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Thyroid Profile of the Reference United States Population: Data from NHANES 2007-2012

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Abstract

Objectives: This study was undertaken to describe the thyroid profile of reference U.S. population including generating reference ranges for thyroid stimulating hormone (TSH), free and total triiodothyronine (FT3, TT3), free and total thyroxine (FT4, TT4), and thyroglobulin.

Design and methods: Publically available data from National Health and Nutrition Examination Survey (NHANES) for the cycles 2007-2012 were analyzed for this purpose.

Results: The prevalence rate of clinical hypothyroidism in general U.S. population was 2.4%. Non-Hispanic white had the highest prevalence of 2.9% and non-Hispanic black the lowest at 0.6%. Females had higher prevalence (2.7%) than males (2%). Median TSH level in 2007-2012 was 1.5 mIU/L as compared to the median for 1988-1994 which was 1.37 mIU/L. The upper half of the distribution (meaning at or above 50th percentile) for TT4 has shifted to the left during 2007-2012 (median for U.S. population = 7.4 µg/dL) as compared to 1988-1994 (median for U.S. population = 8.48 µg/dL) resulting in lower median levels.

Conclusion: The rise in TSH levels and a decrease in total thyroxine levels in 2007-2012 as compared to 1988-1994 levels should be of concern because higher TSH levels even within normal range are associated with adverse cardiovascular and other events.

Keywords: Thyroid stimulating hormone, Thyroxine, Antibodies, Prevalence

Introduction

Thyroid function/dysfunction is associated with adverse lipid profile, hypertension, elevated risk of cardiovascular morbidity and mortality, osteoporosis, and increased insulin resistance. Relatively high levels of thyroid stimulating hormone (TSH), even within the normal reference range have been associated with (i) higher mortality due to coronary heart disease [1], (ii) high blood glucose levels, serum triglycerides, HDL-cholesterol, and hypertension [2], (iii) higher risk of vascular dementia among ≥ 65 years old [3], (iv) higher risk of heart failure events [4], (v) increased arterial stiffness [5], (vi) higher triglyceride levels [6], (vii) increased risk of myocardial infarction [7], and (vii) lower subendocardial viability ratio [8]. Subclinical hypothyroidism has been found to be associated with (i) increased systolic and diastolic blood pressure [9], (ii) alterations in kidney function [10], (iii) high frequency of bone loss [11], and (iv) higher odds of severe preeclampsia during pregnancy [12]. Clinical hypothyroidism is associated with (i) high BMI, diastolic hypertension, dyslipidemia, hyperinsulinemia, insulin resistance, and raised serum C-peptide [13], decreased patient survival [14], and (ii) elevated total cholesterol levels [15]. Subclinical hyperthyroidism is associated with (i) relatively higher heart failure rates among patients with known cardiovascular risk factors [10], (ii) higher risk for developing major cardiovascular events including stroke [16], and (iii) increased risk of developing cardiovascular disease, dementia, and dysrhythmia [17].

Adverse health consequences of thyroid function/dysfunction necessitate that thyroid health of the general population be evaluated. The first and the only study to do this in the general US population, published in 2002 [18] used data from National Health and Nutrition Examination Survey (NHANES) III conducted during the years 1988-1994. NHANES III collected data on TSH, total thyroxine (TT4), thyroglobulin antibodies (TgAb), and thyroid peroxidase antibodies (TPOAb) only. For the NHANES cycles 2007-2012 (http://www.cdc.gov/nchs/nhanes.htm), data for FT3, free thyroxin (FT4), total triiodothyronine (TT3), and thyroglobulin (Tg) have also become available. Consequently, this study was undertaken to re-evaluate the thyroid health of reference U.S. population.

Materials and Methods

NHANES (www.cdc.gov/nchs/nhanes/htm) data from demographic, medical questionnaire, prescription drug use, serum cotinine, urinary iodine, and thyroid profile files for the cycles 2007-2012 were downloaded and match merged. The sampling plan for NHANES is a complex, stratified, multistage, probability cluster designed to be representative of the civilian, non-institutionalized U.S. population. Sampling weights were created in NHANES to account for the complex survey design, including oversampling, survey non-response, and post-stratification. The description of assays used to measure various thyroid variables are provided elsewhere (http://www.cdc.gov/nchs/nhanes/nhanes2011-2012/THYROD_E.htm#Description_of_Laboratory_Methodology). There was a change in laboratories performing the total thyroxine (TT4) in 2010 and the newly evaluated values of TT4 for the years 2010 and onwards needed to be changed by using the equation TT4 (modified) = 4.067036 + 5.492497*((TT4/10.0)**3)-5.673583*((TT4/10.0)**3)*log(TT4/10.0) (http://wwwn.cdc.gov/nchs/nhanes/2011-2012/THYROD_G.htm#Analytic_Notes). While data for 2010 were corrected to be

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compatible for 2007-2009 before being released in the public domain, data for 2011-2012 released in the public domain used the values obtained from the new lab started being used in 2010. To maintain compatibility in the data for the entire period of 2007-2012, we re-computed TT4 data for 2011-2012 using the equation given above.

Data were available for 10544 participants aged ≥ 12 years with non-missing values of thyroid variables. After excluding 87 pregnant females from these data, a total of 10457 participants were available for computing prevalence of TgAB, TPOAb, subclinical and clinical hyper-and hypothyroidism by age, race/ethnicity, gender, smoking status, and iodine sufficiency status.

Age was categorized as 12-19 years (N = 1809), 20-64 years (N = 6490), and 65+ years (N = 2158). Race/ethnicity was categorized as non-Hispanic whites (NHW, N = 4563), non-Hispanic blacks (NHB, N = 2155), and all Hispanics (HISP, N = 2987). The statistics for those who could not be classified as NHW, NHB, or HISP were not computed separately but they were included in computations for the total population.Those who had urine iodine levels below 100 µg/L (N = 3422) were defined as iodine deficient and those who had urine iodine levels ≥ 100 µg/L (N = 7566) were defined as iodine replete. Those with serum cotinine < 10 ng/mL (N = 8305) were defined as non-smokers and those with serum cotinine ≥ 10 ng/mL (N = 2502) were defined as smokers. Smoking status was missing for 831 participants and iodine sufficiency status was missing for 650 participants.

Subclinical hyperthyroidism was defined as TSH ≤ 0.45 mIU/L and FT4 withinits normal reference range of 0.6-1.6 ng/dL as given at http://www.cdc.gov/data/nhanes/nhanes_11_12/thyrod_G_met_free_T4.pdf. Clinical hyperthyroidism was defined when TSH ≤ 0.45 mIU/L and FT4 above 1.6 ng/dL. Subclinical hypothyroidism was defined as having TSH levels ≥ 4.5 mIU/L and FT4 within the normal reference range. Those who had TSH levels ≥ 4.5 mIU/L and FT4 below 0.6 ng/dL were defined as having clinical hypothyroidism.

A reference population was created by excluding those who were pregnant (N = 87), taking prescription thyroid treatment drugs (N = 589),using estrogen drugs (N = 228), reported having current thyroid problems (N = 619), those who had clinical hypo-or hyperthyroidism as defined above, and those tested positive for thyroglobulin antibodies (TgAb) or ≥ 4 IU/mL (N = 734), and/or TPO antibodies (TPOAb) or ≥ 0.9 IU/mL (N = 4114). Reference population data were used to compute reference ranges and percentile distribution for thyroid variables. Total sample size for the reference population was 5792. The detailed sample sizes are given in Table 1. All data were analyzed using SAS version 9.4 (www.sas.com). SAS Proc SURVEYMEANS and SURVEYREG were used to analyze all data.

Results

Percentile distribution of thyroid stimulating hormone (TSH)

Percentile distributions of TSH between males and females were similar (Table 2). The same was true for the distributions of those who were aged 12-19 and 20-64 years old but the distribution of those aged 65+ years was displaced to the right, for example, while 75th percentiles for those aged 12-19 years were 1.9 mIU/L, for those aged 20-64 years and 65+ years were 2.0 and 2.5 mIU/L respectively (Table 2). There was no consistent pattern of displacement for the distributions for non-Hispanic white (NHW), non-Hispanic black (NHB), and Hispanics (HISP) though to a degree the distribution for NHB was displaced to the left of the distributions for other race/ethnicities, for example, while 95th percentile for NHW and HISP was 3.2 and 4.1 mIU/L respectively, it was 3.3 mIU/L for NHB (Table 2). The distribution of TSH for nonsmokers was displaced to the right of the distribution for smokers (Table 2).

Percentile distribution of free triiodothyronine (FT3)

The distribution of FT3 for females was displaced slightly to the left of the distribution for males (Table 2). With increase in age, the distributions of FT3 were displaced to the left (Table 2). For example, the 5th percentiles for those aged 12-19, 20-64, and 65+ years old were 3, 2.7, and 2.5 pg/mL respectively (Table 2), and 95th percentiles were: 4.3, 3.8, and 3.4 pg/mL respectively (Table 2).

Percentile distribution of free thyroxine (FT4)

Higher percentiles, namely 75th and higher, for those aged 65+ years were displaced to the right of the percentiles for those aged 12-19 and 20-64 years old (Table 2). There were almost no differences between the distributions of FT4 by race/ethnicity (Table 2).

Percentile distribution of total triiodothyronine (TT3)

The distribution of TT3 for females was displaced to the left by about 2-6 ng/dL as compared with the distribution for the males (Table 2). For example, 25th and 75th percentiles for females were 99.1 and 125.1 ng/dL respectively as compared to 103 and 131.6 ng/dL respectively for males (Table 2). With increase in age, the percentile distributions of TT3 continued being displaced to the left and the magnitude of displacement widened with increase in percentiles (Table 2). For example, 50th percentiles for those aged 12-19, 20-64, 65+ years were 130.3, 114.6, and 105.7 ng/dL respectively (Table 2), 95th percentiles were: 169.7, 152.9, and 135.1 ng/dL respectively (Table 2). While the percentile distributions of NHW and NHB were similar, the distribution for HISP was displaced to the right of the distributions of NHW and NHB (Table 2). The percentile distributions of smokers and nonsmokers as well as those who were iodine deficient and iodine replete were similar.

Table 1: Geometric means with 95% confidence intervals for thyroid stimulating hormone (TSH) in µIU/mL, free triiodothyronine (FT3) in pg/mL, free thyroxine (FT4) in ng/dL, total triiodothyronine (TT3) in ng/dL, total thyroxine (TT4) in µg/mL, and thyroglobulin (TGN) in ng/mL by gender, race, smoking status, and iodine deficiency for U.S. reference population. Data from National Health and Nutrition Examination Survey 2007-2012.

Demographic Variable	N	TSH	FT3	FT4	TT3	TT4	TGN
All	5794	1.46 (1.42-1.51)	3.22 (3.19-3.25)	0.8 (0.79-0.82)	115.38 (113.71-117.07)	7.47 (7.38-7.56)	10.54 (9.92-11.19)
Male	3179	1.5 (1.42-1.58)	3.31 (3.26-3.35)*	0.8 (0.79-0.82)	116.76 (114.61-118.95)*	7.32 (7.22-7.42)*	9.8 (9.2-10.44)*
Female	2613	1.42 (1.36-1.49)	3.11 (3.08-3.14)*	0.8 (0.78-0.82)	113.74 (111.87-115.65)*	7.65 (7.53-7.78)*	11.49(10.43-12.66)*
Age: 12-19 Years	1100	1.4 (1.3-1.51)^	3.58 (3.52-3.64)^	0.81 (0.79-0.82)	130.93 (128.32-133.58)^	7.27 (7.14-7.39)^	8.9(8.17-9.69)^,^^
Age: 20-64 Years	3593	1.43 (1.37-1.48)^^	3.21 (3.17-3.24)^	0.8 (0.78-0.81)^	114.82 (112.87-116.79)^	7.46(7.36-7.56)^	10.76(10.01-11.57)^
Age: 65+ Years	1099	1.75 (1.56-1.97)^,^^	2.94 (2.9-2.99)^	0.82 (0.81-0.84)^	104.32 (101.83-106.86)^	7.72 (7.56-7.88)^	11.18 (10.11-12.36)^^
Non-Hispanic White (NHW)	2389	1.54 (1.46-1.62)*	3.2 (3.17-3.24)*	0.8 (0.78-0.81)	115.05 (112.75-117.41)	7.38 (7.25-7.5)*,**	10.69 (9.92-11.52)*
Non-Hispanic Black (NHB)	1379	1.23 (1.19-1.28)*,**	3.22 (3.18-3.26)**	0.81 (0.79-0.82)	115.8 (112.72-118.96)	7.66 (7.45-7.87)	14.39 (13.38-15.49)*
Hispanic (HISP)	1616	1.43 (1.35-1.51)**	3.3 (3.24-3.35)*,**	0.81 (0.79-0.83)	118.46 (115.8-121.17)	7.63 (7.48-7.78)*	8.44 (7.78-9.16)*
Nonsmoker	4323	1.52 (1.46-1.58)^	3.21 (3.17-3.24)	0.8 (0.79-0.82)	115.1(113.28-116.94)	7.45 (7.35-7.55)	9.88 (9.21-10.6)^
Smoker	1465	1.31 (1.23-1.38)^	3.25 (3.2-3.3)	0.81 (0.79-0.82)	116.26 (113.37-119.22)	7.52 (7.37-7.69)	12.84 (11.79-13.99)^
Iodine Deficient	1780	1.4 (1.33-1.47)*	3.23 (3.19-3.27)	0.81 (0.8-0.82)	116.8 (114.92-118.72)	7.51 (7.39-7.63)	11.43 (10.47-12.47)*
Iodine Replete	3820	1.5 (1.45-1.56)*	3.21 (3.17-3.26)	0.8 (0.78-0.81)	114.78 (112.6-117.01)	7.45 (7.35-7.56)	10.08 (9.43-10.78)*
Morning Session	2802	1.56 (1.48-1.65)^	3.29 (3.26-3.32)^	0.81 (0.79-0.82)	117.92 (115.38-120.5)^	7.51 (7.39-7.62)	10.81 (10.16-11.51)
Late Session	2990	1.38 (1.3-1.46)^	3.15 (3.11-3.19)^	0.8 (0.78-0.81)	113.03 (111.25-114.84)^	7.43 (7.3-7.57)	10.28 (9.52-11.1)

Table 2: Selected percentile points with 95% confidence intervals for thyroid stimulating hormone (TSH), free triiodothyronine (FT3), free thyroxine (FT4), total triiodothyronine (TT3), total thyroxine (TT4) thyroglobulin (TGN) by gender, age, race/ethnicity, smoking status, and iodine sufficiency status for reference U.S. population. Data from National Health and Nutrition Examination Survey 2007-2012.

Demographic Variable	Percentile	TSH in µIU/mL	FT3 in pg/mL	FT4 in ng/dL	TT3 in ng/dL	TT4 in µg/mL	TGN in ng/mL
Total	5	0.6 (0.6-0.6)	2.7 (2.6-2.7)	0.6 (0.6-0.6)	84.3 (82-86.7)	5.7 (5.6-5.9)	3.3 (3.1-3.5)
	10	0.7 (0.7-0.8)	2.8 (2.7-2.8)	0.7 (0.6-0.7)	89.3 (87.3-91.4)	6 (5.9-6.1)	4.1 (3.8-4.4)
	25	1 (1-1.1)	3 (2.9-3)	0.7 (0.7-0.7)	101.8 (100.1-103.5	6.6 (6.5-6.7)	6.6 (6.2-7)
	75	2.1 (2-2.2)	3.5 (3.4-3.5)	0.9 (0.9-0.9)	129.4 (127.5-131.3	8.3 (8.2-8.4)	16.8 (15.6-18)
	90	2.9 (2.7-3)	3.7 (3.7-3.8)	1 (1-1)	145.7 (142.9-148.5	9.3 (9.1-9.5)	27.8 (25.2-30.3)
	95	3.4 (3.2-3.7)	3.9 (3.9-4)	1 (1-1)	156.3 (152.6-160)	10.2 (10-10.4)	37.2 (34.7-39.7)
Male	5	0.6 (0.6-0.7)	2.7 (2.6-2.8)	0.6 (0.6-0.6)	84.4 (81.8-87)	5.6 (5.5-5.7)	3.2 (3-3.5)
	10	0.8 (0.7-0.8)	2.8 (2.8-2.9)	0.7 (0.6-0.7)	90.3 (86.3-94.4)	6 (5.9-6.1)	4 (3.6-4.4)
	25	1.1 (1-1.2)	3.1 (3-3.1)	0.7 (0.7-0.7)	103 (100.5-105.6)	6.5 (6.4-6.6)	6.3 (5.7-7)
	75	2.1 (2-2.2)	3.6 (3.5-3.6)	0.9 (0.9-0.9)	131.6 (129.1-134.2	8.2 (8-8.3)	15.4 (14.3-16.5)
	90	2.9 (2.7-3.1)	3.8 (3.7-3.9)	1 (1-1)	146.7 (144.1-149.3	9 (8.8-9.2)	22 (20.1-23.8)
	95	3.6 (3.3-3.9)	4 (4-4.1)	1 (1-1)	155.4 (152.1-158.6	9.9 (9.4-10.3)	30 (26.3-33.6)
Female	5	0.5 (0.5-0.6)	2.6 (2.5-2.7)	0.6 (0.6-0.6)	84.2 (81-87.3)	5.8 (5.7-5.9)	3.3 (2.9-3.8)
	10	0.7 (0.7-0.8)	2.7 (2.6-2.8)	0.7 (0.6-0.7)	88.8 (87.3-90.3)	6.2 (6-6.3)	4.1 (3.5-4.7)
	25	1 (1-1)	2.9 (2.8-2.9)	0.7 (0.7-0.7)	99.1 (96.5-101.7)	6.8 (6.7-6.9)	6.8 (6-7.5)
	75	2.1 (1.9-2.2)	3.3 (3.3-3.4)	0.9 (0.9-0.9)	125.1 (122.6-127.6	8.5 (8.4-8.6)	19.3 (16.7-21.9)
	90	2.8 (2.6-3)	3.6 (3.6-3.7)	1 (0.9-1)	144.3 (140.3-148.3	9.6 (9.3-9.9)	33.3 (30.3-36.3)
	95	3.3 (3.1-3.5)	3.8 (3.7-3.9)	1 (1-1.1)	157.7 (149.6-165.7	10.6 (10.2-11)	44.8 (39.7-49.9)
Age: 12-19 Years	5	0.6 (0.5-0.7)	3 (2.8-3.1)	0.6 (0.6-0.7)	99.1 (95-103.2)	5.7 (5.6-5.9)	3 (2.3-3.7)
	10	0.7 (0.6-0.8)	3.1 (3-3.2)	0.7 (0.6-0.7)	107 (103.2-110.9)	6.1 (5.9-6.3)	4.1 (3.2-5)
	25	1 (0.9-1.1)	3.3 (3.2-3.4)	0.7 (0.7-0.7)	116.5 (113.3-119.7	6.6 (6.4-6.7)	5.9 (5.2-6.6)
	75	1.9 (1.8-2.1)	3.8 (3.7-3.9)	0.9 (0.9-0.9)	145.4 (140.2-150.6	8 (7.9-8.1)	13.1 (11.5-14.7)
	90	2.6 (2.4-2.8)	4.1 (4-4.2)	1 (0.9-1)	161.3 (154.5-168.2	8.8 (8.5-9.1)	19.1 (16.2-21.9)
	95	3.2 (2.9-3.5)	4.3 (4.2-4.4)	1 (1-1.1)	169.7 (156.8-182.7	9.2 (8.8-9.6)	25.5 (20.8-30.3)
Age: 20-64 Years	5	0.6 (0.5-0.6)	2.7 (2.6-2.7)	0.6 (0.6-0.6)	85.4 (83-87.8)	5.7 (5.6-5.9)	3.3 (3-3.6)
	10	0.7 (0.7-0.8)	2.8 (2.7-2.8)	0.7 (0.6-0.7)	90 (88.2-91.7)	6 (5.9-6.1)	4 (3.7-4.4)
	25	1 (1-1.1)	3 (3-3)	0.7 (0.7-0.7)	101.5 (99.6-103.4)	6.6 (6.5-6.7)	6.7 (6.1-7.2)
	75	2 (1.9-2.1)	3.4 (3.4-3.5)	0.9 (0.9-0.9)	127.8 (125.6-130)	8.3 (8.2-8.5)	17.4 (15.7-19.1)
	90	2.8 (2.7-2.9)	3.7 (3.6-3.7)	1 (0.9-1)	142.5 (138.6-146.3	9.4 (9.1-9.6)	29.1 (25.9-32.2)
	95	3.3 (3-3.6)	3.8 (3.7-3.9)	1 (1-1)	152.9 (148.5-157.3	10.3 (9.9-10.6)	37.5 (31.9-43)
Age: 65+ Years	5	0.7 (0.4-1)	2.5 (2.4-2.5)	0.6 (.-.)*	76 (71.3-80.8)	6 (5.6-6.5)	3.4 (2.5-4.2)
	10	0.9 (0.7-1.1)	2.6 (2.5-2.7)	0.7 (0.6-0.7)	80.9 (76.9-85)	6.3 (6.1-6.5)	4.2 (3.7-4.8)
	25	1.3 (1.1-1.4)	2.8 (2.7-2.8)	0.7 (0.7-0.8)	91.5 (87-95.9)	6.9 (6.6-7.1)	6.6 (5.6-7.5)
	75	2.5 (2.2-2.8)	3.2 (3.1-3.2)	0.9 (0.9-0.9)	119.2 (115.8-122.6	8.6 (8.3-8.8)	17.5 (15.7-19.3)
	90	3.4 (2.9-3.8)	3.3 (3.3-3.3)	1 (1-1)	129.6 (125.6-133.7)	9.5 (9-10.1)	31.7 (25.9-37.4)
	95	4.1 (3-5.2)	3.4 (3.3-3.5)	1 (1-1.1)	135.1 (127.7-142.5)	10.5 (9.8-11.1)	42.1 (34.6-49.6)
Non-Hispanic White	5	0.6 (.-.)*	2.6 (2.6-2.7)	0.6 (0.6-0.6)	84.3 (81-87.6)	5.7 (5.5-5.9)	3.3 (2.9-3.7)
	10	0.7 (.-.)*	2.8 (2.7-2.8)	0.7 (0.6-0.7)	88.7 (86.3-91.2)	6 (5.8-6.1)	4.1 (3.7-4.5)
	25	1 (.-.)*	3 (2.9-3)	0.7 (0.7-0.7)	101.1 (98.9-103.3)	6.6 (6.4-6.7)	6.7 (6.3-7.2)
	75	1.9 (.-.)*	3.5 (3.4-3.5)	0.9 (0.9-0.9)	128.8 (126.7-130.8)	8.2 (8-8.4)	16.9 (15.2-18.6)
	90	2.6 (.-.)*	3.7 (3.6-3.8)	1 (0.9-1)	144.8 (141.2-148.3)	9.1 (8.8-9.3)	28 (24.4-31.5)
	95	3.2 (.-.)*	4 (3.9-4)	1 (1-1)	156.5 (150.1-162.9)	9.9 (9.5-10.3)	37.2 (34.3-40.1)
Non-Hispanic Black	5	0.6 (.-.)*	2.7 (2.6-2.7)	0.6 (0.6-0.6)	82.8 (78.2-87.4)	5.7 (5.6-5.9)	4.4 (4-4.9)
	10	0.7 (.-.)*	2.8 (2.7-2.8)	0.7 (0.7-0.7)	89.6 (86.1-93.1)	6.1 (5.9-6.3)	5.8 (5.3-6.2)
	25	1 (.-.)*	3 (2.9-3)	0.7 (0.7-0.8)	101.5 (98.3-104.7)	6.8 (6.7-6.9)	8.5 (8.1-9)
	75	2 (.-.)*	3.4 (3.4-3.5)	0.9 (0.9-0.9)	130.3 (126.3-134.2)	8.5 (8.2-8.8)	22.8 (20.7-24.9)
	90	2.8 (.-.)*	3.8 (3.7-3.8)	1 (0.9-1)	148 (143.2-152.9)	9.7 (9.3-10.1)	33.2 (27.9-38.5)
	95	3.3 (.-.)*	4 (3.9-4.1)	1 (1-1)	158.9 (148.3-169.5)	10.7 (10-11.3)	47.4 (36.3-58.5)
Hispanic	5	0.7 (.-.)*	2.7 (2.7-2.8)	0.6 (0.6-0.6)	87.4 (83.1-91.7)	5.8 (5.7-5.9)	2.7 (2.1-3.3)
	10	0.9 (.-.)*	2.8 (2.8-2.9)	0.7 (0.6-0.7)	93.7 (91.2-96.1)	6.1 (6-6.2)	3.5 (3.1-3.8)
	25	1.3 (.-.)*	3 (3-3.1)	0.7 (0.7-0.7)	105.5 (101.9-109)	6.8 (6.6-7)	5.5 (4.9-6)
	75	2.5 (.-.)*	3.5 (3.5-3.6)	0.9 (0.9-0.9)	133 (129.1-136.9)	8.5 (8.3-8.7)	13.7 (12.7-14.6)
	90	3.4 (.-.)*	3.8 (3.7-3.8)	1 (0.9-1)	149.7 (146.6-152.8)	9.5 (9.1-9.9)	19.5 (17.6-21.4)
	95	4.1 (.-.)*	3.9 (3.7-4.1)	1 (1-1.1)	157.7 (153.9-161.5)	10.4 (10-10.8)	25.8 (22-29.5)
Non-smoker	5	0.6 (0.6-0.7)	2.6 (2.6-2.7)	0.6 (0.6-0.6)	84.4 (81.9-87)	5.7 (5.6-5.9)	3.1 (2.8-3.4)
	10	0.8 (0.7-0.8)	2.8 (2.7-2.8)	0.7 (0.6-0.7)	89.3 (87.2-91.4)	6.1 (6-6.2)	3.9 (3.7-4.1)
	25	1.1 (1-1.1)	3 (2.9-3)	0.7 (0.7-0.7)	101.7 (99.7-103.6)	6.6 (6.5-6.7)	6.1 (5.6-6.7)
	75	2.2 (2.1-2.3)	3.5 (3.4-3.5)	0.9 (0.9-0.9)	128.7 (126.3-131.2)	8.3 (8.1-8.4)	15.4 (14.2-16.6)
	90	3 (2.8-3.1)	3.7 (3.7-3.8)	1 (1-1)	145.2 (141.8-148.5)	9.3 (9.1-9.5)	24.6 (21.6-27.7)
	95	3.6 (3.3-3.8)	3.9 (3.8-4)	1 (1-1)	155.5 (152.2-158.8)	10.1 (9.9-10.3)	36.4 (32.2-40.6)
Smoker	5	0.5 (0.4-0.6)	2.7 (2.6-2.7)	0.6 (0.6-0.6)	84.1 (80-88.3)	5.7 (5.5-5.9)	3.8 (3.2-4.4)
	10	0.6 (0.5-0.7)	2.8 (2.7-2.9)	0.7 (0.6-0.7)	89.3 (85.1-93.6)	5.9 (5.8-6.1)	5.2 (4.5-5.9)

	25	0.9 (0.8-1)	3 (3-3)	0.7 (0.7-0.7)	102 (98.7-105.4)	6.7 (6.4-6.9)	7.9 (6.8-8.9)
	75	1.9 (1.7-2)	3.5 (3.4-3.6)	0.9 (0.9-0.9)	130.4 (127.4-133.4)	8.4 (8.1-8.7)	20.1 (17.4-22.9)
	90	2.7 (2.4-3)	3.8 (3.7-3.9)	1 (0.9-1)	146.9 (141.2-152.7)	9.3 (8.8-9.8)	32.4 (29.8-35)
	95	2.9 (2.7-3.1)	3.9 (3.8-4.1)	1 (1-1.1)	161.7 (151.6-171.7)	10.4 (9.8-10.9)	39.5 (34.1-44.9)
Iodine Deficient	5	0.6 (0.5-0.7)	2.7 (2.6-2.8)	0.6 (0.6-0.6)	85.9 (83.1-88.7)	5.9 (5.7-6)	3.4 (3-3.7)
	10	0.7 (0.6-0.8)	2.8 (2.7-2.9)	0.7 (0.6-0.7)	91.6 (88.3-94.8)	6.1 (6-6.2)	4.4 (3.9-4.8)
	25	1 (0.9-1.1)	3 (3-3.1)	0.7 (0.7-0.7)	105 (102.6-107.4)	6.7 (6.6-6.7)	7.1 (6.4-7.8)
	75	2 (1.9-2.1)	3.5 (3.4-3.5)	0.9 (0.9-0.9)	130.2 (127.7-132.7)	8.3 (8.1-8.6)	18.3 (16.4-20.2)
	90	2.8 (2.6-2.9)	3.7 (3.6-3.8)	1 (0.9-1)	145.6 (141.3-149.9)	9.3 (8.9-9.6)	29.7 (25.9-33.6)
	95	3.3 (2.9-3.6)	3.9 (3.8-4)	1 (1-1.1)	154.3 (148.6-160)	10.2 (9.7-10.6)	38.1 (33.6-42.6)
Iodine Replete	5	0.6 (0.5-0.7)	2.6 (2.6-2.7)	0.6 (0.6-0.6)	82.7 (79.4-86.1)	5.7 (5.5-5.9)	3.2 (2.9-3.4)
	10	0.8 (0.7-0.8)	2.8 (2.7-2.8)	0.7 (0.6-0.7)	88.4 (86-90.8)	6 (5.9-6.2)	4 (3.7-4.2)
	25	1.1 (1-1.1)	3 (2.9-3)	0.7 (0.7-0.7)	100.9 (98.7-103.1)	6.6 (6.5-6.7)	6.3 (5.8-6.9)
	75	2.1 (2-2.2)	3.5 (3.4-3.5)	0.9 (0.9-0.9)	129.2 (126.8-131.5)	8.3 (8.2-8.4)	15.4 (14.1-16.8)
	90	2.9 (2.7-3.1)	3.8 (3.7-3.8)	1 (0.9-1)	145.7 (142-149.3)	9.3 (9.1-9.5)	25.4 (22.7-28.1)
	95	3.5 (3.2-3.8)	4 (3.9-4)	1 (1-1)	158.1 (153.4-162.9	10.2 (9.9-10.4)	36 (32-39.9)
*Not enough variability in the data to compute confidence intervals.							

Percentile distribution of total thyroxine (TT4)

Percentile distribution of TT4 for females was displaced to the right of the distribution for males and the gap widened for higher percentiles (Table 2). There was a statistically significant increase in TT4 levels with increase in age (7.46, 7.72, and 7.72 μg/mL for those aged 12-19, 20-64, and 65+ years, Table 1). While lower percentiles were similar for the three age groups, higher percentiles, namely 25th and higher, for the age groups 20-64 and 65+ years were displaced to the right of the percentiles for 12-19 years old and the gap became wider with increase in percentiles, in particular between 12-19 years and ≥ 20 years old (Table 2). NHB had the highest TT4 (7.66 μg/mL) and NHW, the lowest (7.38 μg/mL). The same applies to almost all percentile points (Table 2).

Percentile distribution of thyroglobulin (Tg)

While the distribution of males and females for Tg was similar until the 50th percentile, higher percentiles for females were displaced to the right of the percentiles for males and the gap became wider with increase in percentiles (Table 2). Similarly, the distribution of Tg by age was similar until about the 50th percentile, but the distributions for those aged ≥ 20 years was displaced to the right of the distribution of those aged 12-19 years old, and the gap became wider with increase in percentiles (Table 2). Irrespective of the percentiles, NHB had the highest and NHW the lowest levels of Tg and the gap became wider and wider with increase in percentiles (Table 2).

Prevalence of hypo-and hyperthyroidism

The prevalence rate for subclinical hyperthyroidism was 3.1% for the total U. S. population and females had statistically significantly higher prevalence than males ($p < 0.01$, Table 3). Prevalence of clinical hyperthyroidism for the total population was 0.3% (Table 3).

The percent population with subclinical hypothyroidism was 3.5% (Table 3).For those aged 65+ years, prevalence of subclinical hypothyroidism was almost double of what it was for those aged < 65 years (Table 3). NHB had the lowest prevalence of subclinical hypothyroidism and NHW, the highest ($p < 0.01$, Table 3). HISP had statistically significantly higher prevalence of subclinical hypothyroidism than NHB ($p < 0.01$, Table 3). Percent prevalence of hypothyroidism for the total population was 0.2%. Those who were iodine deficient had four times the prevalence of hypothyroidism than those who were iodine replete (Table 3).

Prevalence of TgAb and TPOAb

Prevalence of positive TgAb among general U.S. population was 7.7% (Table 4) and females had statistically higher prevalence of positive TgAb than males ($p < 0.01$, Table 4). Prevalence of positive TgAb increased with increase in age from 5.1% for 12-19 years old to 11.1% for 65+ years old (Table 4). The order of positive TgAb by race/ethnicity was: NHW > HISP > NHB.

Prevalence of positive TPOAb among general U.S. population was 39.1% (Table 4) and females had higher prevalence of positive TPOAb than males (Table 4). Prevalence of positive TPOAb increased with increase in age from 34.1% for 12-19 years old to 40.4% for 65+ years old (Table 4). The order of positive TPOAb by race/ethnicity was: NHW > HISP > NHB.

Table 3: Percent prevalence of subclinical hyperthyroidism and subclinical and clinical hypothyroidism with 95% confidence intervals by gender, age, race/ethnicity, smoking, and iodine sufficiency status for total U.S. population**. Data from National Health and Nutrition Examination Survey 2007-2012.

Demographic Variable	Subclinical Hyperthyroidism		Clinical Hyperthyroidism		Subclinical Hypothyroidism		Clinical Hypothyroidism	
	Percent Prevalence (95% CI)	Statistically Significant Differences	Percent Prevalence (95% CI)	Statistically Significant Differences	Percent Prevalence (95% CI)	Statistically Significant Differences	Percent Prevalence (95% CI)	Statistically Significant Differences
Total	3.1 (2.2-3.9)		0.3 (0.1-0.4)		3.5 (2.4-4.6)		0.2 (0.1-0.4)	
Males (M)	2 (1.3-2.7)	M < F ($p < 0.01$)	0.4 (0-0.7)		3.1 (1.7-4.6)		0.1 (-0.1-0.3)	
Females (F)	4 (2.7-5.4)		0.1 (0-0.3)		3.8 (2.4-5.2)		0.3 (0-0.6)	
Age: 12-19 Years (A12)	2.6 (1-4.2)		0.1 (-0.1-0.3)		2.5 (0.6-4.4)		0 (0-0)	
Age: 20-64 Years (A20)	3 (2-4.1)		0.3 (0-0.5)		3.3 (1.9-4.6)		0.2 (0-0.4)	
Age: 65+ Years (A65)	3.5 (1.4-5.7)		0.3 (-0.1-0.7)		5.3 (3-7.5)		0.5 (-0.1-1.1)	
Non-Hispanic White (NHW)	3.3 (2-4.6)		0.3 (0-0.5)		4.4 (2.7-6)	NHW < NHB ($p < 0.01$)	0.2 (0-0.5)	NHW < NHB ($p = 0.046$)
Non-Hispanic Black (NHB)	3.1 (2.2-4)		0.1 (-0.1-0.3)		0.6 (0-1.2)	NHB < HISP ($p < 0.01$)	0.1 (-0.1-0.2)	
Hispanic (HISP)	2.1 (0.8-3.4)		0.4 (-0.2-0.9)		3.3 (1.6-4.9)		0.4 (-0.1-0.8)	
Nonsmokers (NSM)	3 (1.8-4.1)		0.2 (0-0.4)		3.6 (2.5-4.7)		0.3 (0-0.5)	
Smokers (SM)	3.3 (1.7-4.9)		0.3 (-0.1-0.8)		3 (1.2-4.8)		0.1 (0-0.3)	
Iodine Deficient (IOD)	3.9 (1.9-5.9)		0.1 (0-0.3)		3.1 (1.5-4.7)		0.4 (0.1-0.7)	
Iodine Replete (IOR)	2.6 (1.9-3.4)		0.3 (0-0.6)		3.7 (2.4-5)		0.1 (-0.1-0.4)	
**Excludes pregnant females.								

Table 4: Prevalence of positive thyroglobulin antibodies (TgAb) and thyroid peroxidase antibodies (TPOAb) in percent with 95% confidence intervals by gender, age, race/ethnicity, smoking, and iodine sufficiency status for total U.S. population**. Data from National Health and Nutrition Examination Survey 2007-2012.

Demographic Variable	TgAb		TPOAb	
	Percent Positive (95% CI)	Statistically Significant Differences	Percent Positive (95% CI)	Statistically Significant Differences
Total	7.7 (6.4-9.1)		39.1 (36.4-41.8)	
Males (M)	5.8 (4.1-7.4)	M < F (p < 0.01)	36.1 (32.6-39.6)	M < F (p < 0.01)
Females (F)	9.6 (7.6-11.7)		42.1 (39-45.1)	
Age: 12-19 Years (A12)	5.1 (2.9-7.3)	A12 < A65 (p = 0.01)	34.1 (29.9-38.3)	A12 < A20 (p < 0.01)
Age: 20-64 Years (A20)	7.5 (5.7-9.2)	A20 < A65 (p = 0.04)	39.8 (36.8-42.7)	
Age: 65+ Years (A65)	11.1 (7.8-14.3)		40.4 (33.6-47.3)	
Non-Hispanic White (NHW)	8.6 (6.7-10.6)	NHW < NHB (p < 0.01)	39.9 (36-43.8)	
Non-Hispanic Black (NHB)	3.5 (2.4-4.7)	NHB < HISP (p < 0.01)	34.1 (29.7-38.6)	
Hispanic (HISP)	6.5 (5.4-7.6)		38.7 (34.8-42.6)	
Nonsmokers (NSM)	8.1 (6.6-9.6)		40.1 (37.2-42.9)	
Smokers (SM)	6.6 (3.7-9.4)		36 (31.9-40.1)	
Iodine Deficient (IOD)	8.1 (5.9-10.3)		40.5 (36.9-44.2)	
Iodine Replete (IOR)	7.5 (5.9-9.1)		38.4 (35.1-41.6)	

**Excludes pregnant females.

Geometric means and reference ranges

The geometric mean (GM) for TSH (Table 1) for the reference U.S. population was 1.46 mIU/L. TSH levels were statistically significantly higher for those aged 65+ years (1.75 mIU/L) than those aged 12-19 years old (1.40 mIU/L) and 20-64 years old (1.43 mIU/L). The TSH levels by race/ethnicity were in the order: NHW > HISP > NHB and NHB had statistically significantly lower TSH levels than NHW and HISP (Table 1). Nonsmokers had statistically significantly higher TSH levels than smokers (Table 1). Those who were iodine replete had higher levels than those who were iodine deficient (Table 1, $p < 0.05$). Those who were tested in the morning had statistically significantly higher TSH levels than those who were tested later during the day (1.56 vs. 1.38 mIU/L, Table 1).

The reference range for TSH for the reference U.S. population determined by the 2.5th and 97.5th percentiles was 0.5-4.0 mIU/L (Table 5). The reference ranges for males and females were similar. The reference ranges for 12-19 years and 20-64 years old were similar (0.5-3.5 mIU/L and 0.5-3.9 mIU/L) but the reference range for 65+ years old was substantially wider (0.3-5.4 mIU/L). The reference ranges for NHW, NHB, and HISP, were 0.5-4.3 mIU/L, 0.4-3.6 mIU/L, and 0.5-4.2 mIU/L respectively.

Prevalence of TSH < 0.45 mIU/L was higher among females than males (Table 6). NHB had the highest (2.99%) and HISP (0.76%) had the lowest prevalence of TSH < 0.45 mIU/L. Those aged 65+ years had the highest prevalence (2.6%) of TSH < 0.45 mIU/L. Prevalence of TSH > 4.5 mIU/L was higher among males than females (Table 6). NHW had the highest (2.4%) and NHB (0.29%) had the lowest prevalence of TSH > 4.5 mIU/L. Those aged 65+ years had the highest prevalence (3.69%) of TSH > 4.5 mIU/L.

GM for FT3 for U.S. population was 3.23 pg/mL (Table 1). Males had statistically significantly higher levels of FT3 than females (Table 1). Levels of FT3 decreased with age from 3.58 pg/mL for 12-19 years old to 2.94 pg/mL for 65+ years old. NHW had the lowest levels of FT3 (3.2 pg/mL) and HISP, the highest (3.3 pg/mL). Those who were tested in the morning session had statistically significantly higher FT3 levels than those who were tested later during the day. In most cases, the width of reference ranges was about 1.6 pg/mL. However, the width of reference range for 65+ years old was 1.1 pg/mL (Table 5).

Levels of FT4 were slightly higher for those aged 65+ years than two other age groups (Table 1). GM for TT3 for U.S. population was 115.38 ng/dL (Table 1). Males had statistically significantly higher TT3 than females (Table 1). The levels of TT3 decreased by more than 25% with increase in age (Table 1). Compared to other racial/ethnic groups, HISP had the highest levels of TT3 (Table 1). Those who were tested in the morning had statistically significantly higher levels of TT3 than those who were tested later during the day (Table 1). The reference range for TT3 for the overall U.S. population was 78.9-69.3 ng/dL (Table 5).

GM for TT4 for U.S. population was 7.47 µg/dL (Table 1) and the reference range was 5.5-11.0 µg/dL (Table 5). Females had statistically significantly higher TT4 levels than males ($p < 0.05$, Table 1).

GM for Tg for the U.S. population was 10.54 ng/mL (Table 1) and the reference range was 2.5-48.4 ng/mL (Table 5). Females had statistically significantly higher levels of Tg than males (Table 1). In addition, the reference range was much shorter for males (2.5-37.6 ng/mL) as compared to females (2.5-52.0 ng/mL). GM for Tg increased with age (Table 1). Width of the reference ranges became wider with increase in age. There was a major difference between the Tg levels for NHB as compared with other race/ethnicities (14.39 ng/mL for NHB, 10.69 ng/mL for NHW, and 8.44 ng/mL for HISP). Smokers had more than 25% higher Tg levels as compared to non-smokers and iodine deficients had about 15% higher Tg levels than those who were iodine replete.

Discussion

The differences between the study by Hollowell et al. and this study need to be noted before the results from the two studies can be compared. First, TSH and TT4 were the only thyroid hormone data analyzed by Hollowell et al.. In this study, we also analyzed data for FT3, FT4, TT3, and Tg. Second, TT4 for Hollowell's data was measured using an immunoassay with a normal reference range of 4.5 µg/dL to 13.2 µ/dL and TSH for their data was measured with a chemiluminescence immunometric assay with a normal reference range of 0.39 to 4.6 mIU/L. For this study, TSH was measured by a 3rd generation two-site immunoenzymatic ("sandwich") assay with a normal reference range of 0.24 to 5.4 mIU/L and TT4 by a competitive binding immunoenzymatic assay with a normal reference range of 6.09 to 12.23 µg/dL (http://wwwn.cdc.gov/nchs/nhanes/2011-2012/THYROD_G.htm#Description_of_Laboratory_Methodology). Third, Hollowell et al. defined subclinical hyperthyroidism when TSH < 0.1 mIU/L and TT4 < 169.9 nmol/L. Clinical hyperthyroidism was defined when TSH < 0.1 mIU/L and TT4 ≥ 169.9 nmol/L. For this study, the definition provided by Surks et al. were used to define subclinical hyperthyroidism when TSH < 0.45 mIU/L and 0.6 ≤ FT4 ≤ 1.6 ng/dL. Clinical hyperthyroidism was defined when TSH < 0.45 mIU/L and FT4 >1.6 ng/dL. Hollowell et al. defined subclinical hypothyroidism when TSH > 4.5 mIU/L and TT4 < 57.9 nmol/L, and subclinical hypothyroidism when TSH > 4.5 mIU/L and TT4 ≥ 57.9 nmol/L. For this study, subclinical hypothyroidism was defined when TSH > 4.5 mIU/L and 0.6 <= FT4 <= 1.6 ng/dL, and clinical hypothyroidism when TSH > 4.5 mIU/L and FT4 < 0.6 ng/dL. Fourth, for the data used by Hollowell et al., Hollowell reported using a direct RIA assay for measuring TPOAb and TgAb while the assay used in NHANES 2007-2012 for both TbAb and TPOAb was a sequential two-step immunoenzymatic "sandwich" assay (http://www.cdc.gov/nchs/nhanes/nhanes2011-2012/THYROD_E.htm#Description_of_

Table 5: Selected percentile points with 95% confidence intervals for thyroid stimulating hormone (TSH), free triiodothyronine (FT3), free thyroxine (FT4), total triiodothyronine (TT3), total thyroxine (TT4) thyroglobulin (TGN) by gender, age, race/ethnicity, smoking status, and iodine sufficiency status for reference U.S. population. Data from National Health and Nutrition Examination Survey 2007-2012.

Demographic Variable	Percentile	TSH in µIU/mL	FT3 in pg/mL	FT4 in ng/dL	TT3 in ng/dL	TT4 in µg/mL	TGN in ng/mL
Total	2.5	0.5 (0.4-0.5)	2.5 (2.5-2.6)	0.6 (0.6-0.6)	78.9 (75.8-82.1)	5.5 (5.4-5.6)	2.5 (2.3-2.8)
	50	1.5 (1.4-1.6)	3.2 (3.2-3.2)	0.8 (0.8-0.8)	115.3 (113.4-117.3	7.4 (7.3-7.5)	10.4 (9.7-11.2)
	97.5	4 (3.6-4.5)	4.1 (4-4.2)	1.1 (1.1-1.1)	169.3 (161-177.7)	11 (10.6-11.4)	48.4 (43.5-53.2)
Male	2.5	0.5 (0.4-0.6)	2.6 (2.5-2.7)	0.6 (0.6-0.6)	78 (72.8-83.1)	5.4 (5.3-5.6)	2.5 (2.2-2.9)
	50	1.5 (1.4-1.6)	3.3 (3.3-3.3)	0.8 (0.8-0.8)	116.9 (114-119.9)	7.2 (7.1-7.3)	10 (9.2-10.7)
	97.5	4.1 (3.1-5.1)	4.2 (4.1-4.3)	1.1 (1-1.1)	163.6 (159.6-167.7	10.5 (10.1-10.9)	37.6 (29.9-45.3)
Female	2.5	0.4 (0.4-0.5)	2.4 (2.3-2.5)	0.6 (0.6-0.6)	80 (76.7-83.3)	5.7 (5.4-6)	2.5 (2-3.1)
	50	1.5 (1.4-1.6)	3.1 (3.1-3.1)	0.8 (0.8-0.8)	113.1 (111.1-115)	7.6 (7.5-7.7)	11 (9.7-12.4)
	97.5	3.9 (3.4-4.4)	4 (3.9-4)	1.1 (1.1-1.1)	171.5 (162.8-180.1	11.4 (10.9-11.8)	52 (35.9-68.1)
Age: 12-19 Years	2.5	0.5 (0.3-0.6)	2.8 (.-.)	0.6 (.-.)	94.5 (88.7-100.3)	5.6 (5.4-5.8)	2.5 (1.9-3.1)
	50	1.5 (1.4-1.6)	3.6 (3.5-3.7)	0.8 (0.8-0.8)	130.3 (126.7-133.9	7.2 (7-7.4)	8.8 (8-9.7)
	97.5	3.5 (3.3-3.7)	4.4 (4.1-4.8)	1.1 (1-1.2)	183.6 (163.1-204.2	10 (9.6-10.3)	29.8 (23.1-36.5)
Age: 20-64 Years	2.5	0.5 (0.4-0.5)	2.6 (2.5-2.7)	0.6 (0.6-0.6)	80.9 (77.2-84.5)	5.5 (5.3-5.7)	2.5 (2.2-2.9)
	50	1.4 (1.4-1.5)	3.2 (3.2-3.2)	0.8 (0.8-0.8)	114.6 (112.3-116.9	7.4 (7.2-7.5)	10.8 (9.9-11.7)
	97.5	3.9 (3.4-4.3)	4 (3.9-4.1)	1.1 (1-1.1)	166.3 (154.7-177.9	11 (10.5-11.5)	48.4 (40.3-56.6)
Age: 65+ Years	2.5	0.3 (.-.)*	2.4 (2.3-2.4)	0.6 (.-.)*	68.5 (59.7-77.4)	5.5 (.-.)*	2.5 (.-.)*
	50	1.8 (1.6-2)	2.9 (2.9-3)	0.8 (0.8-0.8)	105.7 (102.5-108.9	7.6 (7.4-7.8)	10.4 (8.9-11.9)
	97.5	5.4 (.-.)*	3.5 (.-.)*	1.1 (1-1.2)	147.6 (137.6-157.6	11.5 (10.7-12.2)	57.1 (29.4-84.7)
Non-Hispanic White	2.5	0.5 (0.4-0.6)	2.5 (2.4-2.6)	0.6 (0.6-0.6)	78.8 (74.6-83)	5.4 (5.2-5.6)	2.7 (2.3-3)
	50	1.6 (1.5-1.7)	3.2 (3.1-3.2)	0.8 (0.8-0.8)	115.3 (112.9-117.7	7.3 (7.1-7.5)	10.5 (9.6-11.4)
	97.5	4.3 (3.2-5.4)	4.1 (4-4.2)	1.1 (1-1.1)	169.6 (159.8-179.4	10.8 (10.2-11.4)	46.4 (40.4-52.4)
Non-Hispanic Black	2.5	0.4 (0.4-0.5)	2.6 (2.5-2.7)	0.6 (0.6-0.6)	76.3 (72.7-79.9)	5.5 (5.3-5.6)	3.6 (3.1-4.1)
	50	1.2 (1.2-1.3)	3.2 (3.2-3.2)	0.8 (0.8-0.8)	114.4 (110.9-117.9	7.6 (7.4-7.8)	14.2 (12.7-15.8)
	97.5	3.6 (3.3-3.9)	4.2 (4.1-4.3)	1.1 (1-1.2)	182.3 (162.7-201.9	11.4 (10.6-12.2)	67 (45.6-88.3)
Hispanic	2.5	0.5 (0.5-0.6)	2.7 (2.6-2.8)	0.6 (0.6-0.6)	82.9 (75.7-90)	5.6 (5.5-5.8)	1.9 (0.8-2.9)
	50	1.5 (1.4-1.5)	3.3 (3.2-3.3)	0.8 (0.8-0.8)	117.1 (113.6-120.7	7.5 (7.3-7.8)	8.8 (8.2-9.4)
	97.5	4.2 (3.6-4.8)	4.2 (4-4.3)	1.1 (1.1-1.1)	164.9 (154.1-175.8	11.2 (10.7-11.8)	31.9 (20-43.9)
Non-smoker	2.5	0.5 (0.4-0.6)	2.5 (2.4-2.6)	0.6 (0.6-0.6)	78.5 (74.9-82.1)	5.6 (5.4-5.7)	2.3 (1.9-2.8)
	50	1.6 (1.5-1.6)	3.2 (3.2-3.2)	0.8 (0.8-0.8)	115.2 (113.1-117.2	7.3 (7.2-7.5)	9.7 (9-10.4)
	97.5	4.3 (3.7-5)	4.1 (4-4.2)	1.1 (1.1-1.1)	166.5 (160.8-172.2	10.9 (10.5-11.3)	46.5 (41.3-51.8)
Smoker	2.5	0.4 (0.3-0.5)	2.6 (2.4-2.8)	0.6 (0.6-0.6)	80.3 (75.7-84.9)	5.4 (5.1-5.8)	3 (2.4-3.6)
	50	1.3 (1.2-1.4)	3.2 (3.2-3.3)	0.8 (0.8-0.8)	115.9 (111.6-120.2	7.5 (7.3-7.7)	12.8 (11.4-14.3)
	97.5	3.3 (2.9-3.7)	4.1 (3.9-4.4)	1.1 (1-1.1)	175.5 (162.6-188.5	11 (10.1-11.9)	50.9 (44.9-56.9)
Iodine Deficient	2.5	0.5 (0.3-0.6)	2.6 (2.5-2.7)	0.6 (0.6-0.6)	83.3 (78.7-88)	5.6 (5.4-5.9)	2.7 (2.3-3.2)
	50	1.4 (1.3-1.5)	3.2 (3.2-3.3)	0.8 (0.8-0.8)	116.5 (114.1-118.8	7.5 (7.3-7.7)	11.3 (10-12.6)
	97.5	3.8 (3.4-4.3)	4.1 (4-4.2)	1.1 (1.1-1.1)	163.7 (150.8-176.6	10.7 (10.2-11.2)	49.3 (37.6-61)
Iodine Replete	2.5	0.5 (0.4-0.5)	2.5 (2.4-2.6)	0.6 (0.6-0.6)	77.2 (73.6-80.8)	5.4 (5.2-5.6)	2.5 (2-2.9)
	50	1.5 (1.5-1.6)	3.2 (3.1-3.2)	0.8 (0.8-0.8)	114.5 (112.3-116.7	7.4 (7.2-7.5)	10 (9.3-10.8)
	97.5	4.1 (3.4-4.9)	4.1 (4-4.2)	1.1 (1-1.1)	169.9 (159.7-180.2	11 (10.5-11.4)	48.4 (41-55.7)

*Not enough variability in the data to compute confidence intervals.

Table 6: Prevalence of TSH < 0.45 mIU/L, > 4.5 mIU/L, and > 10 mIU/L with 95% confidence intervals by age, gender, race/ethnicity, smoking and iodine deficiency status. Data from National Health and Nutrition Examination Survey 2007-2012.

	TSH < 0.45 mIU/L	TSH > 4.5 mIU/L	TSH > 10 mIU/L
Total	1.88 (1.14-2.63)	1.88 (1.07-2.69)	0.13 (-0.13-0.39)
Males	1.38 (0.46-2.29)	2.19 (0.87-3.51)	0.24 (-0.24-0.72)
Females	2.49 (1.3-3.67)	1.51 (0.51-2.5)	0 (0-0)
Age: 12-19 Years	1.55 (0.16-2.94)	1.08 (-0.87-3.03)*,^^	0 (0-0)
Age: 20-64 Years	1.8 (0.98-2.63)	1.68 (0.78-2.59)*,^	0.18 (-0.18-0.55)
Age: 65+ Years	2.61 (-0.51-5.74)	3.69 (0.67-6.7)^	0(0-0)
Non-Hispanic White	1.7 (0.67-2.73)	2.4 (1.17-3.63)^^	0.2 (-0.2-0.61)
Non-Hispanic Black	2.99 (1.44-4.55)*	0.29 (-0.06-0.64)	0 (0-0)
Hispanic	0.76 (0.08-1.44)*	1.49 (0.33-2.66)	0 (0-0)
Other	3.89 (-0.47-8.25)	0.91 (0.05-1.76)	0 (0-0)
Nonsmokers	1.53 (0.74-2.32)	2.29 (1.35-3.24)*	0.17 (-0.17-0.52)
Smokers	2.98 (0.99-4.97)	0.6 (-0.53-1.73)*	0 (0-0)
Iodine Deficient	1.93 (0.4-3.45)	1.41 (0.38-2.43)	0.39 (-0.39-1.16)
Iodine Replete	1.82 (1.02-2.62)	2.13 (1.03-3.23)	0 (0-0)

^^^Pairs with the same symbols *, ^, or ^^ are statistically significantly different at α = 0.05.

Laboratory_Methodology). Hollowell et al. defined positive thyroid antibodies when TPOAb ≥ 0.5 IU/mL and/or TgAb ≥ 1.0 IU/mL. For this study, the normal values for the assay used to detect TPOAb was < 0.9 IU/ML. The normal values for the assay used to detect TgAb was < 4.0. Lastly, while the total population for this study included all NHANES participants aged ≥ 12 years old except for the females who tested positive for pregnancy using a urine assay. Hollowell et al. defined total population in two different ways, first definition (TP1) included all NHANES population, and second definition (TP2) excluded from TP1 those who were pregnant as well those who taking estrogen drugs. Thus, total population as defined for this study is different from either TP1 or TP2. Reference population was defined by Hollowell et al. as those participants who did not self-report any thyroid disease, were not taking any thyroid medication, were not pregnant, were not taking any estrogen, androgen, or lithium drugs, did not have any detectable thyroid antibodies, and had no evidence of hypo-or hyperthyroidism. Hollowell's reference population seems to be equivalent to our reference population.

Prevalence of hypo-and hyperthyroidism

Prevalence of subclinical hyperthyroidism in Hollowell's study for TP1 was 0.7% and 0.8% for TP2. In this study, prevalence of subclinical hyperthyroidism was substantially higher (3.1%, Table 3) than Hollowell's study which should not be surprising because of the different definitions, namely TSH < 0.1 mIU/L vs. TSH < 4.5 mIU/L, used in the two studies. Hollowell et al. also found the prevalence of clinical hyperthyroidism at 0.5% which is somewhat higher than what was found in this study or 0.3% (Table 3). The prevalence of clinical and subclinical hypothyroidism was found to be 0.2% and 3.5% respectively in this study. These rates in Hollowell's study were 0.3% and 4.3%. Some of these differences in prevalence of clinical hypothyroidism may be due to the differences in use of TT4 in defining hypothyroidism by Hollowell and FT4 in this study. It is also possible that some of those who were defined as having subclinical hypothyroidism in Hollowell's study were defined as having clinical hypothyroidism in this study because of differences in definition. Irrespective of the definitional issues between the two studies, if the prevalence of subclinical hyperthyroidism has, in fact, increased from 0.7 to 0.8% in 1988-1994 to 3.1% in 2007-2012, that too should be of concern since even subclinical hyperthyroidism has been associated with higher heart failure rate as compared with those who had euthyroidism [10], risk of developing major cardiovascular events like stroke [16], and increased risk of developing cardiovascular disease, dementia, and dysrhythmia [17].

Prevalence of thyroid antibodies

Hollowell et al. found postive TgAb at 11.5% and positive TPOAb at 13%. In this study, prevalence of positive TgAb was 7.7% and prevalence of positive TPOAb was 39.1%. If these differences are not due to the different assays used in the two studies, it must be that positive antibody prevalence for TPOAb has gone up substantially to 39.1%. More work will be needed to explain the increased prevalence of TPOAb as seen in this study. The differences in cut offs used to define these antibodies by Hollowell et al. and this study may only be one reason.

Reference ranges and percentile distributions

Mean, reference range, and median TSH levels for the reference population reported by Hollowell et al. were 1.4, 0.45-4.12, and 1.39 mIU/L. In comparison, GM, reference range, and median TSH levels for the reference population for this study were found to be 1.46, 0.5-4.0, and 1.5 mIU/L. Percent reference population with TSH > 4.5 mIU/L for this study was found to be 1.88% which is similar to what was found by Hollowell et al. It would indicate that at risk TSH levels in the reference U.S. population may have decreased a bit or remained at the same level for reference US population. However, for NHW and those aged 65+ years, at risk TSH levels were at 2.4% and 3.69% respectively. At risk TSH levels for these two population subgroups were substantially higher than any other population subgroup. This should be of concern since higher TSH even when within the normal range have associated with higher risk of the occurrence of myocardial infarction among patients with clinical manifest vascular disease [7]. However, abnormal TSH levels, too high or too low, affect not only cardiovascular system but also bone mineral density, tissues such as anteriorpituitarygland, hypothalamus, ovary, testis, skin, kidney, immunesystem, bonemarrow, peripheral blood cells, adipose tissue, orbital preadipocyte fibroblasts and others [20]. In a recent review article, [20] discuss the role of abnormal TSH levels on bone, heart, brain, and immune system as well as thyroid and other cancers.

TT4's reference range for this study was 5.5-11.0 μg/dL with median of 7.4 μg/dL. This reference range in Hollowell's study was 5.05-12.62 μg/dL with median of 8.48 μg/dL. These reference ranges for females were: 5.7-11.4 μg/dL with median of 7.6 μg/dL for this study and 5.23-13.06 μg/dL with median of 8.6 μg/dL for Hollowells' study. Thus, while lower half of the distribution has shifted to the right a bit, the upper half of the distribution has shifted to the left during 2007-2012 as compared to 1988-1994. This has resulted in lower medians during 2007-2012 as compared to 1988-1994. This too does not seem to be good news since lower thyroxine levels are associated with increased TSH levels. The results were same irrespective of race/ethnicity and gender.

GM and median for the reference population for FT4 were both 0.8 ng/dL which are just about at the lower limit of the normal reference of 0.8-2.0 ng/dL for FT4 published elsewhere but higher than the lower limit of the reference range used for this study. Even the 97.5th percentile was substantially below the upper limit of this normal range at 1.1 ng/dL. GM and median for the reference population for TT3 were 115.38 ng/dL and 115.3 ng/dL respectively which are below the middle of the normal reference range for the assay used in this study. The 97.5th percentile was 169.3 ng/dL, well below the upper limit of the normal range. GM and median for the reference population for FT3 were 3.22 pg/mL and 3.20 pg/mL respectively which are near the middle of the normal range of 2.5-3.9 pg/mL for FT3 for the assay used in this study. However, 97.5th percentile was above the upper limit of this normal range at 4.1 pg/mL. The GM and median levels for TT4 were 7.4 ng/dL and 7.4 ng/dL respectively. The 97.5th percentile was 11.0 ng/dL. The normal range for TT4 for the assay used for this study is 6.09-12.23 ng/dL. Thus, for the reference U.S. population while TT4 levels were somewhat acceptable, the levels of FT4, FT3, and TT3 were below what would be expected in a population with normal levels of these hormones. This should be of concern since lower levels of these hormones can result in higher levels of TSH.

Gender and racial/ethnic differences

Statistically significant differences for TSH between males and females for the reference population were not observed either in this study or in the study by Hollowell et al.. While Hollowell et al. did not observe statistically significant gender differences for TT4, we did observe females to have statistically significantly higher levels than males (Table 1) for the reference population. Hollowell et al. found NHB to have significantly lower levels of TSH than NHW. Similar findings were observed in this study. Hollowell et al. found Mexican Americans (MA) to have statistically significantly higher TT4 levels than both NHB and NHW. Similar findings were noted in this study.

Age differences

Increase in TSH levels with age was observed in this study as well as by Hollowell et al.. After the age of 20 years, Hollowell et al. found TT4 levels to decrease. The reverse was observed in this study which may be because of age groupings used in the two studies. Compared to Hollowell's 10 year age groups, we used three age groups in this study, namely, 12-19 years, 20-64 years, and 65+ years.

Summary and Conclusion

In this study, we presented updated data on thyroid profile of the reference United States population. Specifically, in addition to GMs for TSH, FT3, FT4, TT3, and TT4, reference ranges, percentile

points, prevalence rates of TPOAb and TgAb were presented. Other researchers may want to compare thyroid profile of US with thyroid profiles of their own countries. This author was not able to have access to thyroid profile data from other regions of the world like Asia, Africa, Europe, and South America.

For this study, iodine and all other measurements used were based on a single spot sample which may have affected the quality of certain measurements. In particular, levels of urinary iodine may be affected by food intake, atmospheric conditions etc. which may influence sample quality and associated measurements.

In summary, for the first time, in this study, we have presented data the prevalence of hypo-and hyperthyroidism, prevalence of thyroid antibodies, and concentrations levels of thyroid hormones for a representative sample of all U.S. Hispanic population rather than just the Mexican Americans. Overall, (i) males had higher levels of FT3 and TT3 but lower levels of TT4 and Tg than females, (ii) TSH, FT4, TT4, and Tg levels increased with age but FT3 and TT3 levels decreased with age, (iii) NHB had the lowest levels of TSH and FT4 but the highest levels of Tg; (iv) HISP had the highest levels of FT3, TT3, and TT4; (v) smokers had lower levels of TSH but higher levels of FT3 and Tg than nonsmokers, (vi) iodine deficiency was associated with lower levels of TSH but higher levels of FT4 and Tg, (vii) TSH, FT3, FT4, and TT3 levels were higher in the morning than later during the day, and (viii) those who were aged 65+ years had the highest levels of TSH (1.75 mIU/L), highest prevalence (3.69%) of TSH > 4.5 mIU/L, lowest levels of FT3 (2.94 pg/mL), and lowest levels of TT3 (104.32 ng/dL).

References

1. Asvold BO, Bjøro T, Platou C, Vatten LJ (2012) Thyroid function and the risk of coronary heart disease: 12-year follow-up of the HUNT study in Norway. Clin Endocrinol (Oxf) 77: 911-917.
2. Boggio A, Muzio F, Fiscella M, Sommariva D, Branchi A (2014) Is thyroid-stimulating hormone within the normal reference range a risk factor for atherosclerosis in women? Intern Emerg Med 9: 51-57.
3. Forti P, Olivelli V, Rietti E, Maltoni B, Pirazzoli G, et al. (2012) Serum thyroid-stimulating hormone as a predictor of cognitive impairment in an elderly cohort. Gerontology 58: 41-49.
4. Gencer B, Collet TH, Virgini V, Bauer DC, Gussekloo J, et al. (2012) Subclinical thyroid dysfunction and the risk of heart failure events: an individual participant data analysis from 6 prospective cohorts. Circulation 126: 1040-1049.
5. Lambrinoudaki I, Armeni E, Rizos D, Georgiopoulos G, Kazani M, et al. (2012) High normal thyroid-stimulating hormone is associated with arterial stiffness in healthy postmenopausal women. J Hypertens 30: 592-599.
6. Nader NS, Bahn RS, Johnson MD, Weaver AL, Singh R, et al. (2010) Relationships between thyroid function and lipid status or insulin resistance in a pediatric population.Thyroid 20: 1333-1339.
7. Westerink J, van der Graaf Y, Faber DR, Spiering W, Visseren FL, et al. (2012) Relation between thyroid-stimulating hormone and the occurrence of cardiovascular events and mortality in patients with manifest vascular diseases. Eur J Prev Cardiol 19: 864-873.
8. Tatar E, Sezis Demirci M, Kircelli F, Gungor O, Yaprak M, et al. (2012) The association between thyroid hormones and arterial stiffness in peritoneal dialysis patients.Int Urol Nephrol 44: 601-606.
9. Cai Y, Ren Y, Shi J (2011) Blood pressure levels in patients with subclinical thyroid dysfunction: a meta-analysis of cross-sectional data. Hypertens Res 34: 1098-1105.
10. Mariani LH, Berns JS (2012) The renal manifestations of thyroid disease. J Am Soc Nephrol 23: 22-26.
11. López PJT, López CF, de Mora FN, Montes JAR, Albero JS, et al. (2011) Osteoporosis in patients with subclinical hypothyroidism treated with thyroid hormone. Clin Cases Miner Bone Metab 8: 44-48.
12. Wilson KL, Casey BM, McIntire DD, Halvorson LM, Cunningham FG (2012) Subclinical thyroid disease and the incidence of hypertension in pregnancy. Obstet Gynecol 119: 315-320.
13. Purohit P (2012) Estimation of serum insulin, Homeostasis model assessment-insulin resistance and C-peptide can help identify possible cardiovascular disease risk in thyroid disorder patients. Indian J Endocrinol Metab 1: S97-S103
14. Lin YC, Lin YC, Chen TW, Yang WC, Lin CC (2012) Abnormal thyroid function predicts mortality in patients receiving long-term peritoneal dialysis: a case-controlled longitudinal study. J Chin Med Assoc 75: 54-59.
15. Risal P, Maharjan BR, Koju R, Makaju RK, Gautam M (2010) Variation of total serum cholesterol among the patient with thyroid dysfunction. Kathmandu Univ Med J (KUMJ) 8: 265-268.
16. Schultz M, Kistorp C, Raymond I, Dimsits J, Tuxen C, et al. (2011) Cardiovascular events in thyroid disease: a population based, prospective study. Horm Metab Res 43: 653-659.
17. Vadiveloo T, Donnan PT, Cochrane L, Leese GP (2011) The Thyroid Epidemiology, Audit, and Research Study (TEARS): morbidity in patients with endogenous subclinical hyperthyroidism. J Clin Endocrinol Metab 96: 1344-1351.
18. Hollowell JG, Staehling NW, Flanders WD, Hannon WH, Gunter EW, et al. (2002) Serum TSH, T(4), and thyroid antibodies in the United States population (1988 to 1994): National Health and Nutrition Examination Survey (NHANES III). J Clin Endocrinol Metab 87: 489-499.
19. Surks MI, Ortiz E, Daniels GH, Sawin CT, Col NF, et al. (2004) Subclinical thyroid disease: scientific review and guidelines for diagnosis and management. JAMA 291: 228-238.
20. Fröhlich E, Wahl R (2015) Mechanisms in Endocrinology: Impact of isolated TSH levels in and out of normal range on different tissues. Eur J Endocrinol.