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Original Article

The TSH levels and risk of hypothyroidism: Results from a population based prospective cohort study in an Iranian adult's population

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ABSTRACT

Objective: The aim of current study was to assess the relationship between serum TSH levels and hypothyroidism risk in the euthyroid population.
Methods: In a population-based cohort study, a total of 615 individuals with a normal baseline TSH, from of total population ($n = 2254$) in 2006, were followed up for 6 years. TSH, total T4, thyroid peroxidase antibody (TPOAb), and thyroglobulin antibody (TgAb) were measured. The relative risk (RR) and 95% confidence interval (95%CI) were calculated based on logistic regression. The Receiver Operating Characteristic (ROC) analysis along with area under the curve (AUC) was used to prediction of future hypothyroidism.
Results: TSH level in 2006 was a significant predictor for overt hypothyroidism, in the total population (RR = 3.5) and female (RR = 1.37) (all, P value < 0.05). A cutoff value of TSH at 2.05 mIU/L [AUC: (CI95 %), 0.68 (0.44–0.92; $P = 0.05$)] was obtained for differentiating the patients with overt hypothyroidism from euthyroid. However, this cut off was not observed when we included only negative TPO and TgAbs people in 2006. The RR of hypothyroidism increased gradually when TSH level increased from 2.06–3.6 mIU/L to >3.6 mIU/L in the total population and both sexes. In women, the risk of overt hypothyroidism was significantly higher in subjects with TSH above 3.6 than those subject with THS levels ≤ 2.05 [RR: (CI95 %), 20.57(2.—207.04), P value < 0.05].
Conclusion: A cutoff value of TSH at 2.05 mIU/L could predict the development of overt hypothyroidism in future. However, it was not applicable for people with negative TPOAb and negative TgAb.

1. Introduction

Hypothyroidism, both overt and subclinical, is a prevalent disorder, and can be found in up to almost 10% of the general population with defined increment levels of serum thyrotropin (TSH) [1–3]. It should be noted that, many of the subjects in studies on hypothyroidism were not aware of their thyroid dysfunction and consequently important cardiovascular consequences [4,5]. This illustrates the importance of being able to predict who is at risk of hypothyroidism.

Since the most sensitive diagnostic marker is a raised serum TSH concentration, it is crucial to have an evidence based reference range for TSH. Conventionally, in most previous studies the upper range of TSH level in healthy individuals, living in iodine-sufficient areas has been defined as 4.0–4.5 mU/L, with a confidence interval of 95% [2,6–9].

It has been recommended that the upper limit of the TSH reference range should be lowered to 2.5 or 3 mU/L [10–15]. The reason for this claim is that people whose TSH levels are in the upper part of the reference range may have increased prevalence of thyroid antibodies and could be at risk of developing hypothyroidism [16,17]. On the other hand, TSH values lying in the upper part of the reference range can be associated with increased risk of future hypothyroidism [16–21]. In the Whickham survey, during a 20 year follow-up, a baseline serum of TSH level above 2 mU/L was associated with an increased risk of hypothyroidism [16]. There is a need for longitudinal studies examining risk factors for hypothyroidism with measurement of thyroid autoantibodies and TSH. A few prospective studies have investigated

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the predictive role of TSH titers in subjects with normal levels of TSH [19,22,23].

In this cohort study, the euthyroid population was followed up for 6 years and the risk of hypothyroidism in relation to baseline serum concentrations of TSH on its own and TSH combined with thyroid antibodies was assessed.

2. Methods and materials

Between 2006 and 2011 year a prospective population based cohort study was conducted in Isfahan, a large city in the central part of Iran. Baseline assessment of TSH was done for all recruited participants. About one fourth of people ($n = 615$) who were euthyroid ($n = 569$) or subclinical hypo ($n = 41$) and subclinical hyperthyroidism ($n = 5$) in 2006 (n total = 2254) had been followed and invited to participate in the second wave of our project. We named this group as, "people with newly thyroid function in 2011", here. In addition, pregnant women were excluded from this population. All participants gave a written informed consent. Details of the study design have been explained previously [24,25]. After being seen by a trained general practitioner and an endocrinologist, a demographic questionnaire was completed about personal details, age of menopause, number of abortions, family history of thyroid diseases, history of goiter, nodule and current medication usage especially medication that interferes with thyroid function. Anthropometric, clinical measurements were recorded.

The fasting serum sample was obtained to measure fasting blood glucose (FPG), T3, T4, TSH, thyroperoxidase antibodies (TPOAb) and thyroglobulin antibody (TgAb) concentrations at baseline (2006) and at the end of 6 years of follow up (2011).

Serum total T4 and total T3 were analyzed by radioimmunoassay (Kavoshyar Co., Tehran, Iran). T4 intra- and interassay CV was 4.7% and 4.9%, respectively. Normal range of T4 concentration was 4.5 μg/dL–12.0 μg/dL. T3 intra- and inter-assay CV was 5.2% and 3.9%, respectively. Normal range of T3 concentration was 0.92 nmol/L–2.79 nml/L.

Serum TSH concentration was assessed by immunoradiometric assay (Kavoshyar Co., Tehran, Iran). Intra-assay and inter-assay coefficient of variation (CV) was 1.5% and 1.9%, respectively. The normal range for TSH was 0.3 mIU/L–3.6 mIU/L. Serum TPOAb and TgAb were measured with Rapid ELISA (Genesis Diagnostic Products Corp.). The intra-assay and inter-assay CV for TPOAb was 7% and 5%, respectively. It was <12% for TgAb.

TPOAb and TgAb concentrations of >75 IU/mL and 100 IU/mL, respectively were considered as positive. FPG (mg/dL) was measured by photometric method (Pars Azmon kit Lot number: 94011). We consider repeated measurement in laboratory exam, if abnormal level T4, T3 and TSH was measured.

For the purpose of the study, euthyroid was defined as TSH between 0.3 mIU/L and 3.6 mIU/L. Hypothyroidism was defined as overt or clinical hypothyroidism by a TSH of above 10 mIU/L, and subclinical hypothyroidism was defined as TSH between 3.6 and 10 mIU/L and total T4 and total T3 within normal range, 4.5 μg/dL–12.0 μg/dL and 0.92 nmol/L–2.79 nmol/L, respectively. Hyperthyroidism was described as overt or clinical hyperthyroidism by a TSH level of <0.1 mIU/L and total T4 of above 12 μg/dL and/or total T3 of above 2.79 nmol/L. Subclinical hyperthyroidism was described as TSH under 0.3 mIU/L and total T4 and total T3 within normal range, 4.5 μg/dL–12.0 μg/dL and 0.92 nmol/L–2.79 nmol/L, respectively.

2.1. Statistical analysis

Continuous and categorical data were presented as Mean ± SD or median (range) as appropriate. Normality of quantitative data was evaluated using Kolmogrov-Smirnov test and Q-Q plot. Positive skewed data was subjected to logarithmic transformation. Chi-square and generalized McNemar tests were used for evaluating the association between categorical data. For comparing the quantitative data between baseline and end of study, paired samples *t*-test or Wilcoxon signed rank test were used. Between groups comparisons of quantitative data were conducted using Analysis of variance (ANOVA) or nonparametric Kruskal-Wallis tests. Crude incidence rate of thyroid dysfunctions per 1000 person-years was calculated in total study sample as well as in age and gender specific categories. To determine the association between TSH levels at baseline (2006) as an independent variable and hypothyroidism, we used binary logistic regression analysis in different models. In all analyses hypothyroidism were considered as endpoints. In these analyses, after obtaining relative risk (RR) and 95% confidence interval (95%CI) in crude model, adjustment was made for age and sex, smoking, BMI, positive family history in the first model. Additional adjustment was made for number of parity and abortion, age of menopause, having history of goiter or nodule in the second model. Finally, adjustment was made for all mentioned variables and positive TPOAb, TgAb and T4 in third model. The predictive values of baseline TSH levels for different hypothyroidism was evaluated using receiver operating characteristic curve (ROC) analysis and area under the curve (AUC) and its 95%CI was calculated. The sensitivity, specificity and positive and negative predictive value for different cut off values of TSH were calculated. Statistical analyses were performed using statistical package for social science (SPSS version 15, SPSS, Inc., IL, USA).

3. Results

TSH, T3 and T4 levels (2011) in different categories of euthyroid characteristics participants at study baseline (2006) have been presented in Table 1. TSH level was significantly higher in females, subjects with positive family history of thyroid disease and those with positive TPOAb. When the sample group was restricted to negative TPO and negative TgAb subjects ($n = 458$) in 2006, this difference was only observed between genders (P value = 0.004).

The thyroid status and TPOAbs' levels of the 615 study subjects at the baseline and follow-up visits are summarized in Table 2. At baseline, 532 subjects (86.5%) had serum TSH concentrations between 0.3 and 3.6 mU/l. At follow-up, 519 subjects (84.4%) had such TSH concentrations. The median concentration of TSH and TPOAb was significantly higher in 2011 when compared with 2006 ($P = 0.001$). This difference was observed especially in the female group.

During the follow up period TPOAb status changed from negative to positive in 16.4% and from positive to negative in 16.1%. The prevalence of positive TPOAb according to quartiles of TSH ranged from 20% in the lowest to 32% in the highest quartile of TSH in the euthyroid range ($P = 0.04$, Fig. 1). Median (range) TSH for TPOAb positive subjects was 2.2(0.01–42) compared to 1.9(0.03–120 mIU/L, $P = 0.04$) in TPOAb negative subjects.

At the end of follow-up, 9 subjects (1.5%) including 5(1.7%) women, 4(1.3%) men had overt hypothyroidism and 72 (11.7%) including 45 women had subclinical hypothyroidism.

Table 3 presents the results of crude and multivariable binary logistic regression analysis in different models about the association of TSH levels at 2006 and hypothyroidism risk in 2011. In crude logistic regression analyses, TSH level in 2006 positively predict the risk of subclinical hypothyroidism (RR = 8.3, RR = 1.47), overt hypothyroidism (RR = 3.5, RR = 1.37) in total population and female group, respectively (all, $P < 0.05$) in 2011. However, in the male group such result was only detected for subclinical hypothyroidism. In multivariable logistic regression analyses adjustments were made for some important potential confounding factors (Models 1, 2, and 3). As illustrated the associations remained significant for subclinical hypothyroidism in the total population and the females. However, splitting the sample group to negative TPO and negative TgAb subjects ($n = 458$), in crude logistic regression analyses, resulted in TSH level in 2006 positively predicting the risk of subclinical hypothyroidism (RR = 6.7, RR = 3.9, all, $P < 0.05$) but this risk was not observed in overt hypothyroidism (RR = 0.72,

Table 1
TSH, T3 and T4 levels (2011) in different categories of characteristics of euthyroid participants at study baseline (2006)

	(*n*)	TSH Median (rang)	*P* value	Total T3 Median (rang)	*P* value	Total T4 Median (rang)	*P* value
Sex	Men (314)	1.8 (0.1–120)	0.001*	1.7 (0.4–17)	0.11	8 (1.4–56.6)	0.01*
	Women (301)	2.1 (0.01–99)		1.6 (1–11.8)		8.3 (1.4–14.1)	
Age (years)	20–40 (177)	2 (0.02–120)	0.94	1.6 (0.7–3.5)	0.99	8 (1.4–14.1)	0.23
	40–60 (325)	2 (0.01–24)		1.7 (0.7–11.8)		8.1 (1.4–56.6)	
	>60 (109)	1.9 (0.03–42)		1.7 (0.4–17)		8.4 (3 − 13)	
BMI (kg/m^2)	<25 (178)	2 (0.03–42)	0.59	1.6 (0.4–5.5)	0.13	8.1 (3–13)	0.88
	25–30 (266)	1.95 (0.02–47)		1.7 (1–17)		8.2 (3–56.6)	
	≥30 (155)	2.1 (0.01–120)		1.7 (0.7–11.8)		8.1 (1.4–14)	
FPG (mg/dl)	<100 (356)	2 (0.02–120)	0.29	1.6 (0.7–11.8)	0.14	8.1 (1.4–56.6)	0.63
	100–126 (197)	1.9 (0.02–24)		1.7 (0.4–3.2)		8.1 (3–14.1)	
	≥126 (56)	2.2 (0.01–15.7)		1.6 (1.2–17)		8.6 (4–14)	
Smoking	Yes (48)	1.7 (0.02–42)	0.26	1.7 (0.7–3.2)	0.31	8.3 (3.9–11.3)	0.56
	No (567)	2 (0.01–120)		1.7 (0.4–17)		8.1 (1.4–56.6)	
Positive family history	Yes (172)	2.1 (0.02–120)	0.03*	1.6 (0.7–10.5)	0.42	8.4 (1.4–56.6)	0.03*
	No (422)	1.9 (0.01–99)		1.7 (0.4–17)		8 (1.4–14.1)	
Number of menopause in participants	301	2.1 (0.01–99)	0.71	1.6 (1–11.8)	0.52	8.3 (1.4–14.1)	0.2
History of abortion	78	2.1 (0.02–99)	0.45	1.6 (1–3.1)	0.68	8.3 (4–12.9)	0.72
History of goiter	92	2 (0.02–99)	0.73	1.6 (1–3.1)	0.29	8.3 (4.8–14.1)	0.67
History of nodule	5	2.1 (0.04–3.3)	0.61	1.9 (1.6–2)	0.32	8.9 (7.9–12.7)	0.9
TPOAb	Positive (153)	2.2 (0.01–42)	0.03*	1.7 (1–4)	0.49	8 (4.7–14.1)	0.78
TgAb	Positive (6)	4.4 (1.1–24)	0.18	2 (1–10.5)	0.12	7.35 (4.9–8.7)	0.28

BMI (body mass index), FPG (fasting plasma glucose), TPOAb (Thyroid peroxidase antibody) as considered positive when level > 75 IU/mL, TgAb (thyroid globulin antibody) as considered positive when level > 100 IU/mL*$P < 0.05$ was statistically considered significant.

RR = 0.70, all, $P > 0.05$) in the total population and the female group, respectively in 2011.

Receiver operating characteristic (ROC) curve analysis was used to determine the cutoff level of TSH in 2006 for predicting hypothyroidism in 2011. The areas under the ROC curves for the occurrence of thyroid dysfunctions in relation to TSH level are shown in Fig. 2. A cutoff value of TSH at 2.05 mIU/L was obtained for differentiating the patients with overt hypothyroidism from euthyroid, with corresponding specificity of 66% and sensitivity of 67% and area under the ROC curve [(AUC) (95% CI(, 0.68 (0.44–0.92), $P = 0.05$]. By Analyzing the data of people ($n = 458$) without antibodies (negative TPO and negative TgAb subjects) in 2006, we did not obtain a cutoff value of TSH to enable differentiate the patients with overt hypothyroidism from euthyroid persons [(AUC) (95% CI), 0.45 (0.15–0.76), $P = 0.74$]. Nevertheless, a cutoff value of TSH at 2.45 mIU/L was obtained to differentiate the patients with subclinical hypothyroidism from euthyroid people, with a corresponding specificity of 75% and sensitivity of 77% and area under the ROC curve of [(AUC) (95% CI(, 0.80 (0.72–0.87), $P = 0.001$]

We used TSH cut off value 2.05 and 3.6 mU/L (resulted from the ROC analysis and the reference range) to examine the relative risks of overt and subclinical hypothyroidism. Table 4 presents the results. The crude RR for subclinical and overt hypothyroidism at 6 year follow-up was significantly increased in subjects with TSH level between 2.06 and 3.6 mIU/L and those with TSH level above 3.6 mIU/L compared to TSH level lower than 2.06 in total population. In women, the risk of subclinical hypothyroidism increased with higher baseline levels of TSH [RR: (95% CI), 7.04 (2.7–18.11) (for those participants with TSH levels 2.06–3.6) *vs* 19.42 (6.88–54.8) (for those participants with TSH levels >3.6), *P* value <0.05], whereas in women, the risk of overt hypothyroidism was significantly higher in subjects with TSH above 3.6 and 2.06–3.6 mU/L than those subject with THS levels ≤2.05 (reference category) [RR: (CI95%), 20.57(2.− 207.04) 1.9(0.11–31.12)], respectively. In men, the risk of future subclinical hypothyroidism significantly increased with higher baseline levels of TSH but the risk of overt hypothyroidism did not. In multivariable logistic regression analyses adjustments were made for some important potential confounding factors (Models 1,2 and 3), the results showed that in overt hypothyroidism, the observed associations were remained significant in all population and female group only for those with TSH >3.6 mIU/L (*P* value < 0.05) however for participants with TSH within 2.06–3.6 mU/L, such results were only observed in total population.

The determined cut of value of 2.05 mU/L of baseline TSH based on ROC analysis was considered as the threshold for further examining outcomes. The positive predictive value of a serum TSH concentration above 2.05 mU/L at baseline for the presence of overt and subclinical hypothyroidism at follow-up was 3.2%, 25.5%, whereas the negative predictive value was 99.1%, 97.4%, respectively (Table 5). By contrast, for baseline TSH above 3.6 mU/L (the upper limit of the reference range), the positive predictive value for overt and subclinical hypothyroidism was 11.4%, 49.2% and the negative predictive value 99.0%,92.1%, respectively (Table 5).

The odds ratio for hypothyroidism at 6 year follow-up was determined in men and women based on TSH mU/L in 2006. The results are shown graphically in Fig. 3; a dose response relationship is observed between TSH levels and odds of hypothyroidism.

Table 2
Characteristics of the 615 study subjects at baseline and follow-up.

		Total population(615)			Female(301)			Male(310)		
		Baseline 2006	Follow up 2011	*P* value	Baseline 2006	Follow up 2011	*P* value	Baseline 2006	Follow up 2011	*P* value
Age, mean (SD) (yr)		40.48 (11.96)	47.37(12.02)		38.79 (11.60)	45.78 (11.81)		42.09 (12.03)	48.92 (12.04)	
TSH level median(range)		1.9(0.05–65.80)	2 (0.01–120)	0.001*	2 (0.05–65.80)	2.1 (0.01–99)	0.006*	1.8 (0.1–30.70)	1.8 (0.1–120)	0.1
TPOAb level median (range)		10.5(0.3–7809)	44.5(1.3–1300)	0.001*	9.35 (0.8–7809)	48 (1.3–1300)	0.001*	11.8 (0.3–2624)	41 (1.5–1300)	0.001*
Serum TSH (mU/L)	<0.3	11 (1.8%)	15 (2.4%)	0.001**	8(2.6%)	13 (4.3%)	0.001**	3 (1%)	2 (0.6%)	0.001**
	0.3 to 3.6	532 (86.5%)	519 (84.4%)		247(81.5%)	240 (79.2%)		285 (91.3%)	279 (89.4%)	
	3.61–10	67 (10.9%)	72 (11.7%)		45(14.9%)	45 (19.4%)		22 (7.1%)	27 (8.7%)	
	≥10	5 (0.8%)	9 (1.5%)		3 (1%)	5 (1.7%)		2 (0.6%)	0 (0%)	

* Results from Wilcoxon signed ranks test.
** Resulted from generalized McNema test.

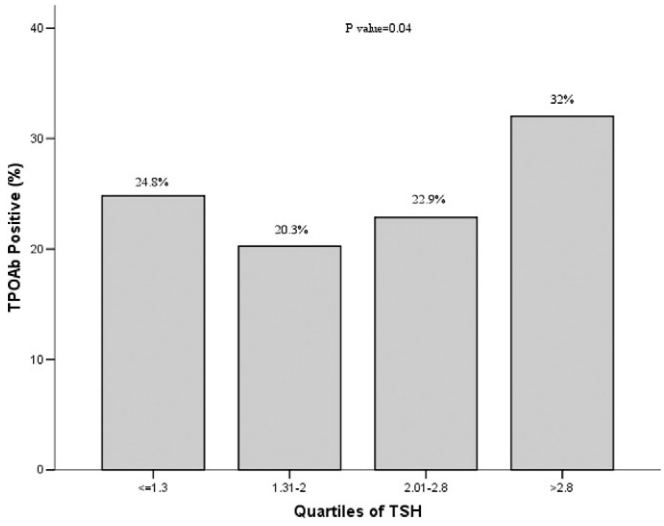

Fig. 1. Prevalence of positive thyroid peroxidase antibody (TPOAb) over the quartiles of TSH within the normal reference range ($n = 615$).

4. Discussion

This study provides longitudinal data on risk factors for hypothyroidism over a 6 year period using current methods for measurement of TSH and thyroid antibodies.

At the end of follow up, TSH level was significantly higher in females, people with positive family history of thyroid disease and positive TPOAb.

The positive association was observed between subclinical and overt hypothyroidism in 2011 and the level of TSH in 2006 in different models, especially in female patients and total population. But in males such results were only detected in subclinical hypothyroidism.

In women, the risk of future overt hypothyroidism at follow-up was significantly higher in subjects with TSH above 3.6 mU/L compared in women with a baseline TSH of 2.06–3.6 mU/L. In men, the risk of future subclinical hypothyroidism increased with higher baseline levels of TSH but did not do so for overt hypothyroidism.

A cutoff value of TSH 2006 at 2.05 mIU/L was obtained for predicting the patients with overt hypothyroidism in 2011.

As reported from previous longitudinal studies [16,19,20] age, female gender, thyroid antibodies, and baseline TSH are associated with hypothyroidism. These results are consistent with our results, not only in women we detected the increasing level of TSH but association with risk of progression to overt hypothyroidism was also observed. Whereas, some factors such as positive family history of thyroid disease was associated with a significant change in TSH level, results of another cross-sectional study [16] were not associated with developing hypothyroidism, but the number of participants when compared are small and statistical power is accordingly limited.

Our findings (in Tables 1, 2) are consistent with earlier studies by Jensen et al. [7] and Hollowell et al. [2], in that the presence of TPOAb was observed both with a higher frequency of levels of TSH outside the reference range and with a tendency for higher levels of TSH within the reference range. Two large cohort studies [16,17] showed that increasing values of serum TSH augmented the odds of developing hypothyroidism, especially when parallel with existence of serum TPOAb. Although positive associations were detected (RR > 1) in twenty years of follow up, an associated risk of 2.1% per year for hypothyroidism was detected in women with positive thyroid antibodies [16].

Our results extend the findings of these studies with the notion that even variation of levels of TSH within the normal range without positive TPOAb in 2011 is important for predicting development of hypothyroidism. Indeed the number of patients with TPOAb positivity was small and could have led to diluting the confounding effects of this variable.

The Iranian population is considered to be iodine sufficient [24–26] with autoimmune thyroiditis being the most common cause of hypothyroidism. Our findings confirmed these data: the median concentration of TSH and TPOAb was significantly higher in 2011 when compared with 2006 especially in the female group (Table 2). This can be considered as evidence for an immunological pattern predisposing to hypothyroidism in our country.

People with autoimmune thyroiditis, diagnosed by thyroid autoantibodies in serum, often have serum TSH in the upper part of the reference range [6,27]. These relatively high TSH levels are probably a response to slightly reduced thyroid hormone levels in the early stage of autoimmune thyroid destruction. Therefore, in some subjects, TSH in the upper part of the reference range may be a marker for mild hypothyroid disease [13,28].

In previous studies [17,23], in addition to TSH level, female gender was the strongest independent predictor of hypothyroidism and this is consistent with our results. In fact we reported a strong association between TSH levels in 2006 and hypothyroidism in 2011 in females and the general population rather than the males. In our study the risk of overt hypothyroidism was significantly (10-fold) higher in women with TSH above 3.6 mU/L compared with a baseline TSH of 2.06–3.6 mU/L. In one study, during a 11 year follow-up, risk of hypothyroidism at follow up was 2 folds higher in women with a TSH of 1.5–1.9 mU/L, 8-fold higher in women with TSH of 2.5–2.9 mU/L, and 30-fold higher in women with TSH of 4.0–4.5 mU/L compared with women with a baseline TSH of 0.50–1.4 mU/L [29].

On the other hand in both sexes, TSH between 2.5 and 4.5 mU/L was positively associated with the risk of subsequent hypothyroidism [14,29]. But in a large Asvold study [29]at any obtained level of TSH, in men, the risk of hypothyroidism was lower than women and agreed with our results that in men, the risk of future subclinical hypothyroidism increased with higher baseline levels of TSH but the risk of overt hypothyroidism did not.

In our study, ROC analysis identified a threshold of 2.05 mU/L for baseline TSH was associated with optimal sensitivity and specificity in predicting hypothyroidism. This is broadly consistent with data from

Table 3
Relationship between TSH levels in 2006 and thyroid dysfunctions in adults in 2011.

	Total sample		Female		Male		Positive TPOAb	
	Subclinical hypothyroidism RR (CI%95)	Overt hypothyroidism RR (CI%95)	Subclinical hypothyroidism RR (CI%95)	Overt hypothyroidism RR (CI%95)	Subclinical hypothyroidism RR (CI%95)	Overt hypothyroidism RR (CI%95)	Subclinical hypothyroidism RR (CI%95)	Overt hypothyroidism RR (CI%95)
Crude model	8.3 (4.81–14.60)*	3.5 (1.27–10.0)*	1.47 (1.20–1.81)*	1.37 (1.08–1.73)*	2.01 (1.51–2.67)*	1.37 (0.95–1.97)	2.84 (0.98–8.19)*	2.96 (0.54–16.12)
Model 1	8.5 (4.8–15.28)*	3.7 (1.24–11.30)*	1.43 (1.16–1.77)*	1.48 (1.11–1.97)*	2.10 (1.55–2.85)*	1.39 (0.93–2.07)	3.37 (0.81–14.0)	
Model 2	5.92 (2.82–12.42)*	3.11 (0.57–16.90)	1.50 (1.18–1.91)*	1.42 (1.06–1.90)*	2.01 (1.48–2.74)*	1.38 (0.93–2.06)	5.49 (0.34–88.41)	
Model 3	3.2 (1.45–7.17)*	3.2 (0.20–52.14)	1.17 (0.78–1.56)		1.12 (0.78–1.61)			

(Crude model) no adjustment was made for confounding variables; (Model 1) adjustment was made for age and sex, smoking, Body max index, positive family history; (Model 2) adjustment was made for age and sex, smoking, Body max index, positive family history, having history of goiter or nodule [and number of parity and abortion, age of menopause only for women];(Model 3) adjustment was made for all mentioned variables and TPOAb (thyroid peroxidase antibody), TgAb (thyroid globulin antibody) and T4.

* P value < 0.05.

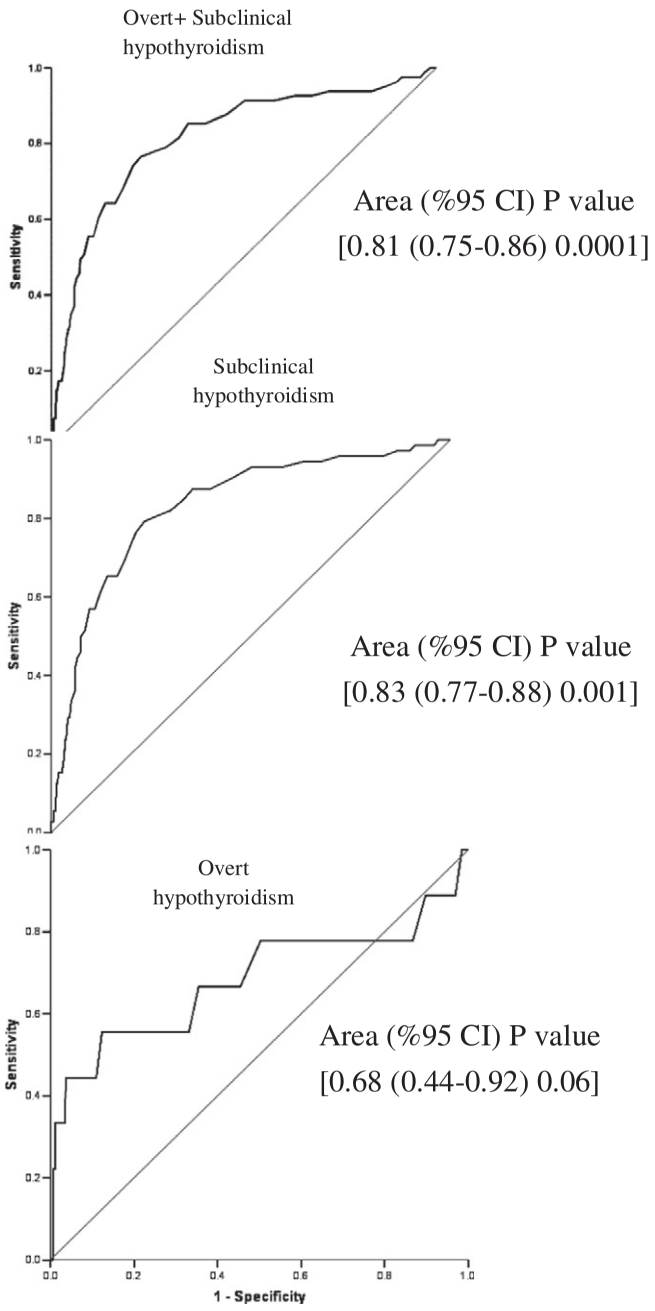

Fig. 2. Receiver operating characteristic curves for peak of TSH level in hypothyroidism (overt and, or subclinical) (A) in Isfahani adults with newly thyroid function ($n = 615$).

Whickham [16] and China [20,22] in which the risk of hypothyroidism was higher if baseline TSH was above 2 mU/L and it is lower but close to the Walsh study [17] where it was 2.5 mU/L. These findings altogether outline the importance of the association between TSH levels range (0.4 and 2.0 mIU/L) with optimal thyroid health [13,18]. However, when we selected subjects without a history of TPO and Tg Abs (in 2006), this cut off point did not apply. The Whickham study [16] also observed that the risk of hypothyroidism progressively increases with increasing TPO antibody concentrations, independent of TSH levels. However, more studies with larger samples and over a longer period of time are needed so the subjects with positive antibodies can be identified at the start. It will then be possible to compare more accurately the role of antibodies *versus* rising TSH towards progressing to hypothyroidism.

Based in part on the Whickham Survey, it has been argued that the upper limit of the TSH reference range should be lowered to 2.5 or

Table 4
The relationship between serum TSH levels with subclinical and overt hypothyroidism.

	Subclinical hypothyroidism RR (CI%95)						Overt hypothyroidism RR (CI%95)					
	TSH ≤2.05	2.06 < TSH ≤3.6			TSH > 3.6		TSH ≤ 2.05	2.06 < TSH ≤ 3.6			TSH > 3.6	
		Total	Female	Male	Total	Female	Male		Total	Female	Male	Total	Female	Male
Crude model	1	8.02 (3.74–17.19)*	7.04 (2.7–18.11)*	8.9 (2.43–33.06)*	36 (15.69–82.67)*	19.42 (6.88–54.8)*	82.76 (20.26–338.)*	1	6.38 (3.22–12.64)*	1.9 (0.11–31.12)	1.22 (0.1–13.69)	30.61 (14.4–65.07)*	20.57 (2.–207.04)*	9.5 (0.79–114.4)
Model 1	1	8.96 (4.01–20.03)*	7.4 (2.83–19.33)*	13.34 (2.86–62.2)*	37.75 (15.66–90.98)*	18.11 (6.31–52.03)*	147.3 (2 7.3–795.4)*	1	6.77 (3.32–13.78)*	1.98 (0.12–32.95)	1.2 (0.10–13.65)	30.9 (14.06–67.92)*	20.43 (2–208.7)*	12.60 (0.88–179.8)
Model 2	1	7.46 (2.82–19.68)*	7.46 (2.82–19.68)*	12.82 (2.74–59.9)*	16.72 (6.55–59.32)*	19.72 (6.55–59.32)*	135 0.6 (24.8–739.3)*	1	6.58 (2.63–16.44)*	2.5 (0.13–49.02)	1.17 (0.1–13.34)	20.46 (7.31–57.2)*	31.57 (1.76–564)*	13.1 (0.92–187.37)
Model 3	1	51.65 (0.59–53.71)	5.09 (0.5–51.83)	0.18 (0.00–0.00)	20 (3.39–118.2)*	10.4 (1.58–68.42)*		1	7.96 (0.98–64.33)*		1.78 (0.00–0.00)	22.78 (3.88–133.6)*		86.19 (0.00–0.00)

Reference category is TSH level ≤ 2.05, (Crude model) no adjustment was made for confounding variables; (Model 1) adjustment was made for age and sex, smoking, Body max index(BMI), positive family history; (Model 2) adjustment was made for age and sex, smoking, BMI, positive family history, having history of goiter or nodule[number of parity and abortion, age of menopause only for women]; (Model 3) adjustment was made for all mentioned variables and positive TPOAb (thyroid peroxidase antibody) , TgAb (thyroid globulin antibody) and T4.

* *P* value < 0.05.

Table 5
Predictive values of baseline serum TSH >2.05 mU/L or >3.6 mU/L for the presence of subclinical and overt hypothyroidism at the end of 6 years follow-up.

	Baseline serum TSH concentration									
	Greater than 2.05					Greater than 3.6				
	Sensitivity	Specificity	PPV	NPV	Accuracy	Sensitivity	Specificity	PPV	NPV	Accuracy
Subclinical hypothyroidism	87.5%	64.5%	25.5%	97.4%	67.3%	41.7%	94.0%	49.2%	92.1%	87.6%
Overt hypothyroidism	66.7%	64.5%	3.2%	99.1%	64.5%	44.4%	94.0%	11.4%	99.0%	93.1%

3 mU/L [11,12,30]. Our study demonstrates that individuals with serum TSH between 2.05 and 3.6 mU/L are at increased risk of hypothyroidism. Such results have been previously reported [17]. For this reason, it is reasonable to regard TSH concentrations of 2.05–3.6 mU/L as a category of intermediate risk in our population, especially in women. It is difficult to compare our results with some others because of differences in assay methods, TSH reference range, and follow-up duration. We found that our risk estimation can be based on whether the baseline TSH is in the upper part of the reference range or not. Also, due to variations in TSH if temporarily low or high [10,14], repeated measurements of TSH at baseline might have better predicted future thyroid dysfunction. Finally, follow-up of thyroid function testing for these subjects may be appropriate, as already recommended [10,13,17].

The limitations of the study were the measurement of thyroid hormones by radioimmunoassay and we did not perform ultrasound features of thyroid to better define for evaluation of predictive factors in onset of hypothyroidism. Though, we had measured the median of urinary iodine in this reported population [26] in 2006, but another our limitation is lack of information about the iodine status of the people included in this study in 2011. Although the result of our study needs to be confirmed with mores studies with repeated measurements of thyroid hormone levels, it can provide some background information towards the reference range for TSH and provide a tool for clinicians to estimate the long-term risk of hypothyroidism in patients based on gender, TSH, and thyroid antibody status.

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Conflict of interest

The authors declare that they have no conflict of interest.

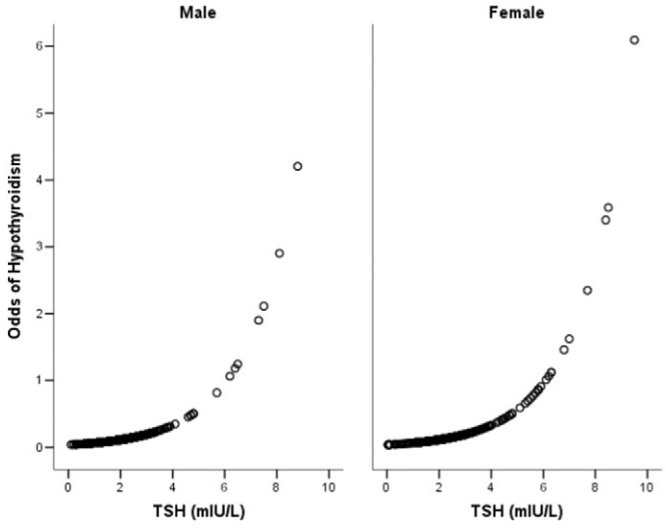

Fig. 3. Predicted odds of hypothyroidism based on baseline TSH mU/L in 2006.

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