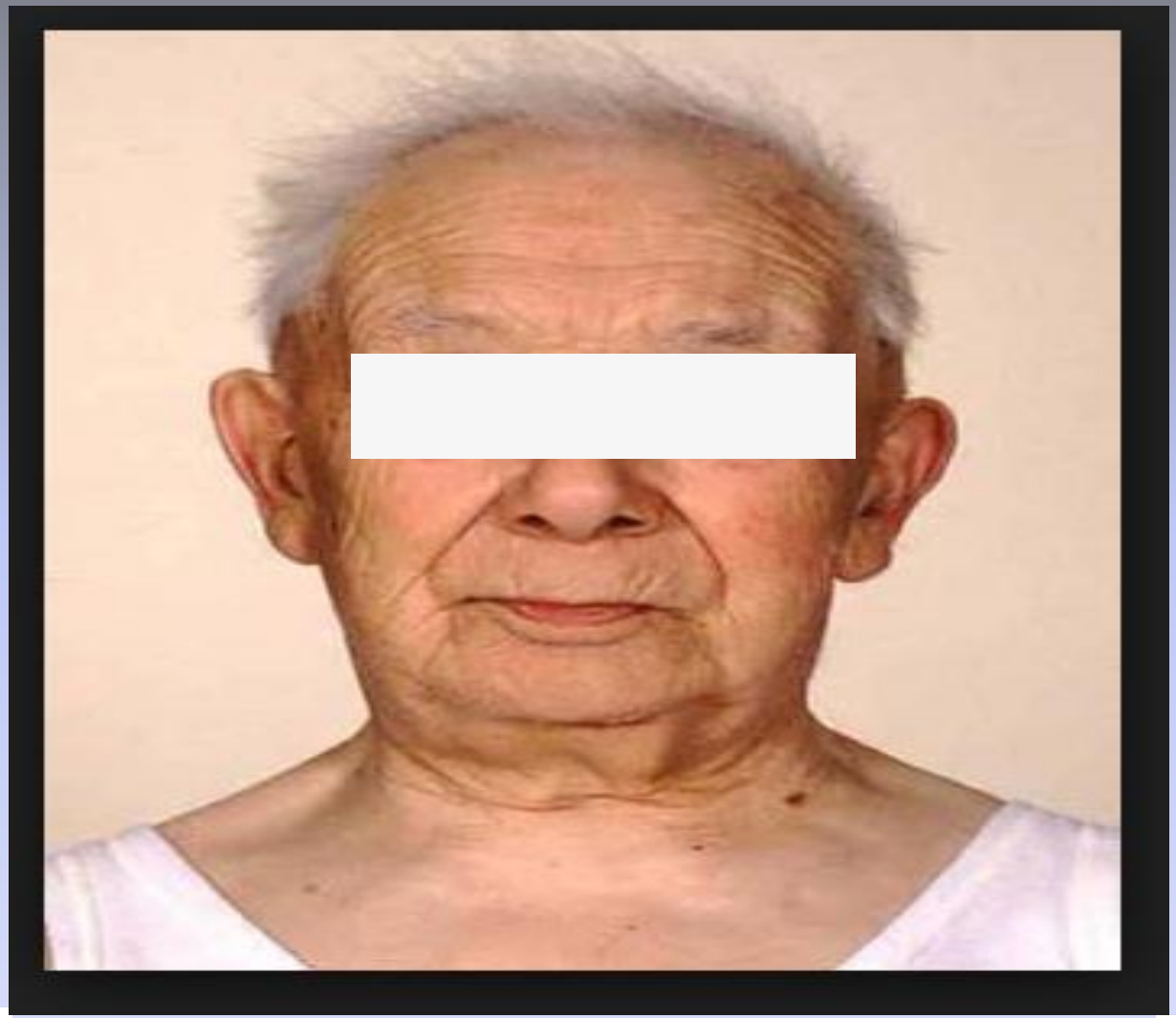
Thyroid disorders in the elderly



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K. Poppe Endocrinologie

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Agenda

- Physiology
- Subclinical hypothyroidism (TSH ↑)
- Subclinical Hyperthyroidism (TSH ↓)

Physiology

Thyroid and Aging or the Aging Thyroid?

Thyroid dysfunction in the elderly

Kristien Boelaert — *Nat. Rev. Endocrinol. 9, 194–204 (2013)*

Thyroid Hormone Signaling and Homeostasis During Aging

(Endocrine Reviews 34: 556–589, 2013)

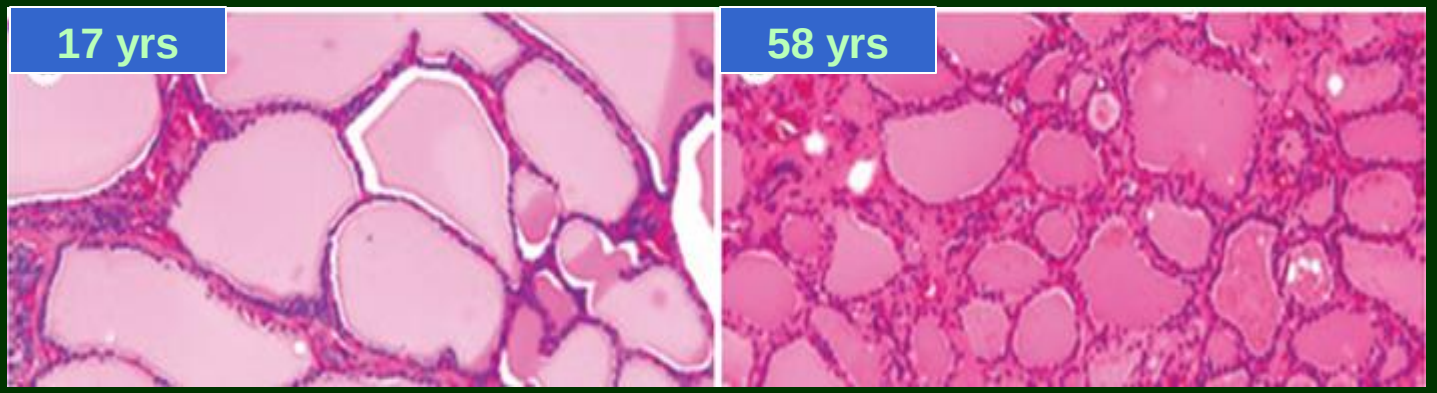
J. Bowers,* J. Terrien,* M. S. Clerget-Froidevaux, J. D. Gothié, M. P. Rozing, R. G. J. Westendorp, D. van Heemst, and B. A. Demeneix

Age-induced changes to thyroid

- Anatomical
  - nodularity
- HP Thyroid- axis
  - thyroid function (TH)
  - thyroid autoimmunity (TAI)

Anatomical changes

- A general trend is thyroid gland atrophy; characterized by a reduction in weight and size of follicles, a decrease in colloid content, and subtle degree of diffuse fibrous interstitial expansion (Figure 1).



… by contrast, several other studies have identified an increase in thyroid size and weight as well as higher incidences of nodular disease with advancing age.

Very high prevalence of thyroid nodules detected by high frequency (13 MHz) ultrasound examination

S. Guth, U. Theune, J. Aberle, A. Galach and C. M. Bamberger

Medical Prevention Center Hamburg at the University Medical Center Hamburg-Eppendorf, Hamburg, Germany

Eur J Clin Invest
2009; 39 (8): 699–706

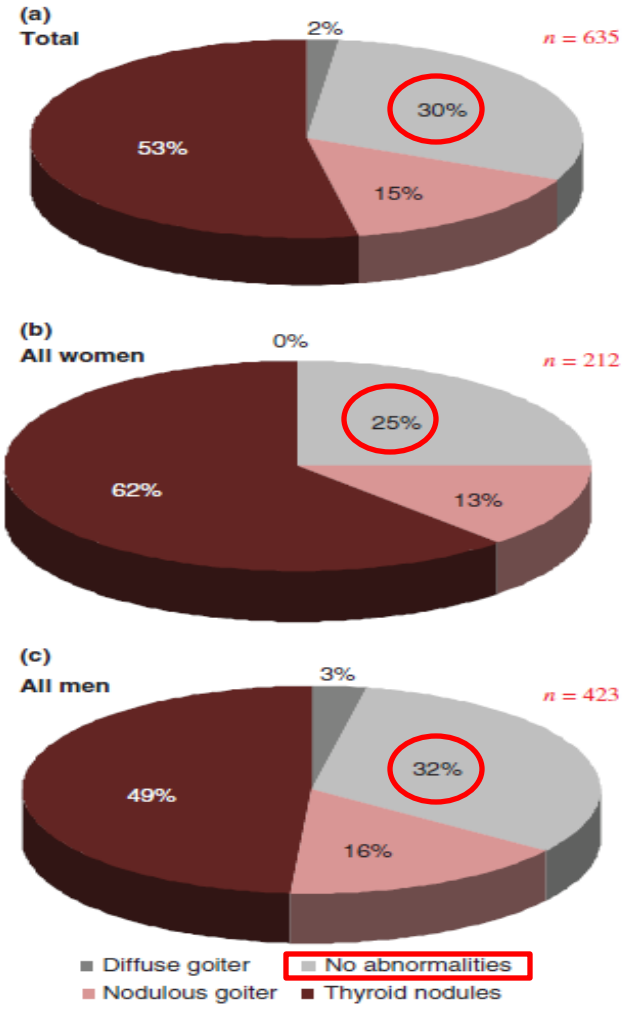


Figure 1 No abnormalities, diffuse goiter, nodulous goiter and non-goiter thyroid nodules in total and gender specific.

Table 1 Study population (age and gender distribution)

	Study population (*n*)	Minimum age (years)	Maximum age (years)	Medium age (years)
Female	212 (33%)	19	86	56·6 ± 11·8
Male	423 (67%)	27	93	56·8 ± 12·0
Total	635 (100%)	19	93	56·7 ± 11·9

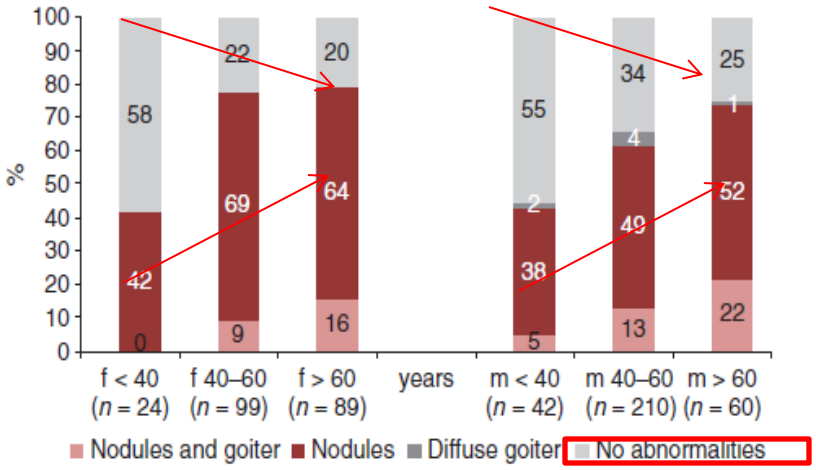


Figure 2 Prevalence of goiter, thyroid nodules and healthy thyroids in women and men of different age groups.

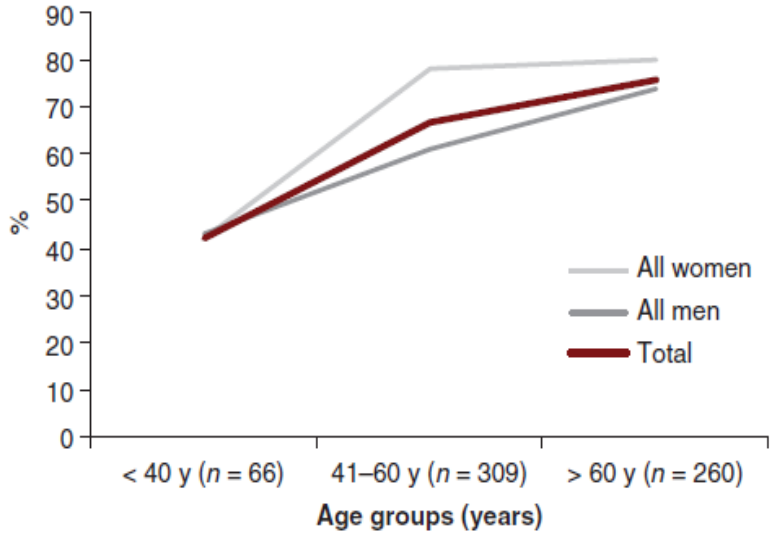


Figure 3 Increasing occurrence of thyroid nodules with age by gender and in total.

HPT axis changes

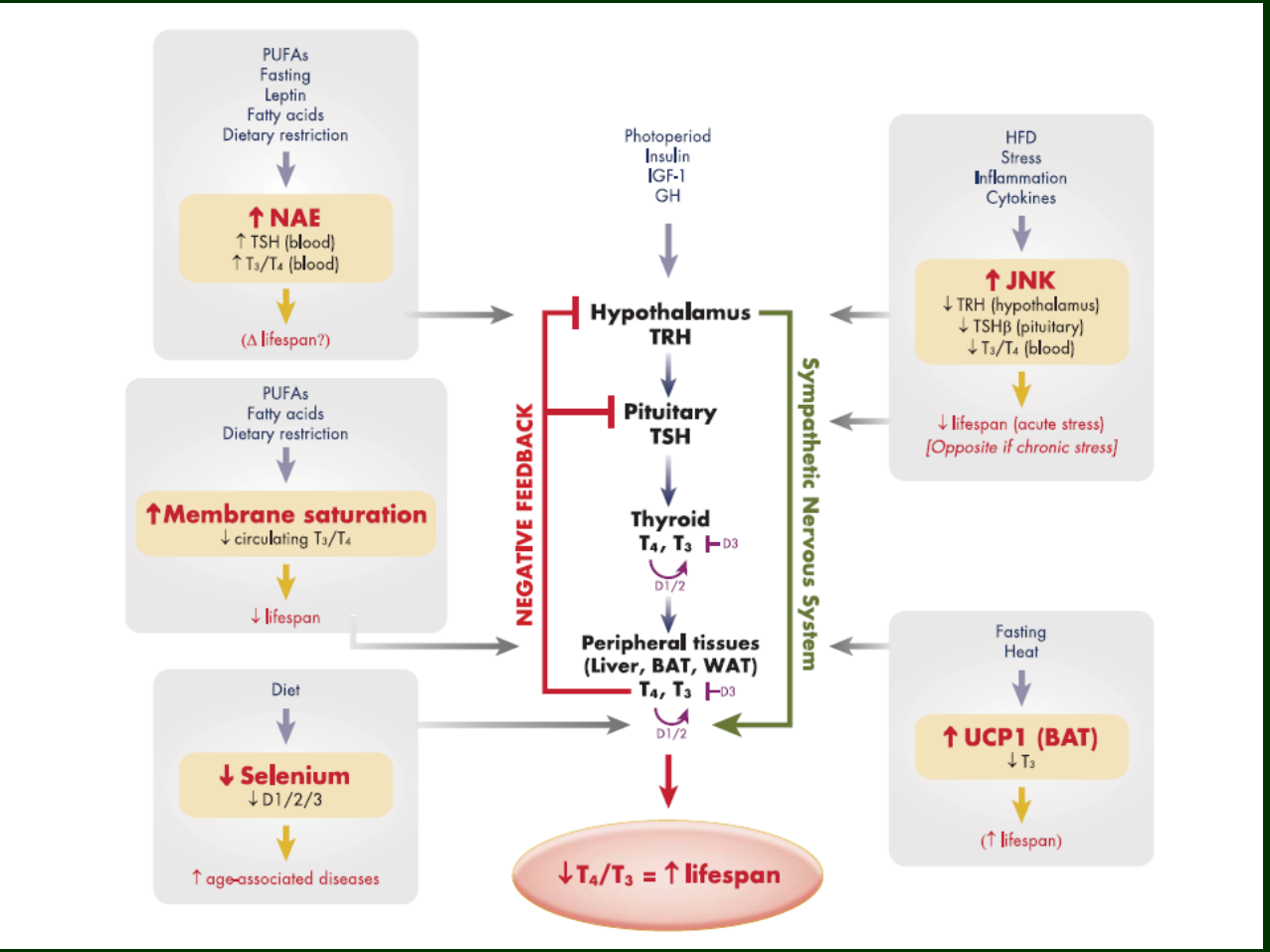


Figure 6. Schematic representation of integrated, age-related influences in the HPT axis activity. Stimulation of the hypothalamus results in TRH release, which increases TSH release from the pituitary. TSH acts to increase TH production and secretion from the thyroid gland. Hypothalamic signals can also directly influence peripheral tissues via the SNS. Low circulating TH levels are associated with longer life span. THs are secreted into the circulation, and they enter target tissues such as liver, BAT, and white adipose tissue (WAT), where they are locally activated by deiodinases D1 and D2 and deactivated by deiodinase D3. Deiodinases contain selenium, higher levels of which are associated with decreased aging-associated disease prevalence in adults. The influence of aging on the HPT axis is more profound in peripheral tissues than in the hypothalamus. Metabolic parameters (nutritional status, diet composition, etc), environmental conditions (food availability, ambient temperature), and immune stimuli will affect NAEs, JNK, and UCP1 activities as well as membrane saturation and then modulate the HPT axis in an integrative manner. The presence of NAEs influences pituitary activity, whereas JNK influences both the hypothalamus and the pituitary gland. Integration of photic and metabolic stimuli (such as insulin, GH/IGF-I) and their age-associated alterations occur at a central level and will therefore influence the functioning of the HPT axis. PUFAs, polyunsaturated fatty acids.

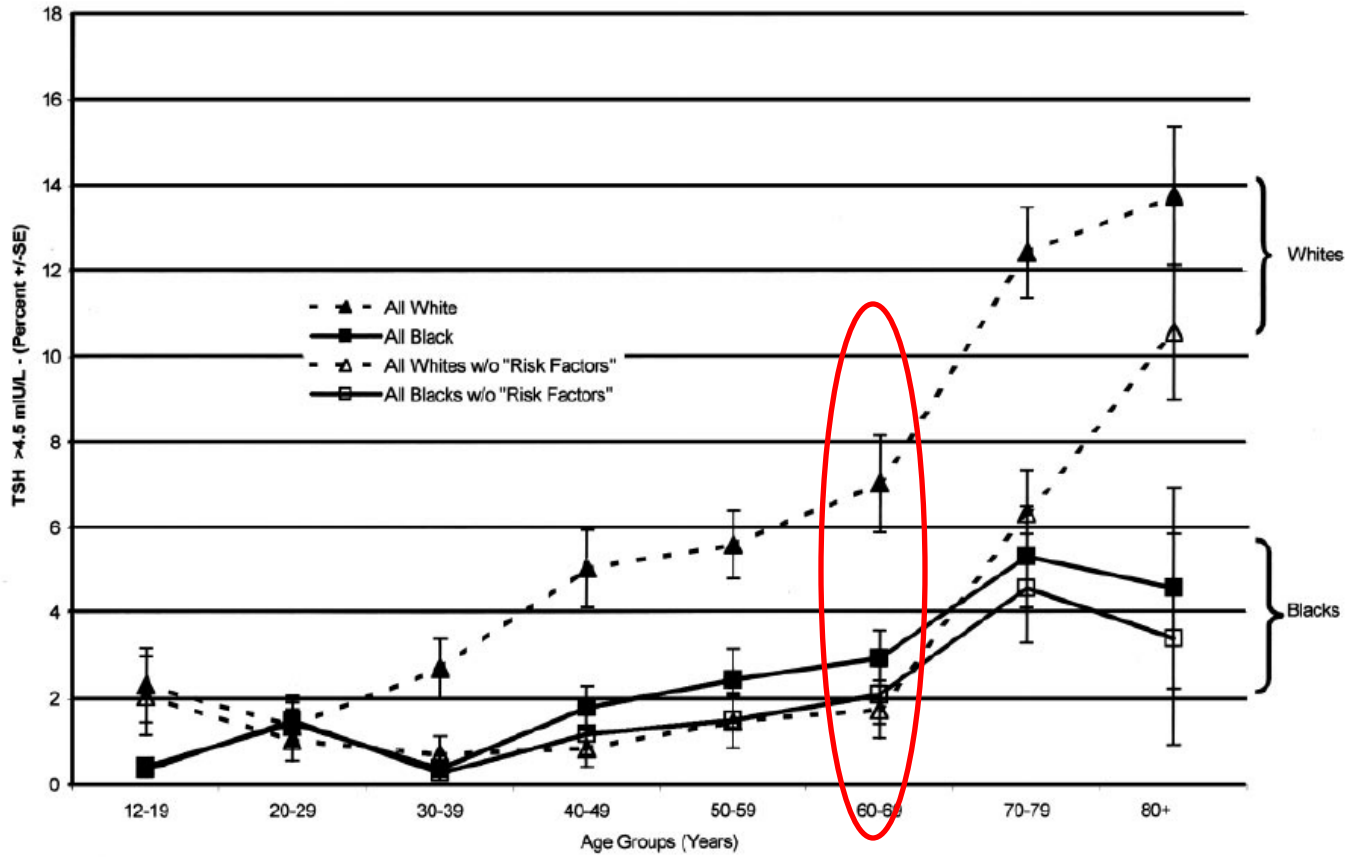
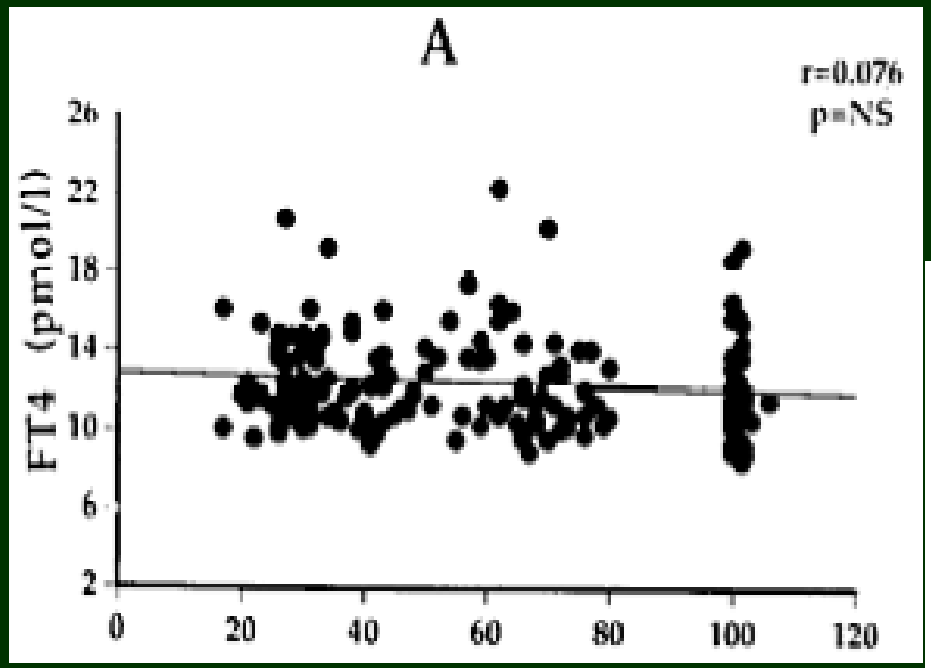
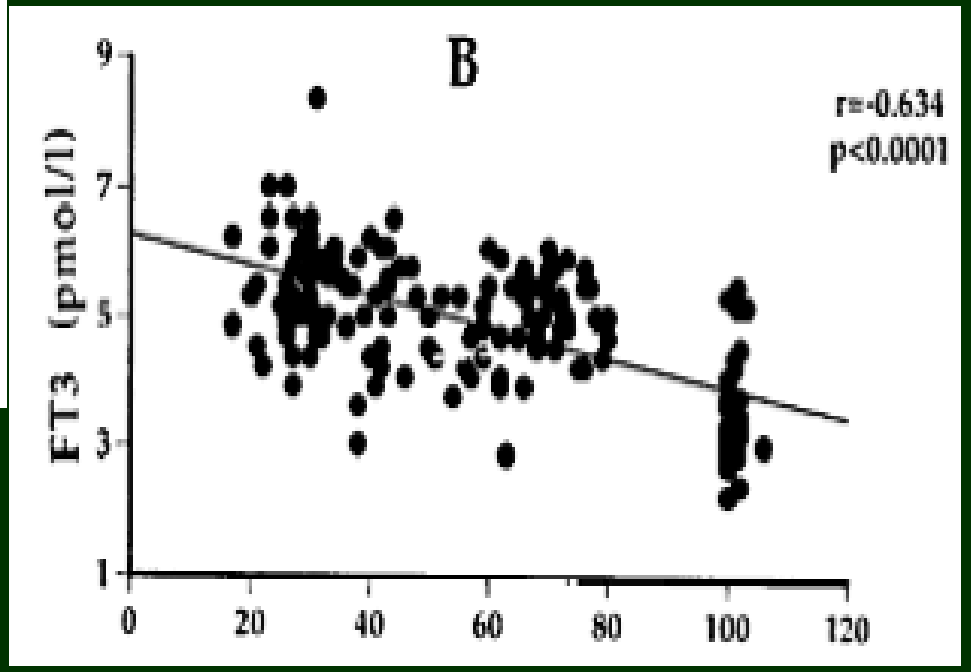


FIG. 4. Comparison of the effect of risk factors on high serum TSH (>4.5 mIU/liter) in blacks and whites. When comparing high TSH concentration in the disease-free population (excludes those people who have reported having thyroid disease, goiter, or taking thyroid medications) with the reference population (excludes those people who reported having thyroid disease, goiter, or taking thyroid medications and who do not have risk factors that include pregnancy, taking estrogen, androgens, or lithium, and are without the presence of thyroid antibodies or biochemical evidence of hypothyroidism or hyperthyroidism), the significant effect of risk factors in whites is not seen in blacks. In the reference population, the prevalence of high TSH in whites does not increase until age 70 yr.

Serum TSH, T(4), and thyroid antibodies in the United States population (1988 to 1994): National Health and Nutrition Examination Survey (NHANES III). Hollowell JG et al. JCEM 2002 87:489-99.



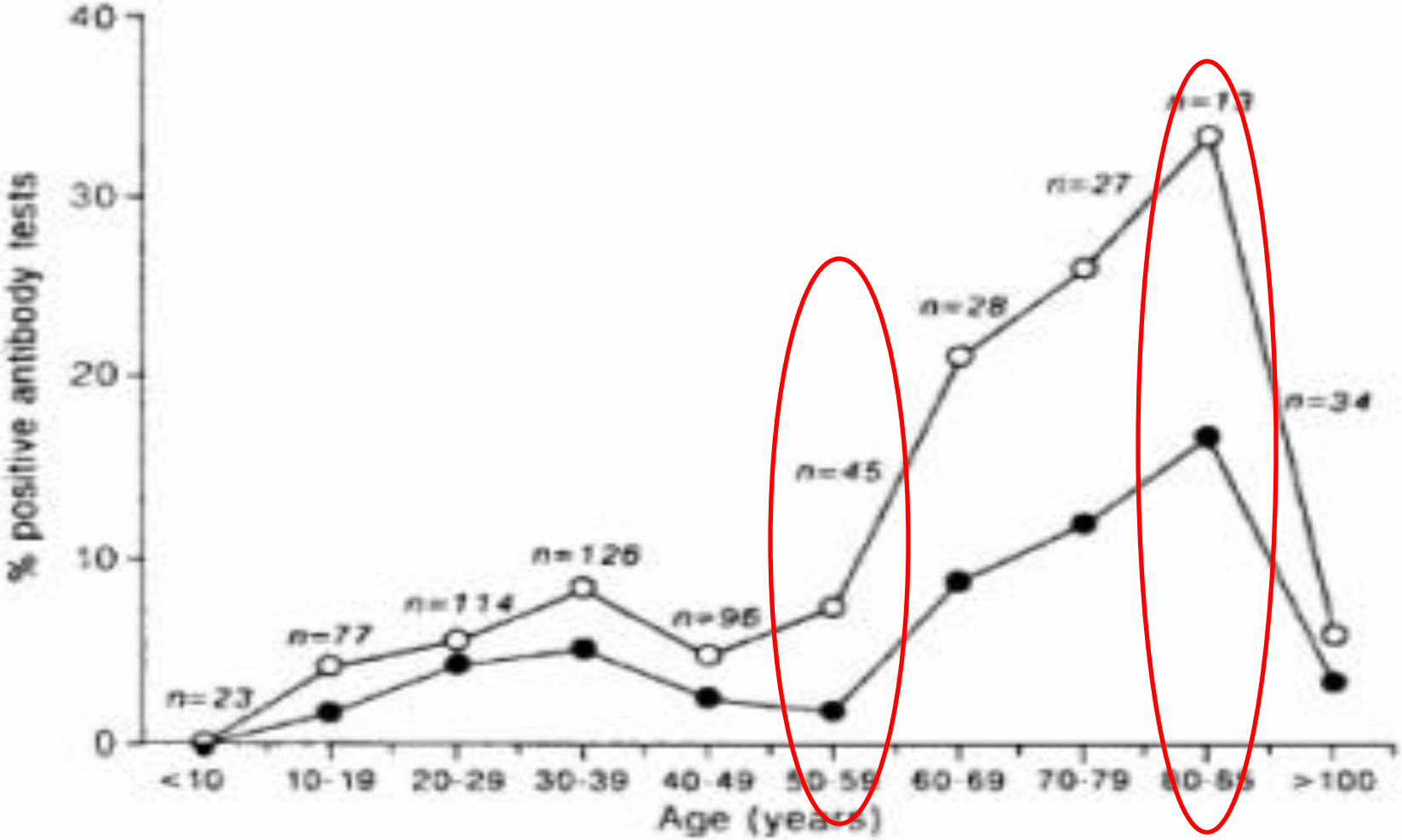


FT4 (and TT4) levels remain constant

Age related decline in T3 levels (ill people excluded)

Mariotti et al. JCEM 1993

Thyroid autoimmunity (TAI)



% positive TPO-Ab (0) and Tg-Ab in healthy people

Mariotti et al. Lancet 1992

Agenda

Subclinical hypothyroidism (TSH ↑)

Subclinical Hyperthyroidism (TSH ↓)

- **MORBIDITY**
  - General symptoms
  - Lipids
  - Atherosclerosis, Cardio Vascular aspects
  - Cognitive aspects
  - Frailty / Bone
- ***MORTALITY***

White slide =

- Definition
- Causes / Prevalence

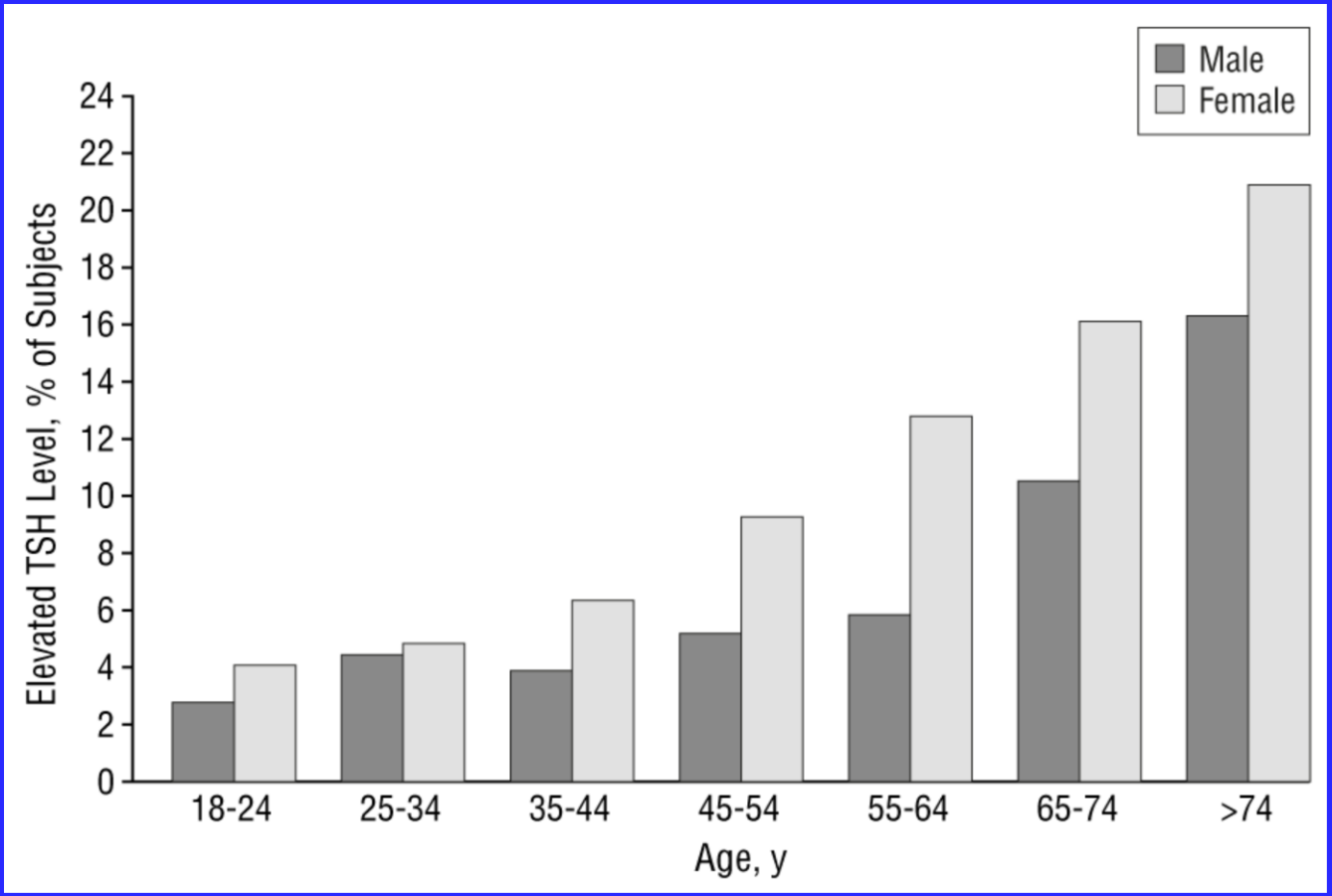
Subclinical hypothyroidism (SCH)

High serum TSH (above the upper limit of the assay)

&

Normal FT4

Prevalence



The Colorado Thyroid Disease Prevalence Study
Arch Intern Med. 2000

Causes of SCH

Table 2 Causes of SHypo and raised TSH levels

Causes	Details
Autoimmune hypothyroidism	Usually associated with positive thyroid autoantibodies and/or hypoechogenic appearance on ultrasound
Previously treated thyroid or neck disease	History of radioiodine or surgical treatment
Drugs	Lithium, amiodarone, anticonvulsants (due to increased T4 metabolism), interferon, sunitinib
Inadequate treatment of thyroid disease	Non-compliance, undertreatment with thyroid hormones, malabsorption, interaction with other substances (iron, calcium); overtreatment with antithyroid drugs
Transiently raised TSH levels	Non-thyroidal illness (recovery phase)
Systemic diseases with thyroid involvement	Sarcoidosis, amyloidosis, lymphoproliferative disorders, haemochromatosis
TSH receptor gene mutations	Several loss of function gene mutations have been found in non-autoimmune SHypo
Pituitary tumours secreting low bioactivity TSH	

SHypo, subclinical hyperthyroidism; TSH, thyroid stimulating hormone; T4, thyroxine.

Spontaneous evolution of SCH

In a study of 422,242 persons with SCH (5.5 to ≤10 mU/L), during 5 years FU, TSH **became normal in 62 % of patients.**

- normalization of serum TSH is more likely to occur in patients

*without TAI / *TSH <10 mU/l / *within the first 2 years after diagnosis

---

20 years FU study of the Wickham survey, evolution to **overt hypothyroidism**

4% / year in women with raised TSH and thyroid antibodies
3% / year if only TSH is raised
2% / year if only thyroid antibodies

Spontaneous normalization of thyrotropin concentrations in patients with subclinical hypothyroidism. Díez JJ, et al. JCEM 2005

Vanderpump et al., Clin Endocrinol, 1995

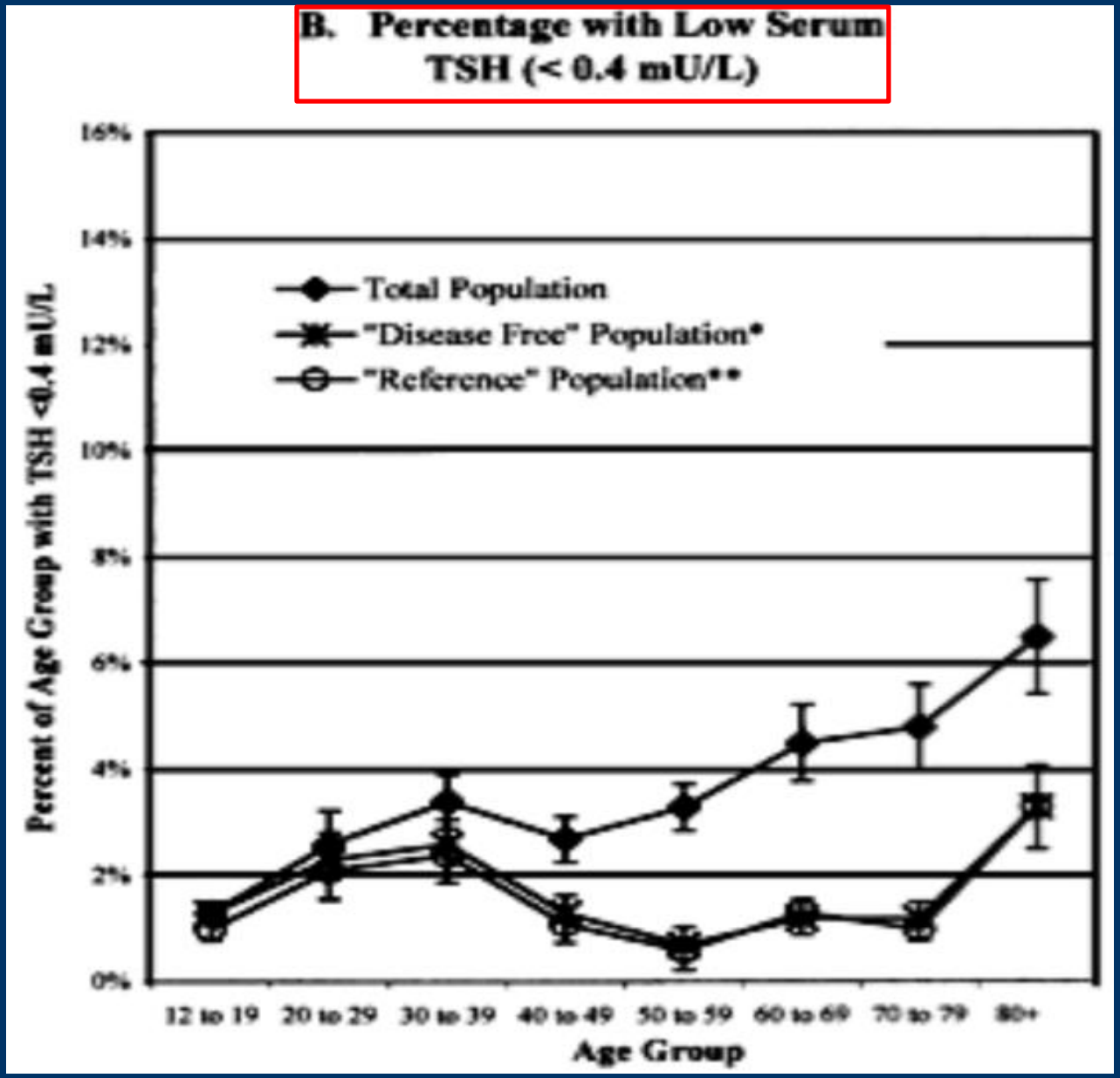
Subclinical Hyperthyroidism (sch)

Low serum TSH & Normal FT4 and FT3

Degrees of (s)hyperthyroidism

	Overt hyperthyroidism	T3 thyrotoxicosis	Grade II subclinical hyperthyroidism	Grade I subclinical hyperthyroidism
TSH	<0.1 mU/l	<0.1 mU/l	<0.1 mU/l	0.1-0.4 mU/l
FT4	Hi	Normal	Normal	Normal
FT3	Hi	Hi	Normal	Normal

Prevalence



NHANES III

Serum thyrotropin measurement in the community

- 422242 patients included
- No history or treatment for thyroid disorders
- 95 % normal TSH (0.35-5.5 mU/l)
- 1.2% decreased TSH (< 0.35 mU/l)
- 3 % were elevated TSH (> 5.5-10 mU/L)
- 0.7 % were highly elevated TSH (> 10 mu/l)

Serum thyrotropin measurements in the community: five-year follow-up in a large network of primary care physicians.
Meyerovitch J et al. Arch Intern Med. 2007

Causes

Thyrotoxicosis with hyperthyroidism (normal or high radioactive iodine uptake)	
Effect of increased thyroid stimulators	
TSH-receptor antibody	Graves' disease
Inappropriate TSH secretion	TSH-secreting pituitary adenoma; pituitary resistance to thyroid hormone
Excess hCG secretion	Trophoblastic tumours (choriocarcinoma or hydatidiform mole); hyperemesis gravidarum
Autonomous thyroid function	
Activating mutations in TSH receptor or $G_s\alpha$ protein	Solitary hyperfunctioning adenoma; multinodular goitre; familial non-autoimmune hyperthyroidism
Thyrotoxicosis without hyperthyroidism (low radioactive iodine uptake)	
Inflammation and release of stored hormone	
Autoimmune destruction of thyroid gland	Silent (painless) thyroiditis; post-partum thyroiditis
Viral infection*	Subacute (painful) thyroiditis (De Quervain thyroiditis)
Toxic drug effects	Drug-induced thyroiditis (amiodarone, lithium, interferon α)
Bacterial or fungal infection	Acute suppurative thyroiditis
Radiation	Radiation thyroiditis
Extrathyroidal source of hormone	
Excess intake of thyroid hormone	Excess exogenous thyroid hormone (iatrogenic or factitious)
Ectopic hyperthyroidism (thyroid hormone produced outside the thyroid gland)	Struma ovarii; functional thyroid cancer metastases
Ingestion of contaminated food	Hamburger thyrotoxicosis[1]
Exposure to excessive iodine	
Jod-Basedow effect	Iodine-induced hyperthyroidism (iodine, iodine-containing drugs, radiographic contrast agents)

TSH=thyroid-stimulating hormone. hCG=human chorionic gonadotropin. $G_s\alpha$=G protein alpha subunit. *Aetiology is not definitive.

Table 1. Clinical characteristics of the patients with hyperthyroid according to the different aetiologies

Aetiology	N	Sex (F/M)	Age† (years)	BMI† kg/m^2	Smoking Habit Current Smoker (%) /Previous or none smoker (%)	Clinical Signs, % (*n*)	Screening , % (*n*)
Graves' disease 1st episode	802	81%/19%	43 ± 14	23 ± 4	23/77	91 (732)	9 (69)
Graves' disease recurrence	350	89%/11%	44 ± 15	24 ± 4	22/78	83 (292)	15 (54)
Multinodular goitre	121	83%/17%	64 ± 16	26 ± 5	15/85	62 (75)	36 (44)
Toxic adenoma	69	78%/22%	59 ± 14	25 ± 5	12/88	64 (44)	36 (25)
Iatrogenic causes*	112	28%/72%	67 ± 13	26 ± 5	3/97	47 (53)	52 (58)
Sub-acute thyroiditis	40	88%/12%	43 ± 14	23 ± 4	21/79	83 (33)	17 (7)
Others	52	67%/33%	58 ± 19	25 ± 5	2/98	81 (42)	19 (10)

*(amiodarone, interferon) †mean ± SEM.

B. Goichot et al. Clinical presentation of hyperthyroidism in a large representative sample of outpatients in France: relationships with age, aetiology and hormonal parameters. Clin Endo 2016

Causes

Thyrotoxicosis with hyperthyroidism (normal or high radioactive iodine uptake)	
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Inflammation and release of stored hormone	
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Viral infection*	Subacute (painful) thyroiditis (De Quervain thyroiditis)
Toxic drug effects	Drug-induced thyroiditis (amiodarone, lithium, interferon α)
Bacterial or fungal infection	
Radiation	
Extrathyroidal source of hormone	
Excess intake of thyroid hormone	
Ectopic hyperthyroidism (thyroid ho produced outside the thyroid gland)	
Ingestion of contaminated food	
Exposure to excessive iodine	
Jod-Basedow effect	Iodine-induced hyperthyroidism (iodine, iodine-containing drugs, radiographic contrast agents)

Exogenous sch is more frequent than the endogenous variant.

Of those taking levothyroxine, 20–40% have a low serum TSH concentration.

TSH=thyroid-stimulating hormone. hCG=human chorionic gonadotropin. $G_s\alpha$=G protein alpha subunit. *Aetiology is not definitive.

High Frequency of and Factors Associated with Thyroid Hormone Over-Replacement and Under-Replacement in Men and Women Aged 65 and Over

JCEM 94: 1342–1345, 2009

Lily L. Somwaru, Alice M. Arnold, Neha Joshi, Linda P. Fried, and Anne R. Cappola

*Take home message

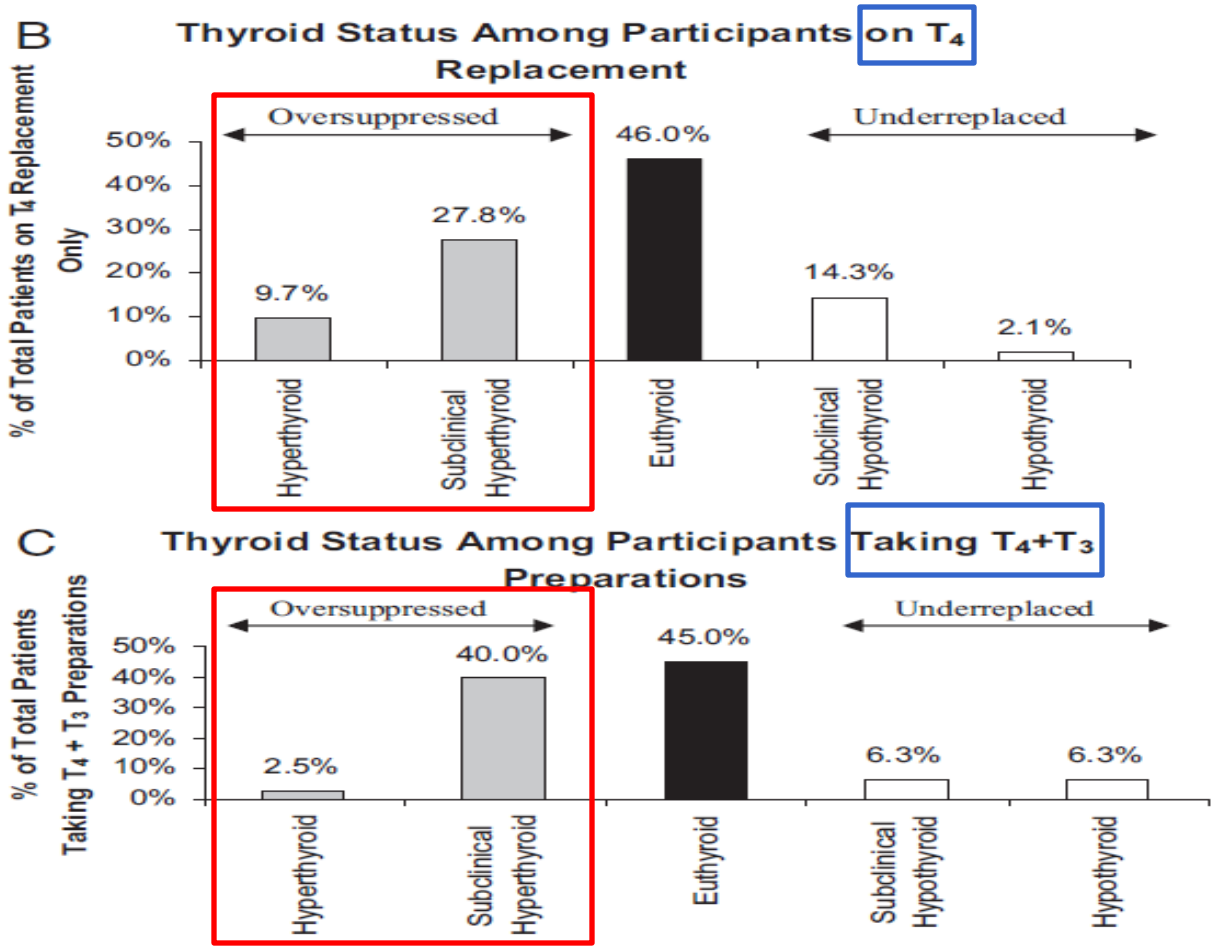


FIG. 1. Thyroid function tests among participants taking all types of thyroid hormone preparations (A), only T_4 preparations (B), and only T_4 plus T_3 preparations (C).

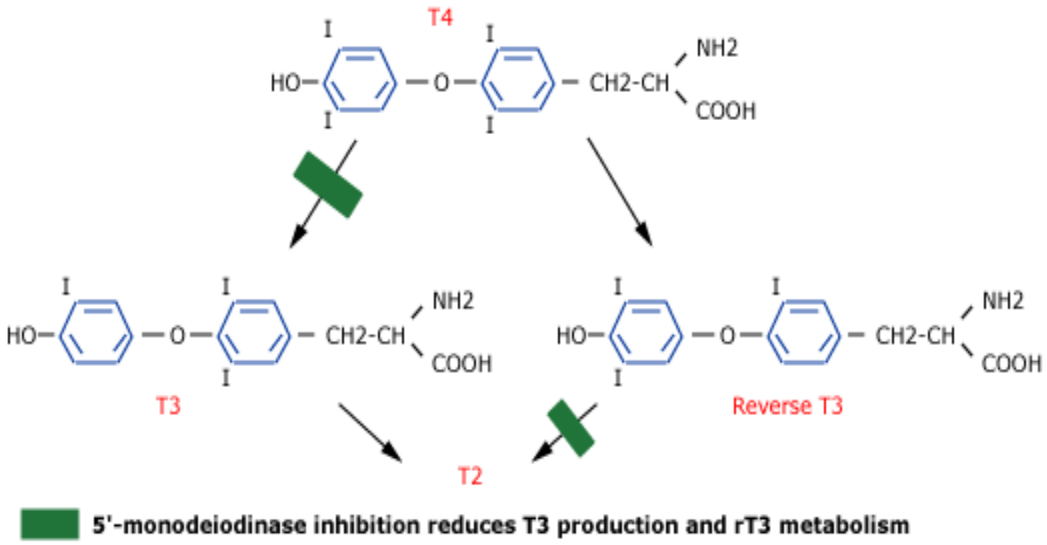
DD

1/ Confounding conditions

2/ Confounding factors

Drugs causing abnormal thyroid function tests without thyroid dysfunction
Low serum TBG - androgens, danazol, glucocorticoids, slow-release niacin (nicotinic acid), l-asparaginase
High serum TBG - estrogens, tamoxifen, raloxifene, methadone, 5-fluouracil, clofibrate, heroin, mitotane
Decreased T4 binding to TBG - salicylates, salsalate, furosemide, heparin (via free fatty acids), certain NSAIDs
Increased T4 clearance - phenytoin, carbamazepine, rifampin, phenobarbital
Suppression of TSH secretion - dobutamine, glucocorticoids, octreotide

T4 metabolism in nonthyroidal illness



The inhibition of 5'- monodeiodinase in nonthyroidal illness leads to decreased conversion of T4 to T3 and reduced metabolism of rT3.

rT3: reverse triiodothyronine; T2: diiodothyronine; T3: triiodothyronine; T4: thyroxine.

NTI

- ↑ cytokines
  - » IL-1, IL-6, TNF-α
  - » inhibiting 5'-D activity
  - » !! also an age-related increase in cytokines
- nutrition status
  - – starvation / low proteins, Se
  - – high corbohydrates, low leptine, low TRH

"protective" low T3 ?

Table 1 | Diagnostic tests of nonthyroidal illness vs subclinical hyperthyroidism

Laboratory tests	Nonthyroidal illness*	Subclinical hyperthyroidism‡
TSH	Normal or low or undetectable	Undetectable or low
Total T_4	Normal or low	Normal to high normal
Free T_4	Normal or low	Normal to high normal
Total T_3	Low	Normal to high normal
Free T_3	Low	Normal to high normal
Reverse T_3	High	Normal

*Take home message

« Try » NOT to determine thyroid function tests during a period of ilness, fever, corticoid treatment …

Evolution of SCH to HT

	Overt hyperthyroidism	T3 thyrotoxicosis	Grade II subclinical hyperthyroidism	Grade I subclinical hyperthyroidism
TSH	<0.1 mU/l	<0.1 mU/l	<0.1 mU/l	0.1-0.4 mU/l
FT4	Hi	Normal	Normal	Normal
FT3	Hi	Hi	Normal	Normal

12 months follow up

87% remained <0.1

76% returned to normal

Parle JV et al. 1991 Clin Endo

Work-up

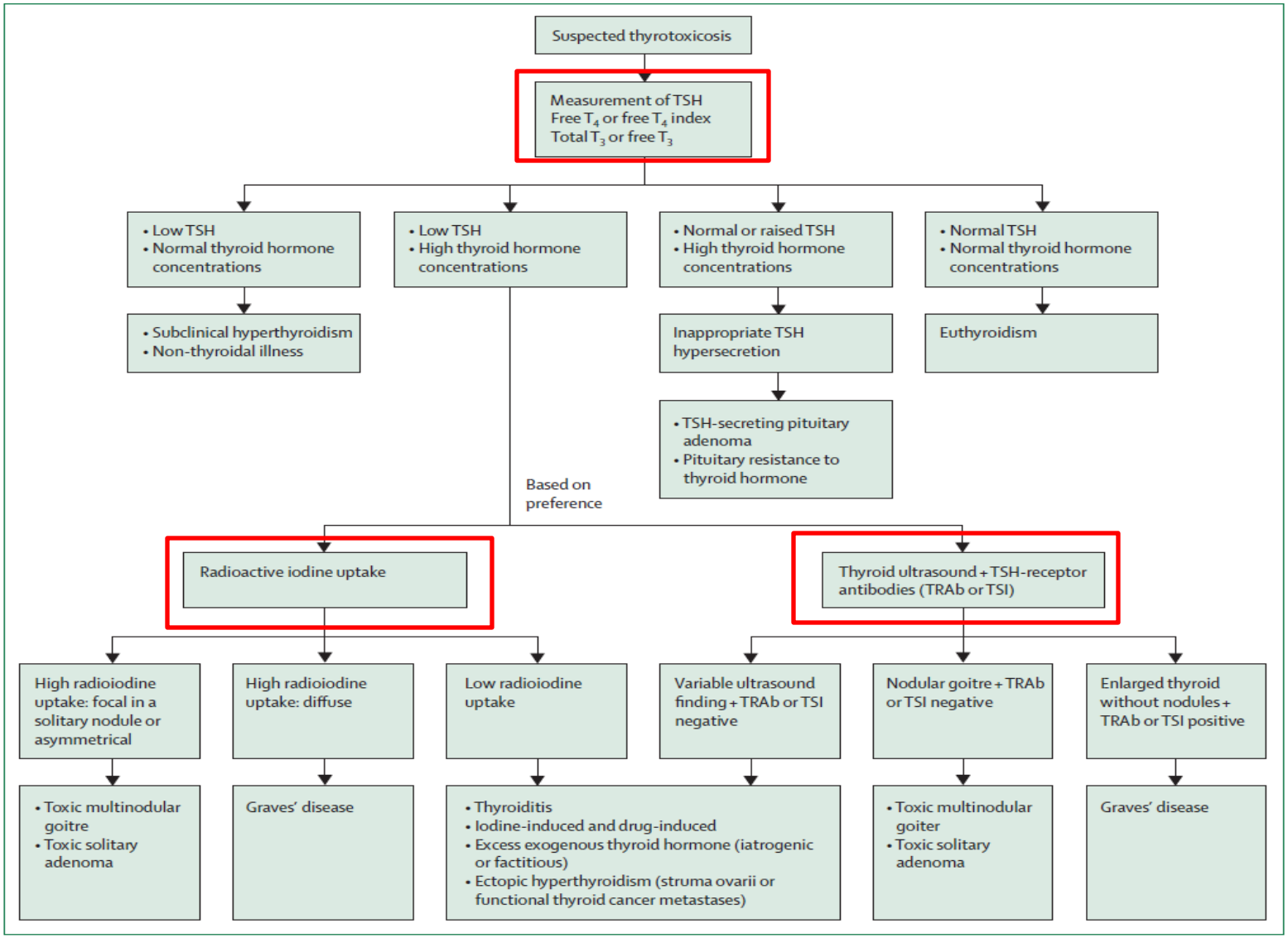


***Figure 2*: Algorithm for the assessment of thyrotoxicosis**
T_3=tri-iodothyronine. T_4=thyroxine. TRAb=TSH-receptor antibodies. TSH=thyroid-stimulating hormone. TRAb=TSH-receptor antibodies. TSI=thyroid-stimulating immunoglobulins.

SCH = high serum TSH (above reference range) and normal FT4

sch = low serum TSH (under reference range/ suppressed) with normal FT4 and FT3

Think about the degrees of sch!

Don’t measure TT in sick patients

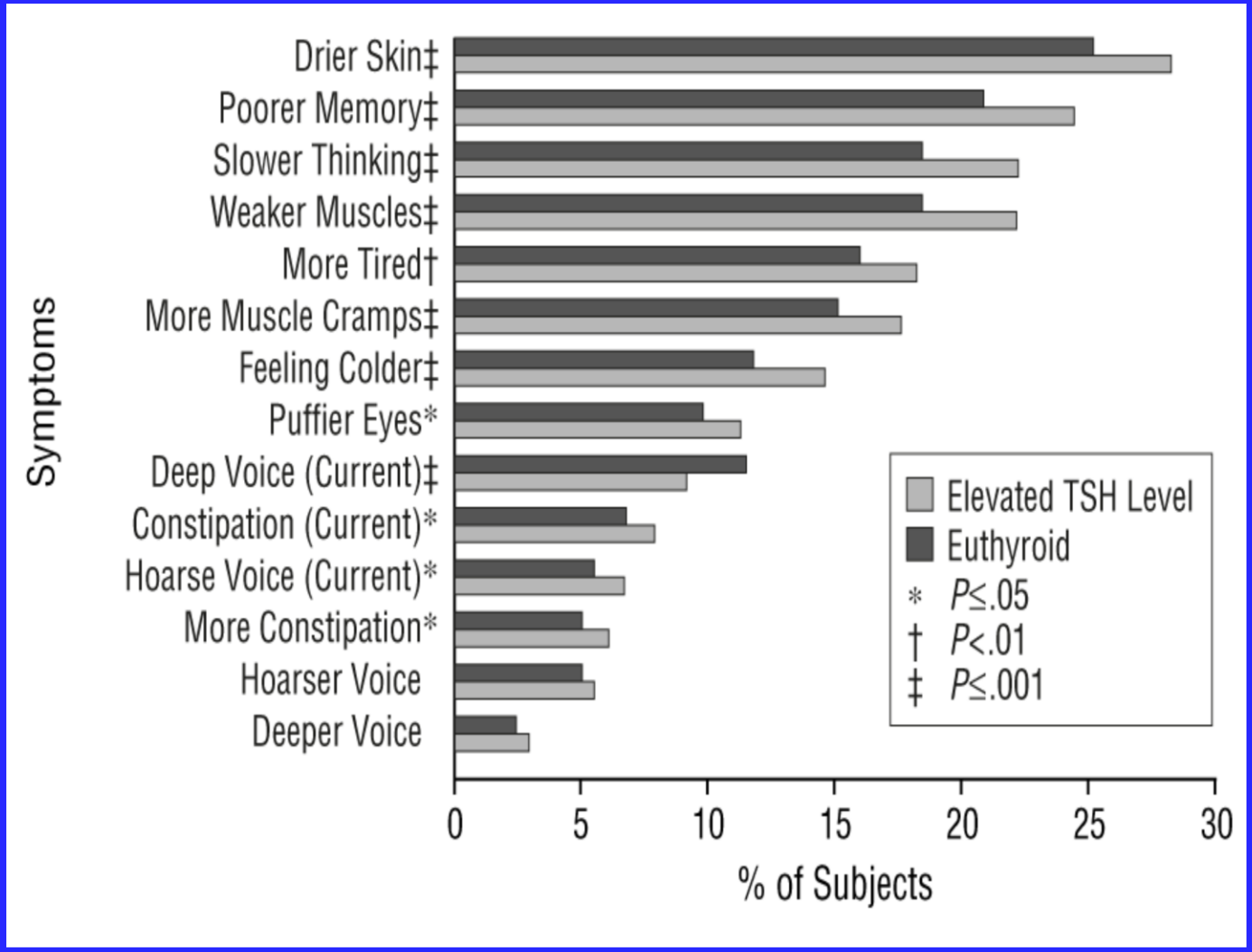
Check sligthly high/low TSH levels 2-3 months later, before starting a treatment

Think about interfering medications ≠ thyroid disease

- **Associations / Treatment evidence**

- **MORBIDITY**
  - General symptoms
  - Lipids
  - Atherosclerosis, Cardio Vascular aspects
  - Cognitive aspects
  - Frailty / Bone
- ***MORTALITY***

- General symptoms

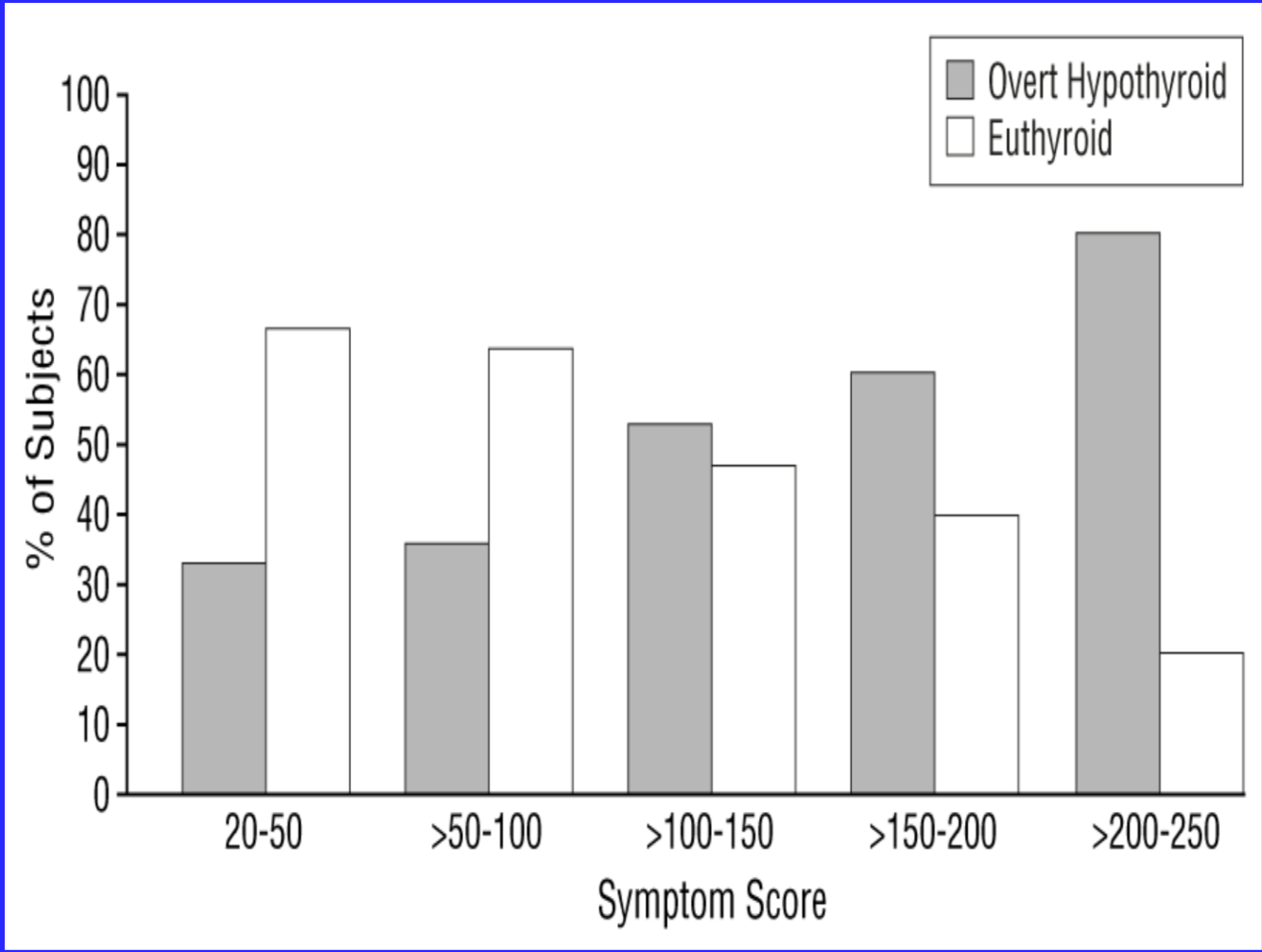


Ravzi et al. J Clin Pathol 2010

Table 6. Individual Symptoms*

Symptom	Sensitivity, %	Specificity, %
Current symptoms		
Hoarse voice	6.7	94.5
Deep voice	9.2	88.5
Constipation	7.9	93.1
Changed symptoms		
Hoarser voice	5.5	95.0
Deeper voice	2.9	97.6
Drier skin	28.3	74.7
Feeling colder	14.6	88.2
More tired	18.3	84.0
Puffier eyes	11.3	90.2
More muscle cramps	17.6	84.9
Weaker muscles	22.2	81.5
More constipation	6.1	95.0
Slower thinking	22.3	81.5
Poorer memory	24.5	79.1

** Total population, elevated thyrotopin level vs euthyroid.*


Overt Hypothyroid
Euthyroid
% of Subjects
100
90
80
70
60
50
40
30
20
10
0
20-50
>50-100
>100-150
>150-200
>200-250
Symptom Score

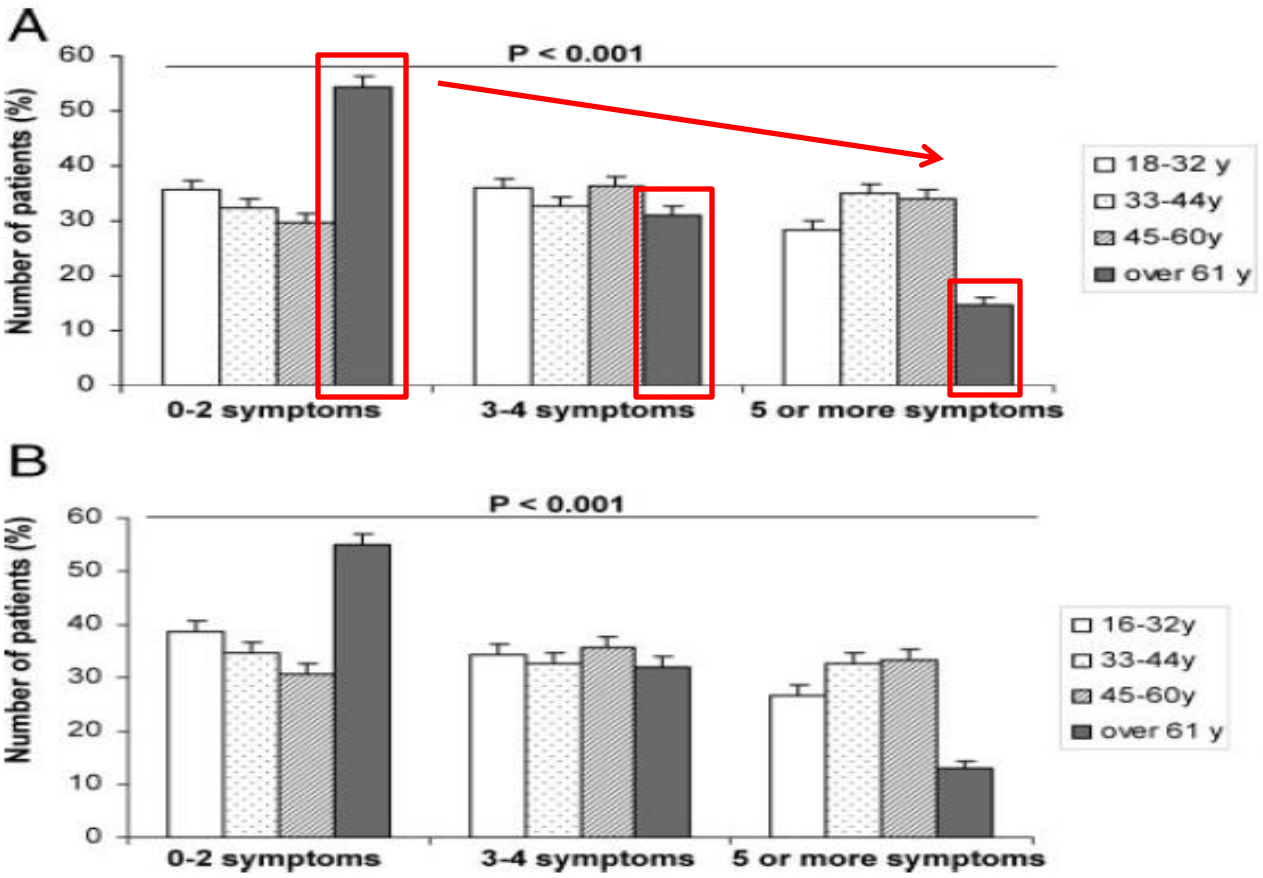


FIG. 1. A, Number of symptoms of hyperthyroidism reported by patients in the respective age groups, indicating that the majority of patients aged older than 61 yr reported a maximum of two symptoms. The lowest proportion of patients reporting five or more symptoms was found in patients older than 61 yr. B, Number of symptoms of hyperthyroidism reported by patients after exclusion of those taking β-blockers or amiodarone.

Boelaert, K., et al. Older individuals with hyperthyroidism present with a paucity of symptoms and signs: a large cross-sectional study. JCEM 2010.

Clinical Endocrinology (2016) 84, 445–451 doi: 10.1111/cen.12816

ORIGINAL ARTICLE

Clinical presentation of hyperthyroidism in a large representative sample of outpatients in France: relationships with age, aetiology and hormonal parameters

B. Goichot*,†, Ph. Caron‡, F. Landron§ and S Bouée¶

Table 4. Influence of age on clinical symptoms and signs of hyperthyroidism

	<65 years old	≥65 years old	*P*-value
	1301	269	
Palpitations	965 (76·0%)	135 (54·4%)	<0·0001
Asthenia	949 (74·7%)	170 (68·5%)	0·0433
Gastrointestinal signs	351 (27·6%)	52 (21·0%)	0·0296
Heat intolerance. polydypsia. excess sweating	692 (54·5%)	74 (29·8%)	<0·0001
Sleep disturbance	543 (42·8%)	70 (28·2%)	<0·0001
Other symptoms	471 (37·1%)	78 (31·5%)	0·0912
Cardiac dysrhythmias. atrial fibrillation or others	134 (11·8%)	77 (33·9%)	<0·0001
Weight loss %	734 (64·6%)	151 (66·5%)	0·5714
Weight loss in kg (standard deviation)	5·9 (4·2)	6·3 (4·2)	0·1932
Tachycardia	780 (68·6%)	100 (44·1%)	<0·0001
Beats/minute	102·1 (14·9)	99·4 (17·8)	0·0366
Visible goitre	437 (38·4%)	35 (15·4%)	<0·0001
Other physical signs	135 (11·9%)	28 (12·3%)	0·8449

European Journal of Endocrinology (2005) 153 747–753 ISSN 0804-4643

CLINICAL STUDY

Cognitive functioning and well-being in euthyroid patients on thyroxine replacement therapy for primary hypothyroidism

Ellie M Wekking, Bente C Appelhof[1], Eric Fliers[1], Aart H Schene, Jochanan Huyser, Jan G P Tijssen[2] and Wilmar M Wiersinga[1]

Department of Psychiatry, [1]Department of Endocrinology and Metabolism, and [2]Department of Cardiology, Academic Medical Centre, University of Amsterdam, Amsterdam, The Netherlands

Abstract

Objective: Hypothyroidism is associated with neurocog.nitive impairment. Sparse data suggest that treatment of hypothyroidism, resulting in a return to euthyroidism, may be associated with only partial recovery of overall neurocognitive functioning. The aim of this study was to assess neurocognitive functioning and well-being in euthyroid patients with primary hypothyroidism on adequate thyroxine (T4) treatment. We also investigated whether serum TSH and thyroid antibodies are determinants of neurocognitive functioning and well-being.

Design: We assessed neurocognitive functioning and well-being in 141 patients with primary hypothyroidism.

Methods: Neurocognitive test results and scores on questionnaires measuring well-being of 141 patients were compared with the reference values for these tests as published and used in Dutch clinical neuropsychological practice. Assessment of neurocognitive functioning included tests for cognitive or psychomotor speed, attention, working memory as well as learning and memory. Well-being was measured with the Symptom Check List-90 total score and the Rand 36-item Health Survey subscales for 'mental health' and 'vitality'.

Results: Patients showed poor performance on various domains of neurocognitive functioning compared with mean standard reference values, especially on a complex attention task and on verbal memory tests. Levels of well-being were significantly lower for patients compared with those of the general population. Neither serum TSH nor thyroid antibodies were determinants of neurocognitive functioning and well-being.

Conclusion: The results of this study suggest that neurocognitive functioning as well as psychological well-being may not be completely restored in patients with hypothyroidism, despite T4 treatment.

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Copyright © 2006 by The Endocrine Society
doi: 10.1210/jc.2005-1775

Neuropsychological Function and Symptoms in Subjects with Subclinical Hypothyroidism and the Effect of Thyroxine Treatment *(mean age 60 years)*

Rolf Jorde, Knut Waterloo, Hilde Storhaug, Audhild Nyrnes, Johan Sundsfjord, and Trond Geir Jenssen

Institute of Clinical Medicine (R.J., K.W.), University of Tromsø, 9037 Tromsø, Norway; Departments of Internal Medicine (H.S., A.N.) and Clinical Chemistry (J.S.), University Hospital of North Norway, 9038 Tromsø, Norway; and Department of Nephrology (T.G.J.), National Hospital, 0027 Oslo, Norway

Conclusion:

In subjects with SHT (TSH in the 3.5–10.0 mIU/L range), there is no neuropsychological dysfunction, compared with healthy controls

! T4 substitution had no effect on any of the parameters measured

Symptoms are less frequent in older patients and not-sensitive for thyroid dysfunction

- Lipids

Colorado survey: statistically higher total and LDL cholesterol in subjects with mild thyroid failure vs. euthyroid subjects (TC 224 mg/dl, vs.216 mg/dl)

Canaris et al., 2000 Arch Intern Med 160(4):526-34

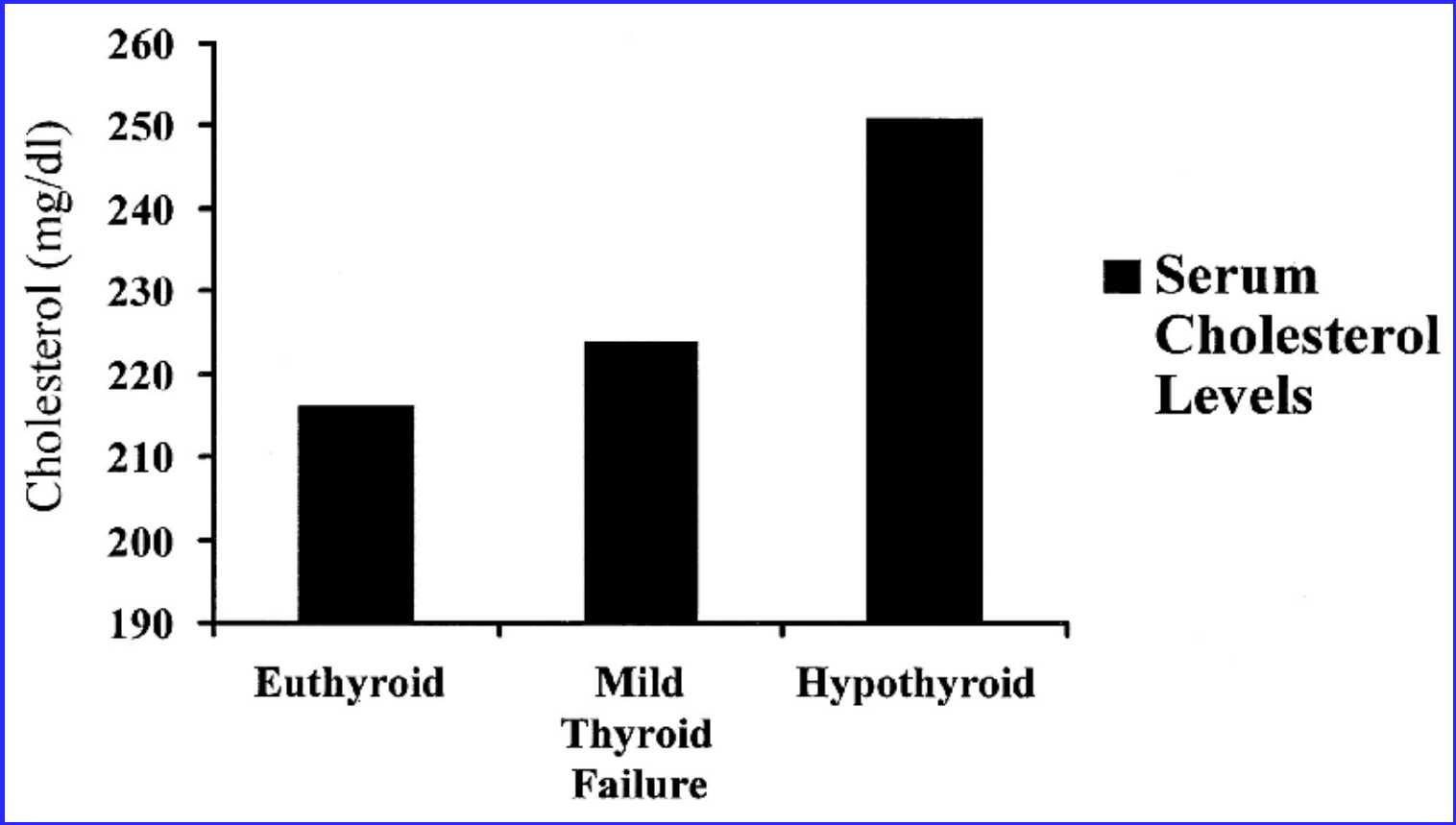

Table 3. Mean Lipid Levels by Disease State*

Disease State	Total Cholesterol,† mmol/L (mg/dL)	LDL Cholesterol,† mmol/L (mg/dL)	HDL Cholesterol, mmol/L (mg/dL)	Triglycerides,‡ mmol/L (mg/dL)
Hypothyroid	6.5 (251)	4.4 (170)	1.4 (53)	2.0 (180)
Subclinical hypothyroid	5.8 (224)	3.8 (146)	1.4 (53)	1.8 (156)
Euthyroid	5.6 (216)	3.6 (140)	1.3 (51)	1.7 (147)
Subclinical hyperthyroid	5.4 (210)	3.4 (131)	1.5 (56)	1.6 (141)
Hyperthyroid	5.2 (202)	3.4 (130)	1.3 (50)	1.6 (140)

*LDL indicates low-density lipoprotein; HDL, high-density lipoprotein.
†Trend analysis, P<.001.
‡Trend analysis, P = .02.

The Colorado Thyroid Disease Prevalence Study Arch Intern Med. 2000

Treatment evidence

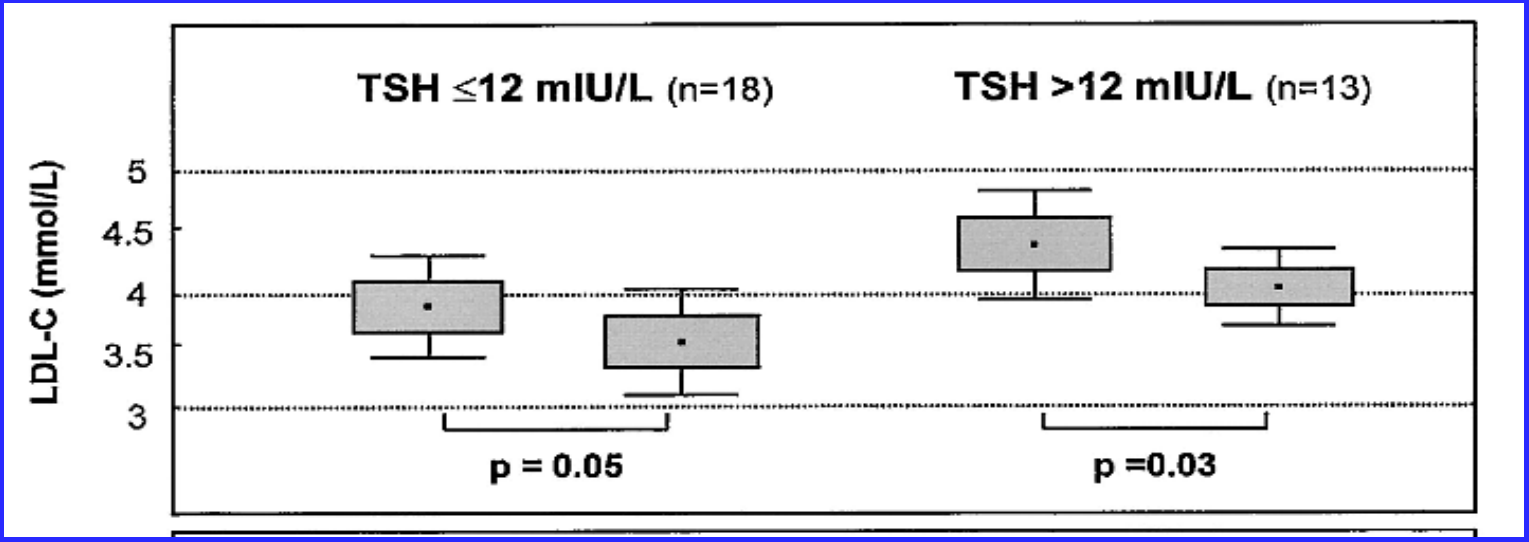

Figure 3. Effect of L-thyroxine treatment on serum LDL-C in subsets of patients in relation to TSH and LDL-C levels at baseline (*points*, mean; *boxes*, ±1.00 SE; *bars*, ±1.96 SE).

Meier et al. 2001

- **Atherosclerosis**

CV system

PRECLINICAL HYPOTHYROIDISM: A RISK FACTOR FOR CORONARY HEART-DISEASE*

P. A. BASTENIE
L. VANHAELST
M. BONNYNS
P. NEVE
M. STAQUET

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Lancet 1971; I: 203

THYROID
Volume 12, Number 6, 2002
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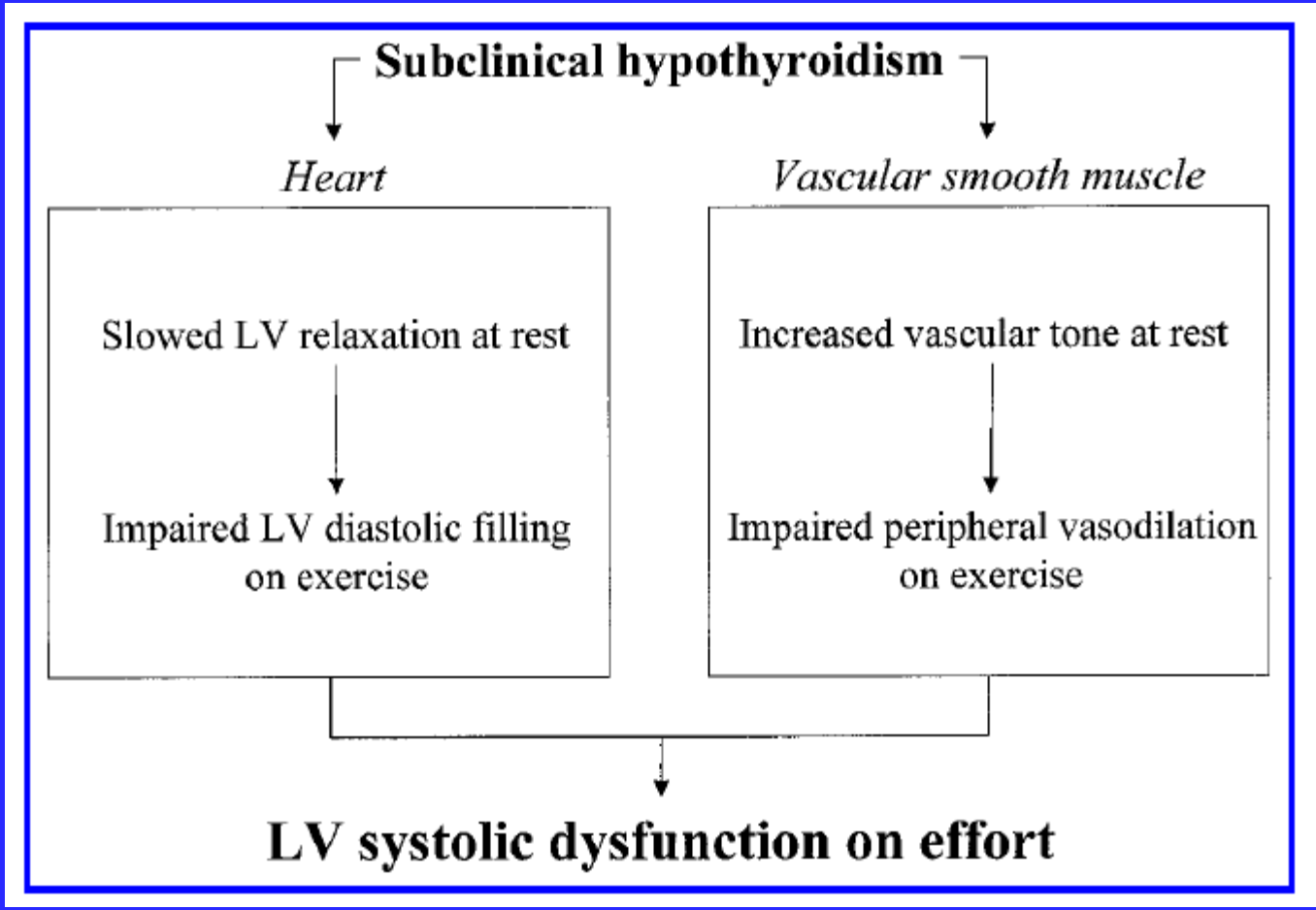
Subclinical Hypothyroidism and Cardiac Function

Bernadette Biondi,[1] Emiliano A. Palmieri,[2] Gaetano Lombardi,[1] and Serafino Fazio[2]



Functional cardiac effects of SHyper

- Resting tachycardia
- LV hypertrophy
- Increase LV mass index
- Increase cardiac workload
- Diastolic dysfunction (impaired relaxation)
- Increased systolic function at rest
- Impaired systolic response to excercise

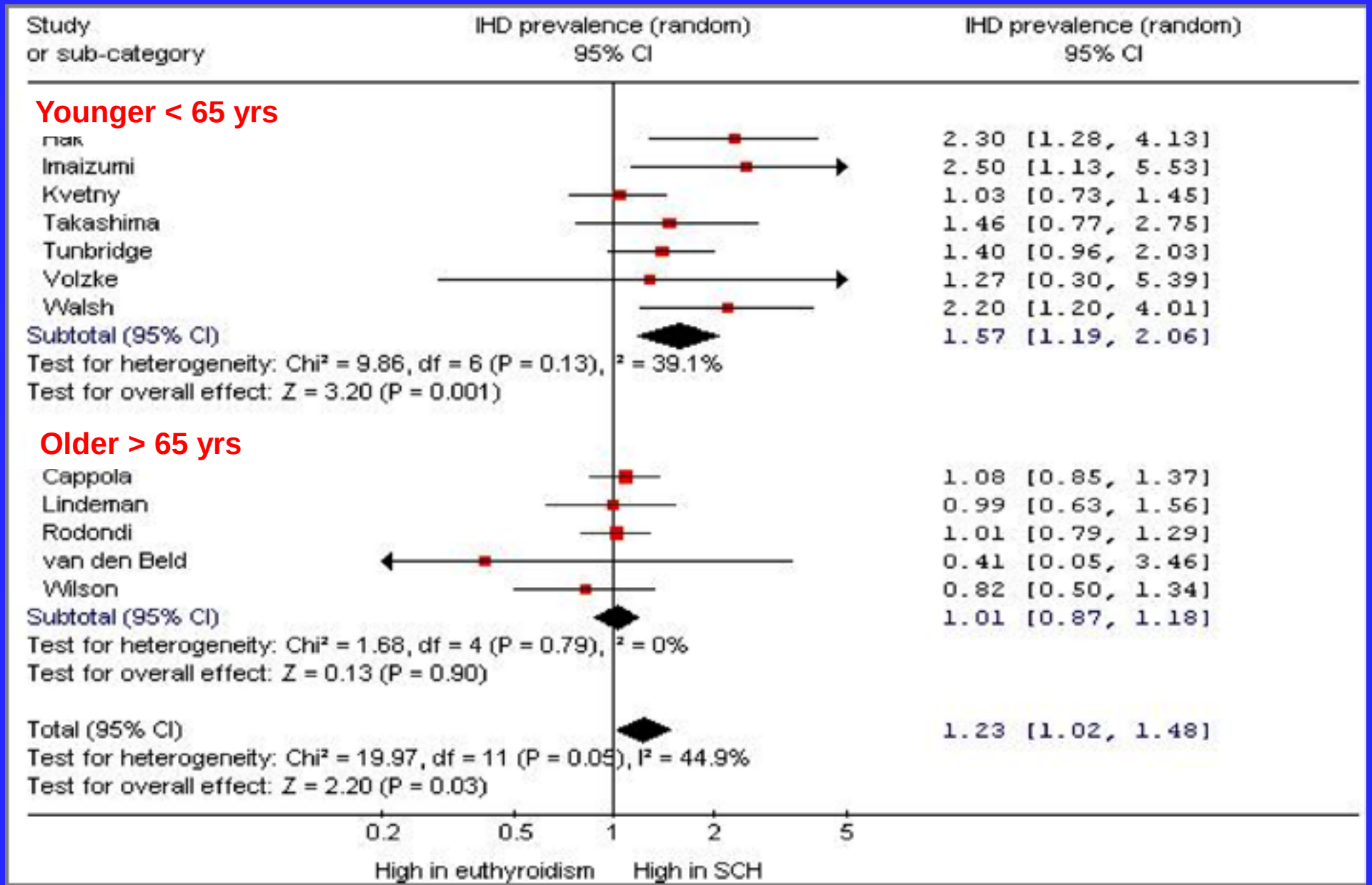
Biondi, Kahaly, Klein and others

The Influence of Age on the Relationship between Subclinical Hypothyroidism and Ischemic Heart Disease: A Metaanalysis **JCEM 2008**

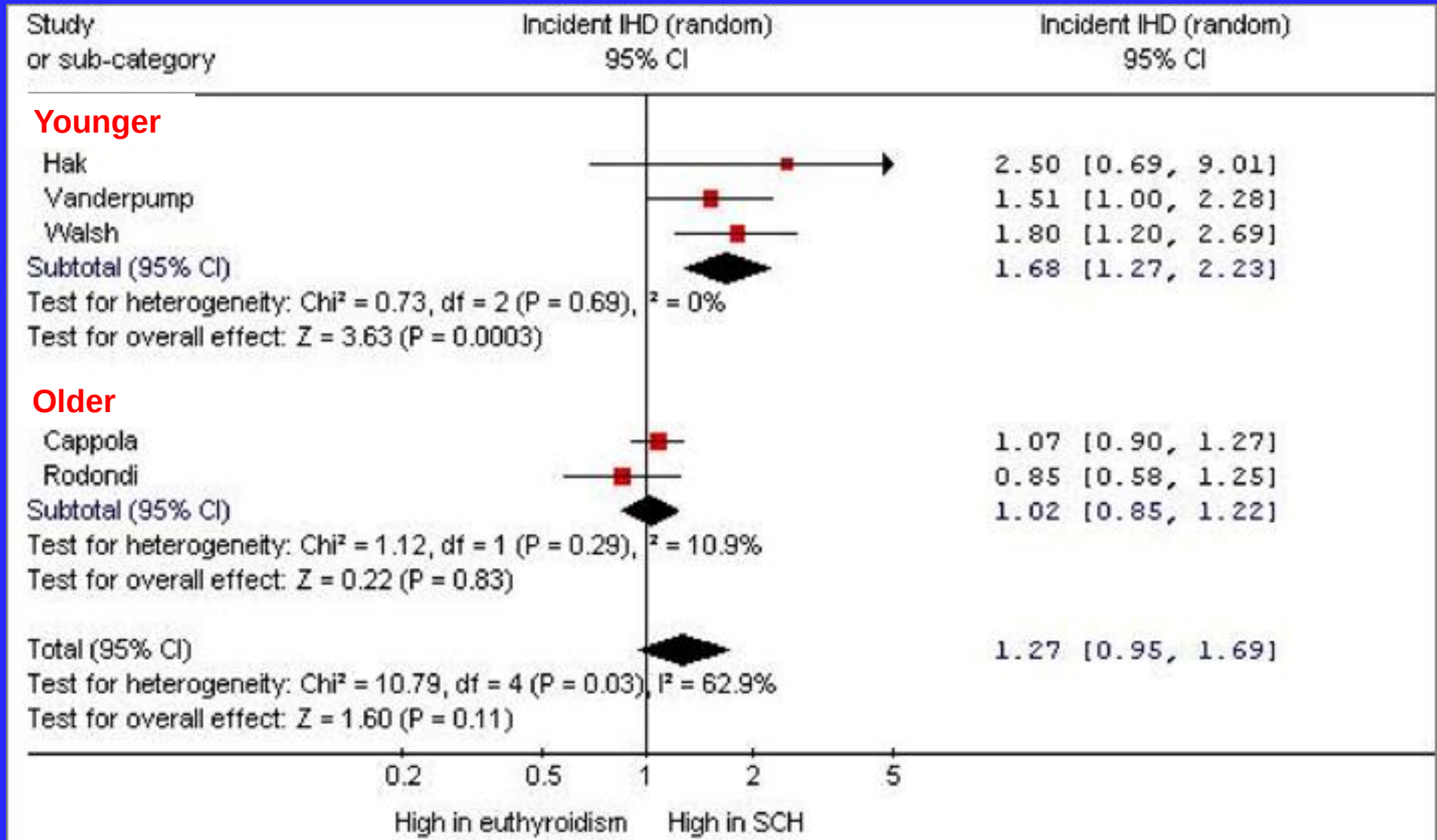
Salman Razvi, Abdul Shakoor, Mark Vanderpump, Jolanta U. Weaver, and Simon H. S. Pearce

- Longitudinal or cross sectional studies of independent community-based subjects
- 14 studies fitted stringent criteria
- 2,531 SCH / 26,491 euthyroid individuals
- Divided studies according to age of inclusion
  - <65 yr vs 65 and above: median 60 & 74 yr

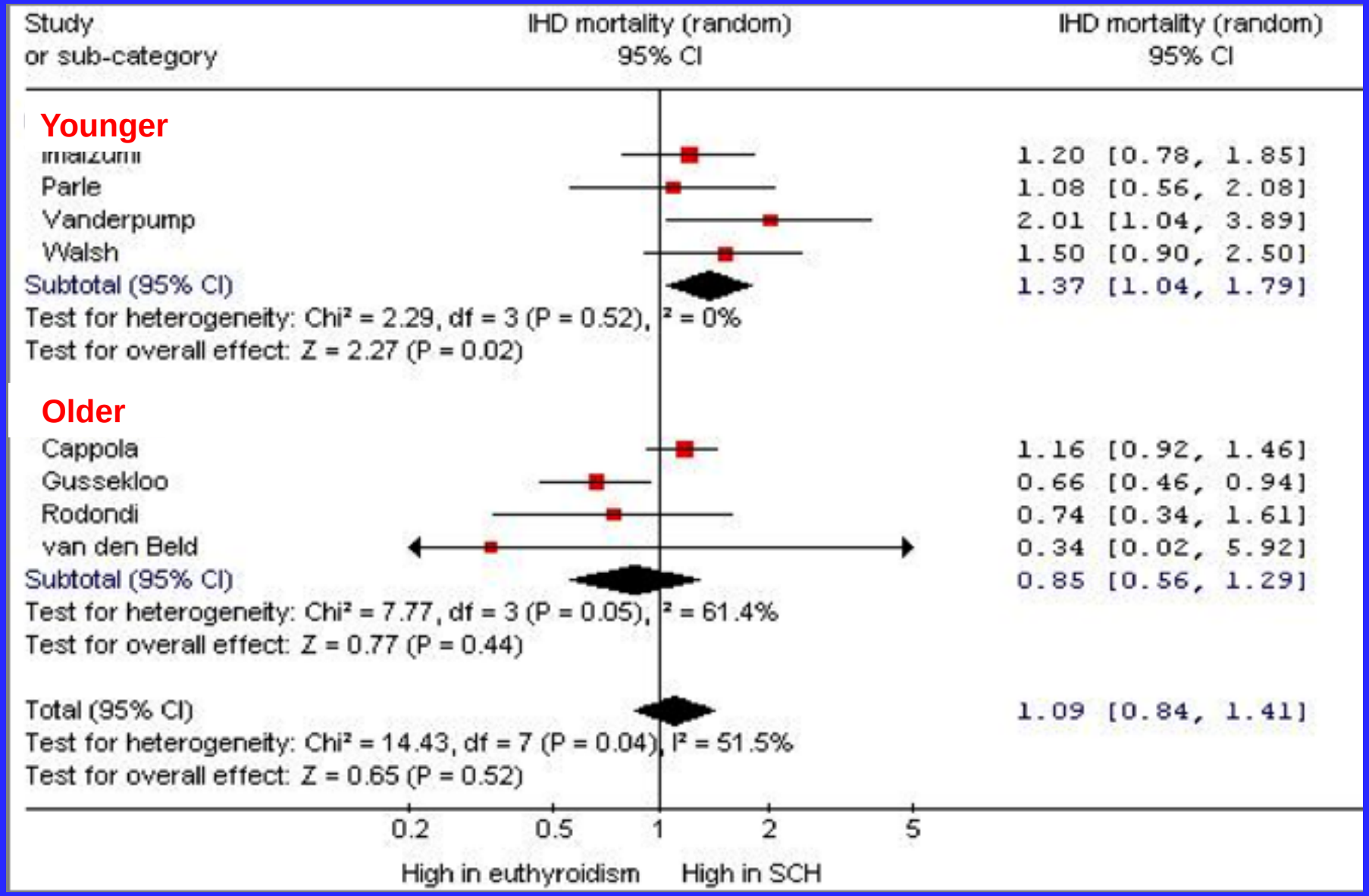
IHD prevalence in cross-sectional studies of SCH & euthyroid controls



IHD incidence in longitudinal studies of SCH & euthyroid controls



Cardiovascular mortality in longitudinal studies of SCH & euthyroid controls



Subclinical Hypothyroidism and the Risk of Coronary Heart Disease and Mortality

JAMA 2010

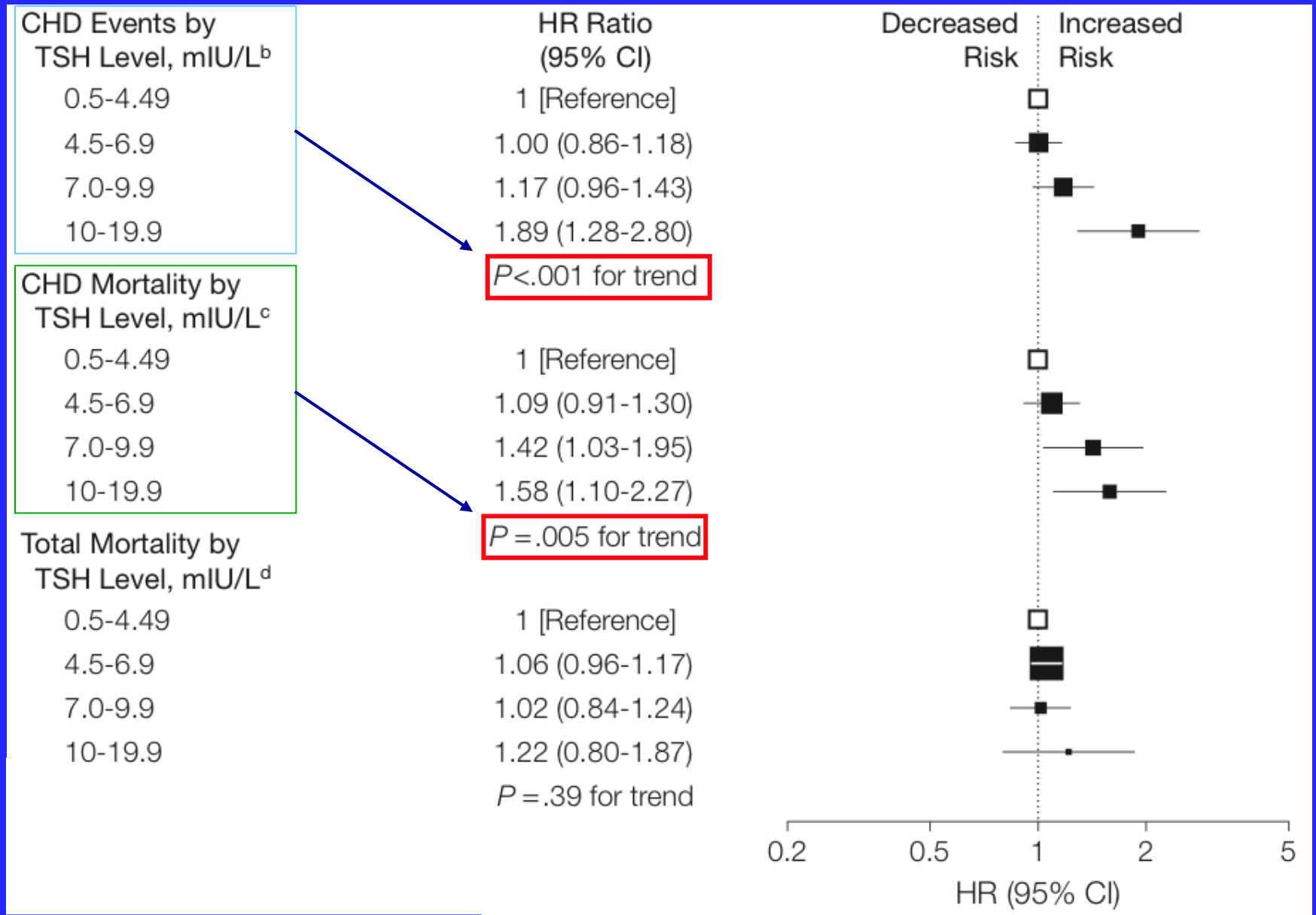
Dr. Nicolas Rodondi, MD, MAS, Ms. Wendy P. J. den Elzen, MSc, Dr. Douglas C. Bauer, MD, Dr. Anne R. Cappola, MD, ScM, Dr. Salman Razvi, MD, FRCP, Dr. John P. Walsh, MBBS, FRACP, PhD, Dr. Bjørn O. Åsvold, MD, PhD, Dr. Giorgio Iervasi, MD, Dr. Misa Imaizumi, MD, PhD, Dr. Tinh-Hai Collet, MD, Dr. Alexandra Bremner, PhD, Mr. Patrick Maisonneuve, Ing, Dr. José A. Sgarbi, MD, Dr. Kay-Tee Khaw, MD, Dr. Mark P. J. Vanderpump, MD, FRCP, Dr. Anne B. Newman, MD, MPH, Dr. Jacques Cornuz, MD, MPH, Dr. Jayne A. Franklyn, MD, PhD, FRCP, Dr. Rudi G. J. Westendorp, MD, PhD, Dr. Eric Vittinghoff, PhD, and Dr. Jacobijn Gussekloo, MD, PhD for the Thyroid Studies Collaboration

- 55,287 participants; 3,450 with SCH (6.2%)
- Information derived from 11 studies
- 9664 deaths; 2168 from CHD

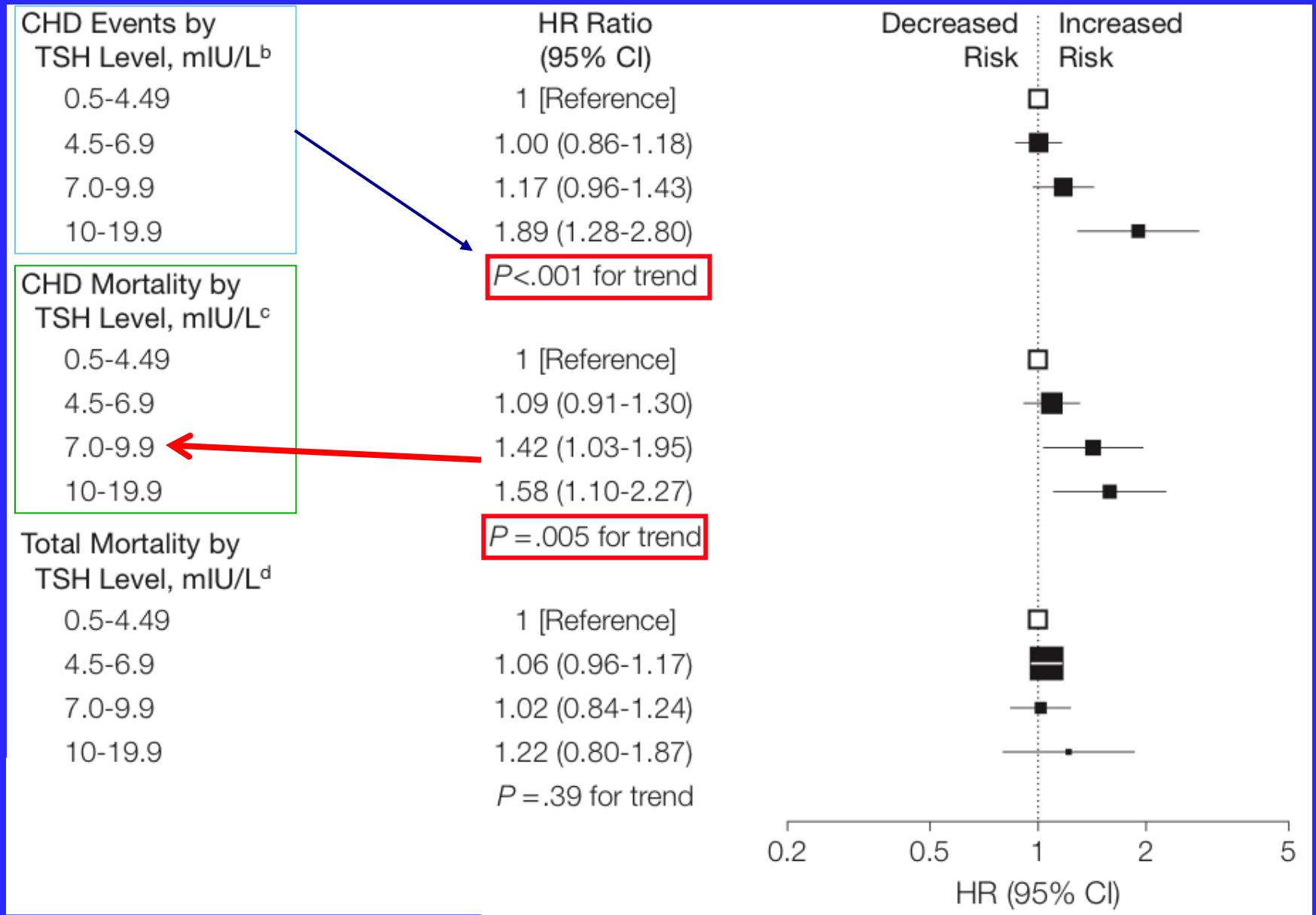
- SCH defined as TSH 4.5-19.99 mU/l (N FT4)

Patient-level analysis

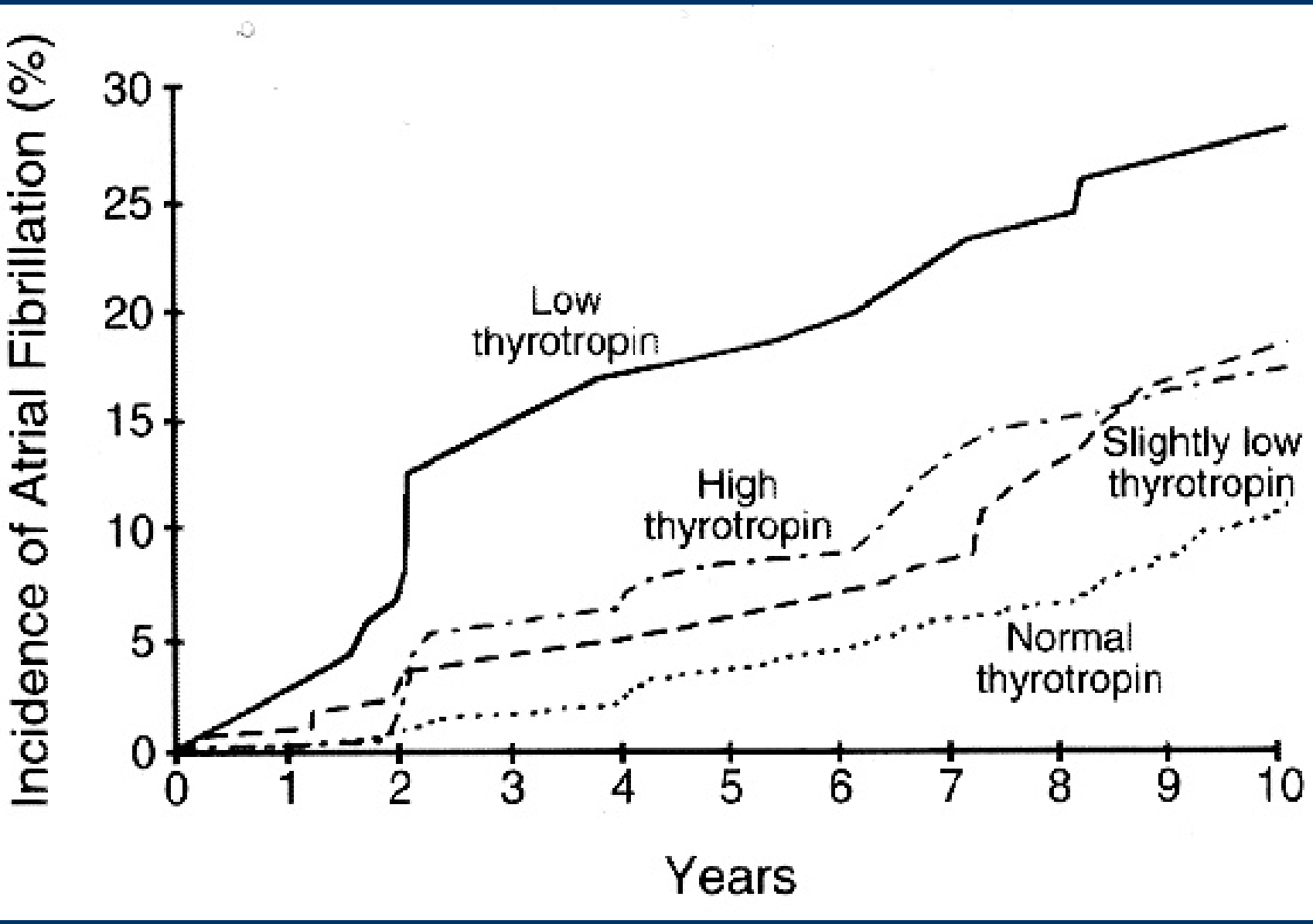
Patient-level analysis: TSH



Patient-level analysis: TSH



AF in Framingham survey



TSH (mU/l)

<0.1

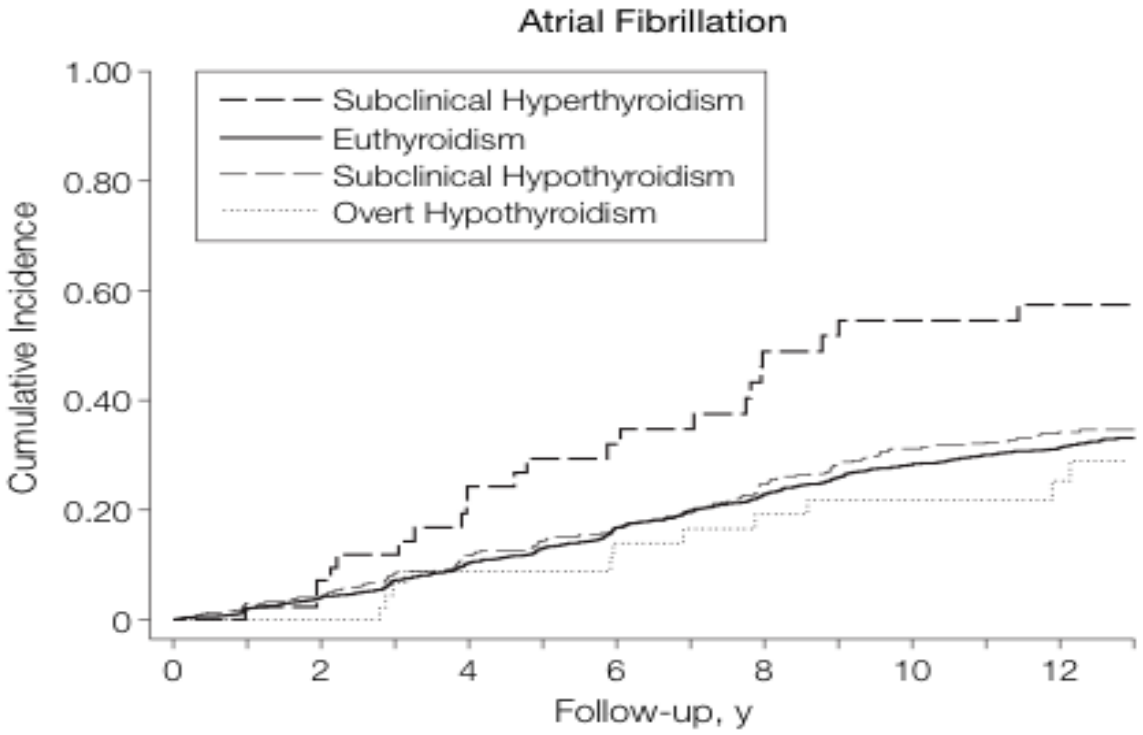
0.1- 0.4

>5.0

0.4- 5.0

Sawin et al. NEJM; 1994

Cardiovascular Health Study



No. at Risk							
Subclinical Hyperthyroidism	47	41	31	27	19	17	14
Euthyroidism	2502	2336	2093	1823	1576	1342	1150
Subclinical Hypothyroidism	472	440	393	348	293	243	208
Overt Hypothyroidism	49	47	40	35	32	29	22

- 3233 US community dwelling individuals over 65, mean age 73
- AF rate 2.0 (CI 1.3-3.0) in SHyper

Cappola et al. JAMA 2006

-No association SCH – CV in patients >70 years

-Association in 60-70 patients especially when serum TSH >7 mIU/L

-Suppressed (>low) serum TSH is associated with and increased prevalence of AF and heart failure

-Lack of treatment evidence on the reversibility of low TSH ~ outcomes

- **Cognitive Aspects**

DEMENTIA

The Rotterdam study **Kalmijn et al. 2000 Clin Endo (Oxf)**

Prospective population based cohort study 1843 participants aged 55 years and over follow up 2 to 4 years

Table 2 Relative risk (95% confidence interval) for incident dementia according to thyroid status, adjusted for age and gender *

	n/N†	Total dementia	*n*/N†	Alzheimer's disease
TSH > 4·0 mU/l	20/1730	0·5 (0·1–3·8)	15/1725	0·6 (0·1–4·6)
Excluding subjects taking beta blockers	20/1662	0·5 (0·1–3·7)	15/1642	0·6 (0·1–4·5)
TSH > 4·0 with positive antibodies§	14/1417	–¶	10/1413	–¶

SD, standard deviation.

* In all analyses thyromimetic or thyrostatic medication users are excluded; †Number of dementia patients and total number in the analyses; ‡One standard deviation = 23·3 nmol/l; §TPO-antibody level > 10 IU/ml; ¶ There were no demented subjects with increased TSH levels and positive antibodies.

Subclinical Hypothyroidism and Cognitive Impairment: Systematic Review and Meta-Analysis

JCEM 2015

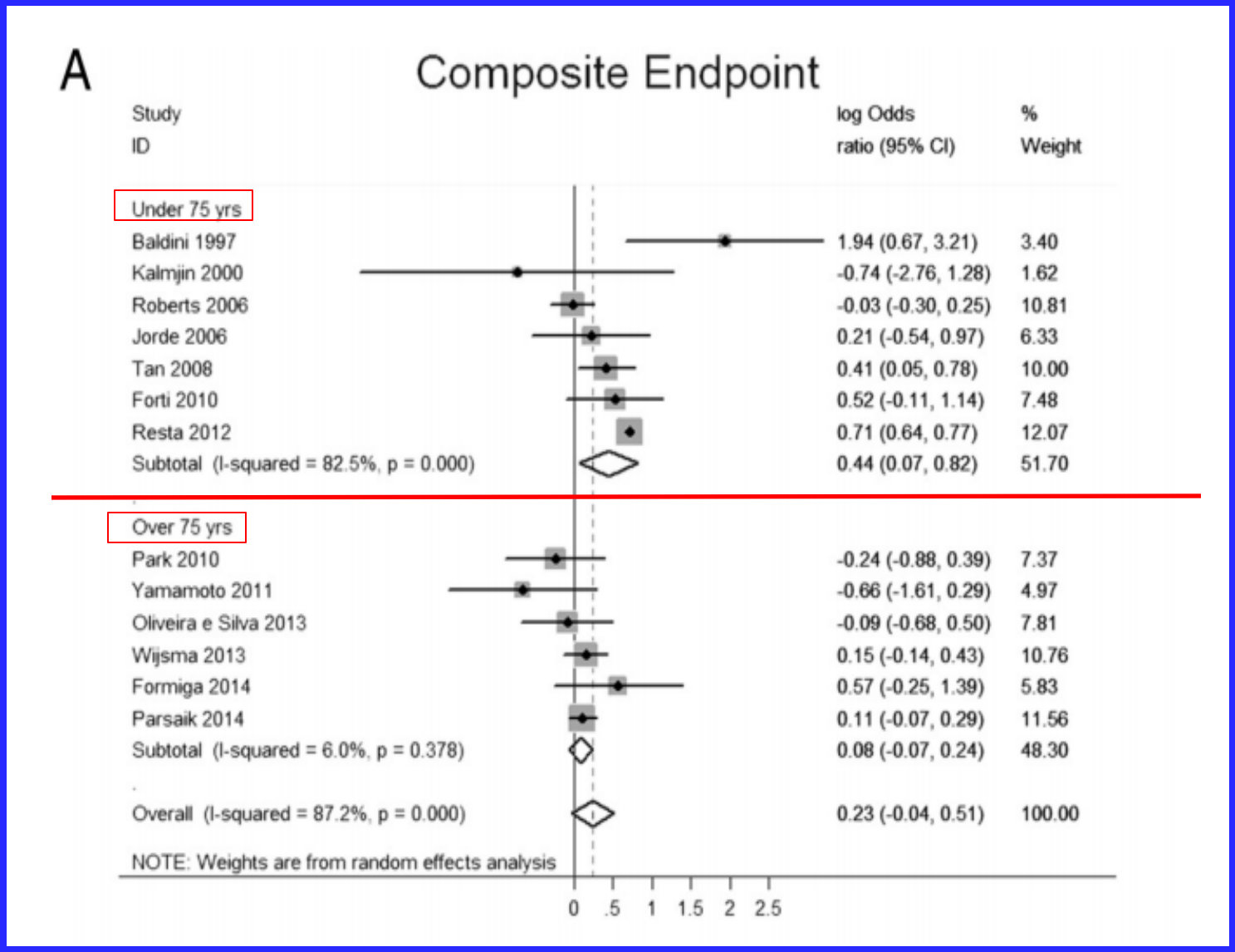
Giuseppe Pasqualetti, Gennaro Pagano, Giuseppe Rengo, Nicola Ferrara, and Fabio Monzani

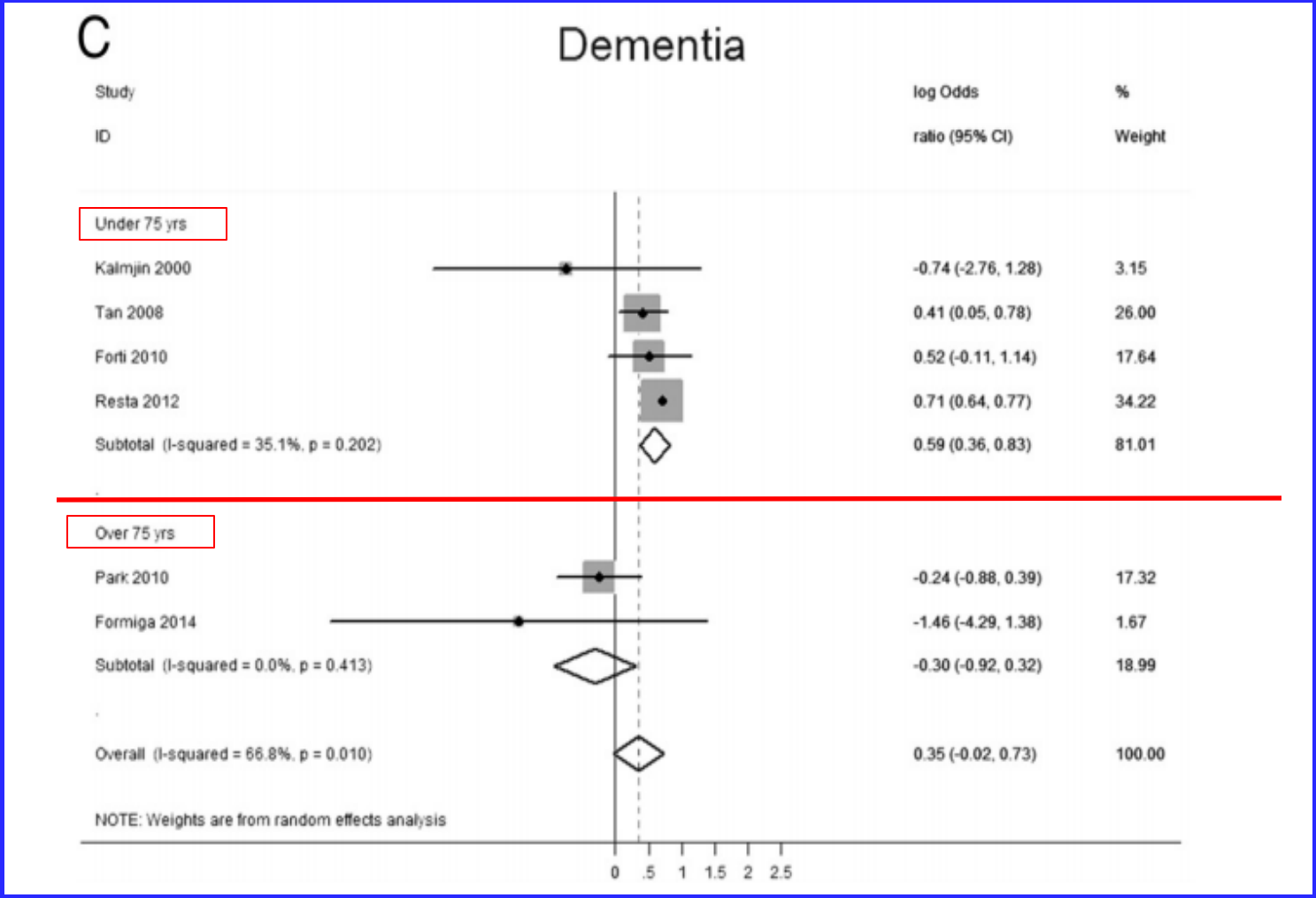
Table 1. Study Characteristic and Quality Score (Newcastle-Ottawa Scale)

Study	Type	sHT Definition	TSH Assay
Baldini et al (1997) (33)	Case control	TSH exceeding the upper normal limits by 20% (4.6 mU/liter) or more (in at least two consecutive occasions) associated with normal FT_4 and FT_3	IRMA Allegro HS-TSH, Nichols Institute Diagnostics, San Juan Capistrano, CA
Formiga et al (2014) (40)	Cohort study	TSH >5 mU/liter, FT_4 10–26 pmol/liter	MABs Roche Diagnostics
Jorde et al (2006) (15)	Cohort study	TSH 5–10 mU/liter, FT_4 9–22 pmol/liter in at least two consecutive occasions	Hoffman-La Roche
Park et al (2010) (17)	Cohort study	TSH >4.1 mU/liter, FT_4 0.7–1.8 ng/liter	TSH: CIS Bio International, Gif-sur-Yvette
Parsaik et al (2014) (32)	Cross-sectional	TSH 5–10 mU/liter, FT_4 1.01–1.79 ng/dl	TSH Mayo Clinic Protocol
Roberts et al (2006) (14)	Cohort study	TSH >5.5 mU/liter, FT_4 9–20 pmol/liter	Adiva Centaur Bayer Diagnostic
Wijsma et al (2013) (34)	Cohort study	TSH >4.5 mU/liter, FT_4 12–18 pmol/liter in at least two consecutive occasions	Roche Elecsys 2010
Yamamoto et al (2011) (35)	Cohort study	NA	NA
Silva et al (2013) (36)	Cross-sectional	TSH 4–19.9 U/liter, FT_4 0.8–1.19 ng/dl	Immunolite 2000
Tan et al (2008) (12)	Cohort study	TSH >1.8–2.1 mU/liter[b]	London Diagnostics, Eden Prairie, Minnesota
Forti et al (2012) (37)	Cross-sectional	TSH >4.50 mU/liter, FT_4 10.3–25.7 pmol/liter	Roche Elecsys 2010
Resta et al (2012) (39)	Cross-sectional	TSH 3.6 mU/liter, FT_4 8–17 pmol/liter	Vedere ILSA Study Ref 24
Kalmijn et al (2000) (38)	Cohort study	TSH >4 mU/liter, FT_4 11–25 pmol/liter	TSH Lumitest (Hennin, Berlin, Germany)

[a] The 97.5th percentile of TSH adjusted for age was obtained by the general National Health and Nutrition Examination Survey cohort values as by Boucai et al (8).

[b] The limits indicated the third percentile for men and women, respectively.


A
Composite Endpoint
Study ID
log Odds ratio (95% CI)
% Weight
Under 75 yrs
Baldini 1997 1.94 (0.67, 3.21) 3.40
Kalmjin 2000 -0.74 (-2.76, 1.28) 1.62
Roberts 2006 -0.03 (-0.30, 0.25) 10.81
Jorde 2006 0.21 (-0.54, 0.97) 6.33
Tan 2008 0.41 (0.05, 0.78) 10.00
Forti 2010 0.52 (-0.11, 1.14) 7.48
Resta 2012 0.71 (0.64, 0.77) 12.07
Subtotal (I-squared = 82.5%, p = 0.000) 0.44 (0.07, 0.82) 51.70
Over 75 yrs
Park 2010 -0.24 (-0.88, 0.39) 7.37
Yamamoto 2011 -0.66 (-1.61, 0.29) 4.97
Oliveira e Silva 2013 -0.09 (-0.68, 0.50) 7.81
Wijsma 2013 0.15 (-0.14, 0.43) 10.76
Formiga 2014 0.57 (-0.25, 1.39) 5.83
Parsaik 2014 0.11 (-0.07, 0.29) 11.56
Subtotal (I-squared = 6.0%, p = 0.378) 0.08 (-0.07, 0.24) 48.30
Overall (I-squared = 87.2%, p = 0.000) 0.23 (-0.04, 0.51) 100.00
NOTE: Weights are from random effects analysis
0 .5 1 1.5 2 2.5


C
Dementia
Study
ID
log Odds
ratio (95% CI)
%
Weight
Under 75 yrs
Kalmjin 2000
-0.74 (-2.76, 1.28)
3.15
Tan 2008
0.41 (0.05, 0.78)
26.00
Forti 2010
0.52 (-0.11, 1.14)
17.64
Resta 2012
0.71 (0.64, 0.77)
34.22
Subtotal (I-squared = 35.1%, p = 0.202)
0.59 (0.36, 0.83)
81.01
Over 75 yrs
Park 2010
-0.24 (-0.88, 0.39)
17.32
Formiga 2014
-1.46 (-4.29, 1.38)
1.67
Subtotal (I-squared = 0.0%, p = 0.413)
-0.30 (-0.92, 0.32)
18.99
Overall (I-squared = 66.8%, p = 0.010)
0.35 (-0.02, 0.73)
100.00
NOTE: Weights are from random effects analysis
0
.5
1
1.5
2
2.5

DEMENTIA

The Rotterdam study Kalmijn et al. 2000 Clin Endo (Oxf)

Prospective population based cohort study 1843 participants aged 55 years and over follow up 2 to 4 years

Table 2 Relative risk (95% confidence interval) for incident dementia according to thyroid status, adjusted for age and gender *

	n/N†	Total dementia	*n*/N†	Alzheimer's disease
TSH < 0·4 mU/l	24/1662	3·5 (1·2–10·0)	18/1656	3·5 (1·1–11·5)
Additional adjustment for atrial fibrillation	24/1662	3·5 (1·2–10·0)	18/1656	3·6 (1·1–11·7)
Excluding subjects taking beta blockers	23/1589	3·0 (1·0–9·5)	17/1583	2·9 (0·8–10·9)
T4 levels (per SD‡)	5/102	2·9 (0·7–12·2)	4/101	2·1 (0·5–8·6)
TSH < 0·4 with positive antibodies§	16/1349	23·7 (4·0–140)	11/1344	14·3 (1·4–141)

SD, standard deviation.

* In all analyses thyromimetic or thyrostatic medication users are excluded; †Number of dementia patients and total number in the analyses; ‡One standard deviation = 23·3 nmol/l; §TPO-antibody level > 10 IU/ml; ¶ There were no demented subjects with increased TSH levels and positive antibodies.

Subclinical Thyroid Dysfunction and the Risk of Cognitive Decline: a Meta-Analysis of Prospective Cohort Studies

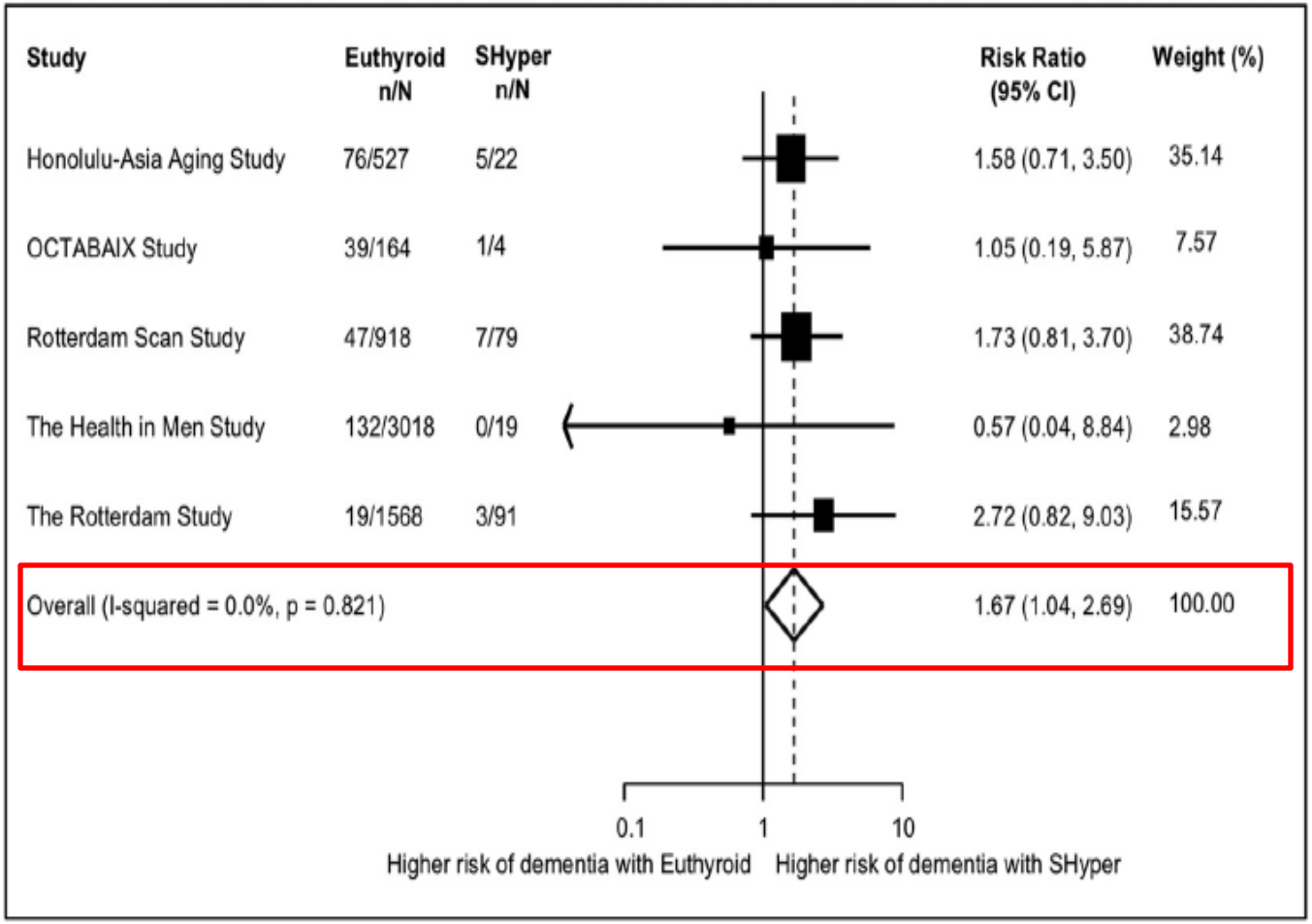
JCEM 101: 4945–4954, 2016

Carole Rieben, Daniel Segna, Bruno R. da Costa, Tinh-Hai Collet, Layal Chaker, Carole E. Aubert, Christine Baumgartner, Osvaldo P. Almeida, Eef Hogervorst, Stella Trompet, Kamal Masaki, Simon P. Mooijaart, Jacobijn Gussekloo, Robin P. Peeters, Douglas C. Bauer, Drahomir Aujesky, and Nicolas Rodondi*

Table 1. Description of Included Studies for the Effect of Subclinical Thyroid Dysfunction on Dementia/Mini-Mental State Examination (MMSE)

Study, Year of Publication	Population, N	Women, %	Mean Age; SD, y	Followup Time, Months	Age, Min–Max, y	TSH Cutoff Level, mU/L		fT_4 Measured	Thyroid Hormone Recipients Excluded?
						SHypo	SHyper		
Rotterdam (31), 2000[c]	1843	61.9	68.8; 7.5	25.2	55–93	>4.0	<0.4	Yes	Yes
Leiden 85-Plus Study (33), 2004	558	66.0	85.0; 0.0	44.4	85	>4.8	<0.3	Yes	In SA
Rotterdam Scan (38), 2006	1077	51.2	72.3[a]; 7.4	66.0	60–90	>4.3	<0.4	Yes	Yes
Health Ageing (36), 2008	1047	51.0	73.6; 6.2	24.0	64–94	>4.8[b]	<0.3[b]	Yes	Yes
Framingham (34), 2008[b]	1864	59.0	71.0; 7.0	152.4				No	In SA
HAAS (30), 2009	665	0.0	78.0	56.4	71–93	>4.3	<0.4	Yes	Yes
Japanese Study (35), 2010	229	65.0	80.9; 4.7	12.0		>4.0	NR	Yes	Yes
Conselice (32), 2012[c]	660	52.9	73.3; 6.0	45.6	65–91	>4.5	<0.45	Yes	In SA
HIMS (29), 2012	3401	0.0	76.8; 3.5	70.8[a]	70–89	>4.0	<0.4	Yes	Yes
PROSPER (20), 2013	5154	49.4	75.0	38.4	80–82	>4.5	<0.45	Yes	Yes
OCTABAIX (37), 2014[d]	307	54.6	85.0; 0.0	36.0	85	>5	<0.25	Yes	Yes

SHyper and Dementia



Received: 17 March 2017 | Revised: 3 August 2017 | Accepted: 22 August 2017
DOI: 10.1111/cen.13458

ORIGINAL ARTICLE

WILEY

The association between subclinical thyroid dysfunction and dementia: The Health, Aging and Body Composition (Health ABC) Study

Carole E. Aubert[1] | Douglas C. Bauer[2] | Bruno R. da Costa[3] | Martin Feller[1,3] | Carole Rieben[4] | Eleanor M. Simonsick[5] | Kristine Yaffe[6,7] | Nicolas Rodondi[1,3] | For the Health ABC Study

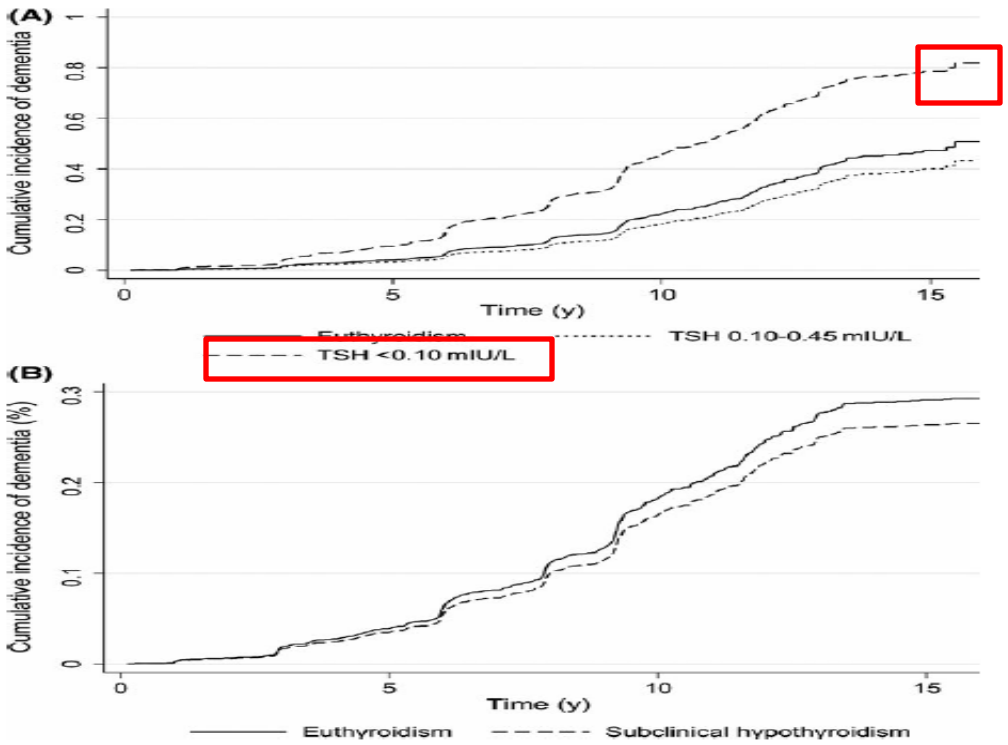


FIGURE 1 Cumulative-adjusted incidence of dementia in subclinical thyroid dysfunction compared with euthyroidism. (A) subclinical hyperthyroidism with suppressed TSH (TSH <0.10 mIU/L) or with mildly decreased TSH (TSH 0.10-0.44 mIU/L) (B) subclinical hypothyroidism. Analyses were adjusted for age, sex, race, education level and baseline 3MS

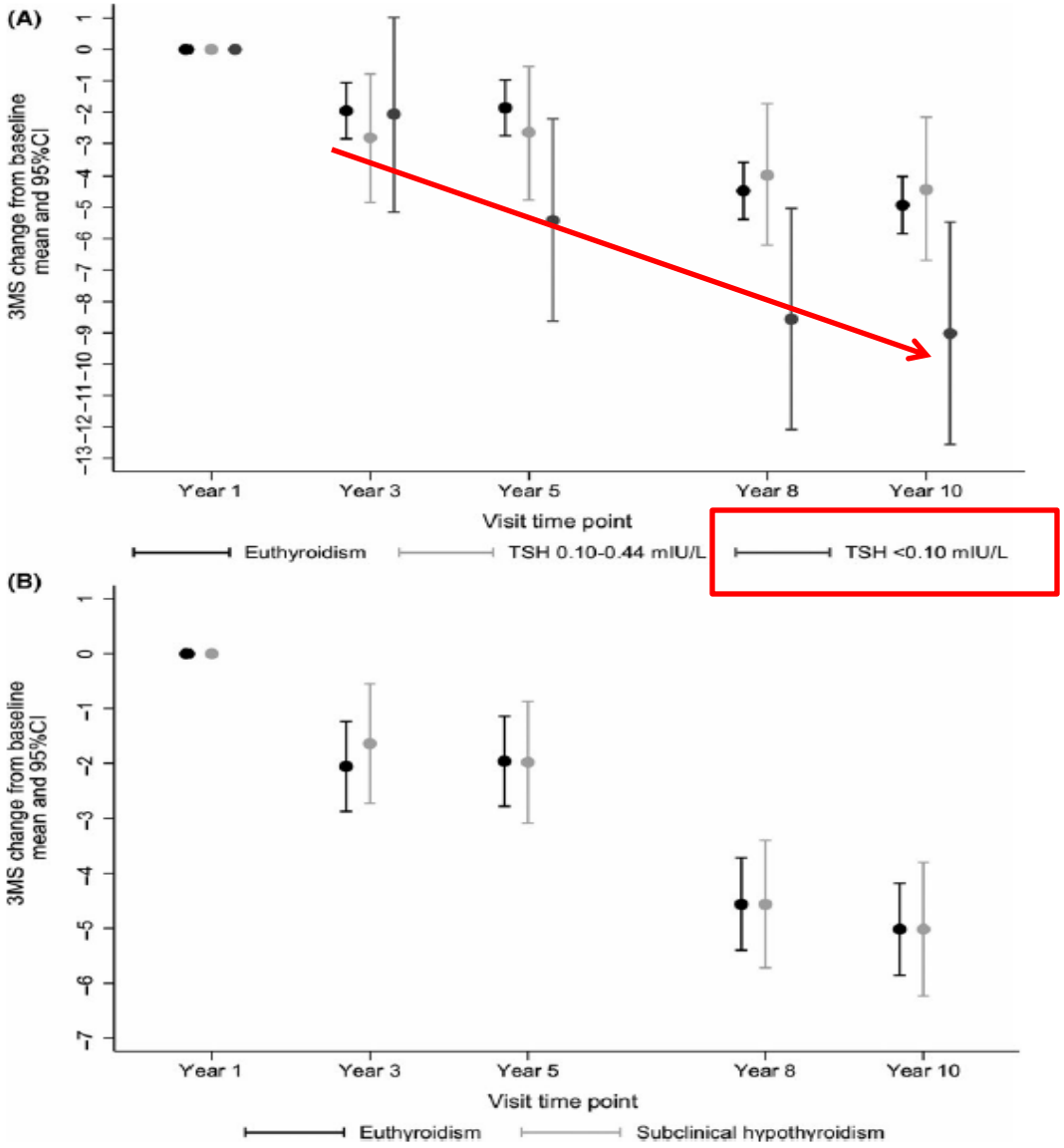


FIGURE 2 3MS change from baseline in subclinical thyroid dysfunction compared with euthyroidism. (A) subclinical hyperthyroidism with suppressed TSH (TSH <0.10 mIU/L) or with mildly decreased (TSH 0.10-0.44 mIU/L) (B) subclinical hypothyroidism. Analyses were adjusted for age, sex, race and education level. Abbreviations: CI, confidence interval; 3MS, Modified Mini-Mental State; SHyper, subclinical hyperthyroidism; SHypo, subclinical hypothyroidism

Dementia-HyperT

- **First,** dementia may be caused by an increase in neuronal necrosis and oxidative stress associated with both HT and Alzheimer's disease.

- **Second,** a genetic susceptibility may exist, as some thyroid hormones target genes are involved in neurogenesis.

- **Third,** dementia could be caused by lower choline in the brain, as described in Alzheimer's disease.
  - In a pilot study, choline/creatine ratio in the brain was indeed lower in patients with untreated Graves' disease, but normalized after treatment.

Aubert C, Clin Endo 2017

-No association SCH – MMS/dementia in patients >75 years

-Possible association SCH- some outcomes in patients <75 years

---

-Suppressed (>low) serum TSH is associated with and increased prevalence of dementia

-Lack of treatment evidence on the reversibility of low TSH ~ cognitive parameters

- **Frailty / Bone**

Subclinical Thyroid Dysfunction and Frailty Among Older Men

JCEM 100: 4524–4532, 2015

Vanessa S. Virgini, Nicolas Rodondi, Peggy M. Cawthon, Stephanie Litwack Harrison, Andrew R. Hoffman, Eric S. Orwoll, Kristine E. Ensrud, and Douglas C. Bauer, for the Osteoporotic Fractures in Men (MrOS) Research Group

Table 1. Baseline Characteristics of Study Participants According to Thyroid Function

Demographics	All (n = 1455)	Thyroid Function: Subclinical Hyperthyroidism (n = 26)	Euthyroidism (n = 1327)	Subclinical Hypothyroidism (n = 102)	*P* Value
Demographics					
Age, y, mean (SD)	73.6 (5.8)	74.6 (6.5)	73.4 (5.7)	76.3 (6.0)	<.001
College education, n (%)	766 (52.2)	13 (50.0)	701 (52.8)	45 (44.1)	.23
Married status, n (%)	1214 (82.8)	21 (80.8)	1106 (83.4)	76 (74.5)	.07
Nonwhite race, n (%)	1336 (91.1)	22 (84.6)	1209 (91.1)	94 (92.2)	.48
Biometrics, mean (SD)					
Weight, kg	83.3 (13.1)	84.5 (17.2)	83.3 (13.0)	83.3 (13.2)	.90
Height, cm	174.2 (6.7)	173.6 (7.2)	174.2 (6.7)	174.8 (7.1)	.62
BMI, kg/m^2	27.4 (3.7)	27.9 (4.4)	27.4 (3.7)	27.2 (3.5)	.67
Appendicular skeletal lean mass, kg	24.2 (3.4)	24.1 (3.8)	24.3 (3.4)	24.1 (3.5)	.91
Fatty composition, % total body	26.4 (5.2)	26.5 (6.0)	26.4 (5.1)	26.3 (5.6)	.99
Walking speed, m/s	1.20 (0.23)	1.17 (0.25)	1.20 (0.22)	1.18 (0.23)	.49
Grip strength, kg	38.4 (7.9)	37.1 (8.4)	38.4 (7.8)	37.8 (8.0)	.53
Medical conditions, n (%)	996 (67.9)	16 (61.5)	904 (68.1)	70 (68.6)	.77
Questionnaires					
Excellent/good self-rated health, n (%)	1265 (86.3)	24 (92.3)	1143 (86.2)	87 (85.3)	.64
Feel full of energy, n (%)	730 (49.8)	17 (62.4)	652 (49.2)	55 (53.9)	.18
PASE score, mean (SD)	148.1 (68.9)	117.8 (60.7)	149.0 (69.2)	144.0 (66.8)	.06
Habits					
Smoking status, n (%)					
Never	539 (36.7)	11 (42.3)	476 (35.9)	46 (45.1)	.26
Past	872 (59.4)	15 (57.7)	798 (60.1)	54 (52.9)	
Current	56 (3.8)	0	53 (4.0)	2 (2.0)	
Drinking, n (%)					
<1 drink/wk	682 (46.5)	13 (50)	611 (46.0)	53 (52.0)	.30
1 drink/wk–14 drinks/wk	606 (41.3)	11 (42.3)	547 (41.2)	43 (42.2)	
>14 drinks/wk	179 (12.2)	2 (7.7)	169 (12.7)	6 (5.9)	
Falls					
Any falls in past year, n (%)	298 (20.3)	5 (19.2)	270 (20.4)	21 (20.6)	.99
≥2 falls in past year, n (%)	130 (8.9)	2 (7.7)	119 (9.0)	8 (7.8)	.91
Frailty components, mean (SD)	0.93 (1.07)	1.38 (0.98)	0.91 (1.06)	1.08 (1.11)	.005
Frailty classification, n (%)					
Robust	652 (44.4)	4 (15.4)	604 (45.5)	38 (37.3)	.02
Intermediate	680 (46.4)	19 (73.1)	602 (45.4)	54 (52.9)	
Frail	135 (9.2)	3 (11.5)	121 (9.1)	10 (9.8)	
Frailty criteria, n (%)					
Sarcopenia	290 (19.9)	7 (28.0)	254 (19.3)	27 (26.5)	.13
Weakness	381 (26.0)	10 (38.5)	336 (25.3)	31 (30.4)	.18
Exhaustion	108 (7.4)	4 (15.4)	96 (7.2)	7 (6.9)	.28
Slowness	283 (19.3)	6 (23.1)	249 (18.8)	27 (26.5)	.15
Low activity level	281 (19.6)	9 (34.6)	258 (19.4)	18 (17.7)	.14

Abbreviations: N, number; sd, standard deviation; BMI, body mass index; PASE, Physical Activity Scale for Elderly.

Table 2. Cross-Sectional Relationship Between Thyroid Function and Frailty at Baseline Visit

	Thyroid Status		
	Subclinical Hyperthyroidism (n = 26)	Euthyroidism (n = 1327)	Subclinical Hypothyroidism (n = 102)
Frailty components, adjusted means (95% CI)	1.29 (0.91–1.68)[a]	0.92 (0.87–0.97)	0.89 (0.70–1.09)
Frailty classifications, OR (95% CI)[b]	2.48 (1.15–5.34)[c]	1.00	0.94 (0.63–1.41)[c]
Frailty criteria			
Sarcopenia	1.55 (0.61–3.94)	1.00	1.38 (0.84–2.26)
Weakness	1.63 (0.68–3.95)	1.00	0.87 (0.54–1.39)
Exhaustion	2.21 (0.71–6.89)	1.00	0.84 (0.38–1.89)
Slowness	0.94 (0.32–2.75)	1.00	1.11 (0.68–1.82)
Low activity	1.91 (0.82–4.44)	1.00	0.81 (0.48–1.39)

Results are adjusted for age, race, BMI, and clinic.

[a] *P* value for interaction compared with that for euthyroidism: 0.2559.

[b] Frailty classifications include frailty, intermediate, and robust. Ordinal logistic model used.

[c] OR for an increased likelihood of greater frailty status (including all frailty categories).

Table 3. Cross-Sectional Relationship Between Thyroid Function and Frailty Depending on Age at Baseline Visit

	Age <74 Yr Thyroid Status			Age ≥74 Yr Thyroid Status		
	Subclinical Hyperthyroidism (n = 13)	Euthyroidism (n = 717)	Subclinical Hypothyroidism (n = 31)	Subclinical Hyperthyroidism (n = 13)	Euthyroidism (n = 610)	Subclinical Hypothyroidism (n = 71)
Frailty components, adjusted means (95% CI)	1.29 (0.80–1.77)[a]	0.63 (0.57–0.70)	0.73 (0.42–1.04)	1.45 (0.83–2.08)	1.23 (1.14–1.32)	1.22 (0.96–1.49)
Frailty classifications, OR (95% CI)[b]	3.59 (1.20–10.72)[c]	1.00 (ref)	1.15 (0.57–2.35)[c]	2.07 (0.71–6.04)[c]	1.00 (ref)	1.00 (0.62–1.60)[c]
Frailty criteria						
Sarcopenia	2.88 (0.81–10.24)	1.00 (ref)	1.88 (0.72–4.90)	0.93 (0.24–3.70)	1.00 (ref)	1.26 (0.71–2.22)
Weakness	3.41 (1.03–11.30)	1.00 (ref)	0.35 (0.08–1.53)	1.10 (0.35–3.45)	1.00 (ref)	1.16 (0.70–1.93)
Exhaustion	1.25 (0.15–10.15)	1.00 (ref)	2.19 (0.72–6.62)[a]	4.06 (0.94–17.57)	1.00 (ref)	0.46 (0.14–1.55)[a]
Slowness	2.76 (0.66–11.50)	1.00 (ref)	2.68 (1.07–6.72)[a]	0.59 (0.15–2.33)	1.00 (ref)	0.97 (0.55–1.70)[a]
Low activity	2.15 (0.63–7.35)	1.00 (ref)	0.67 (0.23–1.98)	1.98 (0.62–6.27)	1.00 (ref)	0.92 (0.49–1.71)

Abbreviation: ref, reference. Results are adjusted for age, race, BMI, and clinic.

[a] *P* value for interactions: <0.10.

[b] Frailty classifications include frailty, intermediate, and robust. Ordinal logistic model used.

[c] OR for an increased likelihood of greater frailty status (including all frailty categories).

Table 4. Prospective Relationship Between Thyroid Function and Frailty After a 5-Year Follow-Up Period

	Thyroid Status		
	Subclinical Hyperthyroidism (n = 22)	Euthyroidism (n = 1102)	Subclinical Hypothyroidism (n = 85)
Frailty components, adjusted means (95% CI)	1.52 (1.00–2.05)[a]	1.24 (1.17–1.32)	1.18 (0.89–1.47)
Frailty classifications, OR (95% CI)[b]	1.09 (0.49–2.42)[c]	1.00	1.00 (0.66–1.52)[c]
Frailty criteria			
Sarcopenia	1.86 (0.50–6.96)	1.00	1.39 (0.63–3.08)
Weakness	1.39 (0.49–3.94)	1.00	0.73 (0.41–1.30)
Exhaustion	1.05 (0.23–4.80)	1.00	1.16 (0.54–2.48)
Slowness	0.65 (0.19–2.25)	1.00	1.23 (0.69–2.22)
Low activity	2.32 (0.86–6.25)	1.00	0.71 (0.38–1.32)

Abbreviation: ref, reference. Results are adjusted for age, race, BMI, and clinic.

[a] *P* value for interaction compared with euthyroidism: 0.3310.

[b] Frailty classifications include frailty, intermediate, robust, and dead. Partial proportional odds test.

[c] OR for an increased likelihood of greater frailty status (including all frailty categories).

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Subclinical Thyroid Dysfunction and Fracture Risk:

A Meta-analysis

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The final sample consisted of 70298 participants (median age 64 years; 61.3% women), a median (IQR) follow-up of 12.1 (8.3–13.0) years

A total of 63 987 (91.0%) of the participants were euthyroid, 4092 (5.8%) had SCH, and **2219 (3.2%) had Shyper:**

- including 1669 (2.4%) with low but not suppressed TSH (0.10–0.44)
- 550 (0.8%) with suppressed TSH (<0.10 mIU/L)

Fracture Outcome by Age and Sex	Euthyroidism		Subclinical Hyperthyroidism		Hazard Ratio (95% CI)	*P* for Interaction
	No. With Fracture	Total No. of Participants	No. With Fracture	Total No. of Participants		
Hip fracture[a]						
Sex						
Men	606	21854	22	468	1.92 (1.26-2.94)	.09
Women	1928	34617	124	1614	1.29 (1.08-1.55)	
Age, y[b]						
<75	1360	47540	78	1646	1.54 (1.22-1.93)	.18
≥75	1162	8462	67	431	1.22 (0.95-1.56)	
Overall	2534	56471	146	2082	1.36 (1.13-1.64)	
Any fracture[c]						
Sex						
Men	796	13091	32	327	1.69 (1.18-2.41)	.12
Women	1407	12810	89	561	1.21 (0.98-1.51)	
Age, y[b]						
<75	1363	20067	69	649	1.33 (1.04-1.69)	.72
≥75	840	5834	52	239	1.24 (0.93-1.65)	
Overall	2203	25901	121	888	1.28 (1.06-1.53)	
Nonspine fracture[d]						
Sex						
Men	592	10326	24	282	1.53 (1.01-2.31)	.17
Women	1153	11396	83	664	1.10 (0.88-1.37)	
Age, y[b]						
<75	1218	18707	69	766	1.17 (0.85-1.59)	.74
≥75	527	2847	36	175	1.08 (0.77-1.53)	
Overall	1745	21722	107	946	1.16 (0.95-1.41)	
Spine fracture[e]						
Sex						
Men	106	10332	7	282	3.61 (1.76-7.41)	.02
Women	149	9996	10	450	1.17 (0.63-2.19)	
Age, y[b]						
<75	167	17476	9	581	1.64 (0.87-3.10)	.82
≥75	86	2732	8	148	1.83 (0.89-3.79)	
Overall	255	20328	17	732	1.51 (0.93-2.45)	

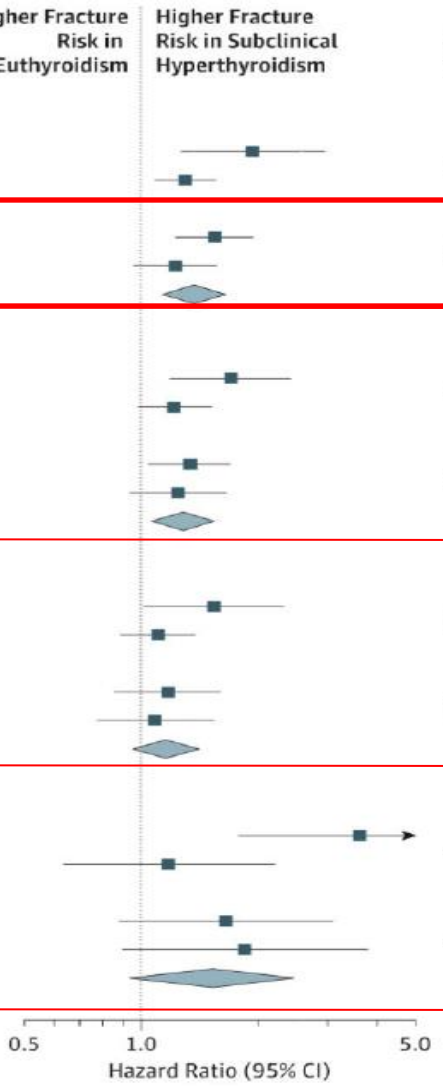


Figure 2. Stratified Analyses for the Association Between Subclinical Hyperthyroidism and Fracture Risk

Fracture Outcome by Thyroid-Stimulating Hormone Levels, mIU/L	Euthyroidism		Subclinical Hyperthyroidism		Hazard Ratio (95% CI)	P for Trend
	No. With Fracture	Total No. of Participants	No. With Fracture	Total No. of Participants		
Hip fracture[a]						
0.45-4.49	2534	56471			1 [Reference]	
0.10-0.44			99	1568	1.34 (1.01-1.77)	.001
<0.10			47	510	1.61 (1.21-2.15)	
Any fracture[b]						
0.45-4.49	2203	25901			1 [Reference]	
0.10-0.44			77	676	1.10 (0.87-1.38)	<.001
<0.10			44	212	1.98 (1.41-2.78)	
Nonspine fracture[c]						
0.45-4.49	1745	21722			1 [Reference]	
0.10-0.44			74	757	1.02 (0.81-1.29)	.07
<0.10			32	185	1.61 (0.96-2.71)	
Spine fracture[d]						
0.45-4.49	255	20328			1 [Reference]	
0.10-0.44			9	566	1.12 (0.59-2.13)	<.001
<0.10			8	162	3.57 (1.88-6.78)	

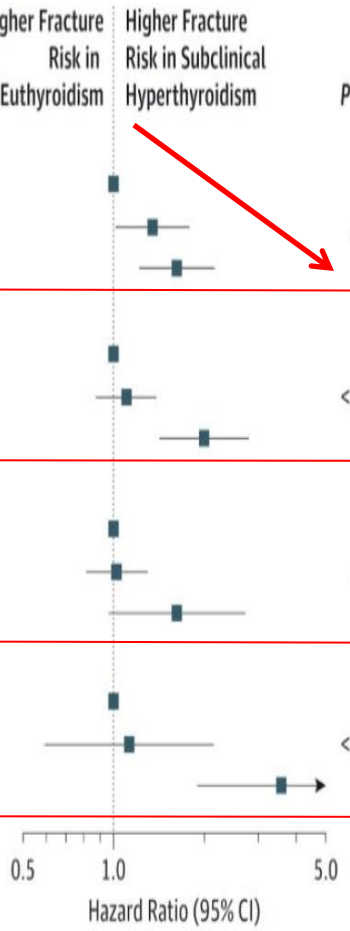


Figure 3. Association Between Subclinical Hyperthyroidism and Fracture Risk Categorized by Thyroid-Stimulating Hormone Level

Does bone benefit from treating postmenopausal women with Shyper?

- Postmenopausal women with SHyper (TSH <0.2 mIU / L) due to multinodular goiter were randomised for I* treatment and followed for two years:
  - treated patients had normal TSH levels
    - had no significant change in lumbar and hip BMD
  - untreated patients with low TSH levels
    - had a continued loss of bone mass of about 1 to 2 percent per year

Faber J et al. Clin Endocrinol (Oxf) 1998

- Significant increase in BMD in persons with SHyper after six months of normalization of thyroid function tests

Greenlund LJ et al. Endocr Pract. 2008

-Suppressed (>low) serum TSH is associated with

- frailty / older men

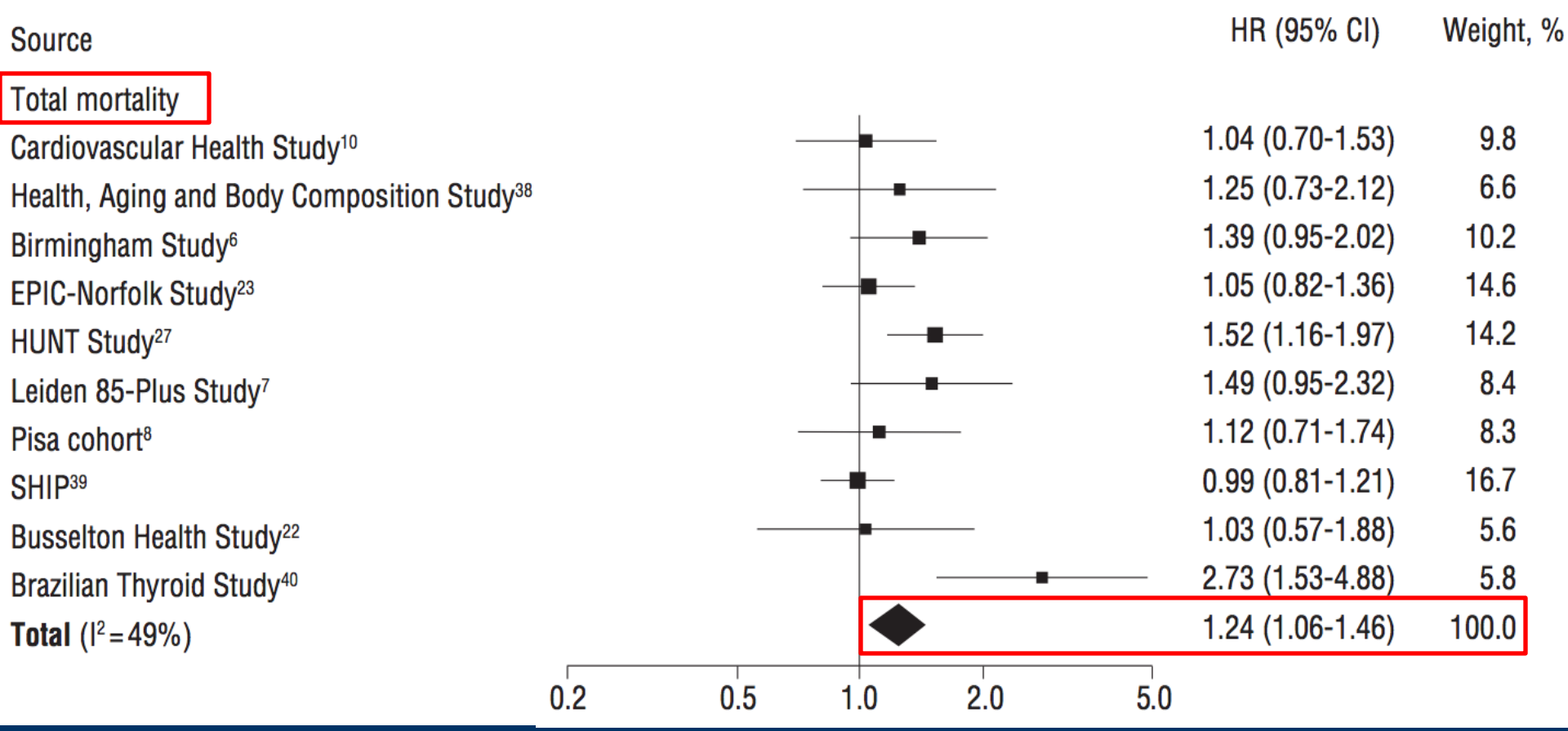
- (hip) fractures

-Lack of treatment evidence on the reversibility of low TSH ~ fracture rate

- ***MORBIDITY***
  - General symptoms
  - Lipids
  - Atherosclerosis, Cardio Vascular aspects
  - Cognitive aspects
  - Frailty / Bone

- **MORTALITY**

Meta-analysis of 10 cohort studies



- 52,000 participants (2188 with SH)

Collet et al. Arch Intern Med 2012

Acute cardiovascular events and all-cause mortality in patients with hyperthyroidism: a population-based cohort study

Olaf M Dekkers[1,2,3], Erzsébet Horváth-Puhó[1], Suzanne C Cannegieter[3], Jan P Vandenbroucke[1,3], Henrik Toft Sørensen[1] and Jens Otto L Jørgensen[4]

EJE (2017) 176, 1–9

Table 1 Characteristics of patients with hyperthyroidism and members of the population comparison cohort at the time of diagnosis/index date.

	Hyperthyroidism cohort (*n* = 85 856)		Population comparison cohort (*n* = 847 057)	
	n	%	*n*	%
Age				
<51 years	22 474	26.5	216 141	26.5
51–60 years	15 865	18.5	158 678	18.5
61–70 years	17 180	20.0	171 722	20.0
>70 years	30 064	35.0	300 516	35.0
Gender				
Female	70 505	82.1	693 588	82.1
Male	15 351	17.9	153 469	17.9
Year of hyperthyroidism diagnosis				
1980–1989	15 603	17.5	–	–
1990–1999	25 414	29.6	–	–
2000–2012	45 379	52.9	–	–
Cancer history				
No	79 002	92.0	787 606	93.0
Yes	6854	8.0	59 451	7.0
Diabetes				
No	81 489	94.9	820 909	96.9
Yes	4367	5.1	26 148	3.1
Hypertension				
No	77 790	90.6	790 443	93.3
Yes	8066	9.4	56 614	6.7
COPD				
No	80 010	93.2	812 156	95.9
Yes	5846	6.8	34 901	4.1

Table 3 Stratified analyses for risk of mortality, venous thromboembolism (VTE), acute myocardial infarction (AMI), ischemic and non-ischemic stroke, arterial embolism, atrial fibrillation (AF) and percutaneous coronary intervention (PCI) in patients with hyperthyroidism. The table presents hazard ratios (adjusted) with 95% confidence intervals.

Outcome	Time since diagnosis	Males (*n* = 15351)	Females (*n* = 70505)	Patients ≤50 years (*n* = 22747)	Patients >50 and ≤60 years (*n* = 15635)	Patients >60 and ≤70 years (*n* = 16798)	Patients >70 years (*n* = 28929)
All-cause mortality	0–1 year	2.47 (2.32, 2.64)	2.57 (2.49, 2.66)	3.37 (2.60, 4.36)	2.81 (2.40, 3.28)	3.03 (2.78, 3.31)	2.46 (2.38, 2.54)
	>1–3 years	1.31 (1.23, 1.40)	1.39 (1.35, 1.44)	1.19 (0.94, 1.50)	1.52 (1.34, 1.73)	1.58 (1.47, 1.71)	1.33 (1.28, 1.37)
	>3–30 years	1.29 (1.24, 1.33)	1.37 (1.35, 1.39)	1.15 (1.09, 1.28)	1.29 (1.24, 1.34)	1.38 (1.34, 1.42)	1.38 (1.35, 1.40)
VTE	0–1 year	2.07 (1.58, 2.70)	1.84 (1.59, 2.12)	2.18 (1.38, 3.42)	2.21 (1.48, 3.30)	2.32 (1.75, 3.07)	1.70 (1.45, 2.00)
	>1–3 years	1.01 (0.76, 1.36)	1.25 (1.10, 1.41)	1.06 (0.70, 1.61)	1.50 (1.07, 2.08)	1.32 (1.04, 1.68)	1.11 (0.95, 1.30)
	>3–30 years	1.13 (0.98, 1.31)	1.13 (1.06, 1.20)	1.07 (0.93, 1.24)	1.18 (1.04, 1.33)	1.19 (1.07, 1.33)	1.06 (0.96, 1.18)
AMI	0–1 year	1.15 (0.93, 1.41)	1.58 (1.40, 1.78)	2.49 (1.31, 4.71)	1.67 (1.19, 2.34)	1.59 (1.27, 1.98)	1.34 (1.18, 1.52)
	>1–3 years	0.93 (0.78, 1.12)	1.03 (0.93, 1.14)	0.87 (0.51, 1.50)	1.23 (0.94, 1.61)	1.03 (0.85, 1.25)	0.95 (0.85, 1.07)
	>3–30 years	1.00 (0.91, 1.10)	1.17 (1.12, 1.24)	1.31 (1.16, 1.49)	1.23 (1.11, 1.35)	1.14 (1.05, 1.24)	1.01 (0.94, 1.09)
Ischemic stroke	0–1 year	1.33 (1.08, 1.63)	1.67 (1.50, 1.85)	1.82 (1.04, 3.19)	2.20 (1.56, 3.12)	1.76 (1.41, 2.21)	1.50 (1.34, 1.67)
	>1–3 years	1.23 (1.04, 1.45)	1.33 (1.22, 1.44)	1.50 (1.01, 2.24)	1.54 (1.18, 2.01)	1.53 (1.29, 1.81)	1.22 (1.11, 1.34)
	>3–30 years	1.06 (0.97, 1.16)	1.28 (1.23, 1.33)	1.27 (1.13, 1.42)	1.31 (1.20, 1.43)	1.23 (1.15, 1.32)	1.19 (1.13, 1.27)
Non-ischemic stroke	0–1 year	1.30 (0.79, 2.16)	1.96 (1.54, 2.49)	1.58 (0.46, 5.40)	2.46 (1.20, 5.04)	2.18 (1.32, 3.61)	1.68 (1.29, 2.19)
	>1–3 years	1.33 (0.89, 1.97)	1.29 (1.05, 1.59)	0.55 (0.17, 1.81)	1.37 (0.78, 2.41)	2.21 (1.56, 3.12)	1.10 (0.86, 1.39)
	>3–30 years	1.13 (0.90, 1.41)	1.22 (1.10, 1.35)	0.72 (0.52, 1.01)	1.28 (1.05, 1.56)	1.21 (1.02, 1.43)	1.32 (1.14, 1.52)
Arterial embolism	0–1 year	1.52 (1.46, 1.58)	2.95 (2.31, 3.77)	4.07 (1.41, 11.77)	2.88 (1.08, 7.64)	3.47 (2.15, 5.61)	2.73 (2.11, 3.54)
	>1–3 years	1.65 (1.03, 2.63)	1.69 (1.37, 2.10)	1.52 (0.52, 4.44)	1.45 (0.73, 2.86)	1.37 (0.83, 2.25)	1.75 (1.39, 2.21)
	>3–30 years	1.64 (1.27, 2.13)	1.69 (1.37, 2.10)	1.76 (1.32, 2.36)	1.49 (1.17, 1.91)	1.66 (1.36, 2.01)	1.65 (1.40, 1.94)
AF	0–1 year	4.47 (3.91, 5.12)	3.56 (3.30, 3.84)	8.47 (5.65, 12.7)	7.13 (5.64, 9.02)	5.36 (4.63, 6.19)	3.09 (2.85, 3.35)
	>1–3 years	1.74 (1.51, 2.01)	1.67 (1.55, 1.81)	2.60 (1.76, 3.84)	2.66 (2.14, 3.30)	1.80 (1.55, 2.09)	1.54 (1.42, 1.67)
	>3–30 years	1.41 (1.31, 1.53)	1.47 (1.42, 1.53)	1.73 (1.57, 1.91)	1.53 (1.42, 1.65)	1.44 (1.36, 1.53)	1.37 (1.30, 1.44)
PCI	0–1 year	1.86 (1.47, 2.36)	2.19 (1.80, 2.66)	3.56 (1.93, 6.56)	1.89 (1.28, 2.81)	2.27 (1.74, 2.96)	1.64 (1.30, 2.07)
	>1–3 years	0.97 (0.76, 1.23)	0.89 (0.72, 1.09)	0.67 (0.32, 1.39)	0.88 (0.59, 1.30)	1.00 (0.76, 1.31)	0.85 (0.68, 1.08)
	>3–30 years	1.05 (0.90, 1.22)	1.07 (0.95, 1.20)	1.34 (1.05, 1.71)	1.16 (0.97, 1.39)	0.99 (0.85, 1.17)	0.87 (0.73, 1.04)

Table 2 Rates and hazard ratios with 95% confidence intervals (95% CIs) for risk of mortality, venous thromboembolism (VTE), acute myocardial infarction (AMI), ischemic and non-ischemic stroke, arterial embolism, atrial fibrillation (AF) and percutaneous coronary intervention (PCI) in patients with hyperthyroidism, stratified by time since diagnosis.

Outcome	Time since diagnosis	Rate (95% CI) per 1000 person-years in hyperthyroidism cohort (n=85 856)	Rate (95% CI) per 1000 person-years in comparison cohort (n=847 057)	Hazard ratio (95% CI), age and sex-adjusted model	Hazard ratio (95% CI), fully adjusted model*
All-cause mortality	0–3 months	122.66 (117.9, 127.4)	27.42 (26.71, 28.14)	4.66 (4.45, 4.89)	4.62 (4.40, 4.85)
	>3–6 months	61.02 (57.59, 64.46)	27.89 (27.16, 28.62)	2.32 (2.18, 2.47)	2.20 (2.06, 2.34)
	>6–12 months	46.13 (44.02, 48.24)	28.06 (27.55, 28.58)	1.76 (1.67, 1.85)	1.68 (1.59, 1.76)
	>1–3 years	38.86 (37.84, 39.89)	29.34 (29.07, 29.62)	1.44 (1.40, 1.48)	1.37 (1.33, 1.41)
	>3–30 years	40.16 (39.64, 40.69)	35.80 (35.65, 35.95)	1.40 (1.38, 1.42)	1.35 (1.33, 1.37)
VTE	0–3 months	6.97 (5.82, 8.11)	2.15 (1.94, 2.35)	3.28 (2.71, 3.97)	3.11 (2.56, 3.77)
	>3–6 months	2.88 (2.13, 3.63)	1.93 (1.73, 2.12)	1.50 (1.13, 1.99)	1.46 (1.10, 1.95)
	>6–12 months	2.62 (2.11, 3.13)	1.91 (1.77, 2.05)	1.43 (1.16, 1.76)	1.36 (1.10, 1.69)
	>1–3 years	2.39 (2.13, 2.65)	1.98 (1.91, 2.05)	1.25 (1.11, 1.40)	1.20 (1.07, 1.35)
	>3–30 years	2.46 (2.33, 2.59)	2.35 (2.31, 2.39)	1.16 (1.09, 1.23)	1.13 (1.06, 1.20)
AMI	0–3 months	9.08 (7.75, 10.40)	3.79 (3.52, 4.07)	2.42 (2.06, 2.85)	2.24 (1.90, 2.65)
	>3–6 months	4.93 (3.94, 5.93)	3.76 (3.48, 4.04)	1.34 (1.08, 1.67)	1.25 (1.00, 1.56)
	>6–12 months	4.48 (3.81, 5.15)	3.71 (3.52, 3.91)	1.24 (1.05, 1.45)	1.12 (0.95, 1.32)
	>1–3 years	3.88 (3.55, 4.21)	3.82 (3.72, 3.92)	1.05 (0.96, 1.15)	1.00 (0.91, 1.10)
	>3–30 years	4.28 (4.11, 4.45)	4.12 (4.07, 4.17)	1.17 (1.12, 1.23)	1.13 (1.08, 1.18)
Ischemic stroke	0–3 months	11.02 (9.56, 12.48)	3.95 (3.67, 4.23)	2.77 (2.38, 3.22)	2.70 (2.31, 3.14)
	>3–6 months	5.03 (4.02, 6.03)	4.32 (4.02, 4.61)	1.18 (0.95, 1.46)	1.11 (0.90, 1.38)
	>6–12 months	5.75 (4.99, 6.51)	4.43 (4.22, 4.64)	1.34 (1.16, 1.55)	1.29 (1.11, 1.48)
	>1–3 years	5.81 (5.41, 6.21)	4.48 (4.37, 4.59)	1.35 (1.25, 1.45)	1.31 (1.21, 1.41)
	>3–30 years	6.43 (6.22, 6.64)	5.83 (5.77, 5.89)	1.27 (1.22, 1.31)	1.24 (1.19, 1.29)
Non-ischemic stroke	0–3 months	1.81 (1.22, 2.40)	0.74 (0.62, 0.86)	2.51 (1.74, 3.63)	2.47 (1.70, 3.58)
	>3–6 months	1.52 (0.96, 2.07)	0.75 (0.62, 0.87)	2.11 (1.41, 3.15)	2.15 (1.42, 3.25)
	>6–12 months	0.91 (0.61, 1.21)	0.70 (0.61, 0.78)	1.34 (0.94, 1.91)	1.30 (0.91, 1.86)
	>1–3 years	0.99 (0.83, 1.16)	0.77 (0.72, 0.81)	1.35 (1.13, 1.62)	1.30 (1.08, 1.55)
	>3–30 years	0.98 (0.90, 1.06)	0.90 (0.87, 0.92)	1.22 (1.11, 1.34)	1.20 (1.10, 1.32)
Arterial embolism	0–3 months	2.62 (1.92, 3.32)	0.45 (0.36, 0.54)	6.08 (4.33, 8.53)	6.08 (4.30, 8.61)
	>3–6 months	1.16 (0.69, 1.64)	0.59 (0.48, 0.69)	2.05 (1.31, 3.22)	1.93 (1.22, 3.07)
	>6–12 months	0.88 (0.59, 1.18)	0.50 (0.43, 0.56)	1.96 (1.36, 2.82)	1.93 (1.33, 2.79)
	>1–3 years	0.87 (0.72, 1.03)	0.54 (0.50, 0.58)	1.73 (1.43, 2.10)	1.66 (1.37, 2.02)
	>3–30 years	0.82 (0.75, 0.90)	0.55 (0.53, 0.57)	1.69 (1.52, 1.87)	1.64 (1.48, 1.82)
AF	0–3 months	34.93 (32.19, 37.67)	4.89 (4.56, 5.22)	7.27 (6.55, 8.07)	7.32 (6.58, 8.14)
	>3–6 months	15.49 (13.62, 17.35)	5.08 (4.75, 5.42)	3.11 (2.71, 3.58)	3.02 (2.62, 3.47)
	>6–12 months	11.92 (10.77, 13.07)	4.94 (4.71, 5.18)	2.43 (2.18, 2.71)	2.36 (2.11, 2.63)
	>1–3 years	8.68 (8.16, 9.20)	5.24 (5.12, 5.37)	1.75 (1.63, 1.86)	1.69 (1.58, 1.81)
	>3–30 years	9.29 (9.02, 9.56)	7.26 (7.19, 7.33)	1.49 (1.45, 1.54)	1.46 (1.42, 1.51)
PCI	0–3 months	7.53 (6.09, 8.97)	2.15 (1.91, 2.40)	3.60 (2.88, 4.51)	3.47 (2.75, 4.37)
	>3–6 months	3.00 (2.07, 3.93)	1.90 (1.67, 2.14)	1.63 (1.17, 2.28)	1.51 (1.08, 2.12)
	>6–12 months	2.45 (1.85, 3.04)	1.75 (1.60, 1.91)	1.42 (1.10, 1.84)	1.35 (1.03, 1.75)
	>1–3 years	1.88 (1.60, 2.16)	2.06 (1.97, 2.15)	0.94 (0.81, 1.10)	0.89 (0.76, 1.04)
	>3–30 years	2.16 (1.98, 2.35)	2.13 (2.08, 2.19)	1.08 (0.99, 1.18)	1.04 (0.95, 1.14)

*Model adjusted for age, sex, calendar time (by study design), cancer, diabetes, hypertension, obesity, chronic obstructive pulmonary disease, liver disease and alcoholism-related diseases.

Conclusions

Results: The study included 85 856 hyperthyroid patients and 847 057 matched population-based controls. Mean follow-up time was 9.2 years. The HR for mortality was highest in the first 3 months after diagnosis of hyperthyroidism: 4.62, 95% CI: 4.40–4.85, and remained elevated during long-term follow-up (>3 years) (HR: 1.35, 95% CI: 1.33–1.37). The risk for all examined cardiovascular events was increased, with the highest risk in the first 3 months after hyperthyroidism diagnosis. The 3-month post-diagnosis risk was highest for atrial fibrillation (HR: 7.32, 95% CI: 6.58–8.14) and arterial embolism (HR: 6.08, 95% CI: 4.30–8.61), but the risks of VTE, AMI, ischemic and non-ischemic stroke and PCI were increased also 2- to 3-fold.

Conclusions: We found an increased risk for all-cause mortality and acute cardiovascular events in patients with hyperthyroidism.

Meta-summary of meta-analyses

- RR (5-95% CI)

Author	Number	Cardiovascular mortality	All cause mortality
Singh 2008	13,267	**1.28 (1.02–1.60)**	1.12 (0.99-1.26)
Ochs 2008	14,449	1.18 (0.98-1.42)	1.12 (0.99-1.26)
Haentjens 2008	14,619	NI	1.22 (0.95-1.57)
Razvi 2008	29,022	1.09 (0.84 –1.41)	NI
Rodondi 2010	55,287	1.14 (0.99- 1.32)	1.09 (0.96-1.24)
Thvilum 2012	35,740	NI	**1.17 (1.00-1.37)**

Treatment evidence ?

ORIGINAL INVESTIGATION

Levothyroxine Treatment of Subclinical Hypothyroidism, Fatal and Nonfatal Cardiovascular Events, and Mortality

Salman Razvi, MD, FRCP; Jolanta U. Weaver, PhD, FRCP; Timothy J. Butler, MRCGP; Simon H. S. Pearce, MD, FRCP

Arch Intern Med. 2012; 172(10):811-817.

UK General Practice Research Database

- Primary care resource linking ~10 million patient records, labs, prescriptions & death certificates
- During 2001 there were 322,291 TSH measurements
- Identified 4,735 people > 40 yrs with TSH 5.0- 10.0 mU/l, nl FT4
- Excluded individuals on L-T4, ATDs, previous thyroid disease, previous IHD, stroke, other vascular disease
- Participants followed 2001-2008 (median 7.6 yrs)
- People aged 40- 70 yrs (n=3093) and >70 yrs (n=1642)
- **53% and 50% were treated with LT4 (median dose 75µg (12.5-175 µg) daily)**
- Primary Care decision

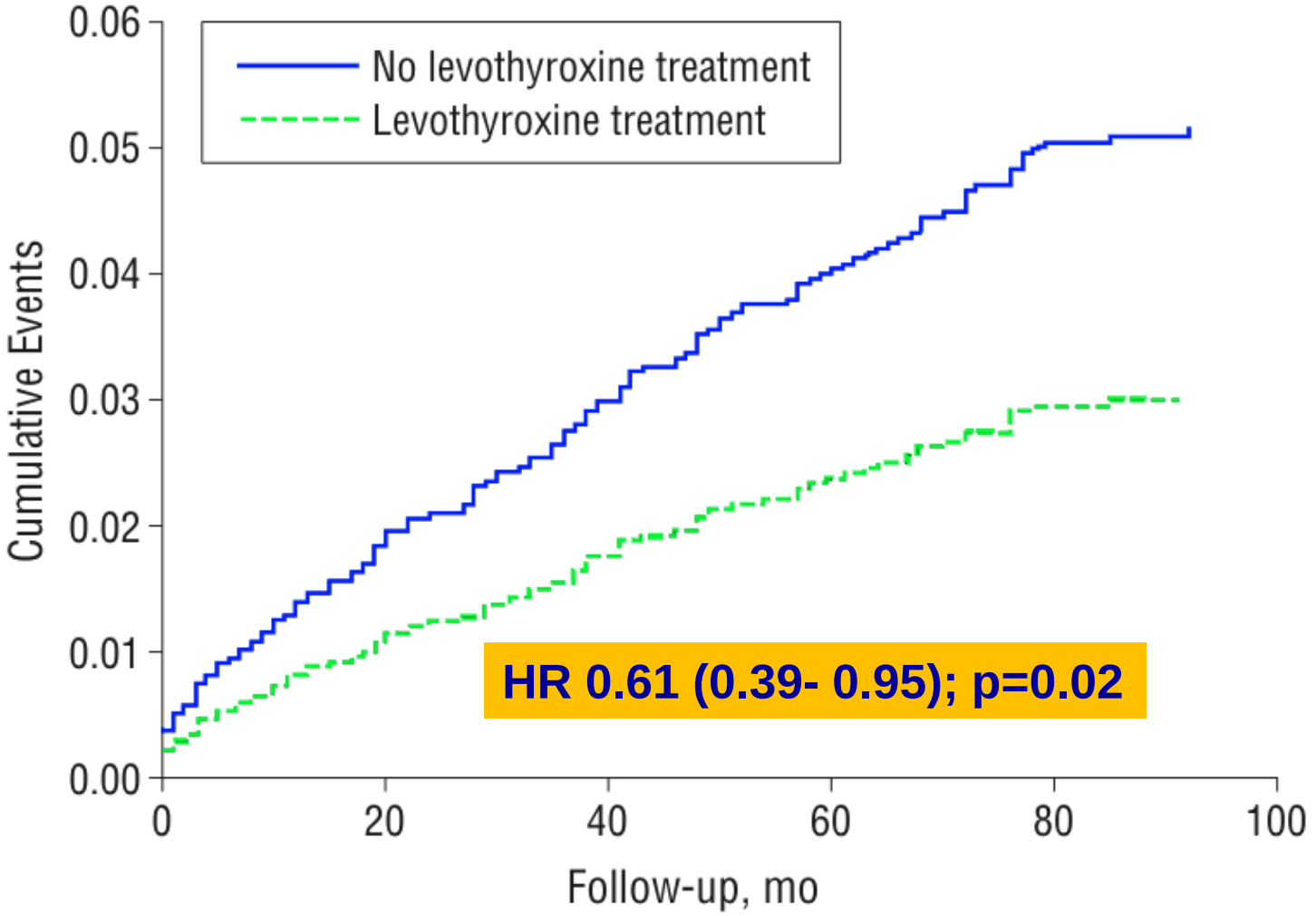
Razvi S et al. Arch Intern Med 2012

Baseline characteristics

	40-70 yrs		>70 yrs	
	Untreated	L-T4 Rx	Untreated	L-T4 Rx
Number	1459	1634	823	819
Age	55.9 ± 8.3	55.9 ± 8.4	79.9 ± 6.5	79.4 ± 6.2
Females	82.5%	87.4%	75.6%	84.6%
Serum TSH (mU/l)	6.3 ± 1.3	6.7 ± 1.4	6.3 ± 1.2	6.8 ± 1.4
Serum FT4 (pM)	13.4 ± 4.4	12.9 ± 3.0	14.6 ± 4.4	13.9 ± 3.4
BMI (Kg/m^2)	27.8 ± 5.9	28.1 ± 6.2	25.4 ± 4.6	26.3 ± 5.1
Systolic BP (mmHg)	136.5 ± 20.0	135.2 ± 19.3	149.4 ± 23.5	149.4 ± 22
T Cholesterol (mM)	5.86 ± 1.34	5.82 ± 1.21	5.93 ± 1.36	5.95 ± 1.25
Diabetes	18.0%	18.1%	26.9%	26.6%
Smokers (current)	18.3%	17.9%	10.9%	10.1%
Deprivation index	17.5	16.75	15.86	16.58
GP contacts/yr	1.2	1.3	2.3	2.4

Fatal & non-fatal vascular events

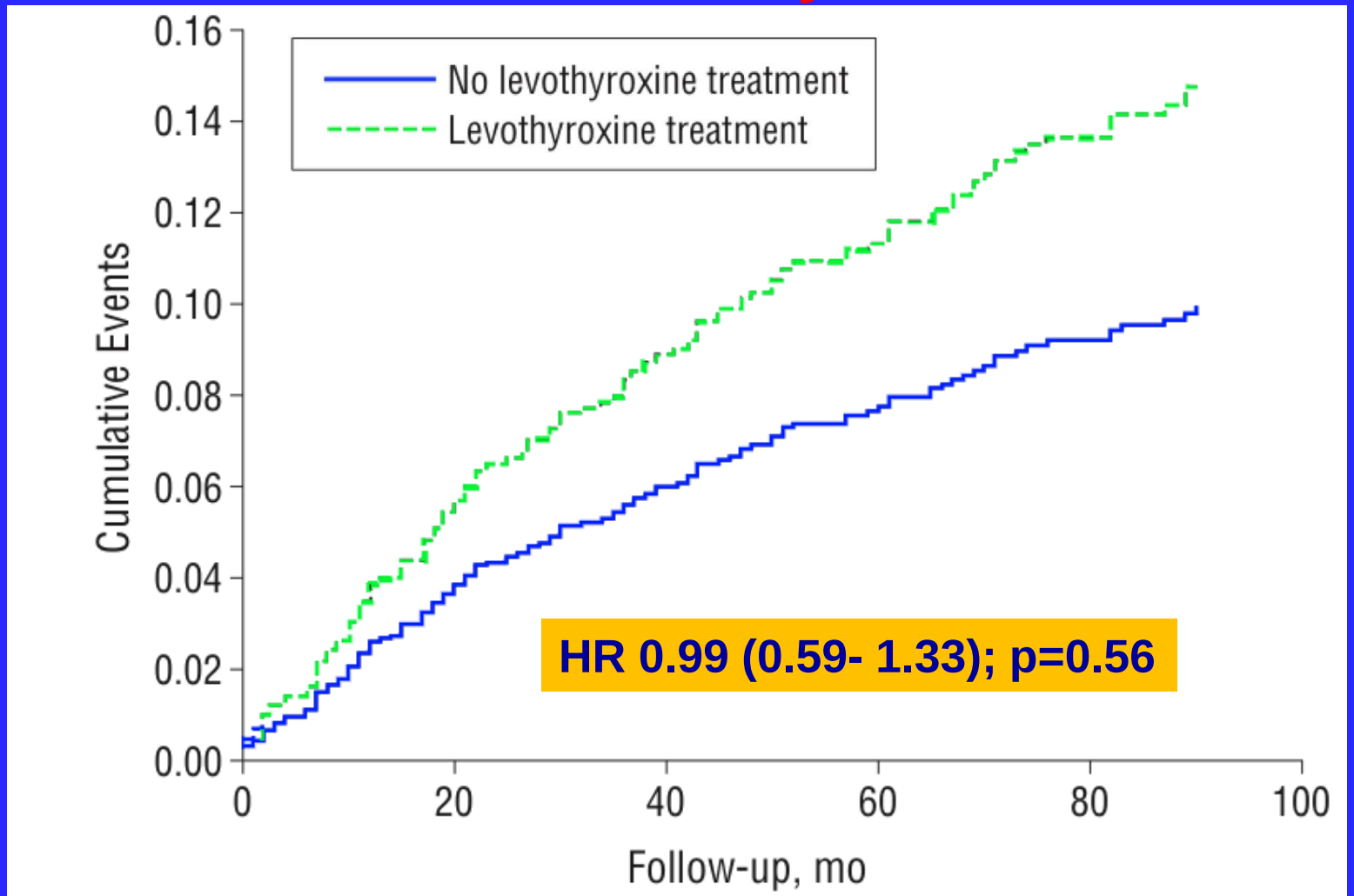
40-70 yrs



Events	58	87	114	138	165
Participants at risk	3035	3006	2979	2955	2928

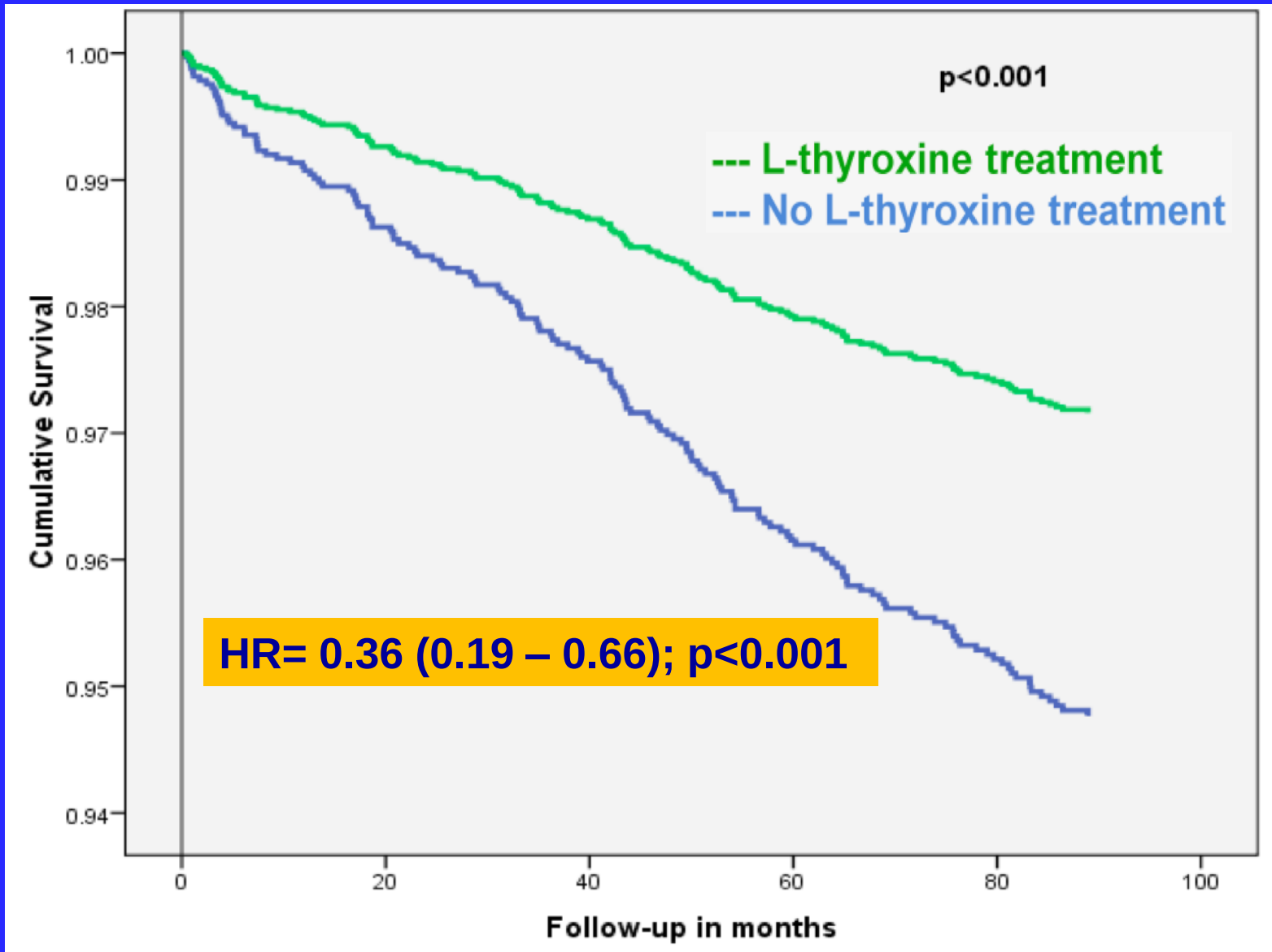
Fatal & non-fatal IHD events

>70 yrs



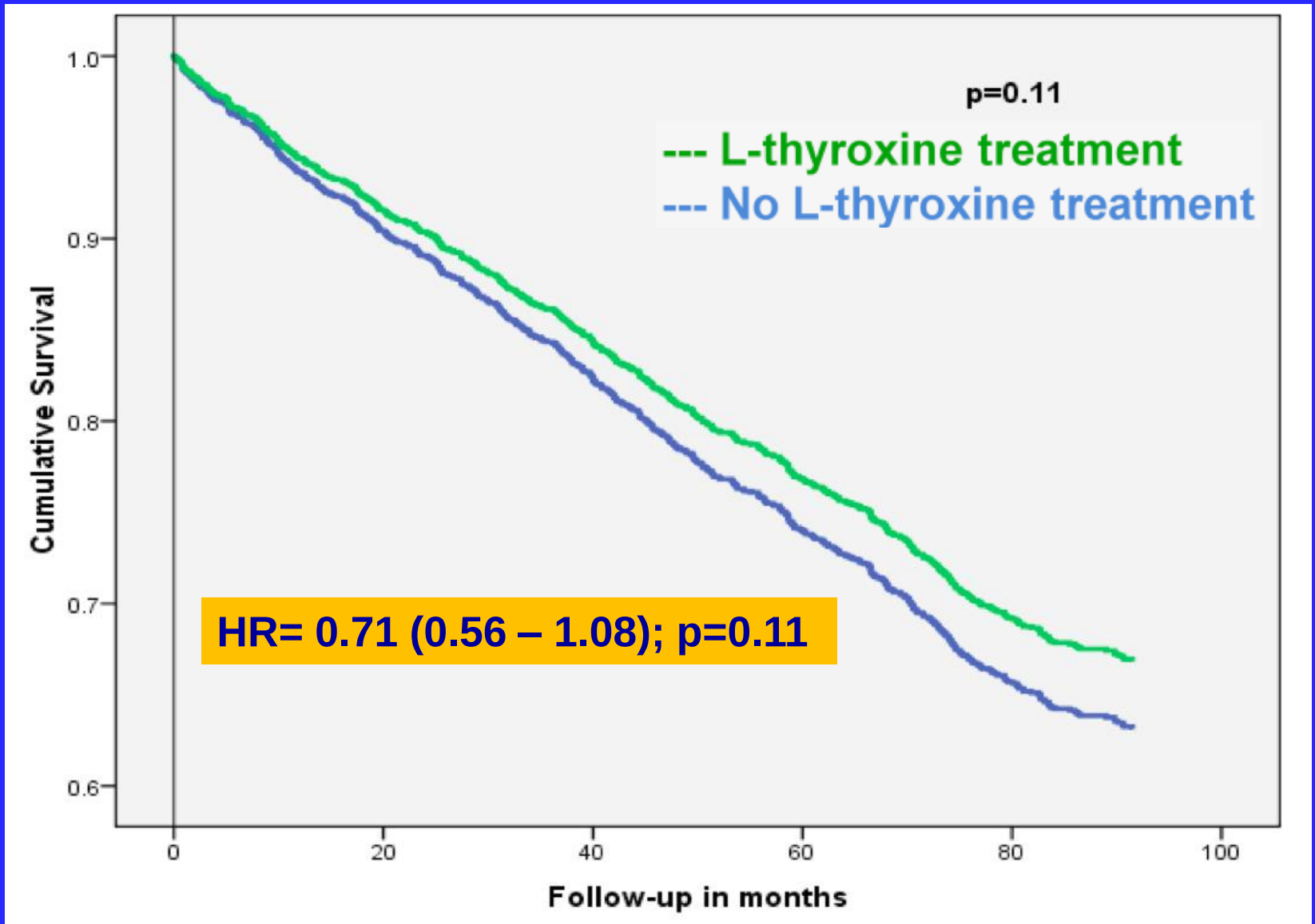
All cause mortality

40-70 yrs



All cause mortality

>70 yrs



Degree of serum TSH elevation

- Median serum TSH: 6.6 mU/l
- Reference group (HR=1) is untreated patients

	Hazard Ratio for vascular events		P value for trend
	TSH 6.6 or less	**TSH > 6.6**	
40-70 yrs	0.62 (0.39-0.96)	0.41(0.26-0.81)	**0.007**
>70 yrs	1.02 (0.66-1.82)	1.19 (0.74-1.80)	NS

Razvi et al. Arch Int Med 2012

- **Strong association with (all-cause) mortality in all age groups and HT, especially during the first year of diagnosis**

- **Weak/absent association with SCH >70 years**

- **This association does however seems to be weaker or even absent in older population (> 70 years)**

- **Two main hypotheses are running to explain this:**
  - **late onset of SCH**
  - **reference range for serum TSH (FT4) are not adapted according to age**

Definition of SCH

High serum TSH (above the upper limit of the assay)

&

Normal FT4

How are normal TSH reference values determined ?

« Normal ranges »

Are determined after correction for

1/ TPO-abs

2/ severe iodine deficiency

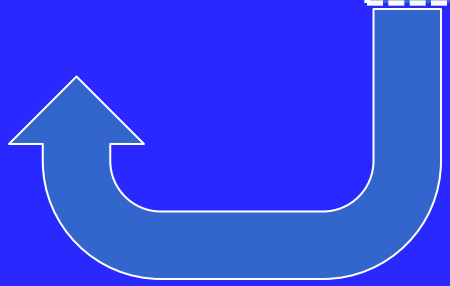
« Normal ranges »

Are determined after correction for

1/ TPO-abs

2/ severe iodine

What about the correction for AGE ?!



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Age-Specific Distribution of Serum Thyrotropin and Antithyroid Antibodies in the U.S. Population: Implications for the Prevalence of Subclinical Hypothyroidism

Martin I. Surks and Joseph G. Hollowell

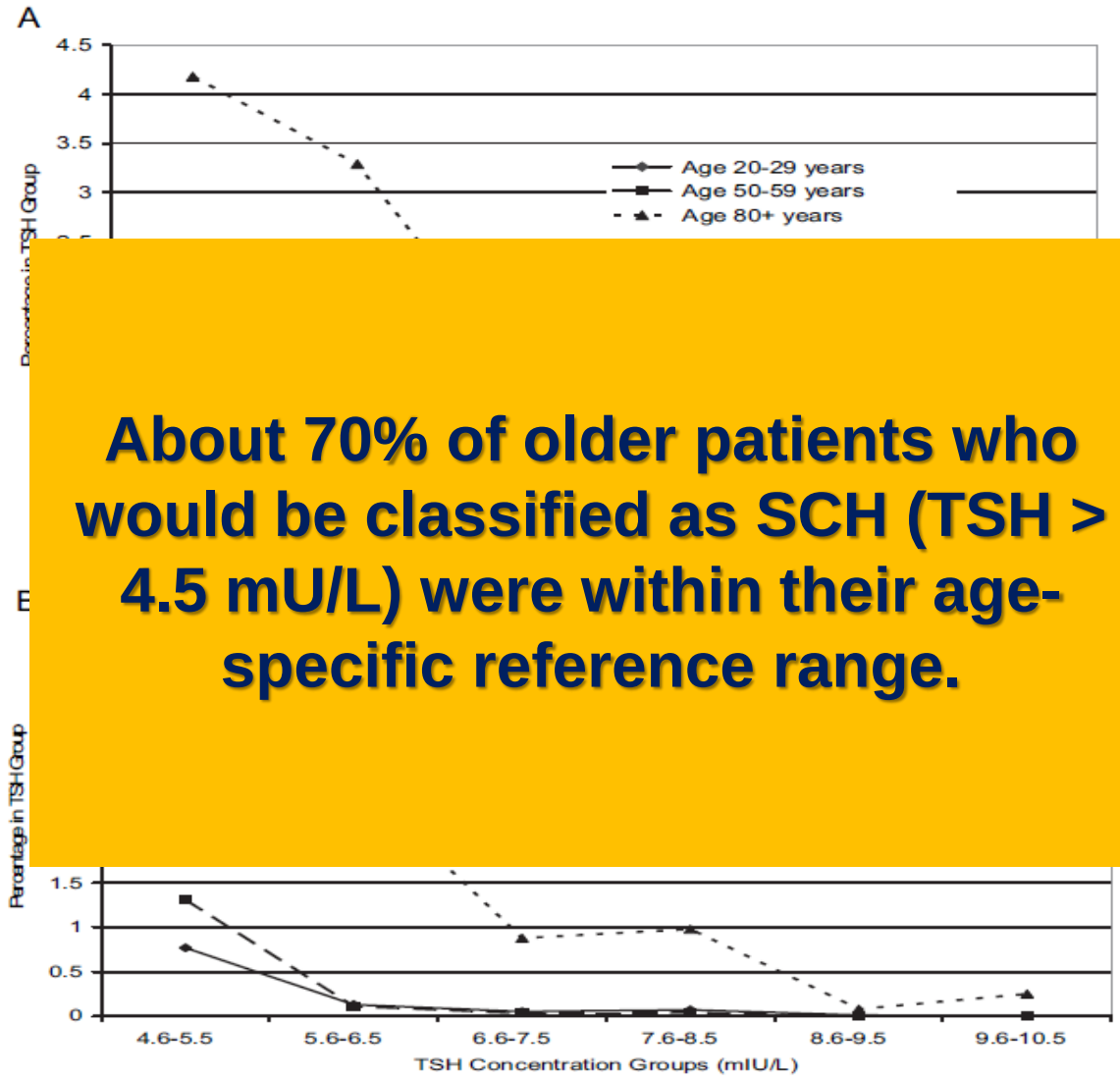
TABLE 3. Mean and median TSH concentration with 97.5 centile (milliinternational units per liter) by age group in disease-free and reference populations, NHANES III (1988–1994)

Age groups (yr)	Sample size	Mean	SE mean	Geometric mean	SE geometric mean	Median	95% confidence limits	97.5 centile	95% confidence limits
A. Disease-free population[a]									
Total	16,533	1.97[b]	0.05	1.50	0.02	1.49	1.46–1.50	5.52	5.24–32.93
12–19	2,431	1.71	0.08	1.39	0.03	1.37	1.31–1.51	4.20	3.82–6.51
20–29	3,186	1.54	0.04	1.27	0.02	1.28	1.25–1.36	4.02	3.76–6.77
30–39	2,981	1.75	0.11	1.36	0.03	1.35	1.31–1.44	4.57	4.04–9.62
40–49	2,290	2.09	0.12	1.60	0.04	1.50	1.46–1.57	5.75	4.99–21.14
50–59	1,554	2.21	0.13	1.67	0.03	1.60	1.57–1.70	5.73	5.28–19.62
60–69	1,834	2.34	0.08	1.83	0.04	1.79	1.71–1.95	7.48	6.21–11.89
70–79	1,333	3.10	0.24	2.03	0.05	1.98	1.87–2.09	9.80	8.58–25.93
80+	924	2.85	0.14	2.02	0.09	2.08	1.92–2.28	9.36	7.71–19.75
B. Reference population[c]									
Total	13,344	1.64[b]	0.02	1.40	0.02	1.39	1.39–1.47	4.12	3.96–6.23
12–19	2,172	1.59	0.04	1.36	0.03	1.35	1.28–1.49	4.07	3.69–4.80
20–29	2,564	1.43	0.03	1.24	0.02	1.26	1.19–1.29	3.56	3.26–4.71
30–39	2,482	1.50	0.04	1.30	0.03	1.29	1.29–1.41	3.69	3.40–4.33
40–49	1,882	1.64	0.04	1.44	0.03	1.40	1.35–1.52	3.82	3.49–4.83
50–59	1,145	1.74	0.03	1.52	0.03	1.50	1.46–1.63	4.03	3.68–4.94
60–69	1,430	1.91	0.05	1.65	0.04	1.67	1.60–1.79	4.33	4.02–5.45
70–79	1,001	2.16	0.06	1.75	0.04	1.76	1.68–1.85	5.90	5.24–8.60
80+	668	2.44	0.12	1.86	0.08	1.90	1.74–2.13	7.49	6.17–10.85

[a] Disease-free population are people who did not report having thyroid disease or taking thyroid medications.

[b] TSH concentration (milliinternational units per liter).

[c] In the reference population, we excluded those who were pregnant; those reporting thyroid disease; those taking estrogens, androgens, lithium, or thyroid medications; and those with antibodies or laboratory evidence of overt hypo- or hyperthyroidism.



About 70% of older patients who would be classified as SCH (TSH > 4.5 mU/L) were within their age-specific reference range.

FIG. 3. Percent TSH concentration greater than 4.5 mIU/liter in the U.S. population by age and concentration groups. A, Disease-free population, antibodies not excluded. B, Reference population, NHANES III (1988–1994).

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Prevalence of thyroid dysfunction and autoimmunity in the older population and implications of age-specific reference ranges

Flora Veltri [a], Francisco Oliveira Rocha [b], Dominique Willems [c], Jean-Philippe Praet [b], Lidia Grabczan [a], Pierre Kleynen [a], Thierry Pepersack [b], Kris Poppe [a,*]

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[b] Endocrine Unit, Department of Clinical Chemistery of the Centre Hosptilalier Universitaire Saint Pierre, Université Libre de Bruxelles (ULB), Rue Haute 322, 1000 Brussels, Belgium
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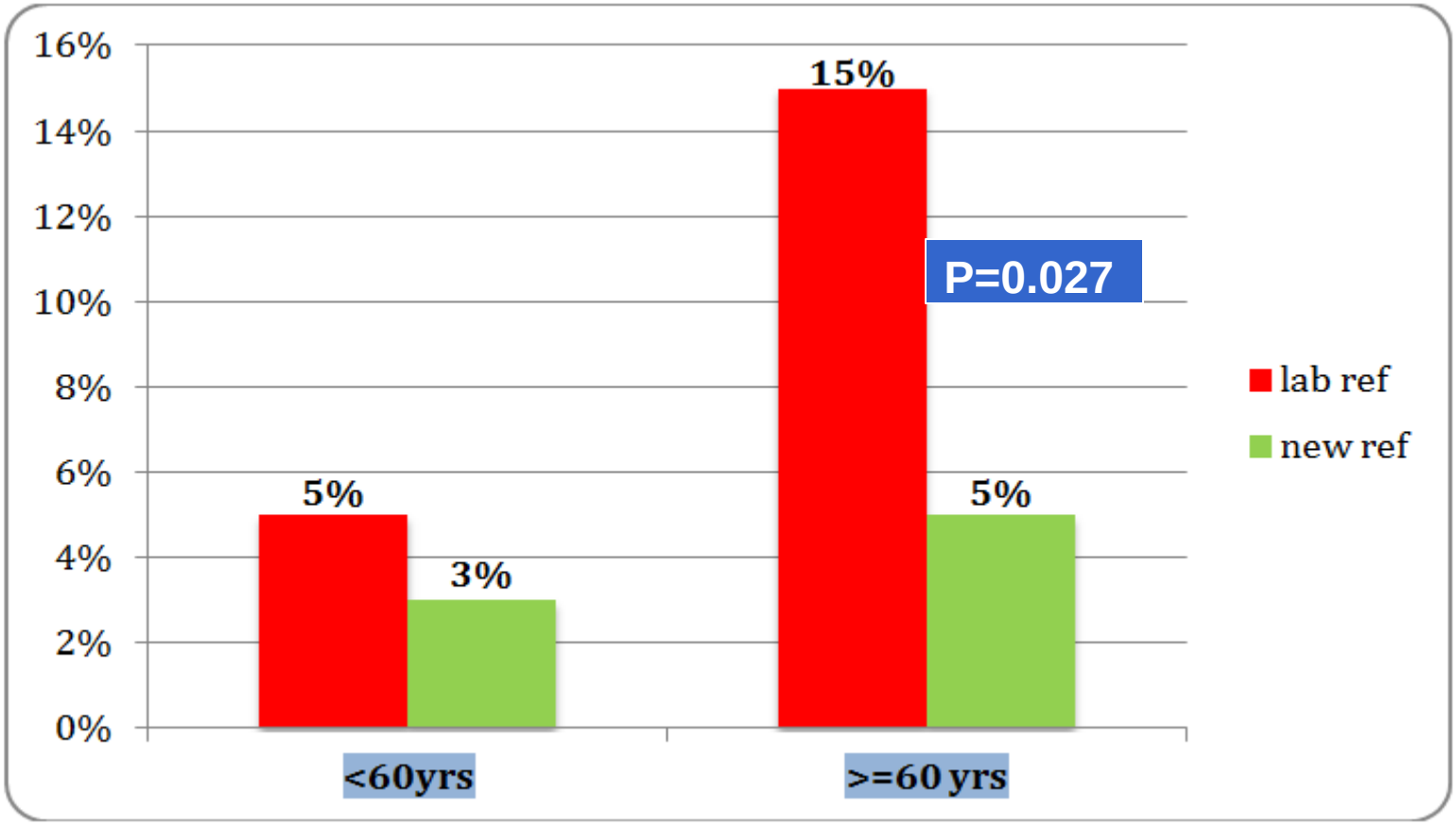
TSH

	<60 yrs		≥60 yrs	p
mean	1,73924569		2,270843373	0,0007
STD	1,135023274		2,040223687	
median	1,5		1,59	
min	0,1		0,09	
max	7,12		8,63	
pc2.5	**0,24575**	**0.30**	**0,153**	
pc97.5	**4,42975**	**4.0**	**8,238**	

Lab refs

Proportion of increased serum TSH according to « new ref for age »

<60 yrs		≥60 yrs	
Lab ref	*New ref*	*Lab ref*	*New ref*
TSH >4.0 mU/L N (%)	TSH >4.43 mU/L N (%)	TSH>4.0 mU/L N (%)	TSH>8.24 mU/L N (%)
30/559 (5%)	17/559 (3%)	17/117 (15%)	6/117 (5%)



REVIEW

Association between increased serum thyrotropin concentration and the oldest old: what do we know?

Associação entre aumento da concentração de tirotropina e longevos: o que sabemos?

Glaucia Cruzes Duarte[1], Maysa Seabra Cendoroglo[1], Lara Miguel Quirino Araújo[1], Clineu de Mello Almada Filho[1]

Einstein. 2015;13(1):117-21

Chart 1. Studies evaluating the association between subclinical hypothyroidism and the oldest old

Author	Year	Study design	n	Age	TSH (upper limit) (mIU/L)	Follow-up	Endpoints	Exclusion criteria	Outcomes/results
Gussekloo et al.[4]	2004	Prospective cohort	704	80-84	4.8	4 years	Thyroid status, disability, cognition, survival	N/A	Abnormally high levels of TSH may prolong life span
Surks et al.[5]	2007	SR of cohort	16,533	12-80+	4.5	N/A	Prevalence of SCH	Report of thyroid disease, goiter, or use of thyroid-related medications	SCH is overestimated, unless an age-specific range for TSH is used
Rodondi et al.[7]	2010	SR of prospective cohort	55,287	18-100	4.5	Variable	CHD and CHD mortality	Mainly symptomatic individuals and/or overt hypothyroidism	SCH associated with risk of CHD and CHD mortality in individuals with TSH>10 mIU/L
Hogervorst et al.[9]	2008	Prospective cohort	1,047	64-94	4.8	2 years	Cognition	Physical frailty or severe cognitive impairment	High log TSH levels associated with lower MMSE scores
Van den Beld et al.[11]	2005	Cross-sectional	403	73-94	4.3	4 years	Thyroid hormones, physical function, mortality	Females, individuals who did not live independently, severe mobility problems, severe systemic disease, physical or mental incapacity to visit study center	Low serum fT4 associated with better 4-year survival, reflecting an adaptive mechanism to prevent excessive catabolism
Atzmon et al.[14]	2009	Case-control	232	97+	4.0	NA	Longevity and TSH	NA	TSH higher in centenarians and may contribute to longevity
Atzmon et al.[15]	2009	Case-control	598	69-85+	4.0	NA	Genetic of high TSH and longevity	NA	SNPs in the TSHR contribute to decreased thyroid function and longevity
Rozing et al.[16]	2010	Cross-sectional	859	89+	4.8	N/A	Longevity and thyroid function	N/A	Low thyroid activity constitutes a heritable phenotype and contributes to familial longevity
Corsonello et al.[17]	2010	Cross-sectional	604	60-85+	4.2	N/A	Longevity and thyroid function	N/A	Decreased thyroid function related to longevity
Spencer et al.[19]	2008	SR of cohort	16,088	12-80+	4.5	NA	TSH and aTPO	Report of thyroid disease or use of thyroid-related medications	Upper limits of TSH may be skewed by aTPO-negative individuals with occult autoimmune thyroid dysfunction
Duarte et al.[20]	2009	Case-control	399	60-92	4.0	NA	Prevalence of thyroid dysfunction in the elderly	Report of thyroid or liver disease, thyroid surgery, radioactive iodine therapy, radiologic tests with contrast media or use of thyroid-related medications	The elderly have higher prevalence of hypothyroidism and thyroid nodules; one-third have elevated urinary iodine excretion and autoimmune thyroiditis
Benseñor et al.[21]	2011	Cross-sectional	1,373	65-80+	5.0	N/A	Prevalence of thyroid dysfunction in the elderly	N/A	Prevalence of thyroid disease in men, and undiagnosed hypothyroidism is higher
Tonial et al.[22]	2007	Cross-sectional	109	60-80	5.6	N/A	Prevalence of hypothyroidism in	N/A	High prevalence of hypothyroidism

Chart 1. Studies evaluating the association between subclinical hypothyroidism and the oldest old

Author	Year	Study design	n	Age	TSH (upper limit) (mIU/L)	Follow-up	Endpoints	Exclusion criteria	Outcomes/results
Gussekloo et al.[4]	2004	Prospective cohort	704	80-84	4.8	4 years	Thyroid status, disability, cognition, survival	N/A	Abnormally high levels of TSH may prolong life span
Surks et al.[5]	2007	SR of cohort	16,533	12-80+	4.5	N/A	Prevalence of SCH	Report of thyroid disease, goiter, or use of thyroid-related medications	SCH is overestimated, unless an age-specific range for TSH is used
Rodondi et al.[7]	2010	SR of	55,287	18-100	4.5	Variable	CHD and CHD	Mainly symptomatic	SCH associated with risk of CHD and CHD mortality in individuals with TSH>10 mIU/L
Hogervorst et al.[9]	2008								High log TSH levels associated with lower MMSE scores
Van den Beld et al.[11]	2005								Low serum fT4 associated with better 4-year survival, reflecting an adaptive mechanism to prevent excessive catabolism
Atzmon et al.[14]	2009								TSH higher in centenarians and may contribute to longevity
Atzmon et al.[15]	2009								SNPs in the TSHR contribute to decreased thyroid function and longevity
Rozing et al.[16]	2010								Low thyroid activity constitutes a heritable phenotype and contributes to familial longevity
Corsonello et al.[17]	2010								Increased thyroid function related to longevity
Spencer et al.[19]	2008								Upper limits of TSH may be skewed by aTPO-negative individuals with occult autoimmune thyroid dysfunction
Duarte et al.[20]	2009							therapy, radiologic tests with contrast media or use of thyroid-related medications	The elderly have higher prevalence of hypothyroidism and thyroid nodules; one-third have elevated urinary iodine excretion and autoimmune thyroiditis
Benseñor et al.[21]	2011	Cross-sectional	1,373	65-80+	5.0	N/A	Prevalence of thyroid dysfunction in the elderly	N/A	Prevalence of thyroid disease in men, and undiagnosed hypothyroidism is higher
Tonial et al.[22]	2007	Cross-sectional	109	60-80	5.6	N/A	Prevalence of hypothyroidism in	N/A	High prevalence of hypothyroidism

No significant increase in risk of CV events, coronary heart disease, or total mortality was observed.

Elevated thyrotropin concentration was associated with longevity.

-Age-specific reference ranges can have an important impact on study results/conclusions/treatment proposals

ESPECIALLY in case of SCH

- **Management in daily practice**

LT4 – SCH ?

Primun non nocere

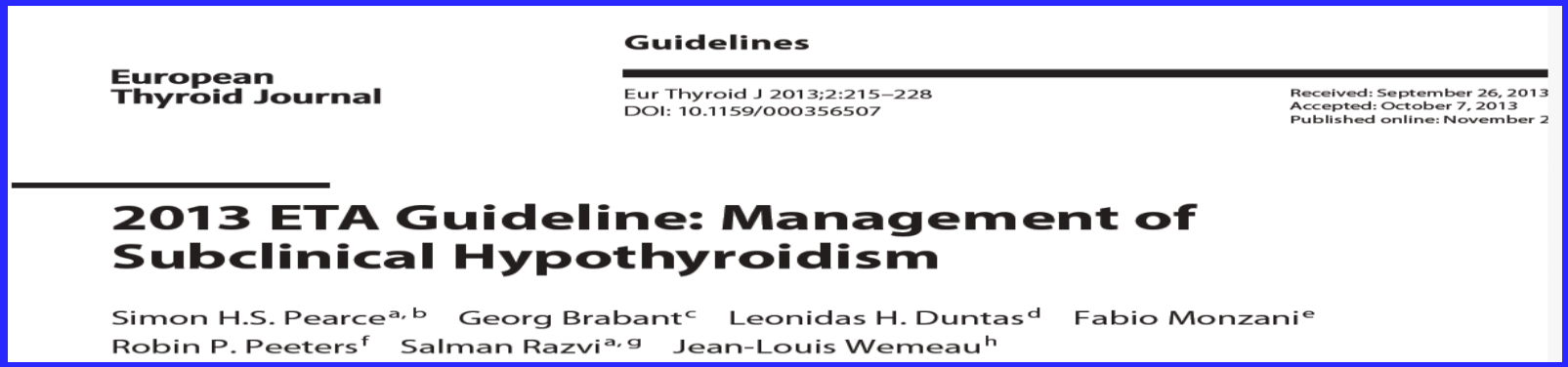
Hipócrates, S. V a AC

Paracelso (1493-1541)

"Dosis sola facit venenum"

Who should we consider treating?

- Symptoms or signs of hypothyroidism
- Age < 70 yrs
- TSH > 7.0 mU/l
- Goitre
- High vascular risk including
  - Ischaemic heart disease
  - Diabetes
  - Dyslipidaemia



Guidelines

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2013 ETA Guideline: Management of Subclinical Hypothyroidism

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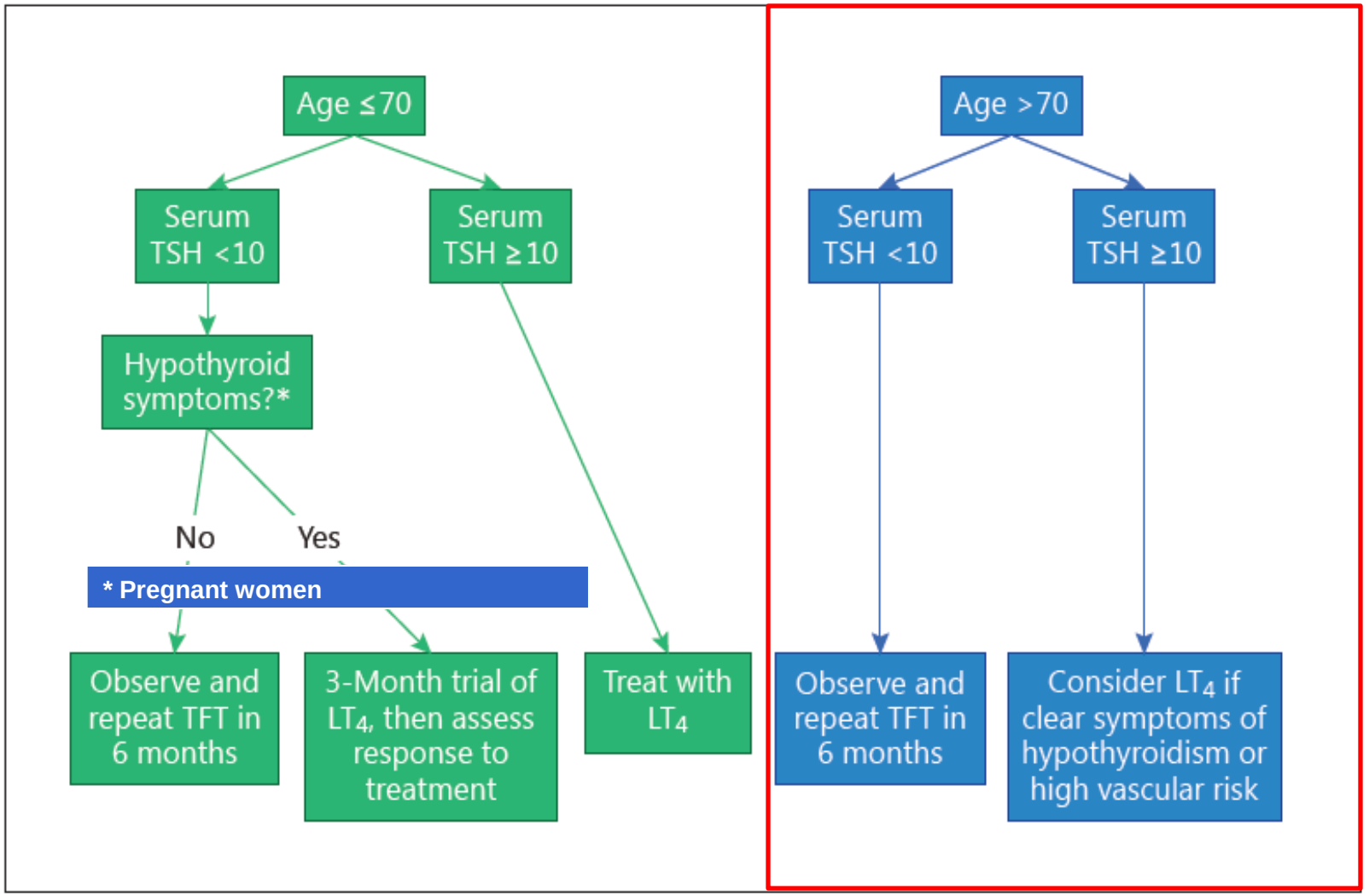
Age ≤70
Serum TSH <10
Serum TSH ≥10
Hypothyroid symptoms?*
No
Yes
* Pregnant women
Observe and repeat TFT in 6 months
3-Month trial of LT4, then assess response to treatment
Treat with LT4
Age >70
Serum TSH <10
Serum TSH ≥10
Observe and repeat TFT in 6 months
Consider LT4 if clear symptoms of hypothyroidism or high vascular risk

MANAGEMENT OF ENDOCRINE DISEASE

L-Thyroxine replacement therapy in the frail elderly: a challenge in clinical practice

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Box 1 | Considerations of levothyroxine replacement in the elderly

- Ideal body weight is best used for dose calculations, and lean body mass is the best predictor of daily requirements;[143] a once-daily dose of 1.6 μg/kg is an optimal starting dose[10]
- Previous reports recommend a low starting dose in elderly individuals (50 μg daily),[144,145] although a retrospective study[146] and a randomized trial[147] demonstrated that full starting doses (100 μg) in asymptomatic individuals are safe
- Current guidelines recommend a starting dose of levothyroxine of 50 μg daily in individuals aged 50–60 years without evidence of coronary heart disease[10]
- Serum TSH level should be rechecked 4–8 weeks after start or change of levothyroxine therapy and every 6–12 months once an adequate replacement dose has been determined[10]
- Absorption of levothyroxine can be reduced owing to interference with a number of medications commonly prescribed to the elderly, including oral bisphosphonates, ferrous sulphate and proton-pump inhibitors[10]
- In patients with known coronary heart disease, the usual starting dose should be reduced (typically to 12.5–25.0 μg daily); clinical monitoring for the onset of angina symptoms is essential[10]
- Overtreatment with levothyroxine should be avoided, especially in elderly patients who are more susceptible to atrial fibrillation[118]
- Postmenopausal women, who constitute a notable proportion of those on levothyroxine replacement, are prone to accelerated bone loss if serum TSH is suppressed as a consequence of excessive levothyroxine replacement[86]
- In view of a physiological increase in the serum TSH concentration with age,[36,39] the threshold for starting levothyroxine replacement in patients with subclinical hypothyroidism aged >60 years should be higher than that in young people

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SPECIAL ARTICLE

2016 American Thyroid Association Guidelines for Diagnosis and Management of Hyperthyroidism and Other Causes of Thyrotoxicosis

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Table 10. Subclinical Hyperthyroidism: When to Treat

Factor	*TSH (<0.1 mU/L)*	*TSH (0.1–0.4 mU/L)*[a]
Age >65 years	Yes	Consider treating
Age <65 years with comorbidities		
Heart disease	Yes	Consider treating
Osteoporosis	Yes	Consider treating
Menopausal, not on estrogens or bisphosphonates	Yes	Consider treating
Hyperthyroid symptoms	Yes	Consider treating
Age <65 years, asymptomatic	Consider treating	Observe

[a]Where 0.4 mU/L is the lower limit of the normal range.

TABLE 8. CLINICAL SITUATIONS THAT FAVOR A PARTICULAR MODALITY AS TREATMENT FOR TOXIC MULTINODULAR GOITER OR TOXIC ADENOMA

Clinical situations	*RAI*	*ATD*	*Surgery*
TMNG			
Pregnancy[a]	x	√√ / !	√ / !
Advanced age, comorbidities with increased surgical risk and/or limited life expectancy	√√	√	x
Patients with previously operated or externally irradiated necks	√√	√	!
Lack of access to a high-volume thyroid surgeon	√√	√	!
Symptoms or signs of compression within the neck	√	-	√√
Thyroid malignancy confirmed or suspected	x	-	√√
Large goiter/nodule	√	-	√√
Goiter/nodule with substernal or retrosternal extension	√	-	√√
Coexisting hyperparathyroidism requiring surgery	-	-	√√

√√ = preferred therapy; √ = acceptable therapy; ! = cautious use; - = not usually first line therapy but may be acceptable depending on the clinical circumstances; X = contraindication.

[a]For women considering a pregnancy within 6 months, see discussion in Section [T2].

- **Global Conclusions**

- Thyroid function results in the elderly (>70 years) should be interpreted with caution as the “normal” range differ from that in younger population.
  - This might explain few associations with SCH

- A single abnormal TSH result should be monitored over time as a substantial number of people with SCH will normalise spontaneously.

- SCH in elderly people should not be treated routinely if TSH is <10 mU/L and if the patient is otherwise well.

- If LT4 is given, start “low & go slow”

- sch is associated with a number of adverse outcomes (and suppressed TSH > low TSH)
- Think about confounding conditions / factors in the DD
- A single abnormal TSH result should be monitored over time as a substantial number of people with SCH will normalise spontaneously
- Endogenous HT seems to be stronger associated with altered outcomes than exogenous HT
- An evidence vacuum remains on the efficacy of the treatment …

Thank you for your attention

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