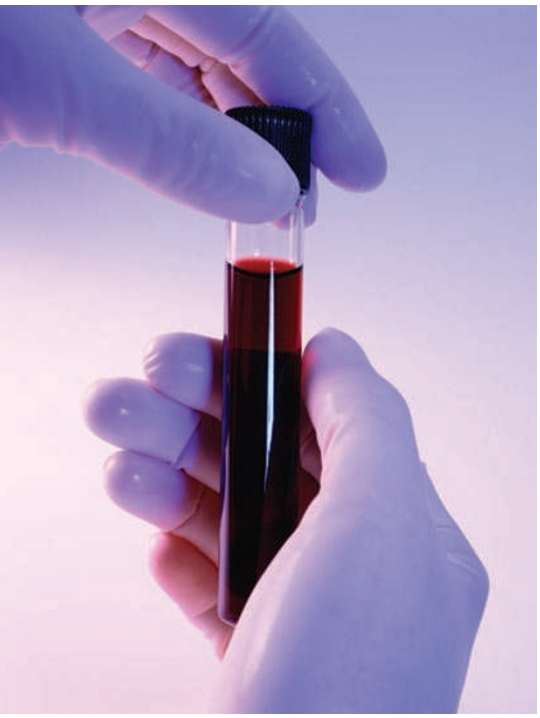
THYROID GLAND

# TSH reference limits specific for age, sex and ethnicity

A recent article published in *Thyroid* provides novel reference limits for TSH that are specific for age, sex and ethnicity in the US population.

Previous studies have increasingly shown that reference limits of serum TSH and free $T_4$ are significantly influenced by race and age; for example, longevity is associated with increased levels of serum TSH. However, the traditional TSH distribution curve and reference limits use measurements from all individuals, irrespective of age, ethnicity or sex, that have been weighted to represent the population of the continental USA.

Using data from the National Health and Nutrition Examination Survey (NHANES) III, Boucai *et al.* determined the TSH median, as well as the 2.5$^{th}$ and 97.5$^{th}$ percentiles as a function of age and antithyroid antibodies in all patients, as well as in subpopulations of non-Hispanic white individuals, non-Hispanic black individuals and Mexican Americans. The investigators then compared the TSH reference limits and median of individuals without thyroid disease ($n$ = 15,277) with those of a reference population ($n$ = 13,344) that was created by exclusion of individuals positive for thyroid antibodies or those with significantly elevated (>10 mIU/l) or suppressed (<0.1 mIU/l) TSH levels.



The results indicate that TSH levels increase with age in all groups and reach levels of nearly 7 mIU/l and 8 mIU/l in the ninth decade in white individuals and in Mexican Americans, respectively. The 'normal' lower limit is approximately 0.5 mIU/l in all groups. However, a slightly lower serum TSH level can be found in black individuals than in Mexican Americans or white individuals. Moreover, women had a reduced lower reference limit and median TSH level compared with that of men, but no significant difference was found for the upper TSH reference limit.

From their results, the investigators derived equations that predict TSH reference limits for specific subpopulations of white, black or Mexican American patients, according to their age and sex. Urine iodine concentration, body weight and BMI showed little or no effect as independent predictors of the 2.5$^{th}$, 50.0$^{th}$ and 97.5$^{th}$ percentiles and were, therefore, not included in any prediction models.

Aside from its physiological interest, what does the study by Boucai *et al.* contribute? "At this time, TSH determinations are nearly universally used as a screening test for thyroid dysfunction," explains thyroid expert P. Reed Larsen (Brigham and Women's Hospital, Boston). "Knowing exactly what the normal range is, and especially that the upper normal limit increases as patients age, is extremely important since a patient with elevated TSH levels, but a normal free $T_4$ concentration, is thought to have a disease which has been termed subclinical hypothyroidism."

Moreover, it is also of interest that the lower TSH reference limit in individuals free of thyroid disease does not decrease with age. A number of elderly patients exist in whom a suppressed TSH level (<0.5 mIU/l) is associated with normal free $T_4$ and $T_3$ concentrations, a condition defined as subclinical hyperthyroidism. As Larsen points out, "these data suggest this is not simply due to a reset of the feedback loop with age."

Compared with overt hypothyroidism and hyperthyroidism, the diagnosis of subclinical thyroid dysfunction is relatively new. Numerous studies on this topic can be found in the literature; nevertheless, the condition must be defined accurately and consistently before discussing whether or not it should be treated.

Whether the formulas presented will be widely applied is open to debate, but the methodology used by Boucai *et al.* can more accurately predict how a distribution of any biomarker changes in different populations than currently employed statistical tools. "That is to say, its applicability is beyond TSH reference limits," adds lead investigator Laura Boucai (Montefiore Medical Center, Albert Einstein College of Medicine, New York). The major, but unavoidable, limitation of the study is that it is sensitive to both the commercial assay method used and to the preparation of the reference sample. Nevertheless, the study may help clinicians to better classify patients within their subpopulation-specific TSH reference range. "A similar analysis would be useful in the pediatric population where such rigorous data are not yet available to define the effect of age on the normal range," concludes Larsen.

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**Original article** Boucai, L. *et al.* An approach for development of age-, gender-, and ethnicity-specific thyrotropin reference limits. *Thyroid* doi:10.1089/thy.2010.0092