

□ 1: Clin Endocrinol (Oxf). 1995 Jul;43(1):55-68.

TSH LIMITS

The incidence of thyroid disorders in the community: a twenty-year follow-up of the Whickham Survey.

Vanderpump MP, Tunbridge WM, French JM, Appleton D, Bates D, Clark F, Grimley Evans J, Hasan DM, Rodgers H, Tunbridge F, et al.

A logit model indicated that increasing values of serum TSH above **2mU/l at first survey increased the probability of developing hypothyroidism which was further increased in the presence of anti-thyroid antibodies.**



**95 %
REFERENCE
INTERVAL**

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1: BMJ 1997 Jun 14;314(7096):1764

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Thyroxine should be tried in clinically hypothyroid but biochemically euthyroid patients.

Skinner GR, Thomas R, Taylor M, Sellarajah M, Bolt S, Krett S, Wright A.

We wish to question present medical practice, which considers abnormal serum concentrations of free thyroxine and TSH - those outside the 95% reference interval - to indicate hypothyroidism but incorrectly considers "normal" free thyroxine and thyroid stimulating hormone concentrations to negate this diagnosis.



TSH LIMITS

**74th Annual Meeting of the American Thyroid Association
Millennium Biltmore Hotel, Los Angeles, California
October 10 – 13, 2002**

Program Number 2 Thyroid Diseases

CONCLUSIONS: (1) Occult thyroid disease is a common occurrence in normal reference populations. (2) Based on TPOAb prevalence, the new normal serum TSH adult reference range approximates **0.4 to 2.0mIU/L**. (3) Pilot results of a highly selected normal sub-population (n=76) supports this new reference range (Spencer). (4) This new TSH reference range should be considered as the optimal end-point for T4 replacement Rx. (5) TPOAb measurement is indicated when the TSH value is outside this new range.

BACKGROUND: The conventional serum TSH reference range in euthyroid subjects approximates 0.4 to 4.0 m IU/L. However, several recent reports indicate that this range may be skewed to the high-end by the presence of occult autoimmune thyroid disease.



Guideline 22. TSH Reference Intervals

TSH Upper Reference Limits

It is likely that the upper limit of the serum TSH euthyroid reference range will be reduced to 2.5 mIU/L because >95% of rigorously screened normal euthyroid volunteers have serum TSH value between 0.4 and 2.5 mIU/L.

LABORATORY MEDICINE PRACTICE GUIDELINES

Laboratory Support for the Diagnosis and Monitoring of Thyroid Disease

The majority (>95%) of healthy euthyroid subjects have a serum TSH concentration below 2.5 mIU/L. Ambulatory patients with a serum **TSH above 2.5 mIU/L, when confirmed by a repeat TSH measurement made after 3-4 weeks, may be in the **early stages of thyroid failure**, especially if TPO Ab is detected.**

LABORATORY MEDICINE PRACTICE GUIDELINES

Laboratory Support for the Diagnosis and Monitoring of Thyroid Disease

Over the last two decades, the upper reference limit for **TSH** has steadily declined from ~10 to approximately ~ **4.0 - 4.5 mIU/L**. This decrease reflects a number of factors including the improved sensitivity and specificity of current assays. The recent follow-up study of the Whickham cohort has found that individuals with a serum **TSH > 2.0 mIU/L** at their primary evaluation had an increased odds ratio of developing hypothyroidism over the next 20 years.

1: [Thyroid](#). 2003 Jan;13(1):3-126.

Laboratory medicine practice guidelines. Laboratory support for the diagnosis and monitoring of thyroid disease.

[Baloch Z](#), [Carayon P](#), [Conte-Devolx B](#), [Demers LM](#), [Feldt-Rasmussen U](#), [Henry JF](#), [LiVosli VA](#), [Niccoli-Sire P](#), [John R](#), [Ruf J](#), [Smyth PP](#), [Spencer CA](#), [Stockigt JR](#); [Guidelines Committee, National Academy of Clinical Biochemistry](#).

In the future, it is likely that the **upper limit** of the serum **TSH** euthyroid reference range will be reduced to **2.5 mIU/L** because **>95%** of rigorously screened normal euthyroid volunteers have serum TSH value between 0.4 and 2.4 mIU/L.

RESEARCH LETTER

**Effects of Reducing the Upper Limit
of Normal TSH Values**

When individuals with thyroid autoantibodies, goiter, or a strong family history of thyroid disease are excluded, the upper bound of the 95% TSH concentration reference range decreases to between 2.5 and 3.0 mIU/L.

1: [J Clin Endocrinol Metab.](#) 2005 Sep;90(9):5483-8.

TSH REFERENCE RANGE

The evidence for a narrower thyrotropin reference range is compelling.

[Wartofsky L](#), [Dickey RA](#).

Debate and controversy currently surround (...) the **definition of the normal reference range for TSH**. It has become clear that **previously accepted reference ranges are no longer valid** as a result of both the development of more highly sensitive TSH assays and the appreciation that reference populations previously considered normal were contaminated with individuals with various degrees of thyroid dysfunction that served to increase mean TSH levels for the group.

1: [J Clin Endocrinol Metab.](#) 2005 Sep;90(9):5483-8.

TSH REFERENCE RANGE

The evidence for a narrower thyrotropin reference range is compelling.

[Wartofsky L](#), [Dickey RA](#).

Recent laboratory guidelines from the National Academy of Clinical Biochemistry indicate that **more than 95% of normal individuals have TSH levels below 2.5 mU/liter.** (...) Importantly, data indicating that African-Americans with very low incidence of Hashimoto thyroiditis have a **mean TSH level of 1.18 mU/liter** strongly suggest that this value is the true normal mean for a normal population.

National Health and Nutrition Examination Survey III Thyroid-Stimulating Hormone (TSH)-Thyroperoxidase Antibody Relationships Demonstrate That TSH Upper Reference Limits May Be Skewed by Occult Thyroid Dysfunction.

TSH REFERENCE RANGE

Conclusions:

TSH upper reference limits may be skewed by TPOAb-negative individuals with occult autoimmune thyroid dysfunction.

NHANES III TSH:TPOAb Relationships Demonstrate that TSH Upper Reference Limits May be Skewed by Occult Thyroid Dysfunction

TSH REFERENCE RANGE

J Clin Endocrin Metab. First published ahead of print August 7, 2007 as doi:10.1210/jc.2007-0287

The American Association of Clinical Endocrinologists has recommended the adoption of a TSH upper limit of 3.0 mIU/L - a value close to the TSH upper limit determined for populations with a low prevalence of thyroid autoimmunity (i.e. NHANES III blacks).

The upper limit of the reference range for thyroid-stimulating hormone should not be confused with a cut-off to define subclinical hypothyroidism.

[Waise A](#), [Price HC](#).

Laboratory Medicine, York Hospital, York, UK. ahmed.waise@nhs.net

TSH REFERENCE RANGE

Decision cut-offs to diagnose and perhaps to consider treatment of mild hypothyroidism are a separate issue and should not be confused with the issue of defining **reference ranges**.

The upper limit of the reference range for thyroid-stimulating hormone should not be confused with a cut-off to define subclinical hypothyroidism

Ann Clin Biochem 2009; 46: 93–98. DOI: 10.1258/acb.2008.008113

Ahmed Waise^{1,2} and Hermione C Price²

TSH REFERENCE RANGE

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Such **cut-offs** may well be lower than the upper limit of reference range reported in many assays and recent studies suggest perhaps **between 2.5 mU/L and 3.0 mU/L.**

TSH REFERENCE RANGE

J Clin Endocrinol Metab. 2013 Sep;98(9):3584-7. doi: 10.1210/jc.2013-2760.

The normal TSH reference range: what has changed in the last decade?

Biondi B.

L-thyroxine has been found to exert a beneficial effect on atherogenic lipid profile and impaired vascular function in patients with TSH levels between 2.5 and 4.5 mIU/L.

J Clin Endocrinol Metab. 2013 Sep;98(9):3584-7. doi: 10.1210/jc.2013-2760.

The normal TSH reference range: what has changed in the last decade?

Biondi B.

A large body of evidence, which began to emerge in 2005, indicates that differences in thyroid function within the euthyroid reference range are associated with negative health outcomes.

Clinical review: A review of the clinical consequences of variation in thyroid function within the reference range.

Taylor PN, Razvi S, Pearce SH, Dayan CM.

T 4 AND HEALTH

CONCLUSION: Common variation in persons with thyroid function in the normal range are associated with adverse health outcomes. These data suggest, by extrapolation, that carefully monitored treatment of even modest elevations of TSH may have substantial health benefits.