.332 (−0.402 to 1.065)	.374
PTFQI	0.326 (−2.544 to 3.196)	.824	12.009 (−12.979 to 36.997)	.346	0.086 (−0.827 to 0.998)	.853
TFQI	0.113 (−0.624 to 0.851)	.763	3.358 (−3.158 to 9.874)	.312	0.027 (−0.208 to 0.261)	.822
TSHI	0.413 (−0.502 to 1.328)	.375	3.794 (−3.796 to 11.385)	.327	0.151 (−0.146 to 0.449)	.319
TT4RI	0.847 (−0.665 to 2.359)	.271	2.932 (−8.938 to 14.801)	.628	0.316 (−0.192 to 0.824)	.223
Men						
TSH	−0.466 (−1.091 to 0.160)	.144	−4.478 (−9.787 to 0.831)	.098	−0.143 (−0.355 to 0.068)	.184
T3	0.384 (−0.329 to 1.098)	.290	3.607 (−2.517 to 9.731)	.248	0.074 (−0.173 to 0.322)	.555
FT4	−0.385 (−1.058 to 0.289)	.262	−6.126 (−12.502 to 0.250)	.060	−0.075 (−0.306 to 0.156)	.523
T3/FT4 ratio	0.030 (−0.006 to 0.065)	.100	0.399 (0.059 to 0.739)	.022	0.005 (−0.008 to 0.018)	.457
TSH/FT4 ratio	−0.371 (−1.179 to 0.437)	.367	−3.256 (−10.266 to 3.753)	.362	−0.133 (−0.401 to 0.135)	.331
TSH/T3 ratio[e]	−0.953 (−2.173 to 0.267)	.126	−7.878 (−17.592 to 1.836)	.112	−0.297 (−0.709 to 0.116)	.159
PTFQI	−1.655 (−3.460 to 0.150)	.072	−20.169 (−38.319 to −2.018)	.029	−0.455 (−1.090 to 0.181)	.161
TFQI	−0.599 (−1.237 to 0.039)	.066	−7.290 (−13.755 to −0.826)	.027	−0.163 (−0.388 to 0.062)	.156
TSHI	−0.676 (−1.395 to 0.043)	.065	−7.274 (−14.089 to −0.459)	.036	−0.200 (−0.449 to 0.050)	.116
TT4RI	−1.166 (−2.376 to 0.043)	.059	−11.648 (−22.048 to −1.247)	.028	−0.338 (−0.750 to 0.075)	.109

Model adjusted for baseline diabetes status, time between visits, diabetes medication at follow-up, age, BMI, waist-hip ratio, acculturation score, recruitment site, Hispanic background, education, statin use, family history of diabetes, gestational diabetes (women only), cigarette use, alcohol use, physical activity, BMI change (V1 – V2), waist-to-hip ratio change (V1 – V2), hypertension, high triglycerides, low HDL, and CRP.
Individual continuous hormone concentrations and hormone indices were standardized using the following SD: women: TSH, 0.86 mIU/L; T3, 18.8 ng/dL; FT4, 0.13 ng/dL; PTFQI, 0.25; TFQI, 0.33; TSHI, 0.51; TT4RI, 12.6; men: TSH, 0.81 mIU/L; T3, 18.6 ng/dL; FT4, 0.14 ng/dL; PTFQI, 0.34; TFQI, 0.35; TSHI, 0.52; TT4RI, 12.5. Hormone ratios are not standardized.
Abbreviations: BMI, body mass index; CRP, C-reactive protein; FT4, free thyroxine; HDL, high-density lipoprotein; HOMA-B, Homeostasis Model Assessment Index of β-Cell Function; HOMA-IR, Homeostasis Model Assessment Index of Insulin Resistance; PTFQI, Parametric Thyroid Feedback Quantile-based Index; T3, total triiodothyronine; TFQI, Thyroid Feedback Quantile-based Index; TSH, thyrotropin; TSHI, TSH Index; TT4RI, Thyrotroph T4 Resistance Index; V, visit.
[a]Adjusted for baseline fasting insulin.
[b]Adjusted for baseline HOMA-B.
[c]Adjusted for baseline HOMA-IR.
[d]β Estimate interpretated as the change in glycemic measure per SD increase in hormone concentration.
[e]Natural log-transformed.

with increased change in insulin resistance after 3 years in a group that was euthyroid at baseline [23]. In contrast with these studies, de Vries et al [24] found no relation between TSH levels within the normal range and incidence of diabetes. Finally, in a 3 year follow-up of euthyroid individuals, Ferrannini et al [25] found that FT3 was positively associated with increases in fasting glucose and decreases in insulin sensitivity. None of the last 3 studies presented data for men and women separately [23-25].

Other longitudinal studies not limited to thyroid values within normal limits have shown mixed results, with the strongest associations seen in those with clinical thyroid disease. In a study that included both euthyroid and subclinically hypothyroid participants, there was no association of TSH or FT4 with incidence of high fasting glucose [26]. Several studies based on large medical databases have found associations of clinical thyroid disease [27], including hyperthyroidism [28, 29] and hypothyroidism [29-32], with diabetes incidence and/or mortality.

The stronger associations below the median ages (56 for women and 52 for men) are consistent with a previous paper by Chen et al [29] noting greater sex differences in relationships of clinical thyroid disease with incident diabetes in those younger than 65 years. Mechanisms for sex differences in the relationships are not clear. Younger individuals have relatively higher sex hormone levels, as well as greater muscle mass available for glucose uptake [33, 34]. Animal models have shown that FT4 decreases with age in female but not male rats, as well as decreased hypothalamic deiodinase 2 activity and decreased thyroid TSH receptor density in ovariectomized rats, consistent with the sex differences in pituitary sensitivity seen in our study [35]. Previous literature on effects of ovariectomy on T3 are not clear [35].

In this study, the more associations observed in cross-sectional vs longitudinal analyses suggest that reverse causation may also be operative. In general, cross-sectional associations of FT4 [36-53] and TSH [37, 38, 40, 41, 43-57] with measures of glucose homeostasis have been variable. The positive associations in this study of T3 with measures of glucose homeostasis are consistent with most [25, 36, 41-43, 47-49, 51, 55, 58], but not all [37, 38, 40, 46, 50, 52], previous cross-sectional studies, including the majority [25, 36, 41-43, 55, 58] of those in

Table 5. Association between hormones and diabetes progression at visit 2 among euthyroid men

	Normoglycemic at baseline→ Prediabetes at follow-up N = 229/440		Normoglycemic at baseline→ Prediabetes or diabetes at follow-up N = 243/447		Prediabetic at baseline→ Diabetes at follow-up N = 198/421	
	IRR (95% CI)	***P***	**IRR (95% CI)**	***P***	**IRR (95% CI)**	***P***
TSH	1.12 (0.87-1.45)	.383	1.09 (0.84-1.40)	.524	0.79 (0.52-1.20)	.265
T3	1.09 (0.95-1.25)	.236	1.08 (0.94-1.24)	.271	0.94 (0.79-1.12)	.516
FT4	0.90 (0.77-1.04)	.141	0.90 (0.78-1.04)	.150	0.84 (0.67-1.05)	.127
T3/FT4 ratio	1.01 (1.00-1.01)	.041	1.01 (1.00-1.01)	.048	1.00 (0.99-1.01)	.691
TSH/FT4 ratio	1.08 (0.93-1.24)	.322	1.06 (0.92-1.22)	.447	0.94 (0.75-1.18)	.610
TSH/T3 ratio[a]	0.97 (0.77-1.22)	.802	0.94 (0.75-1.17)	.582	0.81 (0.59-1.10)	.173
PTFQI	0.82 (0.59-1.14)	.240	0.81 (0.58-1.11)	.190	0.57 (0.35-0.93)	.025
TFQI	0.94 (0.83-1.05)	.255	0.93 (0.83-1.04)	.207	0.82 (0.69-0.98)	.025
TSHI	0.95 (0.83-1.08)	.440	0.93 (0.82-1.06)	.292	0.79 (0.64-0.96)	.019
TT4RI	1.07 (0.88-1.30)	.506	1.04 (0.86-1.27)	.660	0.75 (0.52-1.07)	.111

Model adjusted for age, BMI, waist-to-hip ratio, Hispanic background, acculturation score—MESA, recruitment site, education, statin medication use, family history of diabetes, cigarette use, alcohol use, physical activity, hypertension, high triglycerides, low HDL, and CRP.
Individual continuous hormone concentrations and hormone indices were standardized using the following SD: women: TSH, 0.86 mIU/L; T3, 18.8 ng/dL; FT4, 0.13 ng/dL; PTFQI, 0.25; TFQI, 0.33; TSHI, 0.51; TT4RI, 12.6; men: TSH, 0.81 mIU/L; T3, 18.6 ng/dL; FT4, 0.14 ng/dL; PTFQI, 0.34; TFQI, 0.35; TSHI, 0.52; TT4RI, 12.5. Hormone ratios are not standardized.
Abbreviations: BMI, body mass index; CRP, C-reactive protein; FT4, free thyroxine; HDL, high-density lipoprotein; IRR, incident rate ratio; MESA, Multi-Ethnic Study of Atherosclerosis; PTFQI, Parametric Thyroid Feedback Quantile-based Index; T3, total triiodothyronine; TFQI, Thyroid Feedback Quantile-based Index; TSH, thyrotropin; TSHI, TSH Index; TT4RI, Thyrotroph T4 Resistance Index.
[a]Natural log-transformed.

euthyroid populations [25, 36-38, 40-43, 52, 55, 58]. Only 3 cross-sectional studies that included T3 measurements presented data for men and women separately [43, 47, 52], and of those, 2 [43, 47] found positive associations in men and women and 1 found negative associations both in men and women. Some studies also found associations with FT3/FT4 or T3/T4 ratios, thought to be related to increased deiodinase activity [42, 43, 55].

Whether the cross-sectional associations of T3/FT4 reflect reverse causation or direct effects of T3 on diabetes risk is not clear. Previous studies have shown that adipose tissue-derived leptin augments deiodination of T4 to T3 [3, 59]. The inverse associations with FT4 in this study, along with the positive associations with T3, on cross-sectional analysis are consistent with metabolic dysfunction contributing to deiodination [60]. The persistence of the associations with control both for BMI and WHR, however, argues against obesity-related reverse causation [42, 43, 55]. The lack of association of baseline metabolic dysfunction with incidence of thyroid disease in several studies [61, 62], as well as the positive associations in this study of T3 and T3/FT4 with incidence of diabetes from prediabetes, also support the possibility that T3 may be operative in the development of the disease. Increased thyroid hormones may also reflect a compensatory response to metabolic dysfunction [60].

Mexican American ancestry is associated with the Thr92Ala polymorphism in the *D2 deiodinase* gene, which has been related to risk of diabetes, suggesting a genetic component to the association. Additional mechanisms that have been suggested in the literature for adverse metabolic effects of elevated T3 include mitochondrial uncoupling, increased hepatic gluconeogenesis, increased β-cell apoptosis, increased degradation of insulin, increased gluconeogenic effects of epinephrine, oxidative stress, and increased proinflammatory mediators [2, 3, 25].

In this study, the more consistent associations observed when prediabetes is defined by postload glucose than when it is defined by fasting glucose suggests that the effects are more likely to be operative in muscle rather than liver. Both hyperthyroid and hypothyroid states have been associated with insulin resistance, with hyperthyroidism resulting in increased glucose release from the liver and consequential hyperinsulinemia, while hypothyroidism has been related to decreased glucose disposal resulting from decreased skeletal muscle and adipose tissue sensitivity to insulin [63]. Mechanisms of associations in euthyroid individuals are not well delineated.

Limitations and Strengths

Among the limitations in this study are the single measurements and limited number of thyroid hormones. Not included were total T4, free T3, other thyroid hormones such as reverse T3, or thyroid antibodies. Similarly, single measurements of metabolic parameters may have decreased precision of the end point. Autoimmune thyroid disease has been associated with autoimmune diabetes, which could account for a subgroup of this study population [64]. The biologic basis for that association may differ from the overall associations seen in the present investigation. Unfortunately, we do not have thyroid or diabetes autoantibodies with which to examine associations in this subpopulation. It is, however, anticipated that autoimmune diabetes is unlikely to represent a significant fraction of our population (4.2% in a study of US and European participants) [64].

Despite the large numbers of participants, they may not have been sufficient for selected stratified analyses. Results cannot also be generalized to non-Hispanic populations. Nevertheless, this is the only large study of Hispanic/Latino

	Prediabetes at baseline	Normoglycemic at baseline→ Prediabetes at follow up[a]	Prediabetic at baseline→ Diabetes at follow up
TSH	↓W ↓M	-	↑W
T3	-	-	↑W
FT4	↓M	-	↓W
T3/FT4 Ratio	↑M	↑M	↑W
TSH/FT4 Ratio	↓W	-	↑W
TSH/T3 Ratio	↓W ↓M	-	-
PTFQI	↓M	-	↓M
TFQI	↓M	-	↓M
TSHI	↓W ↓M	-	↓M
TT4RI	↓W ↓M	-	-

Figure 2. Summary of cross-sectional and longitudinal associations of hormones with dichotomous diabetes outcomes among euthyroid men and women. Abbreviations: TSH, thyroid stimulating hormone; T3, total triiodothyronine; FT4, free thyroxine; PTFQI, Parametric Thyroid Feedback Quantile-based Index; TFQI, Thyroid Feedback Quantile-based Index; TSHI, TSH Index; TT4RI, ThyrotrophT4 Resistance Index. ↑W Significant positive association after adjustment among women. ↑M Significant positive association after adjustment among men. ↓W Significant inverse association after adjustment among women. ↓M Significant inverse association after adjustment among men. - Non-significant findings. [a] Results were similar when transition from normoglycemic to prediabetes or diabetes at follow up was investigated.

	HbA1c		Fasting Glucose		Post Load Glucose		Fasting Insulin		Post Load Insulin		HOMA-B		HOMA-IR	
	Cross-sectional	Longitudinal	Cross-sectional	Longitudinal	Cross-sectional	Longitudinal	Cross-sectional	Longitudinal	Cross-sectional	Longitudinal[a]	Cross-sectional	Longitudinal	Cross-sectional	Longitudinal
TSH	↓W	-	-	-	↓W	-	-	-	-	ND	-	-	-	-
T3	-	-	↑W	↑W	↑W	-	↑W ↑M	-	↑W	ND	↑W ↑M	-	↑W ↑M	-
FT4	-	-	-	-	-	-	↓M	-	-	ND	↓M	-	↓M	-
T3/FT4 Ratio	-	-	↑W	↑W	-	-	↑W ↑M	-	↑W ↑M	ND	↑W ↑M	↑M	↑W ↑M	-
TSH/FT4 Ratio	-	-	-	-	↓W	-	-	-	-	ND	-	-	-	-
TSH/T3 Ratio	↓W	-	-	-	↓W	-	↓W	-	↓W	ND	↓W	-	↓W	-
PTFQI	-	-	-	-	-	-	↓M	-	-	ND	↓M	↓M	↓M	-
TFQI	-	-	-	-	-	-	↓M	-	-	ND	↓M	↓M	↓M	-
TSHI	↓W	-	-	-	-	-	-	-	-	ND	-	↓M	-	-
TT4RI	↓W	-	-	-	↓W	-	-	-	-	ND	-	↓M	-	-

Figure 3. Summary of cross-sectional and longitudinal associations of hormones with continuous diabetes outcomes among euthyroid women and men. Abbreviations: TSH, thyroid stimulating hormone; T3, total triiodothyronine; FT4, free thyroxine; PTFQI, Parametric Thyroid Feedback Quantile-based Index; QI, Thyroid Feedback Quantile-based Index; TSHI, TSH Index; TT4RI, ThyrotrophT4 Resistance Index; ND, not done. [a] Post load insulin was not measured at follow-up visit. ↑W Significant positive association after adjustment among women. ↑M Significant positive association after adjustment among men. ↓W Significant inverse association after adjustment among women. ↓M Significant inverse association after adjustment among men. - Non-significant finding.

adults with diverse ethnic backgrounds, one of the only prospective cohorts with the ability to examine the relationships of thyroid hormones with incidence of metabolic dysfunction at various stages in the development of diabetes, and the only study examining sex differences in associations of indices of pituitary sensitivity to thyroid hormones with incidence of diabetes and prediabetes.

Clinical Relevance

Our study indicates that disruptions in the HPT axis may be a marker or mediator of metabolic deterioration later in the development of diabetes and suggests that they are sex specific. A key component of these findings is the application of indices of pituitary sensitivity. In men, there is evidence that increased sensitivity of the pituitary to peripheral thyroid hormones predicts transition from a prediabetic to a diabetic state. In postmenopausal women, associations of higher TSH and T3, lower FT4 and higher TSH/FT4 with conversion from prediabetes to diabetes suggest lower sensitivity of the pituitary with increased risk of diabetes conversion. These findings may provide important insights into mechanisms of metabolic deterioration, potentially arguing for thyroid hormone supplementation in a subpopulation of postmenopausal, prediabetic euthyroid women to overcome this resistance. Identification of such a subpopulation in future studies with repeated measurements over time could assist in determining who is most likely to experience a deterioration in glucose homeostasis and be at risk of consequential complications. Trends in thyroid hormones and easily calculated indices of pituitary sensitivity could be used to prioritize individuals to be targeted with interventions to prevent diabetes development (eg, interventions defined by the Diabetes Prevention Program Diabetes Care) [65].

Conclusions

This study demonstrates positive associations in postmenopausal women of T3 and TSH and inverse associations of FT4 with transition from prediabetes to diabetes, but not with transition from normoglycemia to prediabetes. The results are consistent with decreased sensitivity of the pituitary to thyroid hormones affecting later stages in the pathogenesis of diabetes. In contrast, in men, indices of pituitary sensitivity to thyroid hormones suggest that greater pituitary sensitivity to negative feedback of peripheral hormones influences diabetes risk later in the development of the disease. The study provides justification for future investigations of sex differences in relationships of pituitary sensitivity and deiodinase activity with stages of diabetes development. If specific alterations in thyroid status are confirmed, they would provide novel insights into the pathophysiology of metabolic disorders and could empower implementation of earlier interventions to prevent the development of diabetes and its associated complications.

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Disclosures

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Data Availability

Some or all data sets generated during and/or analyzed during the current study are not publicly available but are available from the corresponding author on reasonable request.

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