



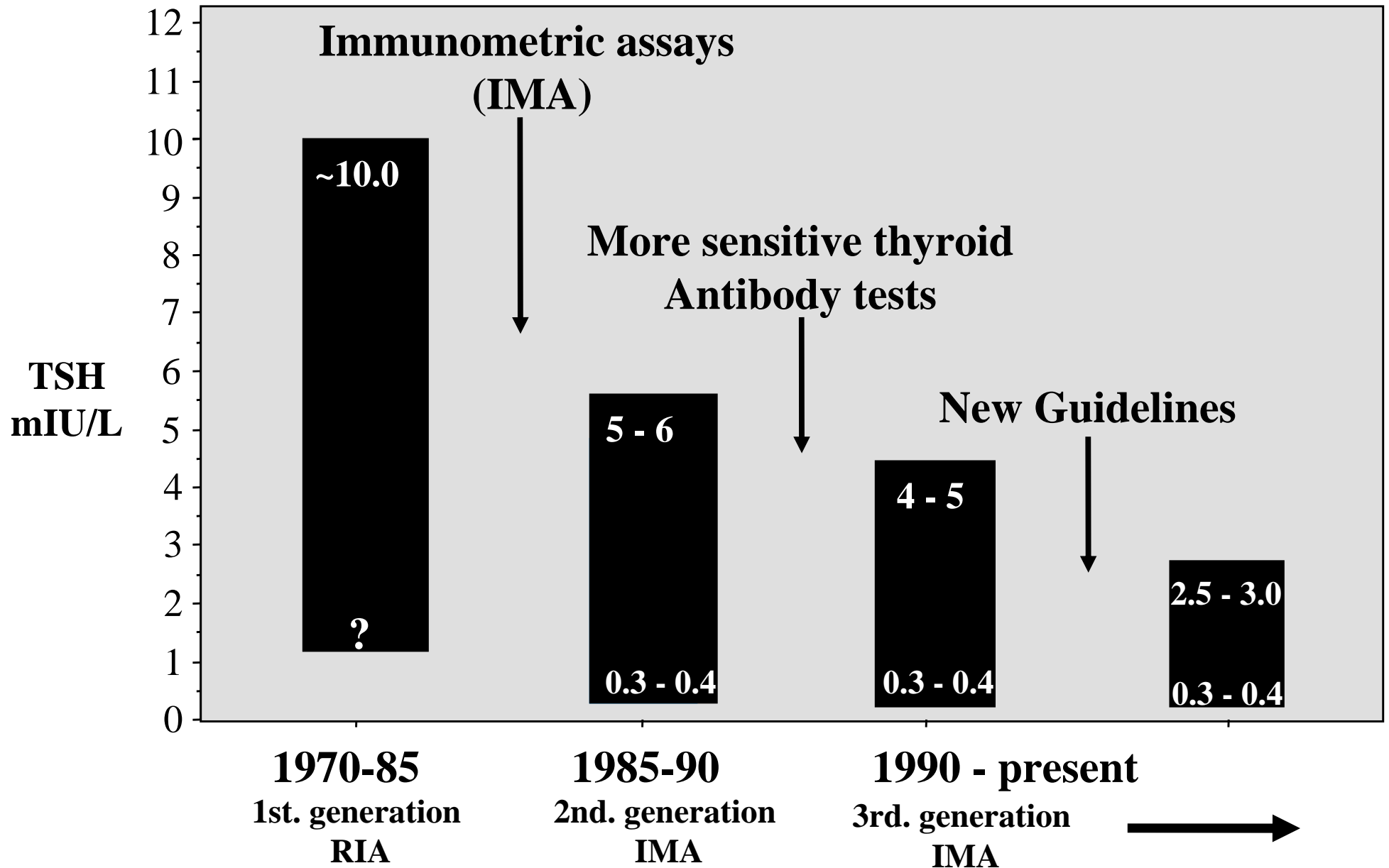
Clinical Implications of the New TSH Reference Range

AACC Expert Access

8/15/06

*Carole Spencer Ph.D., FACB.,
Professor of Medicine
Technical Director, USC Endocrine Services Laboratory
University of Southern California
Los Angeles, California*

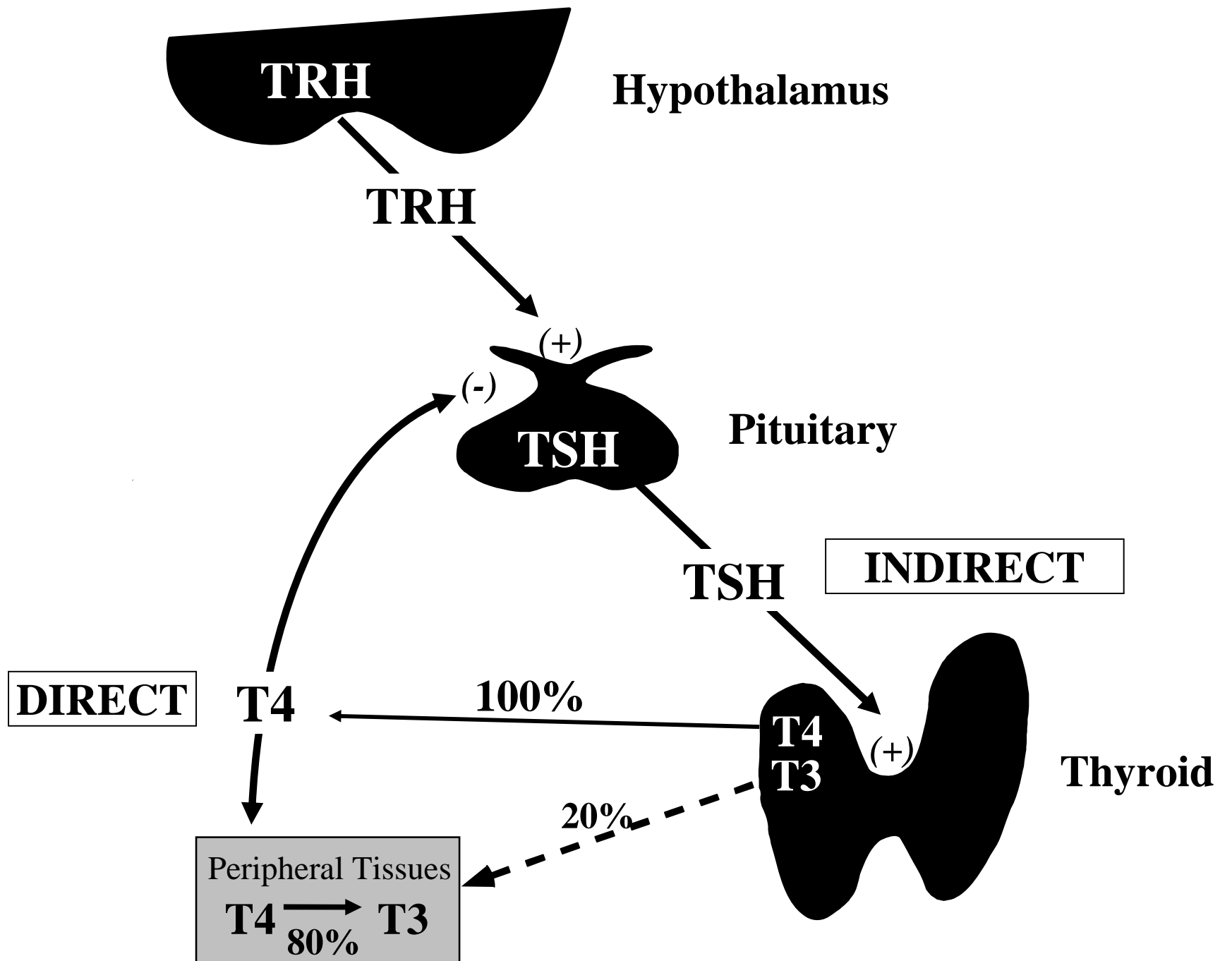
Changing TSH Reference Ranges Over Three Decades



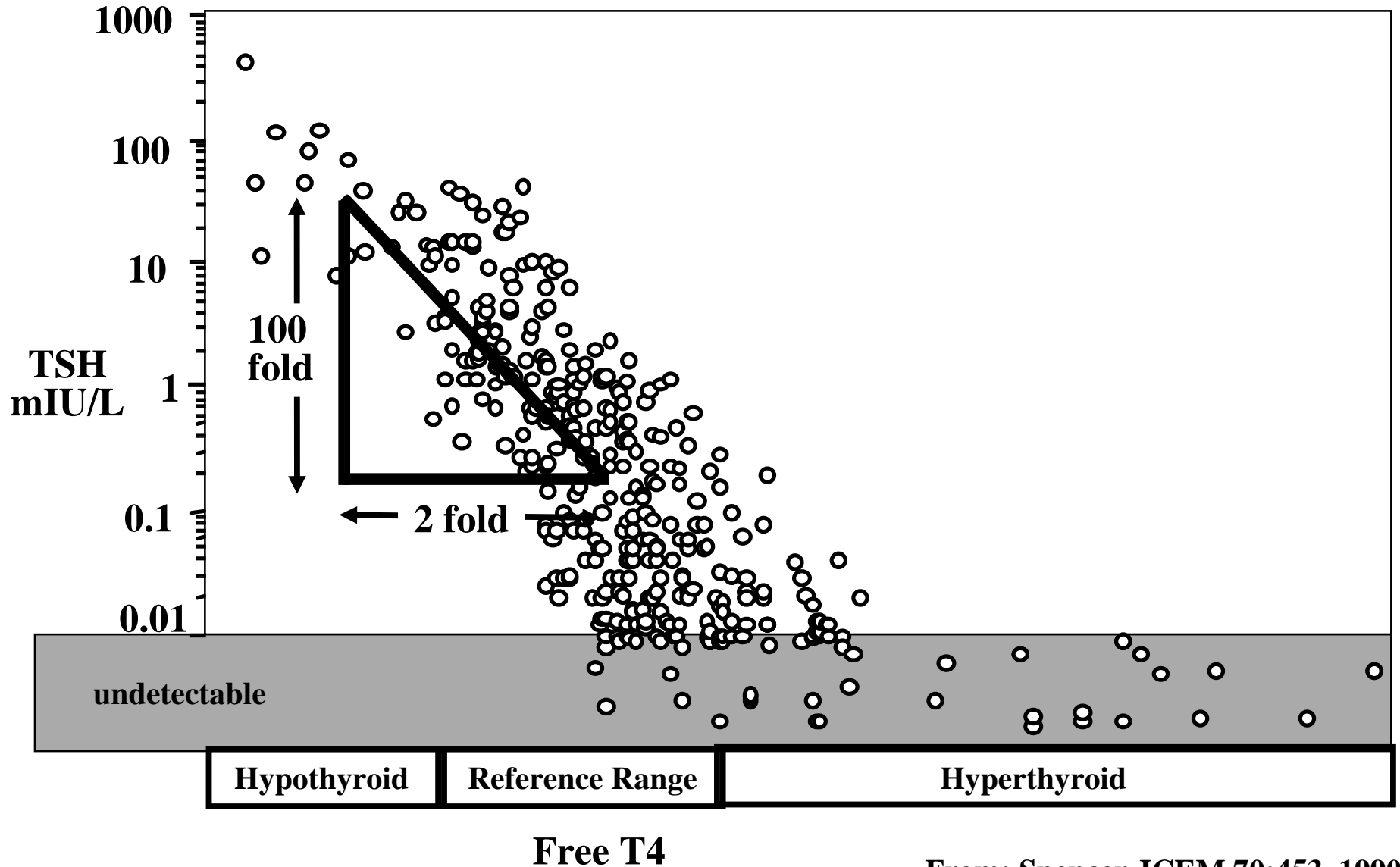
OUTLINE

TSH Testing in Ambulatory Patients

- **Why TSH has become the primary thyroid test**
- **Limitations of using population reference ranges for the thyroid tests - TSH has a low index of individuality**
- **Rationale for a TSH lower reference limit of ~ 0.3 mIU/L**
- **Rationale for an empiric TSH upper reference limit of 2.5-3.0 mIU/L**
- **Clinical Rationale for adopting a TSH reference range 0.3-3.0 mIU/L**

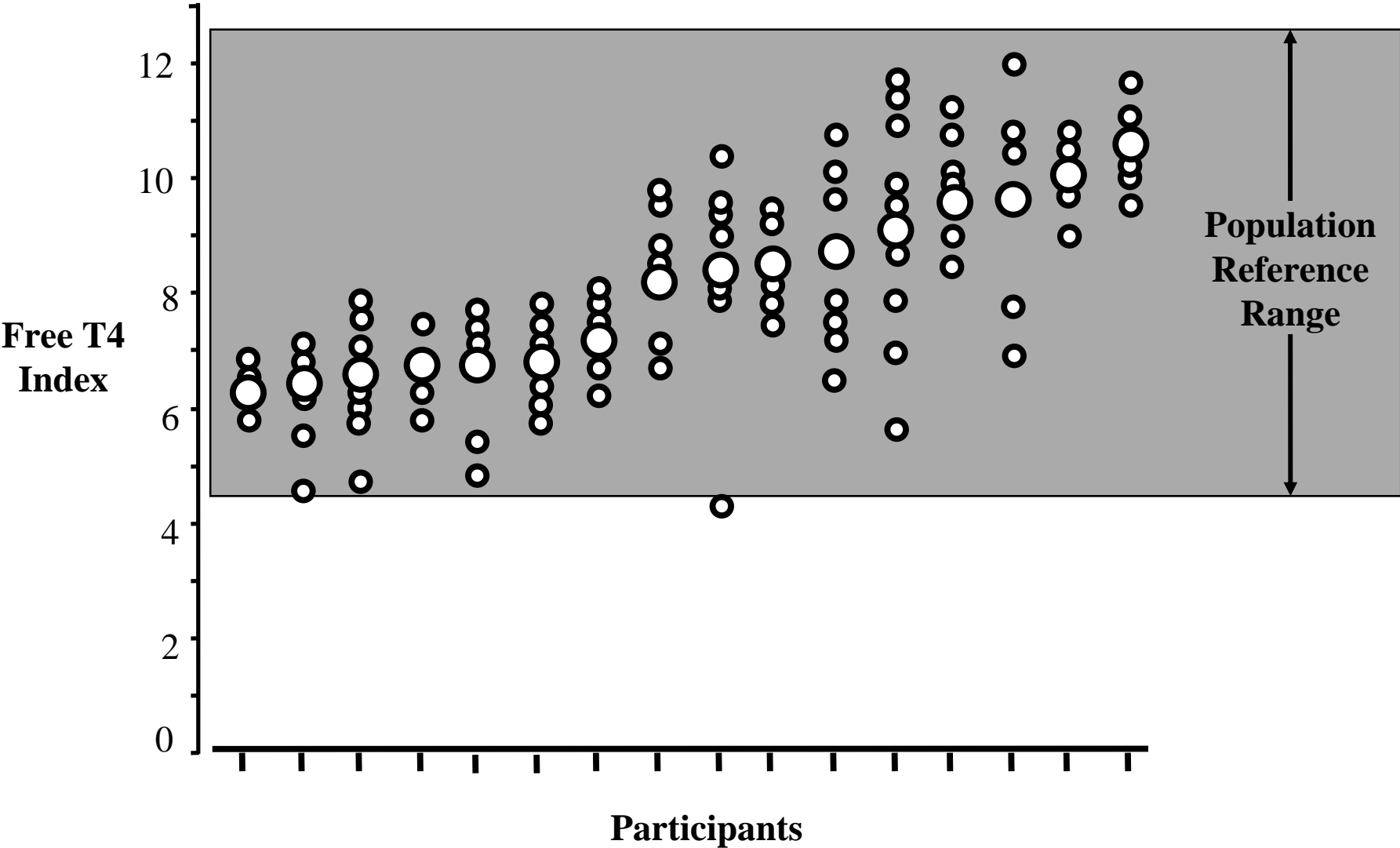


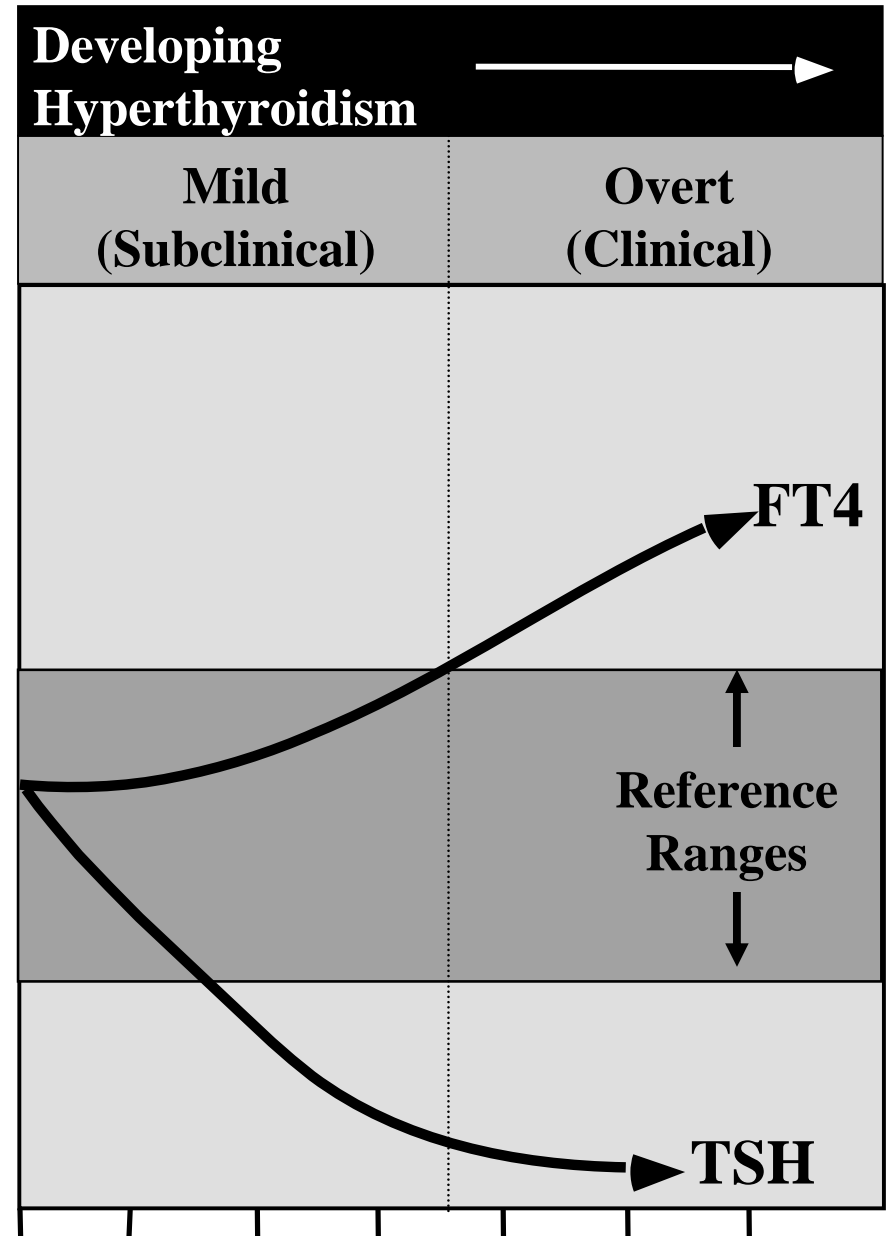
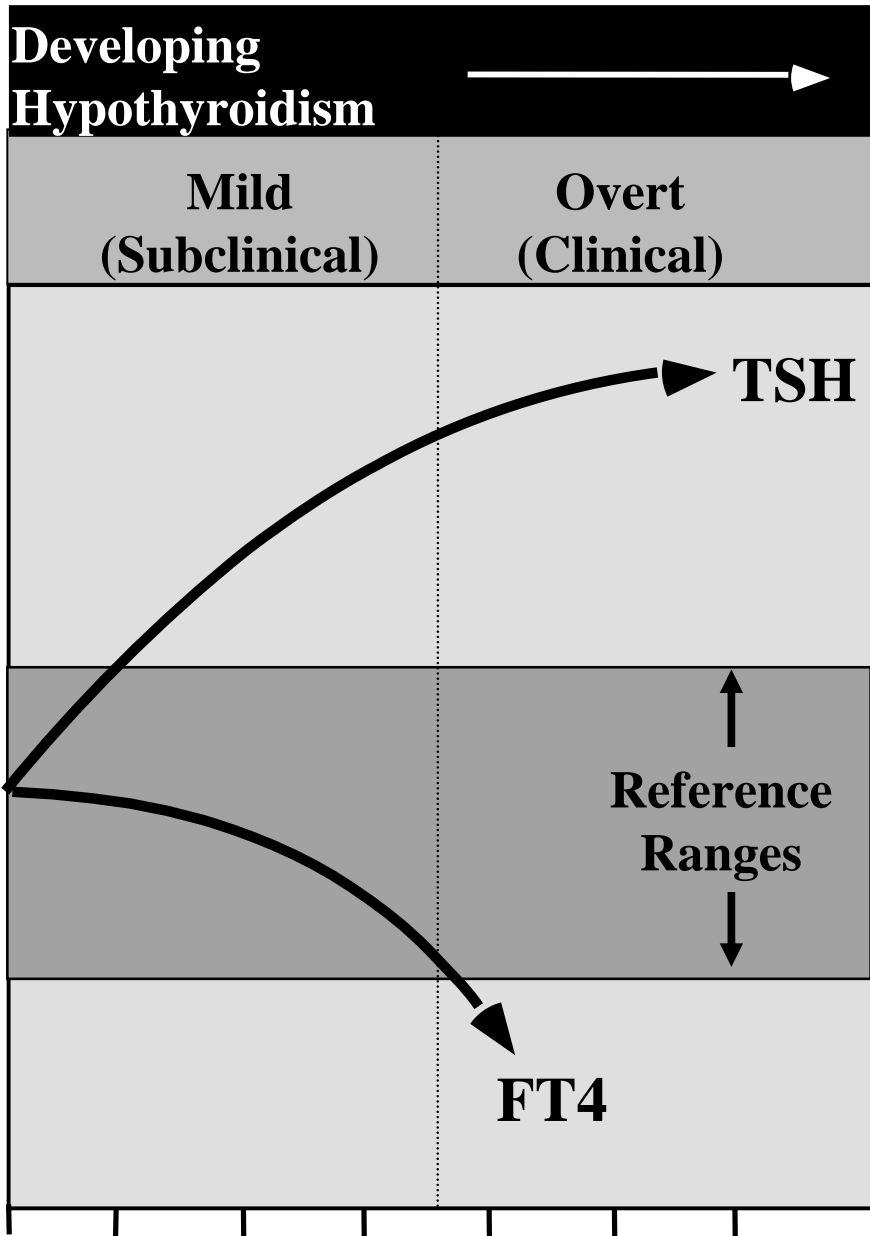
The Diagnostic Power of TSH is Due to the TSH/Free T4 Relationship



From: Spencer JCEM 70:453, 1990

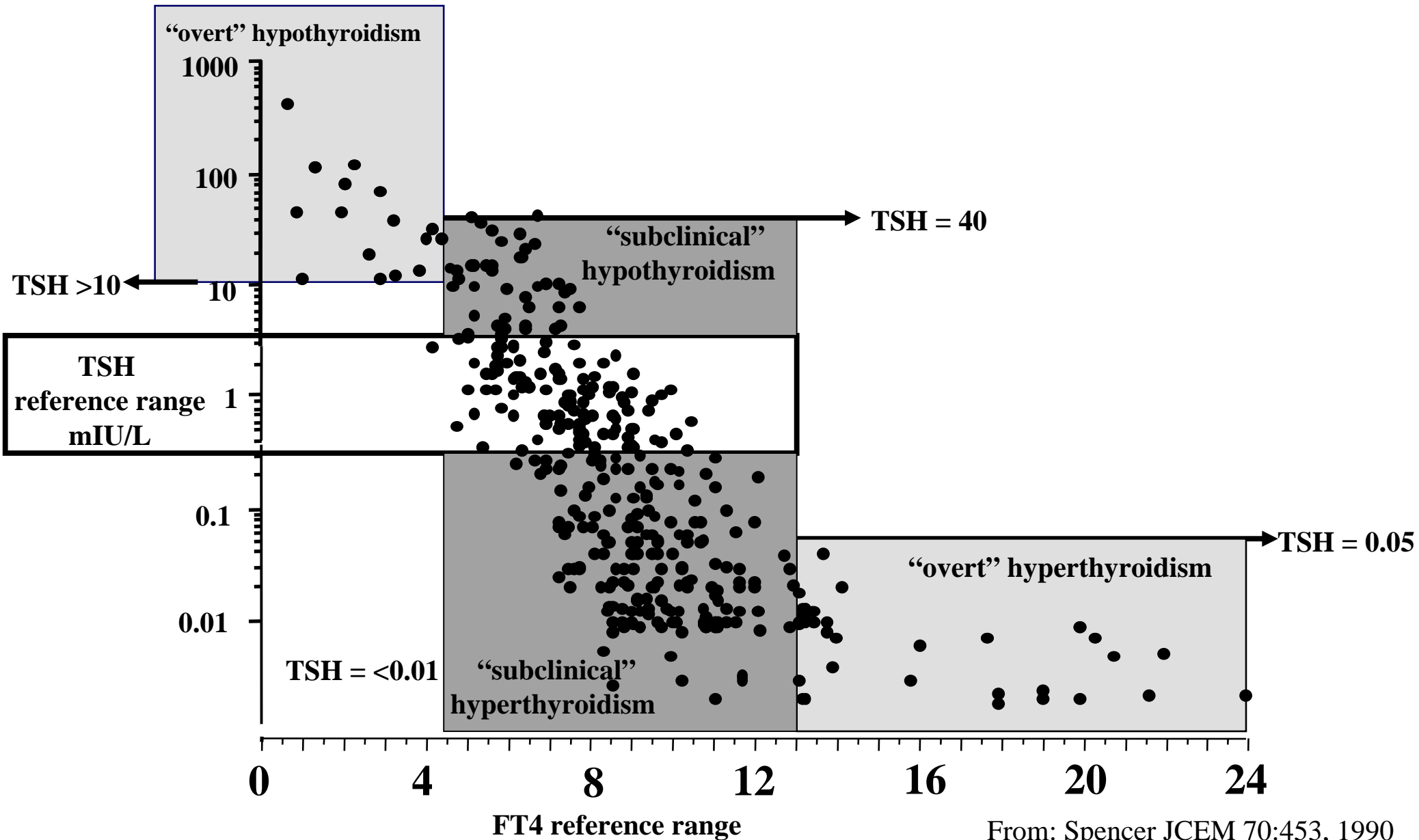
Individuals have a Genetically Controlled Free T4 Set-Point





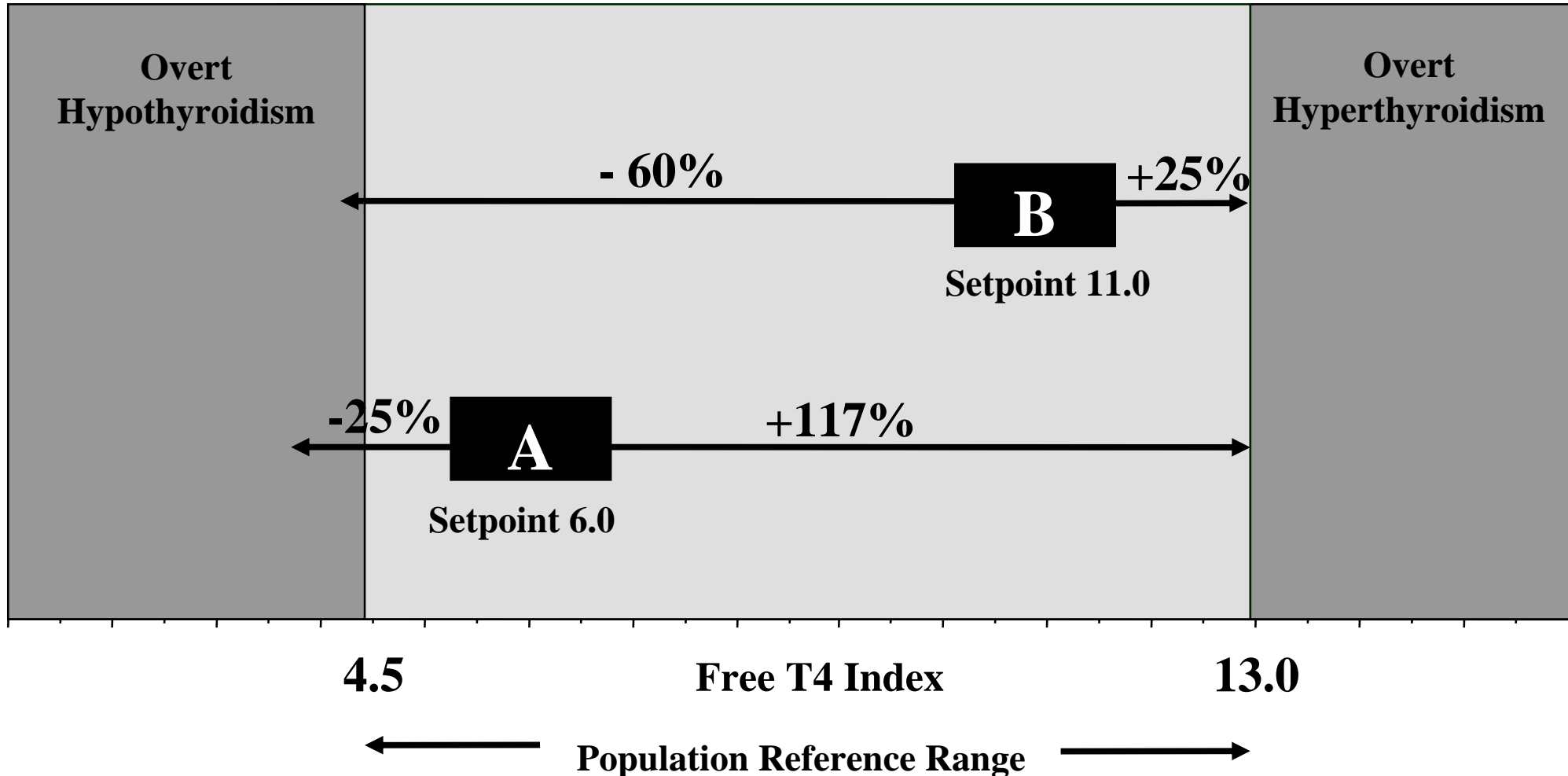
Months / Years

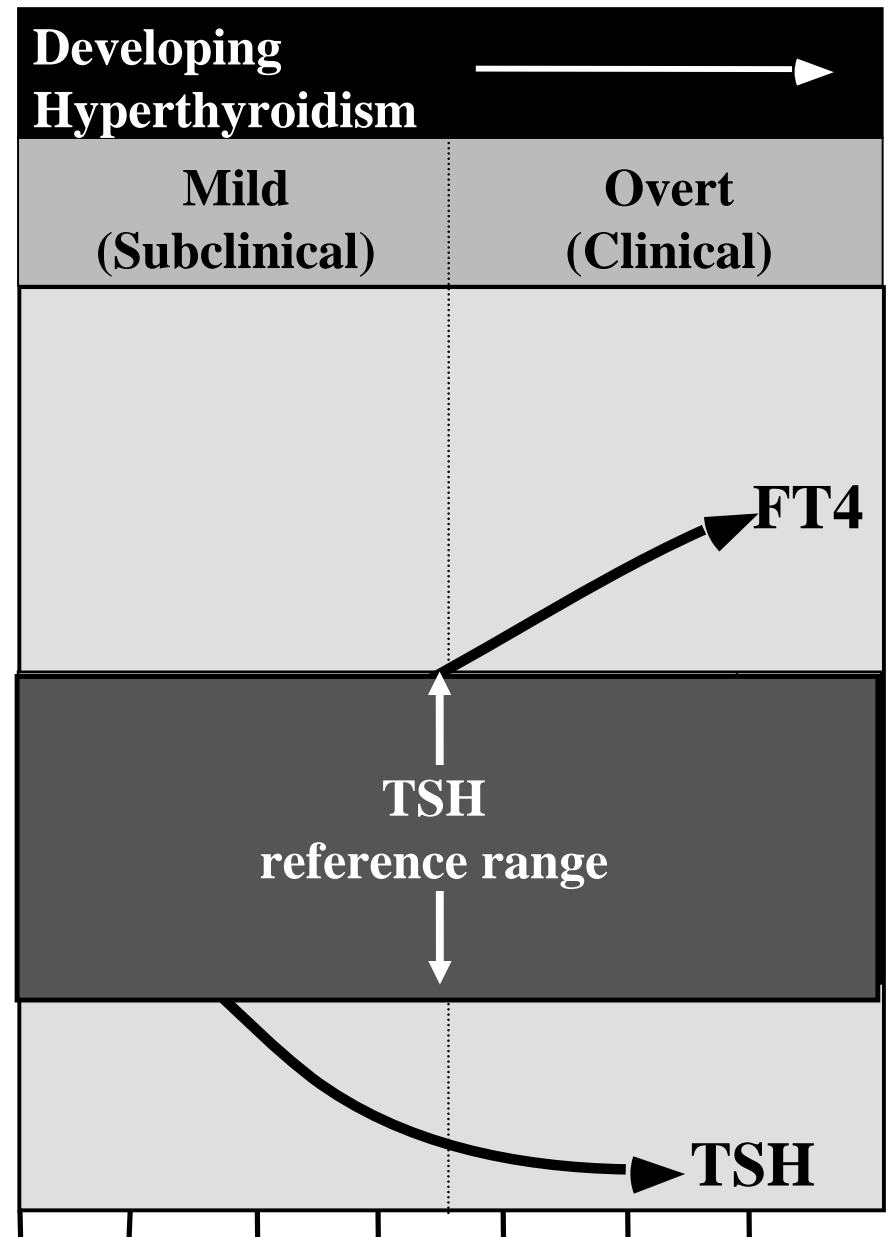
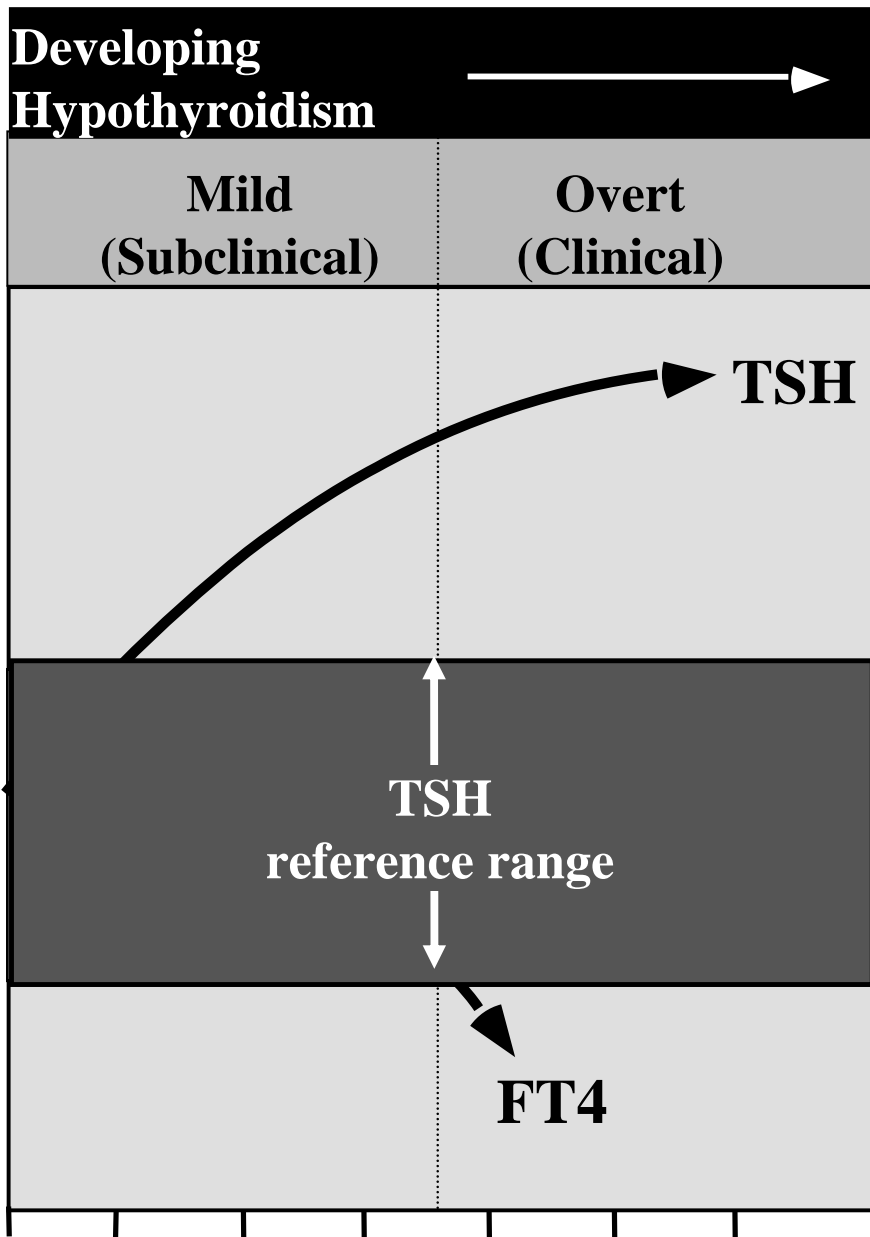
Free T4 Status Does Not Always Indicate the Degree of Thyroid Dysfunction



Classification of Overt Disease is Influenced by the FT4 Set-Point

From Andersen Thyroid 13:1069, 2003





Months / Years

OUTLINE

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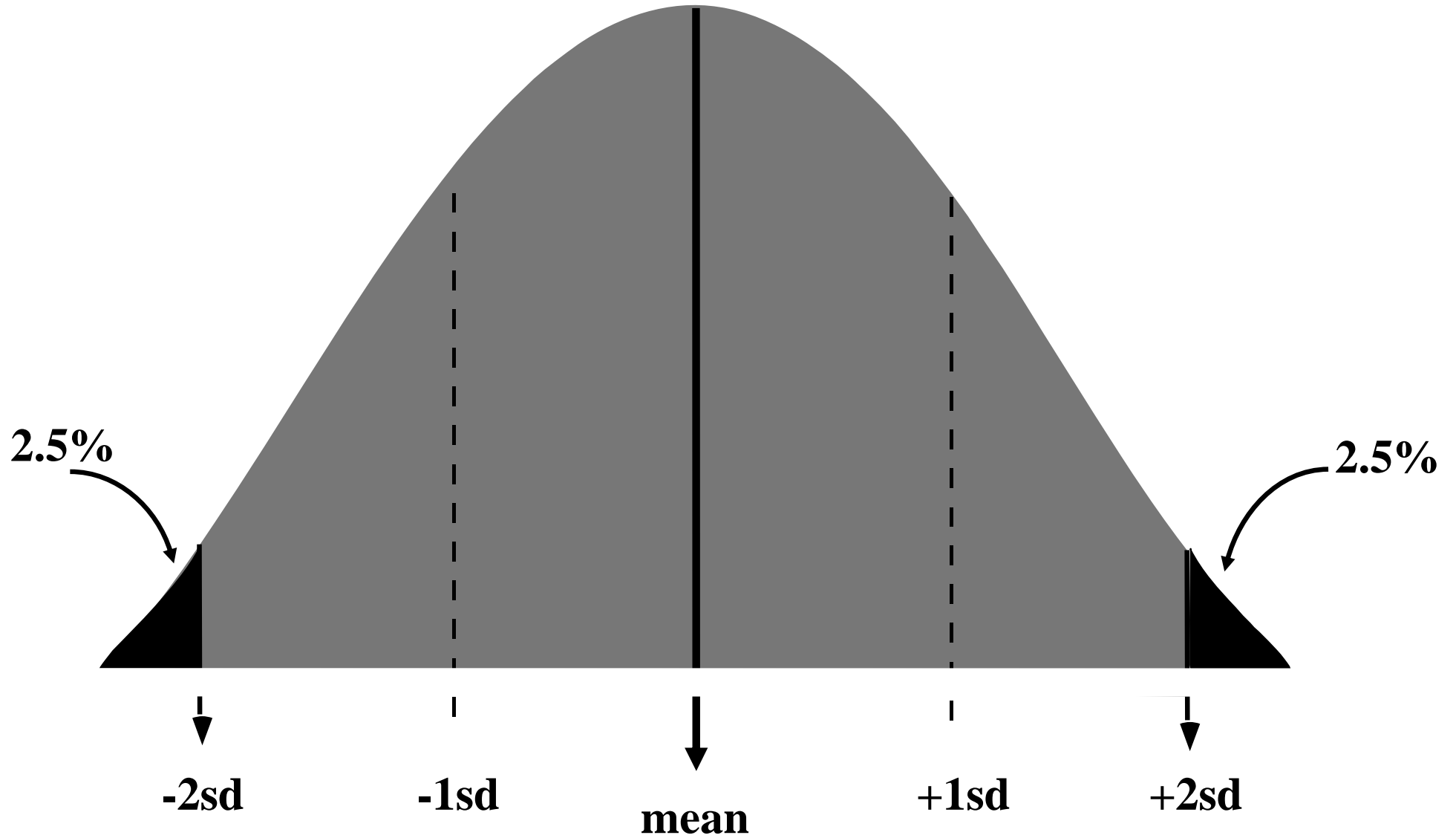
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The TSH Reference Range

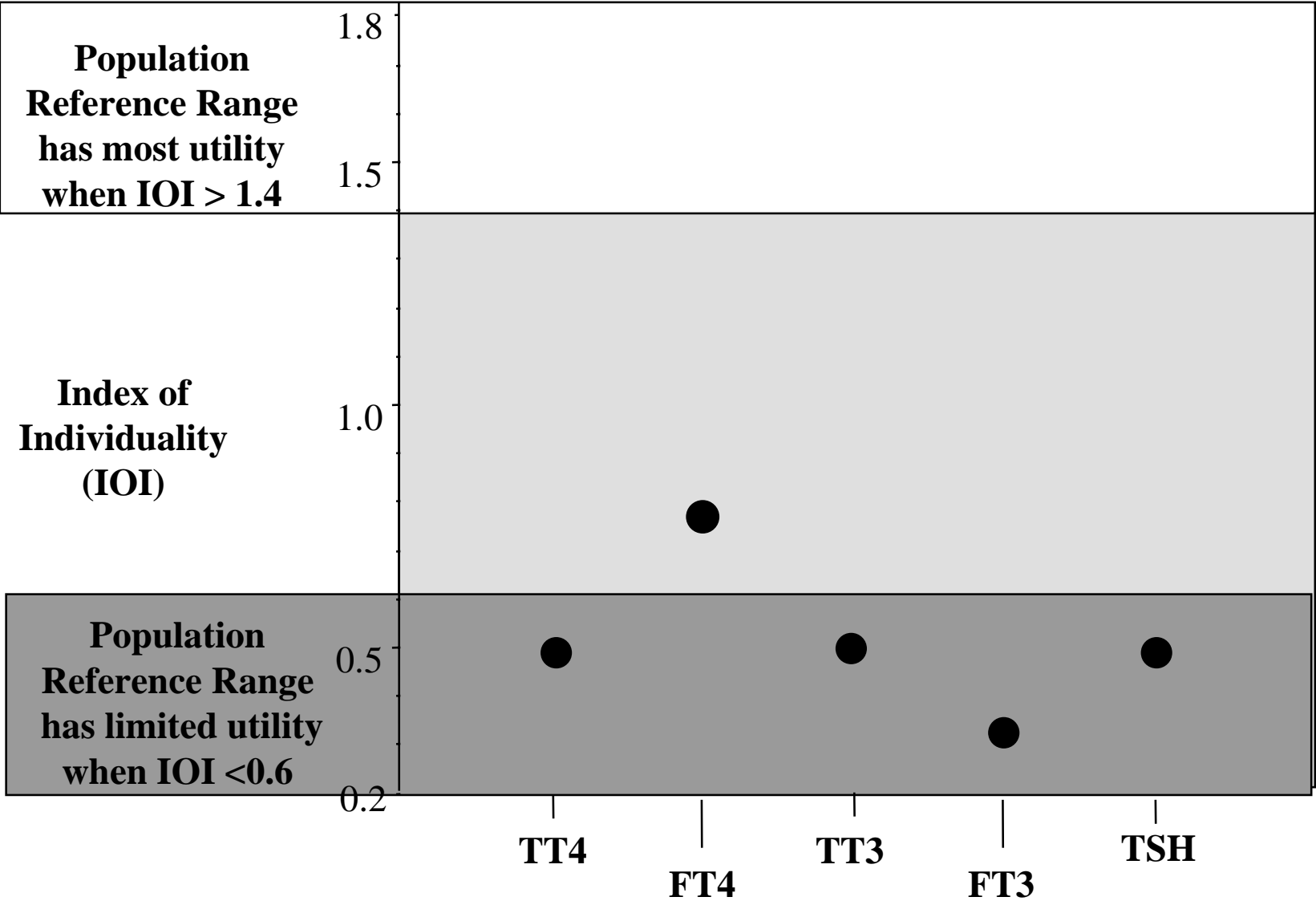
TSH reference intervals should be established from the 95 % confidence limits of the log-transformed values of at least 120 rigorously screened normal euthyroid volunteers with:

- **No personal or family history of thyroid dysfunction**
- **No visible or palpable goiter**
- **No medications (except estrogen)**
- **No thyroid autoantibodies -TPOAb or TgAb (measured by sensitive immunoassay)**

Reference
The TSH ~~Normal~~ Range

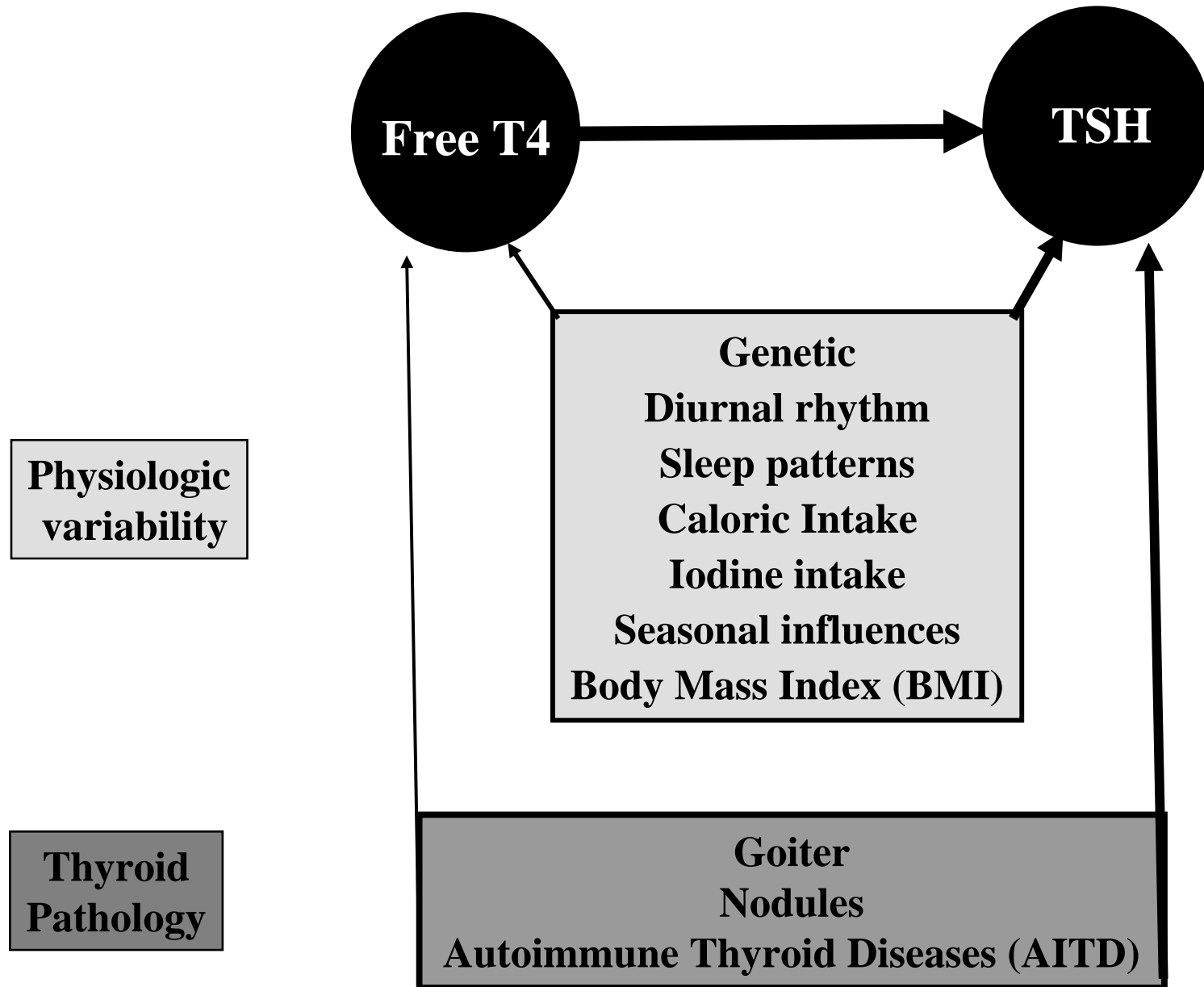


Index of Individuality - Is an Index of the Intra-individual versus Between-individual Variability



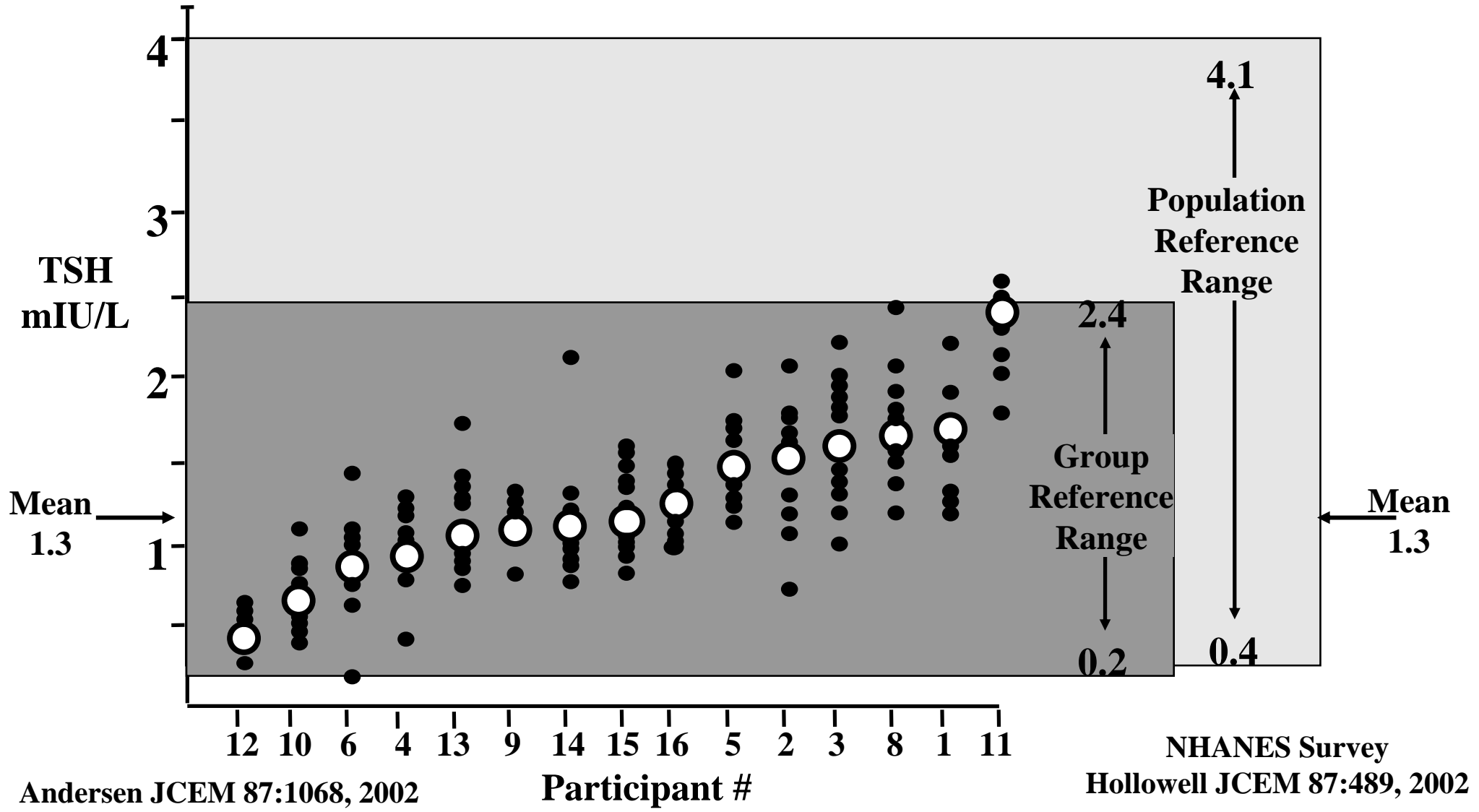
**Browning Clin Chem 32: 962, 1986
Andersen et al JCEM 87: 1068, 2002**

Multiple Variables Contribute to Between-Individual TSH Variability



The Population Reference Range is a Crude Parameter for Assessing the Thyroid Status of Individuals

In an individual, a TSH change that exceeds 0.75 mIU/L is biologically significant.
(NACB Guideline #8. Thyroid 13:18, 2003)



OUTLINE

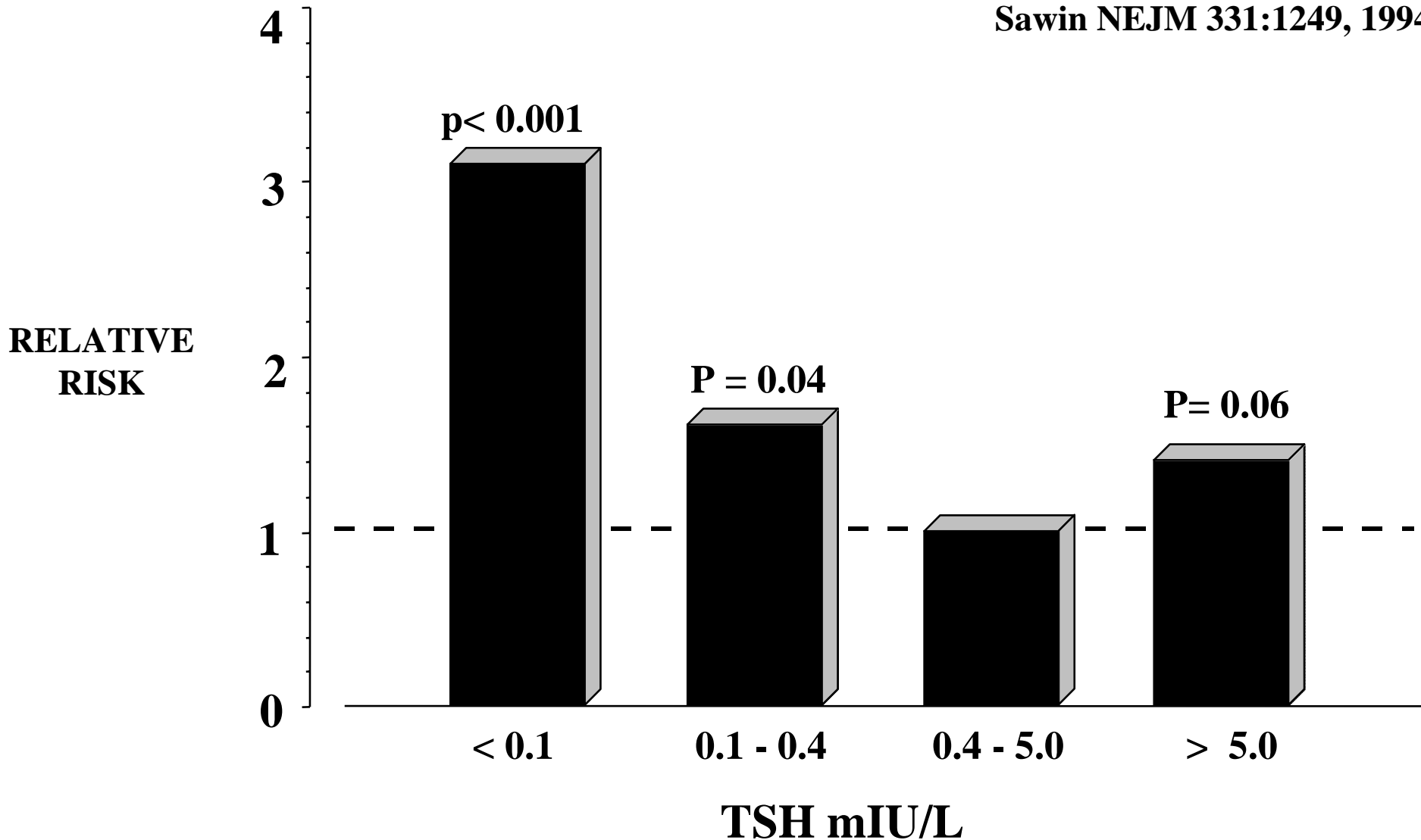
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**A TSH Lower Reference Limit
of 0.3 - 0.4 mIU/L
is supported by methodologic
and clinical studies**

Framingham Study - Relative Risk of Developing Atrial Fibrillation in > 60-Year Old Individuals (no L-T4 Rx.)

Sawin NEJM 331:1249, 1994



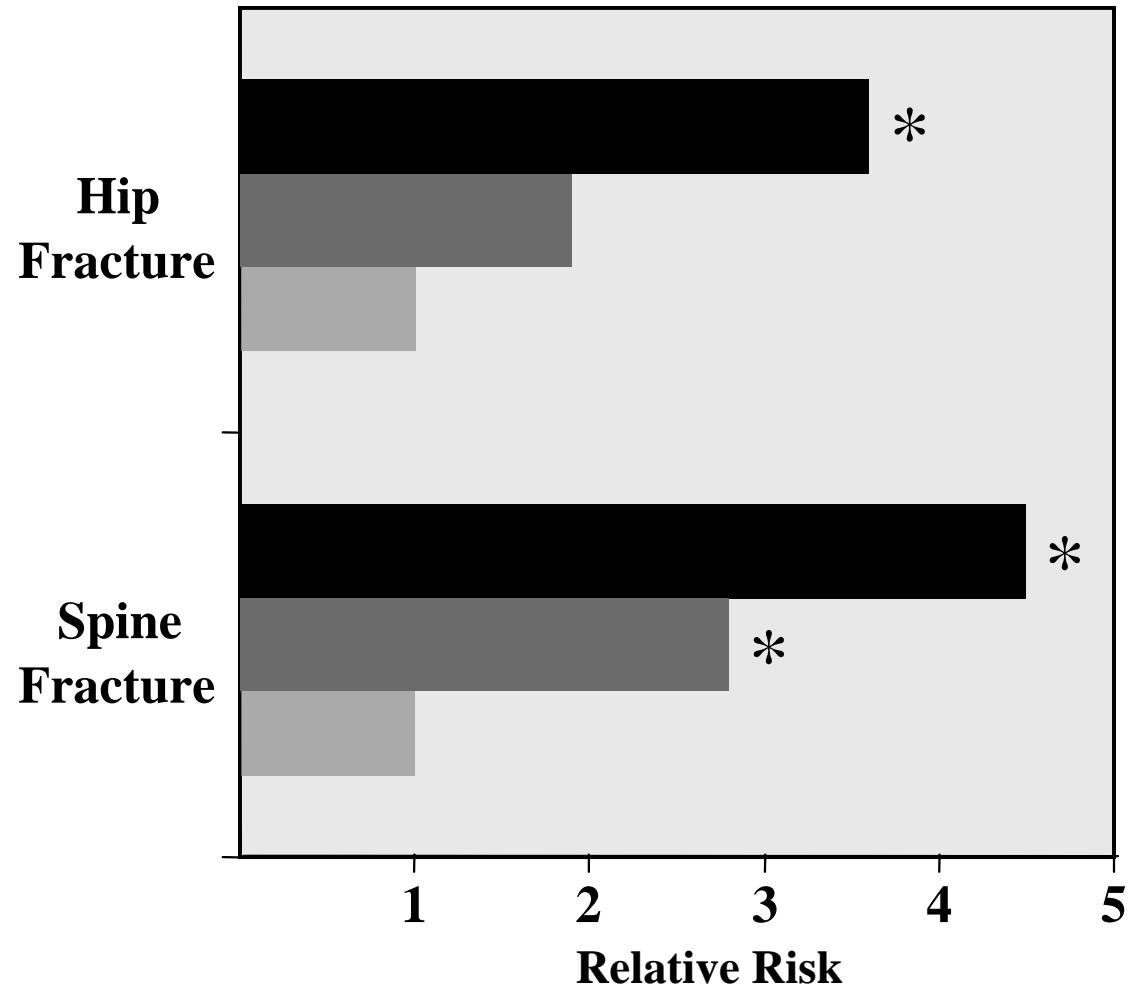
Subclinical Hyperthyroidism - The Study of Osteoporotic Fractures

Bauer DC et al AIM 134:561-568, 2001

- **Prospective Cohort Study**
- **686 from Cohort of 9704 women**
- **Age >65 yrs**
- **Data Adjusted by Multifactorial Analysis**

1. **Previous Hyperthyroidism**
2. **Age**
3. **Self-Rated Health**
4. **Estrogen Use**
5. **Thyroid Hormone Use**

■ **TSH <0.1**
■ **TSH 0.1-0.5**
■ **TSH 0.5-5.5**



TSH Upper Reference Limit

(~ 2.5 - 4.5 mIU/L)

is more controversial!

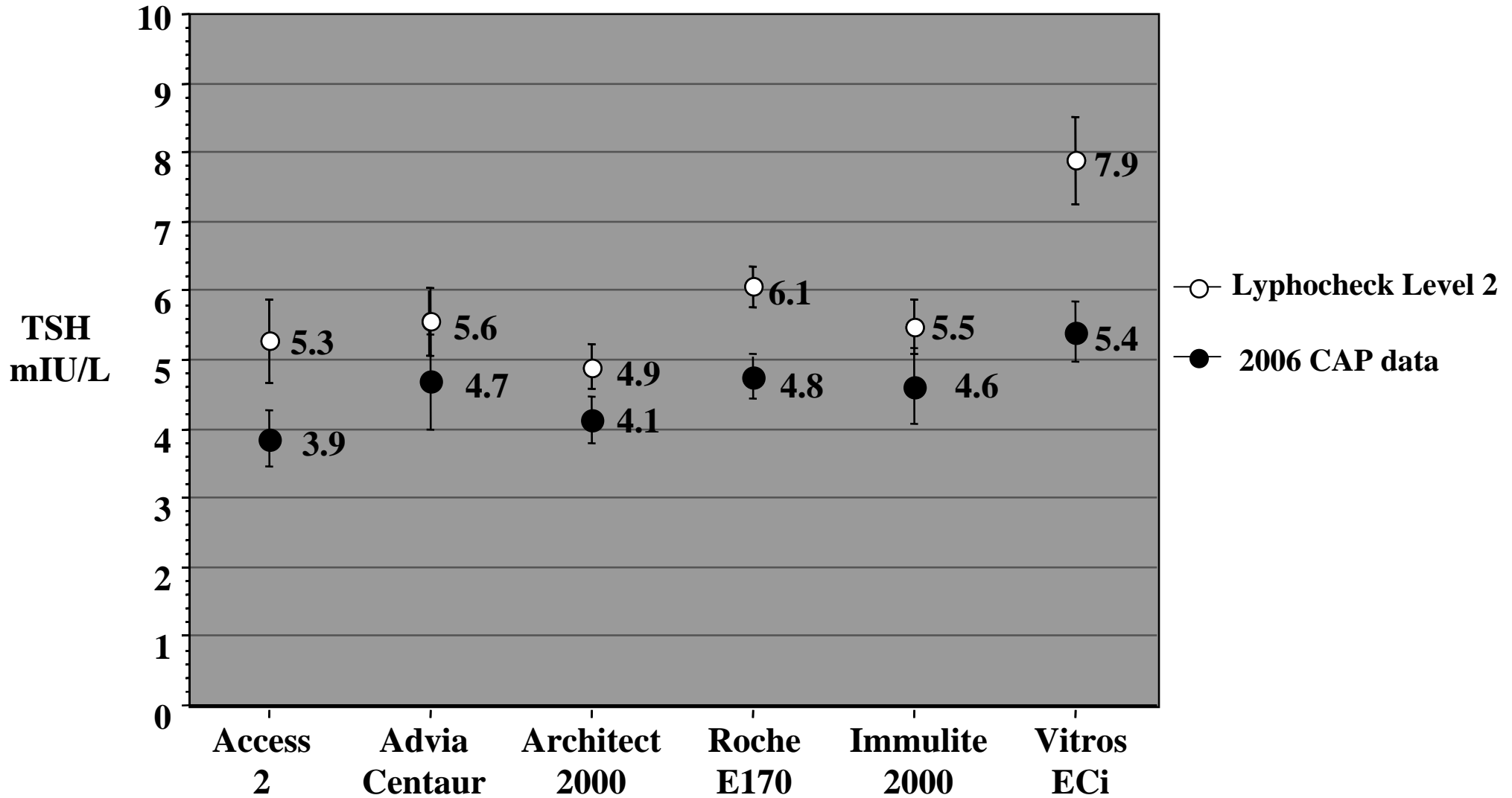
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TSH Methods Likely Measure Different TSH Isoforms

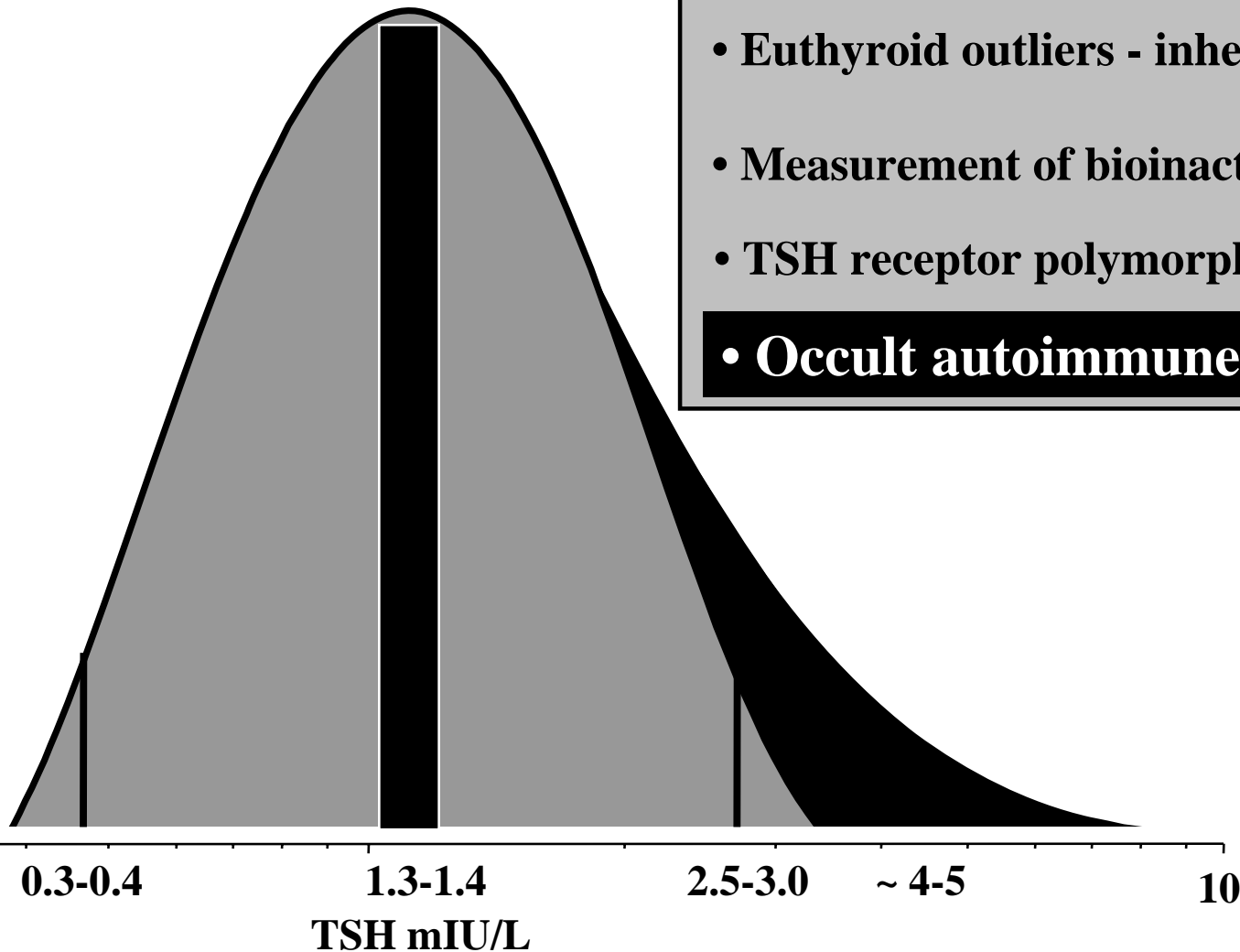
(mean \pm 2sd)



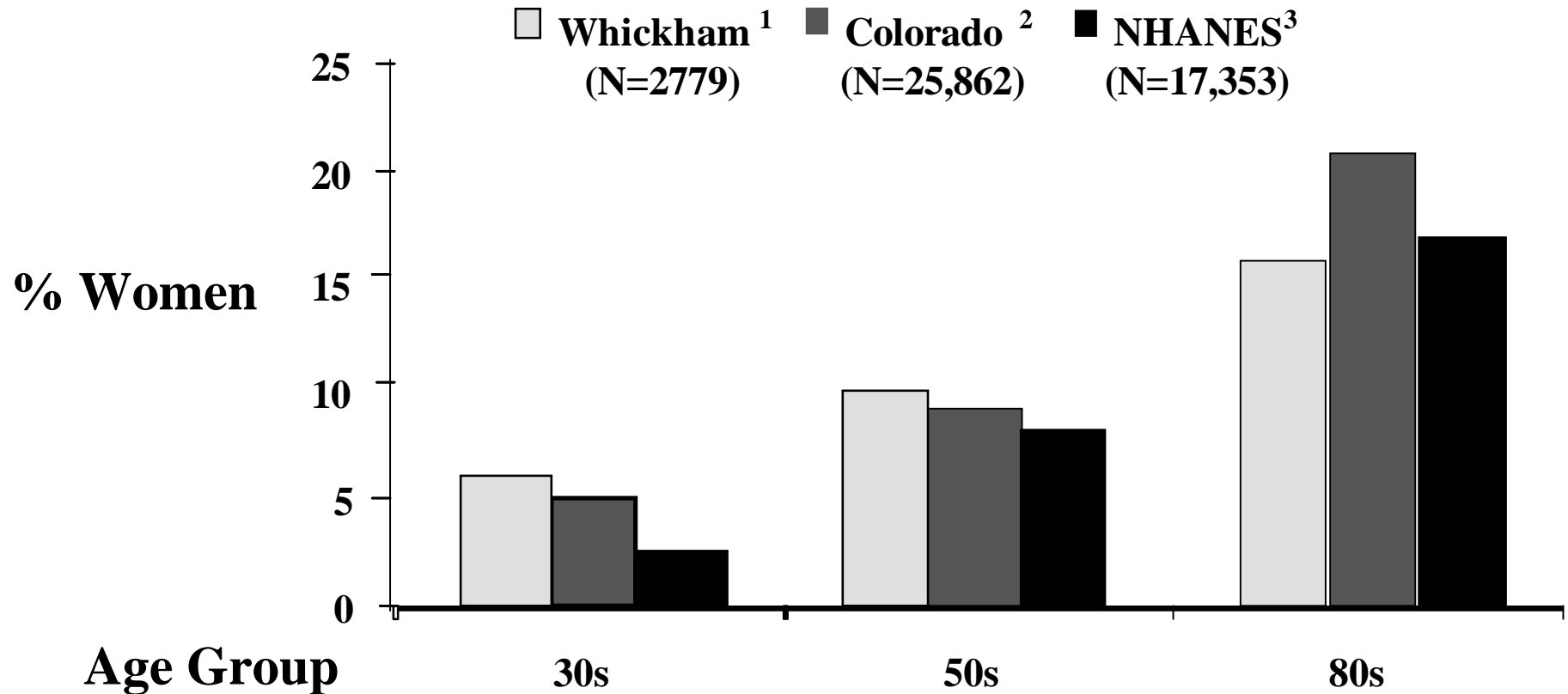
The Predicted versus the Population TSH Upper Reference Limit

Reasons for the skew in the TSH upper reference limit include:

- Euthyroid outliers - inherent TSH lability
- Measurement of bioinactive TSH isoforms
- TSH receptor polymorphisms \downarrow TSH sensitivity
- **Occult autoimmune thyroid dysfunction**



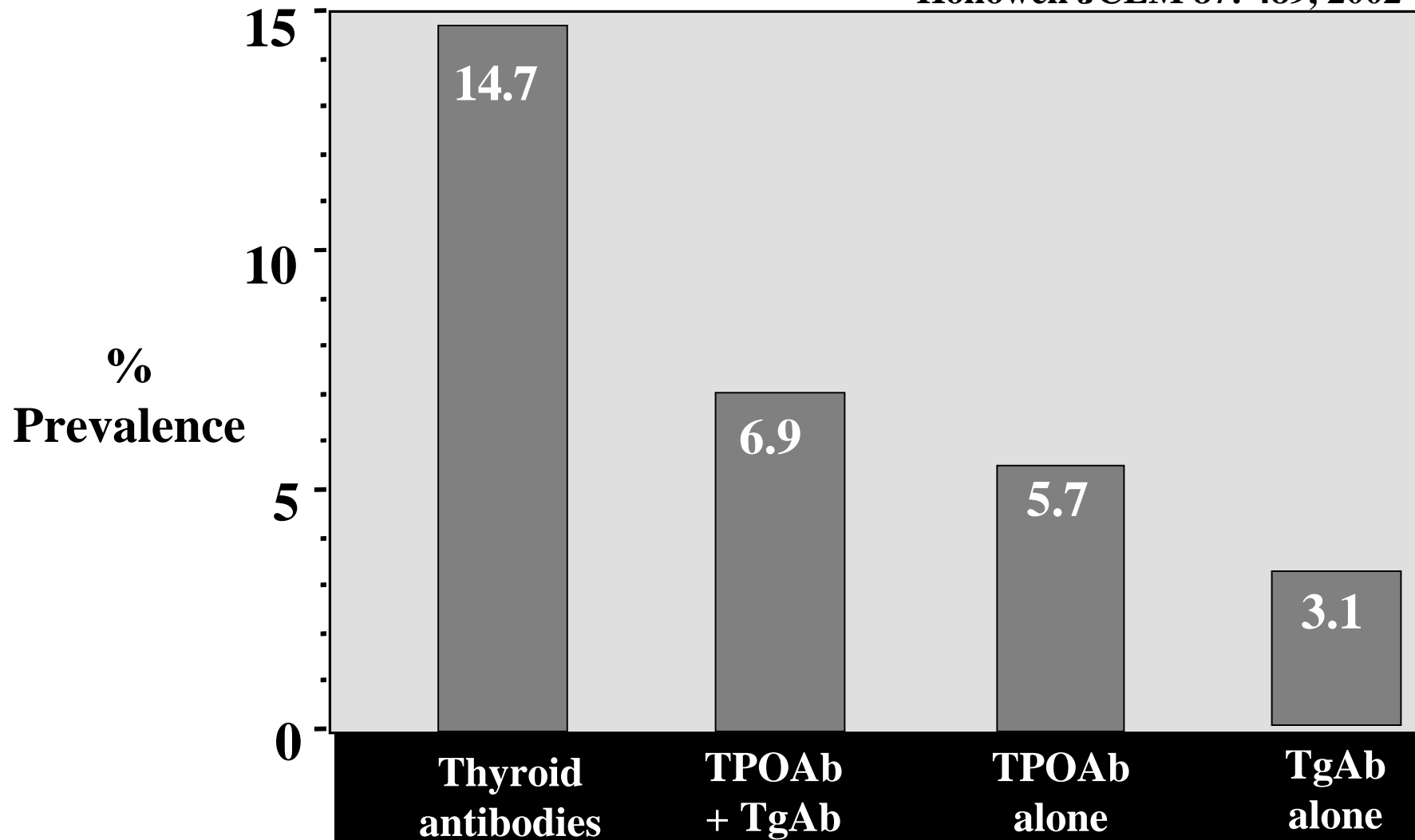
Prevalence of Mild Thyroid Failure (Subclinical Hypothyroidism) in Women in Different Age Groups



1. Tunbridge W, et al. Clin Endocrinol 1977;7:481-493.
2. Canaris G, Arch Intern Med. 2000;160:526-534.
3. Hollowell J, J Clin Endocr Metab. 2002; 87:489-499.

NHANES - Prevalence of Thyroid Antibodies (n= 17,353)

Hollowell JCEM 87: 489, 2002



Odds Ratio for Overt Hypothyroidism

23.5

6.9

1.1

Odds Ratio for Subclinical Hypothyroidism

11.7

4.0

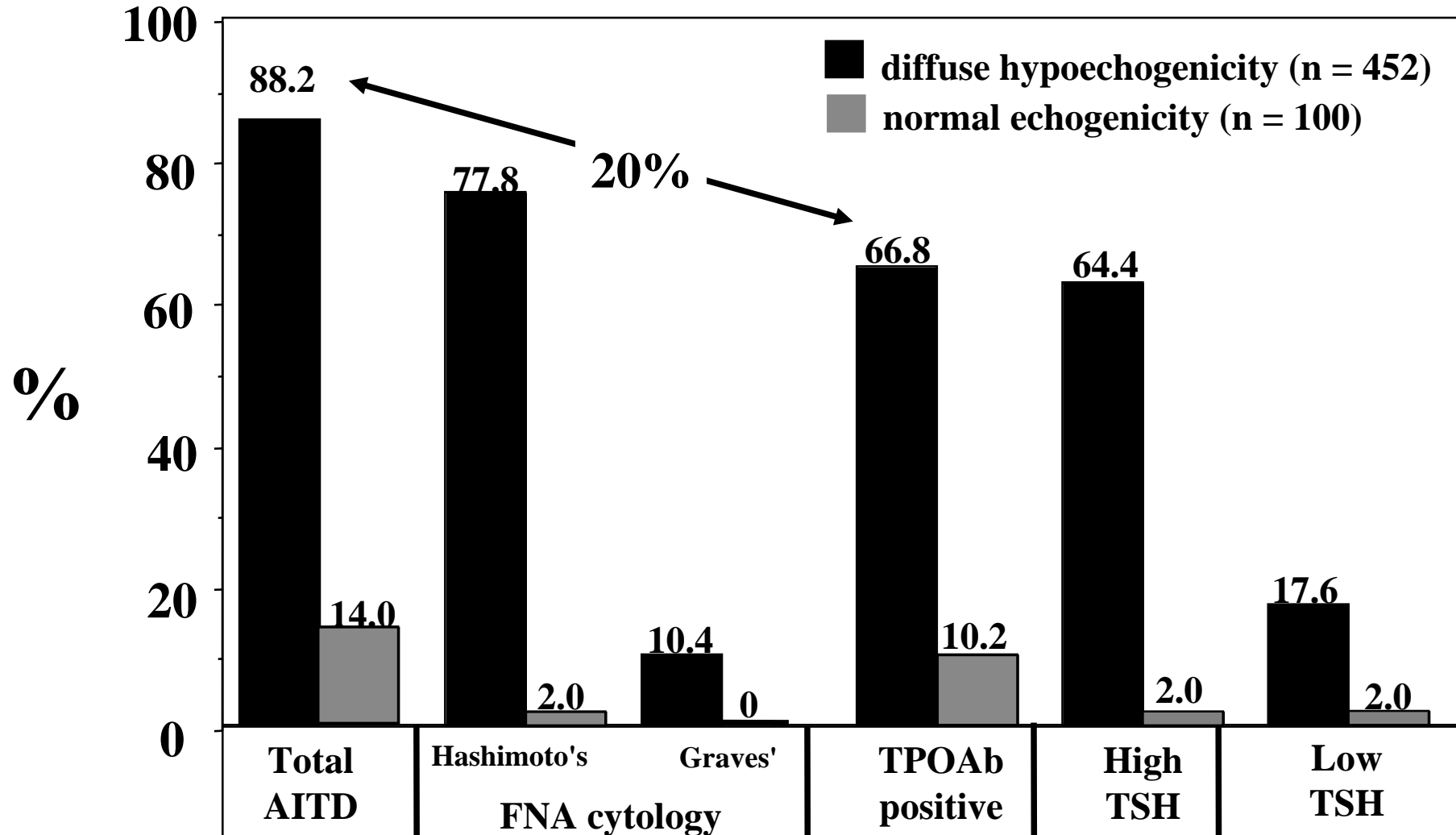
1.5

**The presence of TPO antibodies (TPOAb)
is the primary exclusion criterion for
autoimmune thyroid disease when
establishing TSH reference ranges**

**However, TPOAb is not always detected
in patients with AITD!**

3077 Prospective Ultrasound Evaluations

Hypoechoogenicity Indicative of Autoimmune Thyroid Disease (AITD) in 15%



from: Pedersen Thyroid 10:251, 2000

Occult Thyroid Dysfunction Skews the TSH Upper Limit

Recommendations: Adopt an *Empiric* TSH Upper Limit

- **National Academy of Clinical Biochemistry (NACB) Guidelines:**

Ambulatory patients with a serum TSH above 2.5 mIU/L, when confirmed by a repeat TSH measurement made after 3 weeks, may be in the early stages of thyroid failure, especially if TPOAb is detected.

Thyroid 13:42, 2003 & www.nacb.org

- **Association of Clinical Endocrinologists (ACE) Guidelines:**

Proposes the adoption of a TSH reference range of 0.3 - 3.0 mIU/L

Endocrine Practice 8:457, 2002

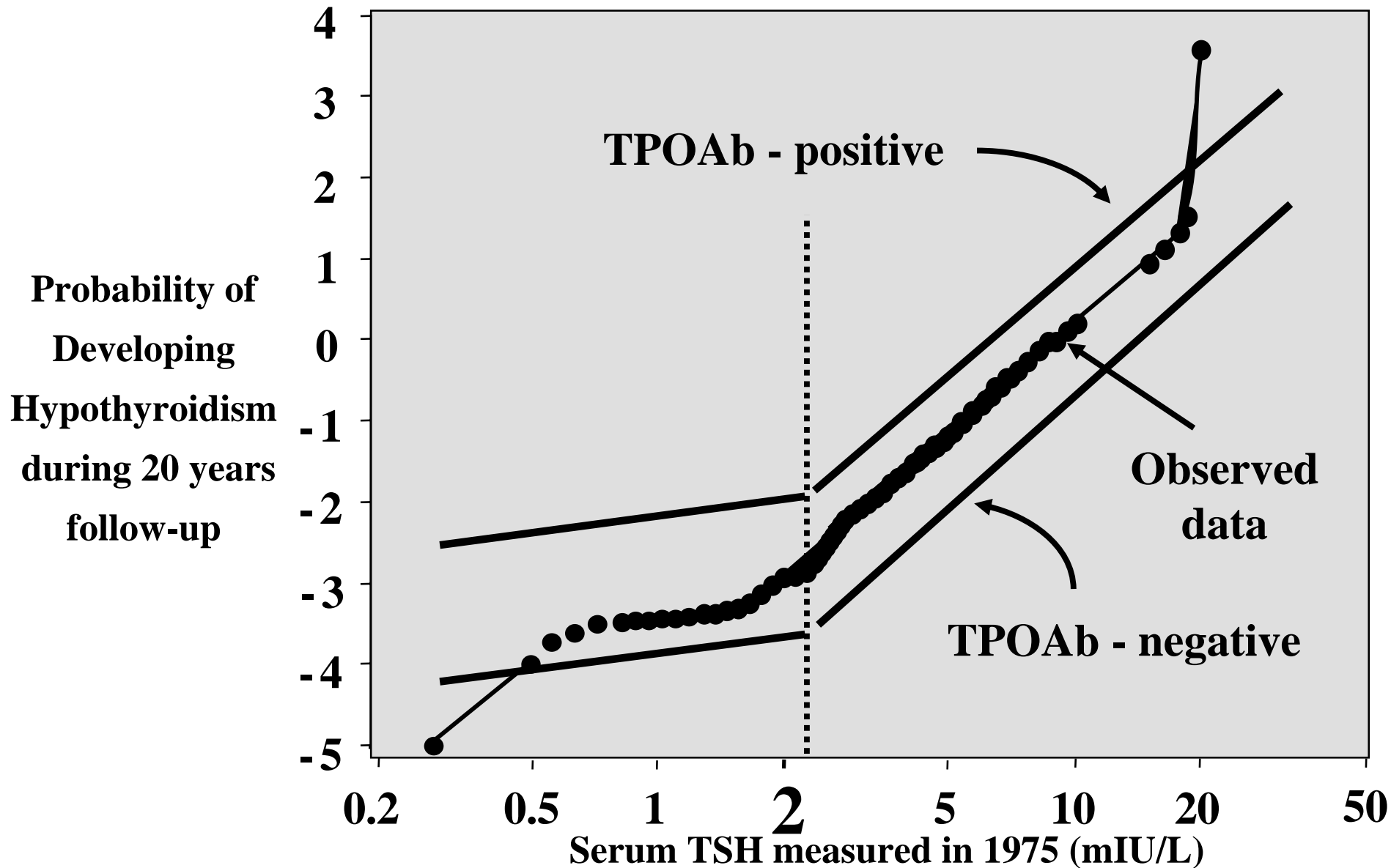
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20-Year Follow-up Study of the Whickham Cohort

Vanderpump Clin Endocrinol 43:55, 1995



A TSH Upper Reference Limit of 2.5 mIU/L is now Considered Optimal for Managing Pregnant Patients.

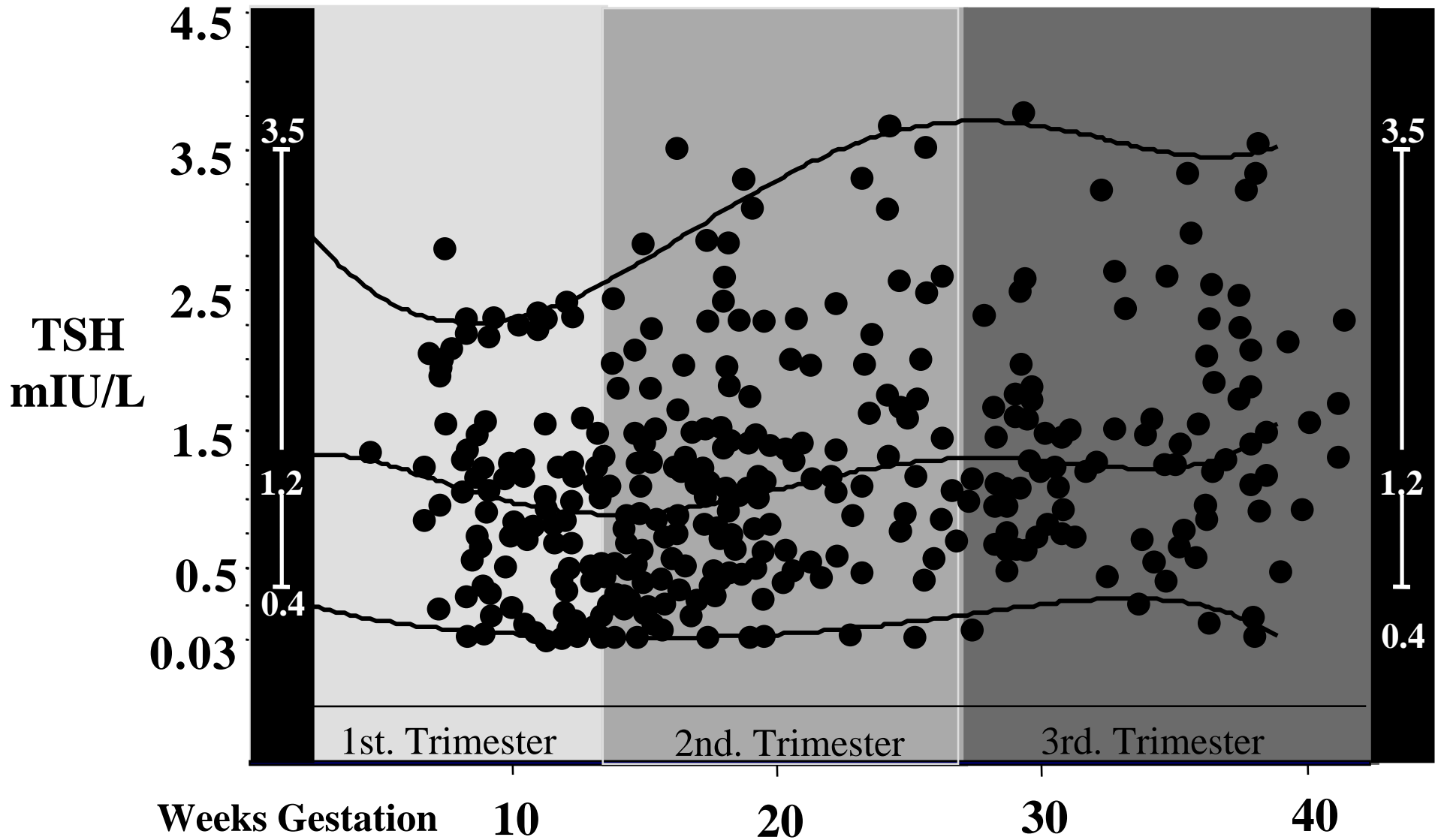
Growing recognition that even mild (subclinical) Thyroxine deficiency in early pregnancy is detrimental to mother and fetus

New guidelines state that a TSH below 2.5 mIU/L is optimal for pregnancy.

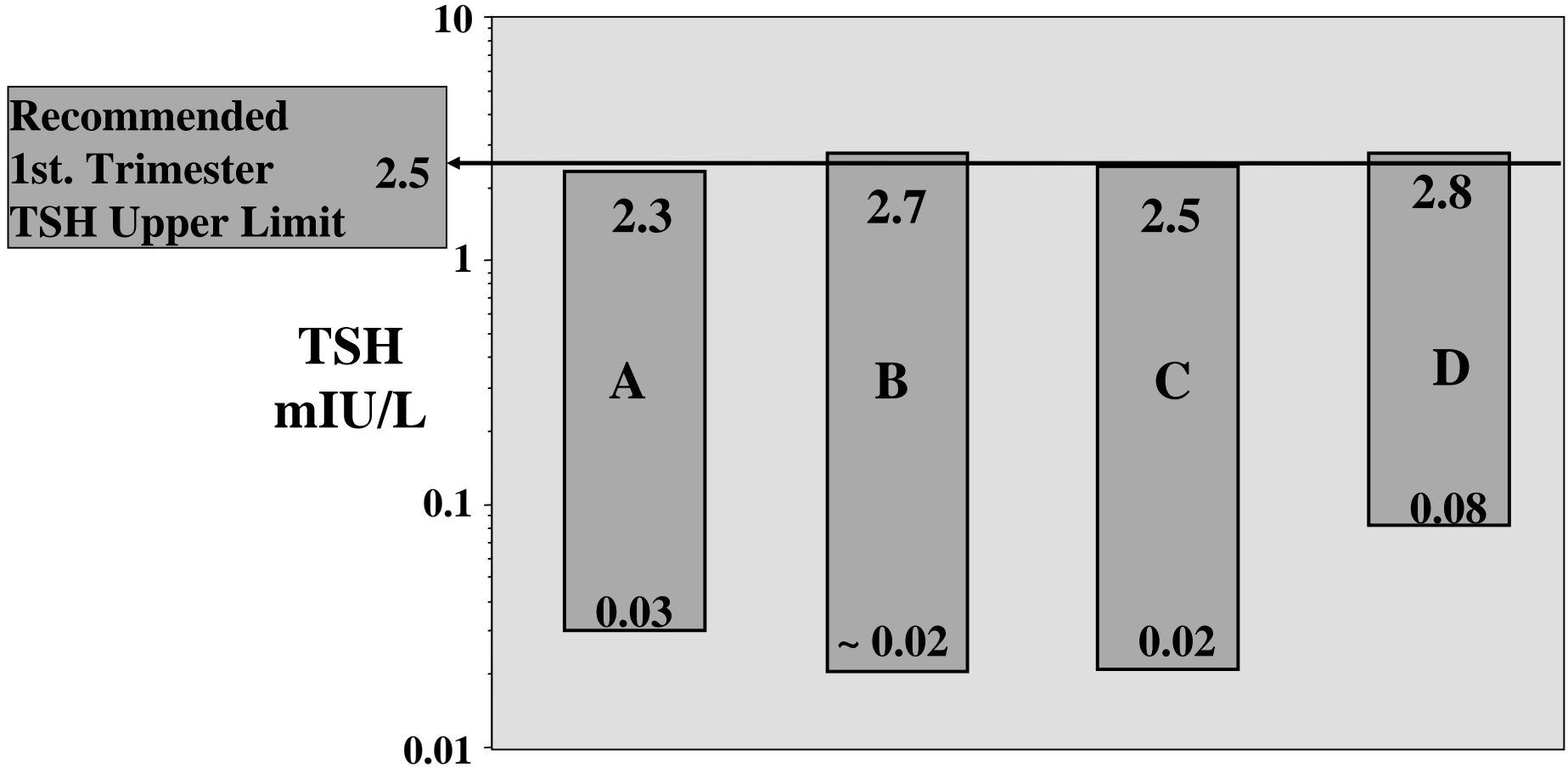
Mandel et al Thyroid 15:44, 2005

Casey et al Obstet Gynecol 105:239,2005

Changes in TSH During Pregnancy



1st. Trimester TSH Reference Ranges (95% confidence limits)



A = n = 343 (Hong Kong) Panesar Ann Clin Biochem 38:329, 2001

B = n = 17,298 (USA) Casey Obstet Gynecol 105:239, 2005

C = n = 115 (USA) Mestman ITC, 2005

D = n = 217 (Europe) Stricker AACCC, 2006

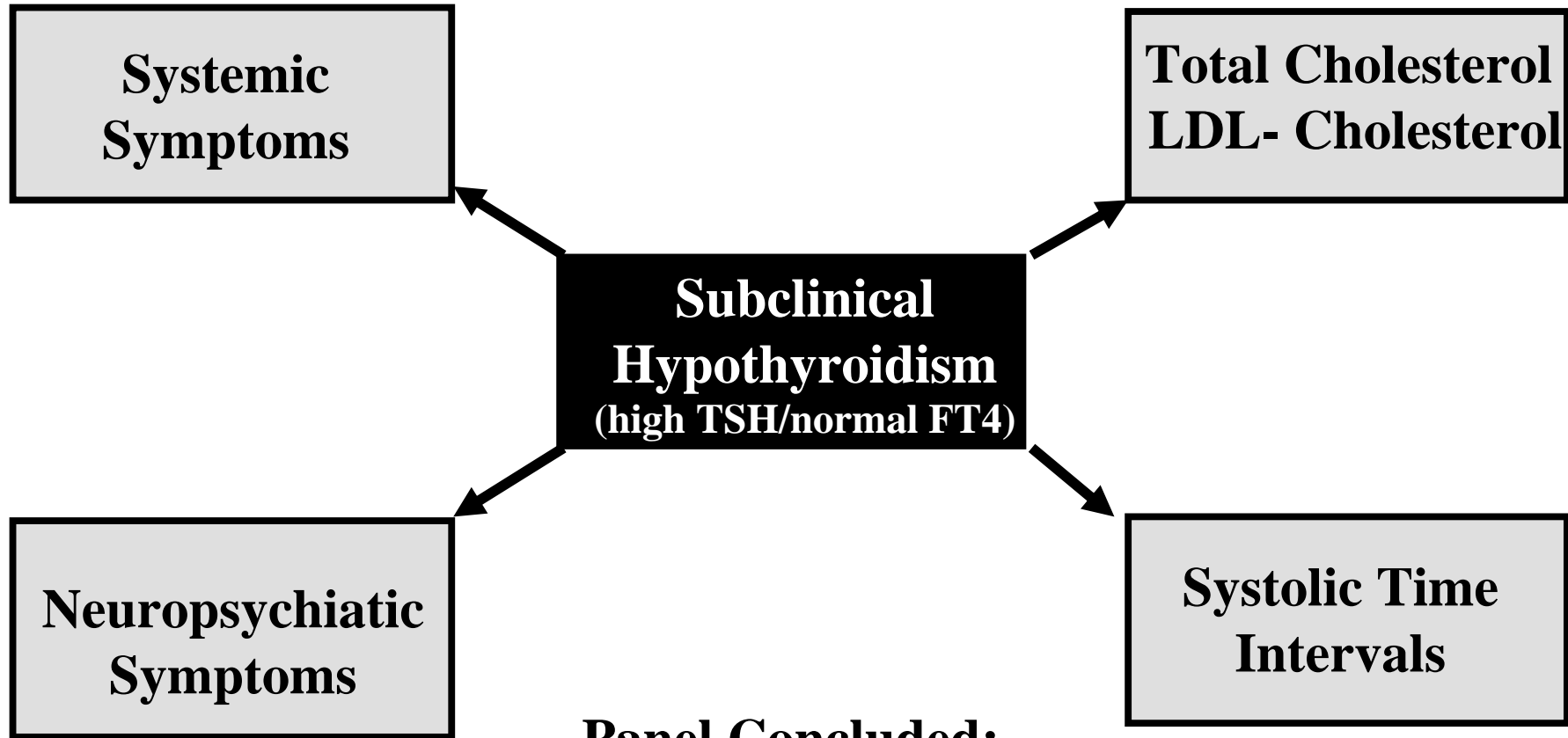
Question

In the non-pregnant patient,

do mild TSH abnormalities

(TSH > 3.0 mIU/L)

have any clinical significance?



Panel Concluded:

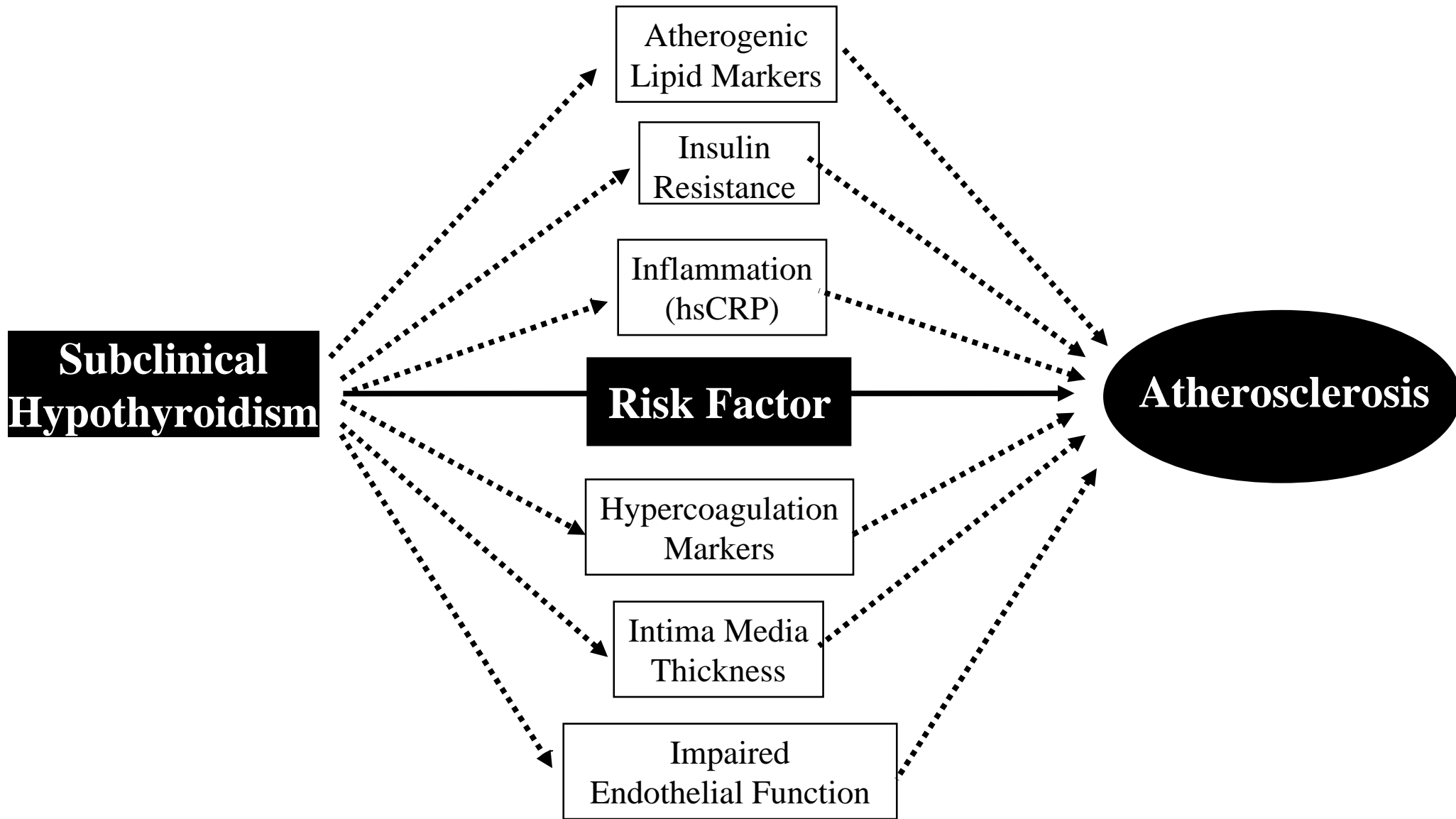
**“Few symptoms and little benefit
in treating Subclinical Hypothyroidism when TSH is < 10 mIU/L”**

2002 Subclinical Hypothyroidism (SCHO) Consensus Conference

Problems

- **Many studies were based on small numbers of subjects and most were not double-blinded, placebo-controlled trials.**
- **SCHO study groups often included individuals with different degrees of severity (i.e. subjects with TSH below & above 10 mIU/L were grouped).**
- **In some studies claiming a lack of a treatment response suboptimal L-T4 treatment was employed that failed to lower TSH below 3.0 mIU/L.**
- **Typically, insensitive parameters (like symptoms & Total Cholesterol) were used to judge the effects of SCHO.**

| Atherosclerosis Risk Factors | Associations with SCHO | # SCHO/contr. | Mean age | entry TSH (mean mIU/L) | mean TSH post Rx. L-T4 |
|--------------------------------------|-------------------------------|----------------------|-----------------|-------------------------------|-------------------------------|
| Atherogenic lipid markers | <i>Michalopoulou, 1998</i> | 26/35 | - | > 0.4 (2.8) | 1.4 (improved) |
| | <i>Meier, 2001</i> | 66/963 RCT | 57 | > 5.0 (12.8) | 3.1 (improved) |
| | <i>Kvetny, 2004</i> | 249/963 | 42 | > 2.9 (3.7) | |
| | <i>Dessein, 2004</i> | 14/55 | 59 | > 4.0 (5.1) | |
| | <i>Serter, 2004</i> | 30/26 | 39 | > 4.0 (6.2) | 1.4 (improved) |
| | <i>Monzani, 2004</i> | 45/32 | 35 | > 3.6 (6.0) | 1.3 (improved) |
| | <i>Milionis, 2005</i> | 28/30 | 54 | > 4.5 (9.9) | 1.6 (improved) |
| | <i>Iqbal, 2006</i> | 84/145 | 62 | > 4.0 (5.7) | 1.0 (improved) |
| Insulin Resistance | | 47 controls | 34 | > 0.2 (1.8) | |
| | <i>Bakker, 2001</i> | 14/55 | 59 | > 4.0 (5.1) | |
| | <i>Dessein, 2004</i> | | | | 3.1 (no effect) |
| Inflammation (hsCRP) | | 63/40 RCT | 57 | > 5.0 (9.9) | |
| | Christ-Crain, 2003 | 249/963 | 42 | > 2.9 (3.7) | |
| | Kvetny, 2004 | 77/80 | 34 | > 4.2 (7.4) | |
| | Tuzcu, 2005 | | | | |
| Hypercoagulation Markers | | 42/66 | 59 | > 4.0 (16.0) | 1.1 (improved) |
| | <i>Muller, 2001</i> | 35/30 | 42 | > 4.0 (8.7) | |
| | <i>Canturk, 2003</i> | | | | 1.3 (improved) |
| Intima Media Thickness | <i>Monzani, 2004</i> | 45/32 | 35 | > 3.6 (6.0) | |
| Impaired Endothelial Function | | 28/7 | 51 | > 2.0 (9.0) | 1.7 (improved) |
| | <i>Lekakis, 1997</i> | 14/28 | 39 | > 3.6 (7.7) | |
| | <i>Taddei, 2003</i> | 25/23 | 32 | > 4.5 (8.9) | |
| | <i>Cikim, 2004</i> | | | | |



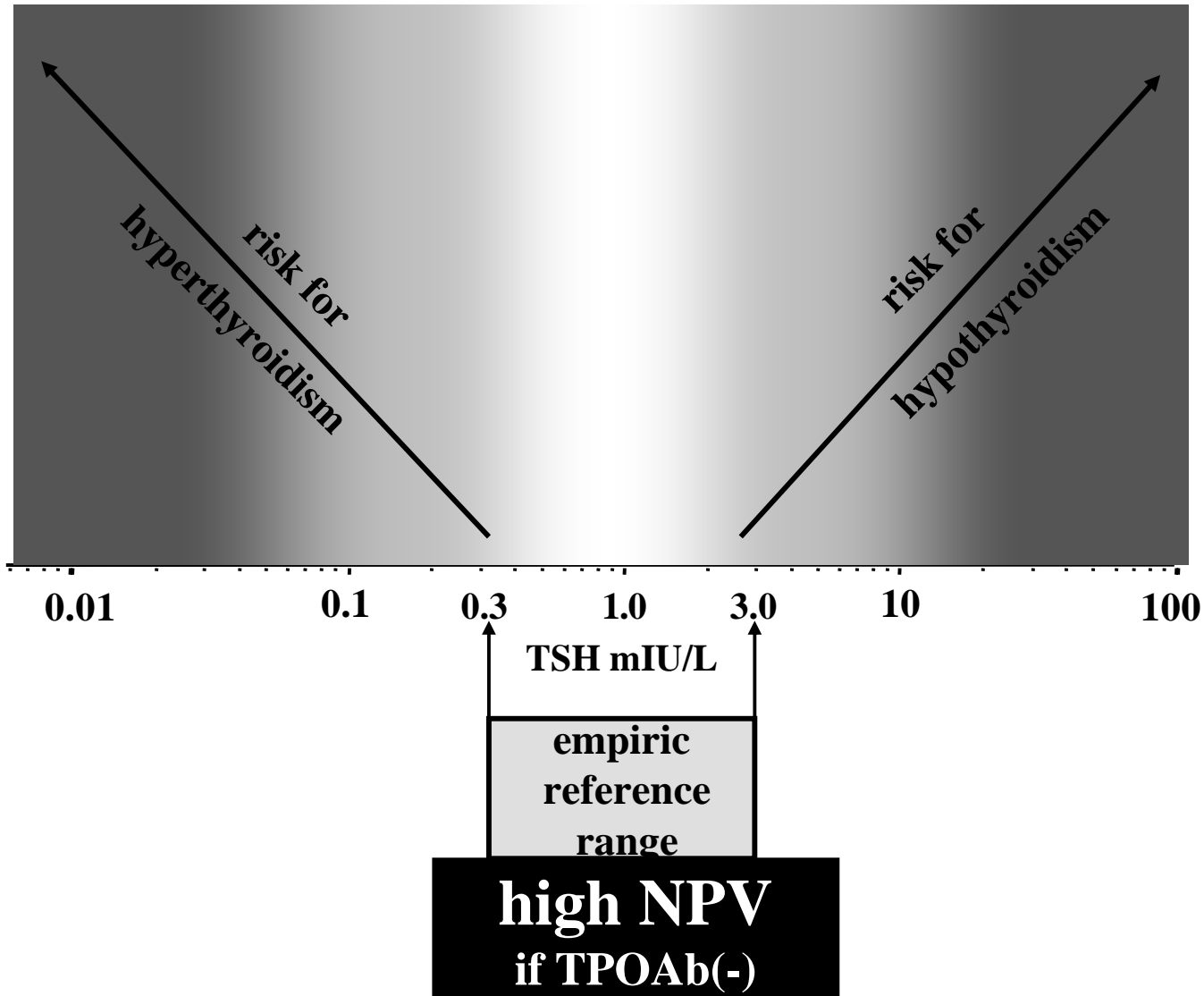
*There is wide between-subject differences in overall cardiovascular risk.
Subject selection (SCHO vs control) likely accounts for the variability among studies.*

Subclinical Thyroid Disease Consensus Panel

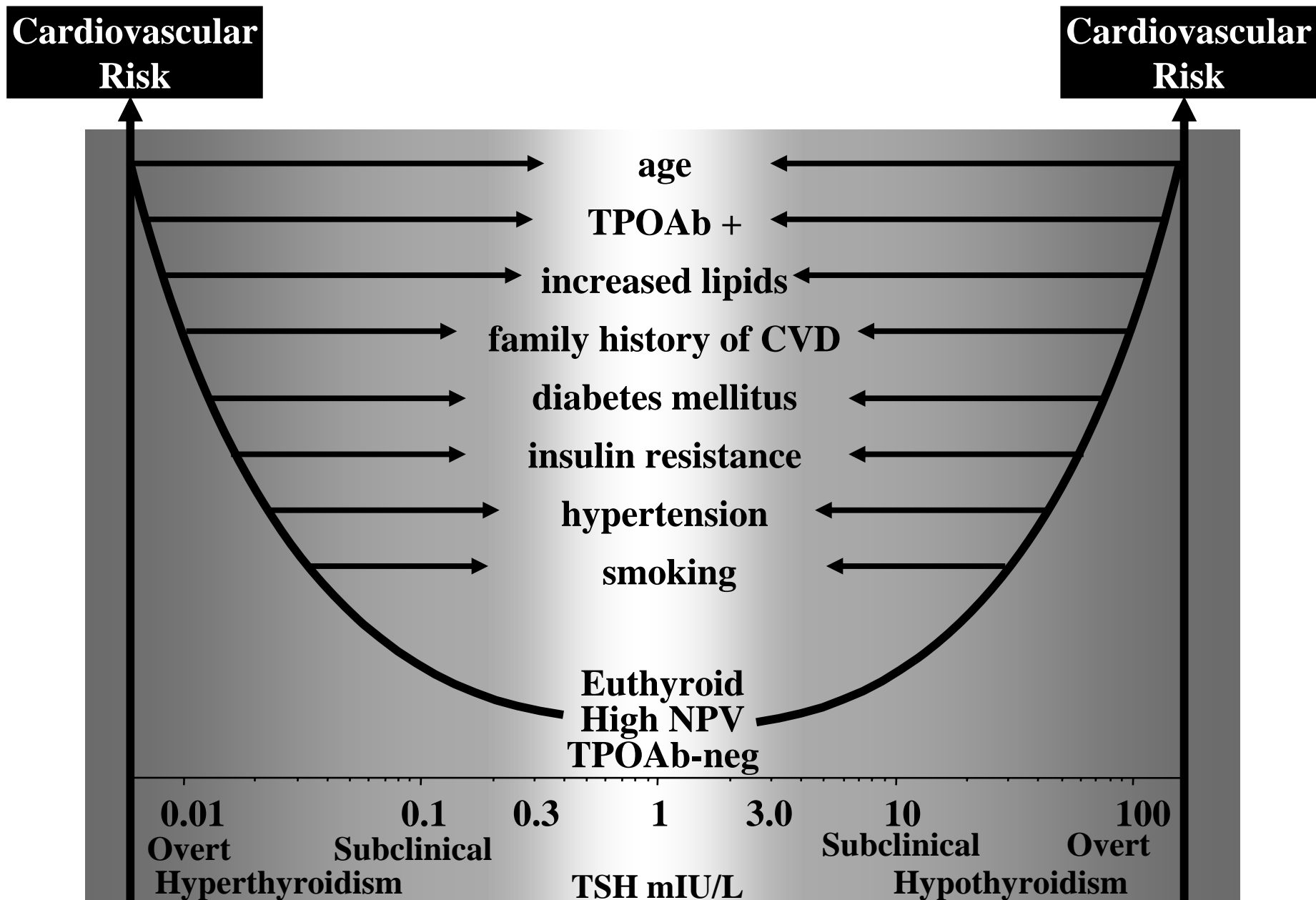
“There is no single level of serum TSH at which clinical action is always either indicated or contraindicated. The higher the TSH the more compelling is the rationale for treatment”.

“It is important to consider the individual clinical context (e.g. pregnancy, lipid profile, TPO antibodies)”.

Patients with TSH Outside the Empiric Reference Range Do Not Necessarily Need Treatment!



Threshold for Treatment Should be Adjusted for Patient-Specific Risk Factors



Threshold for Treatment Should be Patient-Specific!



- risk factors for cardiovascular disease**
- atherogenic lipid profile
 - cardiovascular disease
 - diabetes
 - insulin resistance (high BMI)
 - hypertension
 - ?????

Decision to treat is multifactorial

- Other Factors**
- Age
 - General health
 - Symptoms
 - Family history
 - Compliance
 - Patient preferences

TPOAb Concentration (risk factor for progression)

Conclusions

- **Each individual has their own TSH range that spans ~ 0.75 mIU/L. The population reference range is NOT an individual's 'normal range'**
- **95% of individuals in a population free of thyroid disease have TSH in the 0.3 to 2.5 mIU/L range.**
- **New Guidelines recommend that pregnant patients should have TSH below 2.5 mIU/L - this is critical in the 1st. trimester.**
- **There is growing data suggesting that mild subclinical hypothyroidism (TSH 3-10 mIU/L) can exacerbate the risk for cardiovascular disease in susceptible individuals.**
- **The presence of TPOAb increases the risk of progression to overt disease.**

Conclusions - Therapy

- **TSH is a labile hormone and any TSH abnormality should be confirmed before initiating therapy.**
- **There is no TSH level that either indicates or contraindicates the need for L-T4 therapy, although the higher the TSH the more compelling is the rationale to treat with L-T4.**
- **The threshold TSH for initiating therapy should be patient specific.**
- **The threshold for initiating therapy should be lower for patients with a history of cardiovascular disease, older patients, elevated lipids, hypertension, diabetes or planning pregnancy.**