NAPOLI
25-28 Novembre 2015

60° CONGRESSO NAZIONALE

Simposio
La patologia Tiroidea nell'Anziano

Invecchiamento e Tiroide

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CLUB EndoGer

THE EFFECT OF AGING ON THYROID ECONOMY & SUBTLE THYROID FAILURE

- Modificazioni del profilo ormonale età correlate
- Invecchiamento attivo e funzione tiroidea
- Ipotiroidismo in età geriatrica
- Basi fisiopatologiche del peculiare scenario clinico

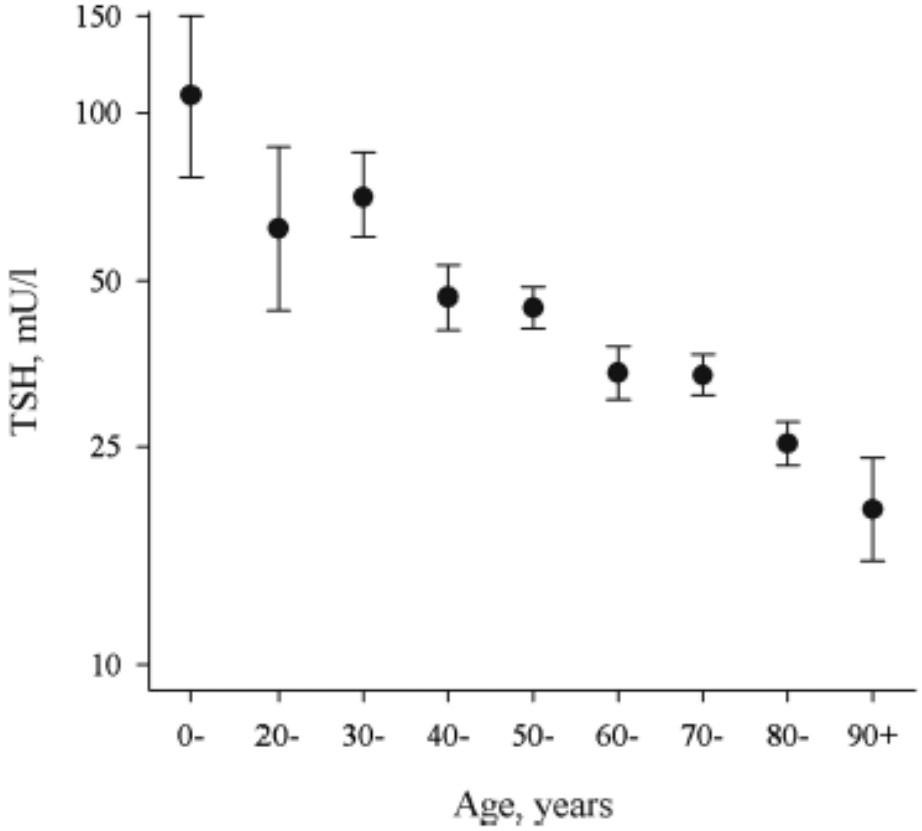
CLUB EndoGer

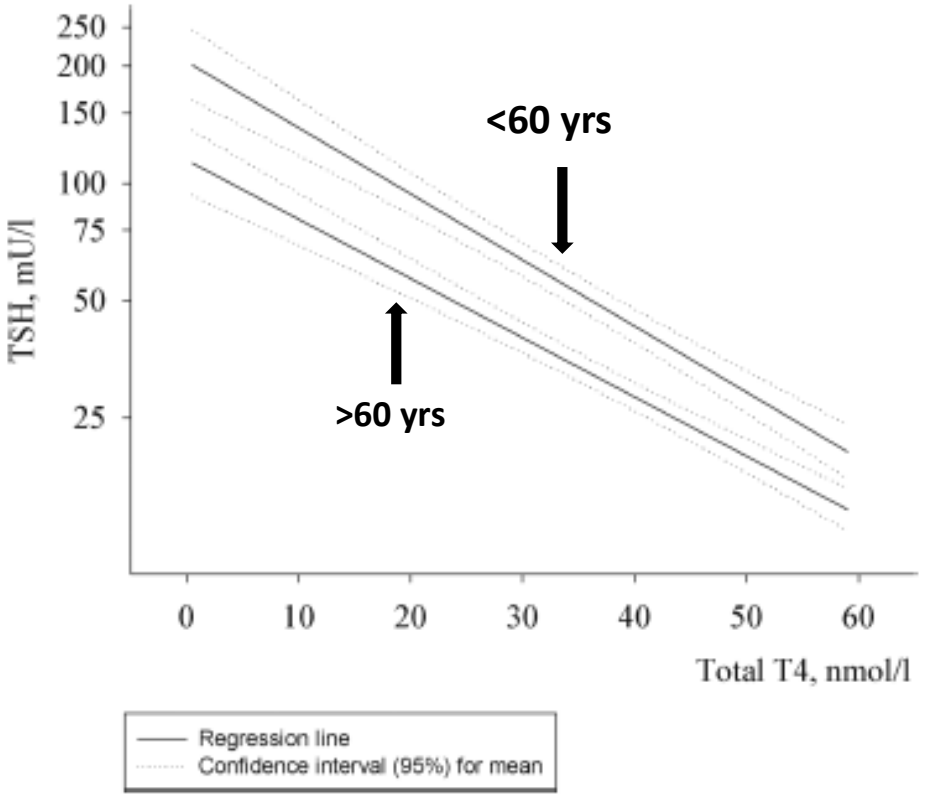
Age-Related Changes in Thyroid Economy

Decreased	No change or decreased	No change	Increased
Production of T4, T3	Thyroid sensitivity to TSH	Pituitary content of TSH	Plasma half-life of T4, T3
Degradation of T4, T3	TSH response to TRH?	Serum levels of *r*T3, TBG. T4	
Pulse amplitude of nocturnal TSH?	Diurnal variation in TSH secretion?		
Thyroid gland uptake of iodine	Serum levels of T3		

Mooradian AD, Drugs Aging 2008 (modif.)

Age Modifies the Pituitary TSH Response to Thyroid Failure

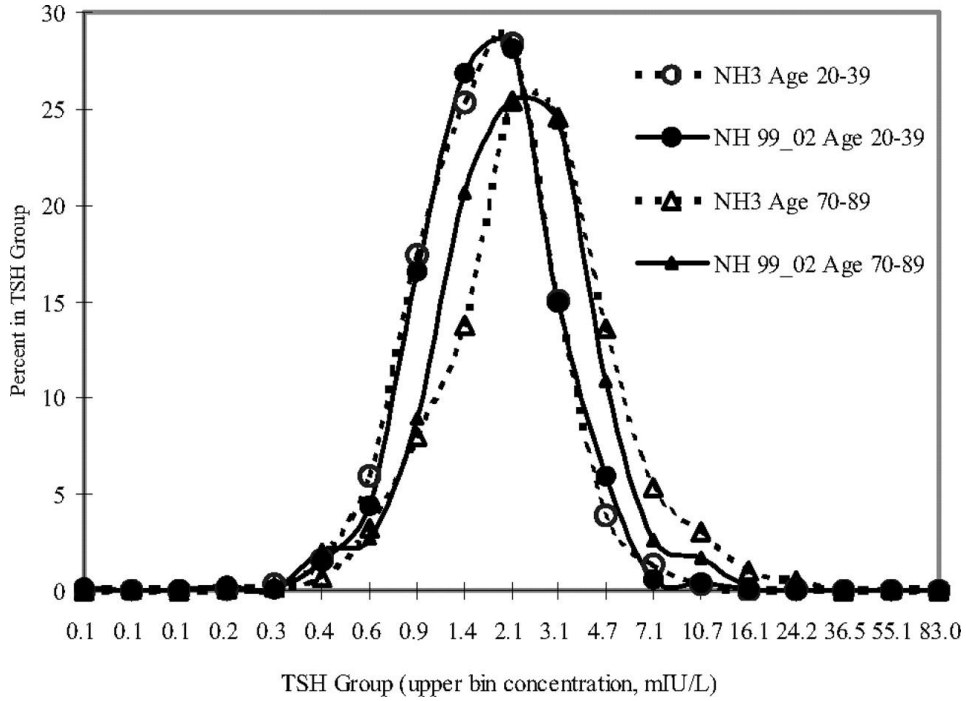




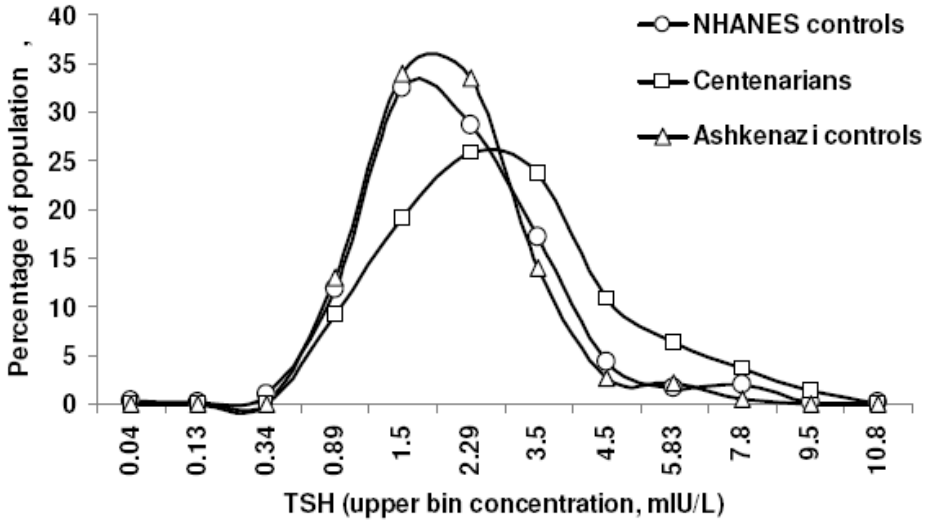
Carlè A et al. Thyroid 2007

TSH distribution by age groups

disease-free populations



NHANES III (1988-1994) and NHANES 1999-2002



236 Ashkenazi Jewish centenarians living independently, median age: 97.7 yrs
188 younger unrelated Ashkenazi Jews (controls), median age: 71.0 yrs
605 NHANES controls, age range 60-79 yrs

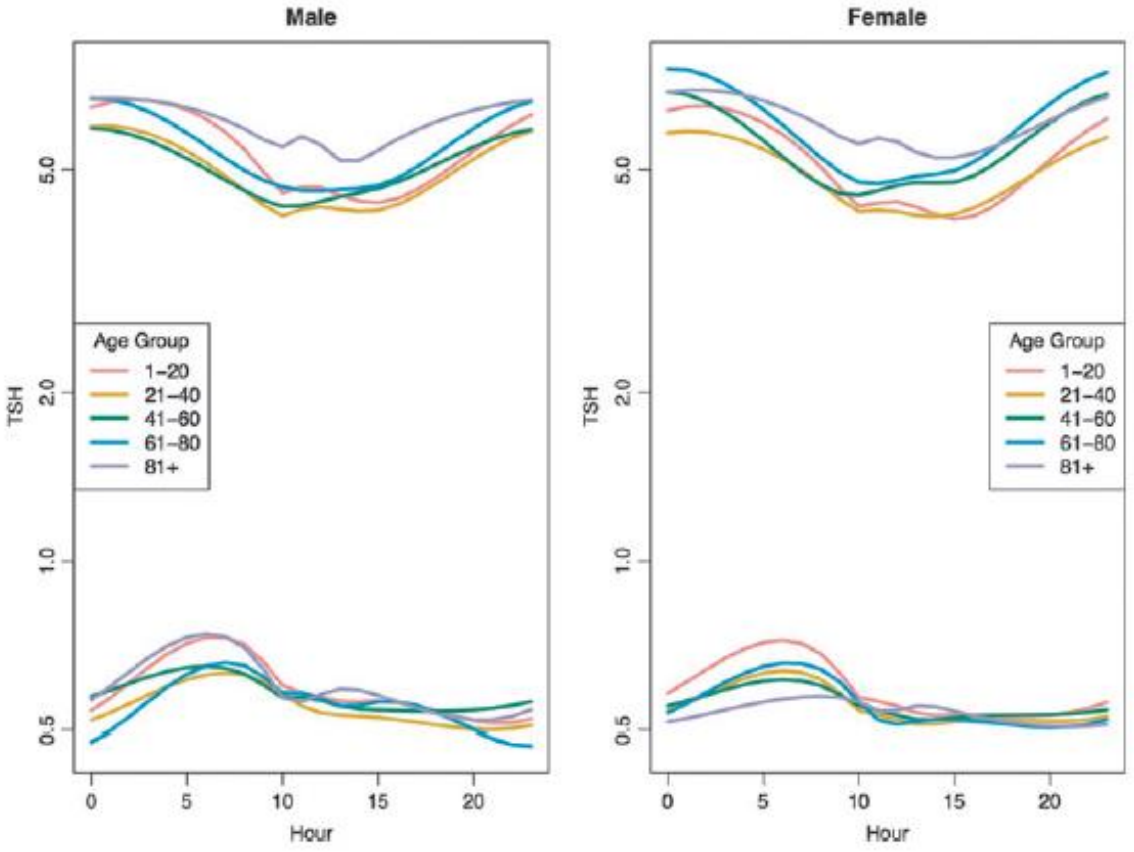
Surks et al. JCEM 2007; Atzmon et al. JCEM 2009

THYROID
Volume 25, Number 8, 2015

DOI: 10.1089/thy.2014.0589

Circadian and Circannual Rhythms in Thyroid Hormones: Determining the TSH and Free T4 Reference Intervals Based Upon Time of Day, Age, and Sex

FIG. 1. Thyrotropin (TSH) circadian reference interval by sex, age, and time of day.

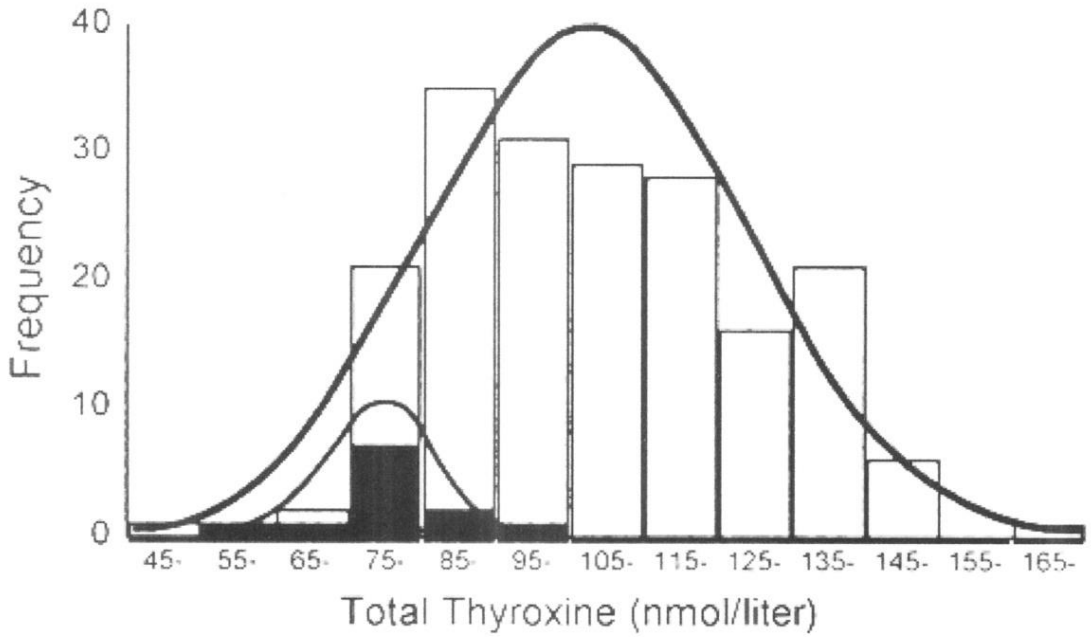


465,593 TSH and 112,994 free T4 measurements from subjects aged 1-104 yrs

Conclusions: The reference interval for TSH varies significantly by age, sex, hour of day, and ethnicity. Time of year does not affect the TSH reference interval, and age, sex, hour of day and time of year do not affect the free T4 reference interval.

Ehrenkranz J et al. 2015

Normal subjects have a narrow individual variation in serum TT_4, TT_3, FT_4 and TSH



Steady state concentrations

Andersen S et al JCEM 2002

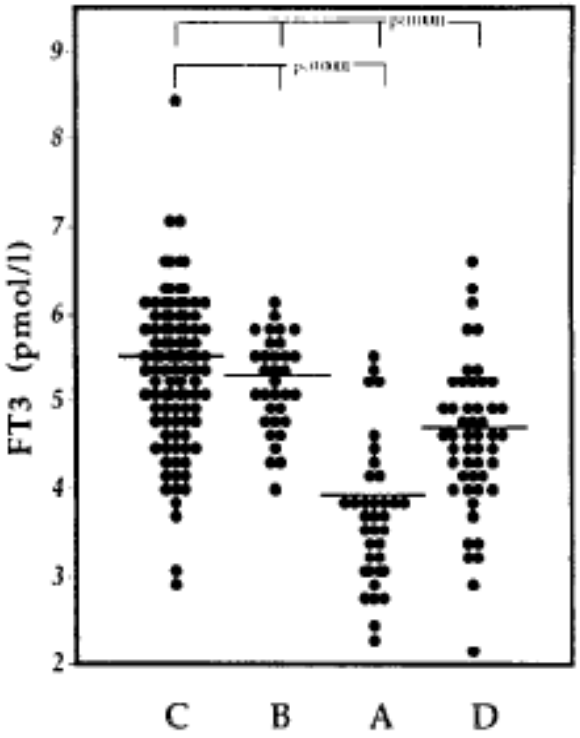
Effect of drugs on thyroid hormone economy

I.	Decreased TSH secretion: corticosteroids, dopamine, octreotide
II.	Increased thyroid hormone secretion: amiodarone, iodide
III.	Decreased thyroid hormone secretion: lithium, amiodarone, iodide
IV.	Increased TBG: estrogens, tamoxifen, methadone, heroin, fluorouracil
V.	Decreased TBG: androgens, anabolic steroids, corticosteroids, slow-release nicotinic acid (niacin)
VI.	Decreased TBG binding: heparin, furosemide, salicylates, fenclofenac, mefenamic acid
VII.	Increased hepatic metabolism: phenytoin, phenobarbitone (phenobarbital), rifampicin (rifampin), carbamazepine
VIII.	Decreased thyroid hormone 5'-deiodinase: propylthiouracil, amiodarone, ß-adrenoceptor antagonists, corticosteroids
IX.	Decreased absorption of levothyroxine sodium (thyroxine): colestyramine, colestipol, aluminium hydroxide, ferrous sulphate, sucralfate
X.	Other causing hyper- or hypothyroidism: interferon-a, interleukin-2

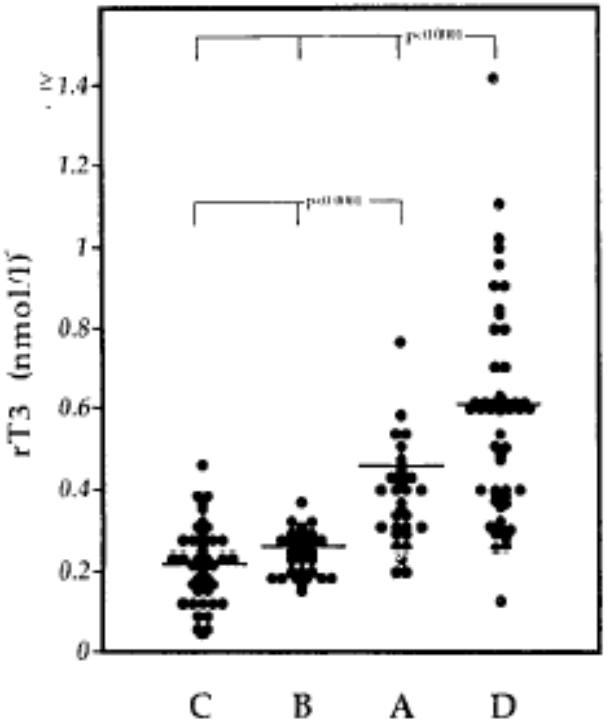
Mooradian AD, Drugs Aging 2008 (modif.)

THYROID HORMONE PROFILE AND WELL AGING

Complex Alteration of Thyroid Function in Healthy Centenarians



Group A aged 100-110 yrs
Group B aged 65-80 yrs
Group C aged 20-64 yrs
Group D patients with NTIS

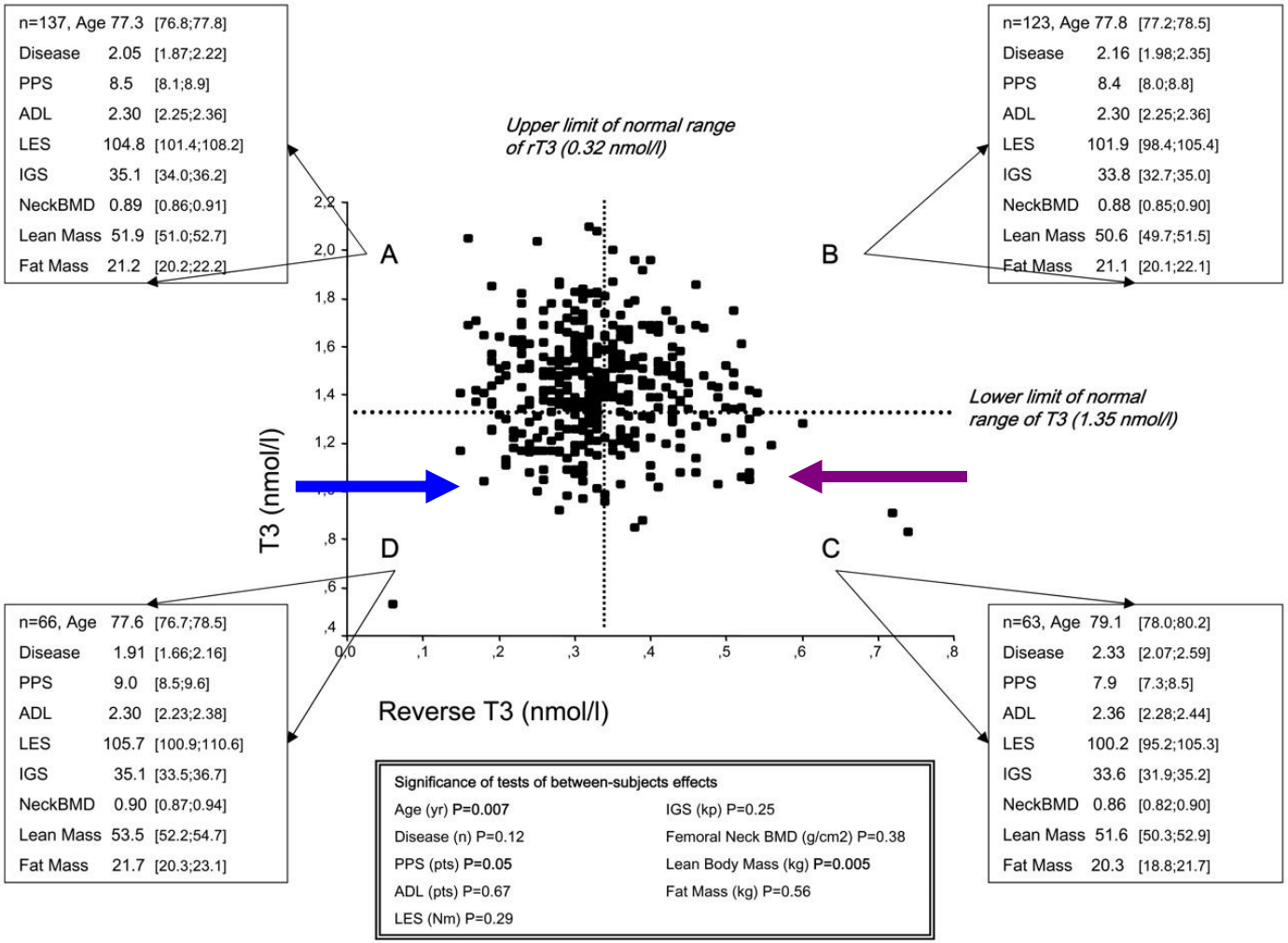


Study groups	FT_4 (pmol/L)	FT_3 (pmol/L)	TSH (mU/L)
A (n = 38)[a]	11.7 (8.5–19.4)	3.68 (2.3–5.5)[b,c]	0.97 (<0.09–2.28)[b,c]
B (n = 33)	11.4 (9.0–20.4)	5.22 (4.0–6.1)	1.17 (0.53–2.74)[d]
C (n = 98)	12.0 (9.4–22.5)	5.38 (2.9–8.4)	1.7 (0.4–4.8)

[b]P < 0.0001 vs group C; [c]P < 0.0001 vs group B; [d]P < 0.01 vs group C.

Mariotti et al. JCEM 1993

Overview of the values of T3 and rT3 within a population of 403 elderly men (>73 yrs)



Low FT_3 and normal rT_3 levels: better 4-yr survival and physical performance

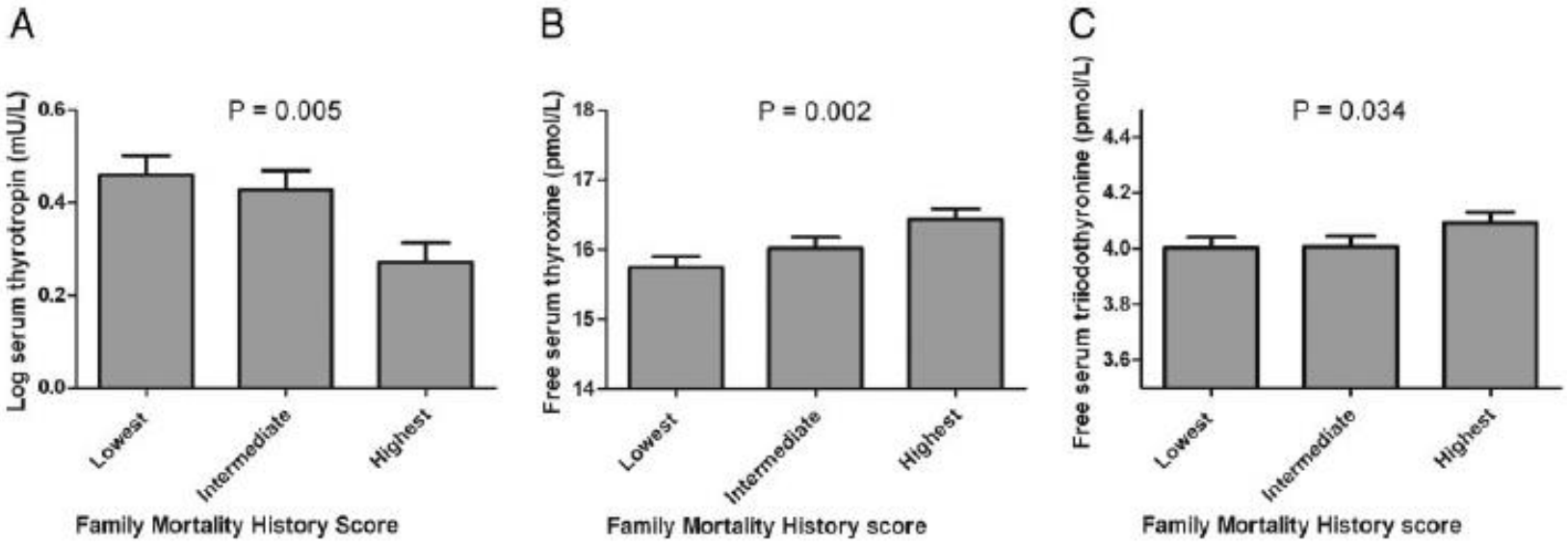
Low FT_3 and high rT_3 levels (NTIS): no survival advantage, lower physical performance

van den Beld et al. JCEM 2005

Longevità Familiare e Funzione Tiroidea

	Study population
Participants (n)	859
Males (n, %)	330 (38.4)
Age (yr)	92.9 (91.4–94.8)
TSH (0.3–4.8 mU/liter)	1.51 (0.95–2.40)
Free T_4 (10–24 pmol/liter)	16.0 (14.4–17.6)
Free T_3 (2.5–5.5 pmol/liter)	4.00 (3.70–4.40)
Hyperthyroidism (n, %)	5 (0.6)
Subclinical hyperthyroidism (n, %)	43 (5.0)
Euthyroidism (n, %)	746 (86.8)
Hypothyroidism (n, %)	7 (0.8)
Subclinical hypothyroidism (n, %)	58 (6.8)

Mortalità familiare relativa ai soggetti con profilo tiroideo nella norma



Rozing MP et al. JCEM 2010

Non-thyroidal illness syndrome and short-term survival in a hospitalised older population

	Non-NTIS group (n = 205)	NTIS group (n = 96)	P^a
Age (years)	79.0 ± 7.8	81.9 ± 7.4	0.003
Gender (% women)	52.7	50.0	0.7
TSH (mIU/l)	1.24 ± 0.90	1.23 ± 0.86	0.9
FT_4 (pmol/l)	14.5 ± 3.5	14.0 ± 3.5	0.3
FT_3 (pmol/l)	3.6 ± 0.7	1.9 ± 0.4	<0.0001
CRP (mg/dl)	49.9 ± 63.3	102.7 ± 83.8	<0.0001
ESR (mm/h)	35.3 ± 24.9	51.8 ± 32.6	<0.0001
Fibrinogen (μmol/l)	13.7 ± 4.5	15.0 ± 5.1	0.03
LDH (IU/l)	410.8 ± 142.2	484.1 ± 205.1	0.0004

Data are expressed as mean ± SD. CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; LDH, lactate dehydrogenase.

Disease	Patients (n)	Gender (%women)	Age (years)	NTIS (%)	P
NYHA IV HF	42	47.6	82.9 ± 6.9	52.4	0.003
NYHA II–III HF	20	30.0	80.6 ± 7.0	20.0	0.37
COPD	42	26.8	81.6 ± 6.8	38.1	0.42
Pneumonia	39	33.3	80.8 ± 7.4	25.6	0.44
Non-controlled DM	19	44.4	75.9 ± 7.1	22.2	0.44
Non-metastatic cancer	27	48.0	85.1 ± 7.2	32.0	0.57
Metastatic cancer	53	50.0	73.3 ± 7.5	53.8	0.0002
Renal failure	42	40.5	82.2 ± 6.2	50.0	0.007
Complicated cirrhosis[a]	9	50.0	75.5 ± 7.3	37.5	0.7
Others[b]	8	37.5	76.2 ± 9.7	0	>0.99

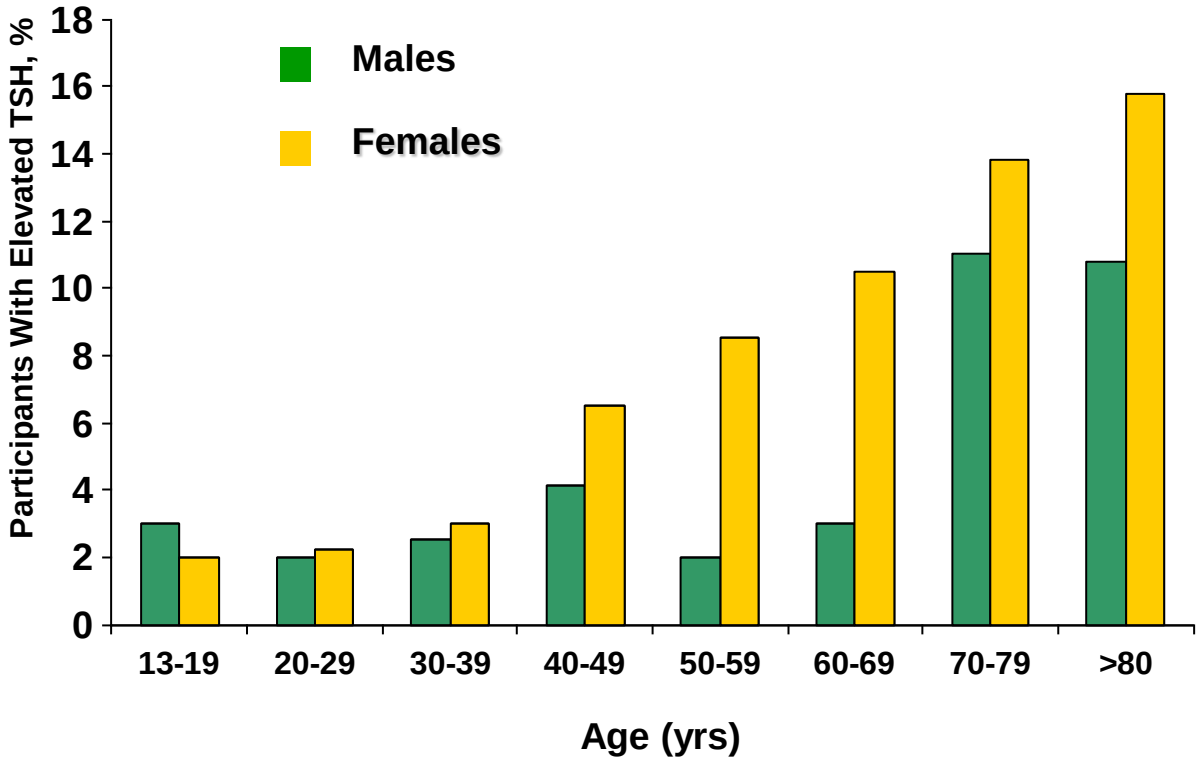
HF, heart failure; COPD, chronic obstructive pulmonary disease (level II–III exacerbation); DM, diabetes mellitus (we assumed for non-controlled DM HbA1c level >8.5%).

Low T3 syndrome is very common in the hospitalized older population (31.9%), emerging as the most sensitive independent predictor of short-term survival (odds ratio: 4.3; 95%CI: 1.7-10.5)

Tognini et al Age & Ageing 2010

THE PECULIAR CLINICAL SCENARIO OF HYPOTHYROIDISM IN OLDER PEOPLE

SUBCLINICAL HYPOTHYROIDISM: PREVALENCE BY GENDER AND DECADE OF AGE



- At <40 years of age, prevalence is relatively low and similar between males and females
- At ≥40 years of age, a higher percentage of female patients have elevated TSH levels

Hollowell et al. JCEM 2002

REVIEW ARTICLE

THE INTERNATIONAL JOURNAL OF CLINICAL PRACTICE

Editor's Choice

Subclinical hypothyroidism: a historical view and shifting prevalence

Table 3 Reported thyroid-stimulating hormone reference ranges by age in reference populations free of thyroid disease and risk factors for thyroid disease

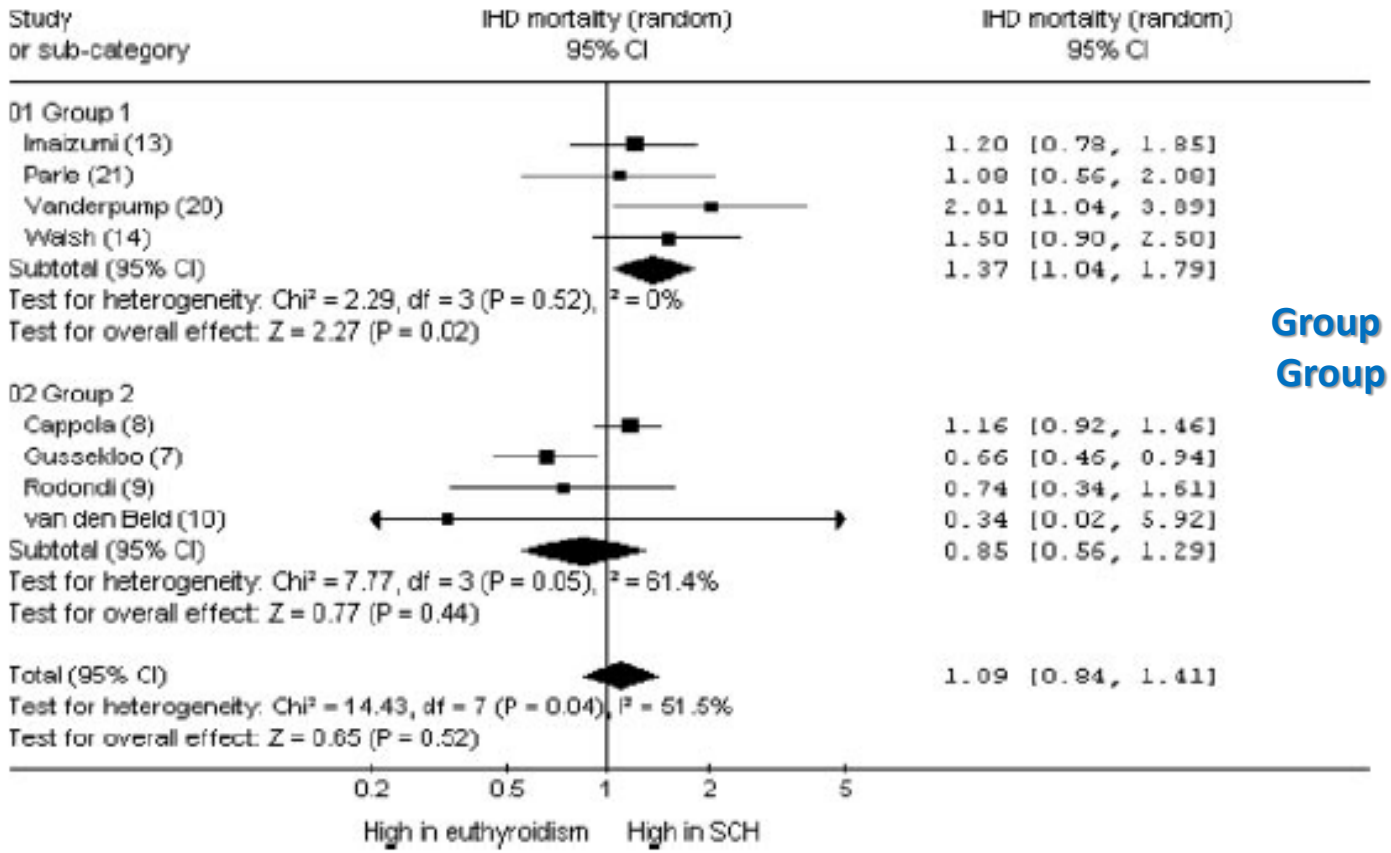
	TSH Concentration, mIU/l										
	Surks and Hollowell, 2007* (26)		Boucai et al., 2011 (28)			Bremner et al., 2012 (67)			Waring et al., 2012† (68)		
Age range, years	Median	97.5th percentile	2.5th percentile	Median	97.5th percentile	Lower limit‡	Mean	Upper limit‡	2.5th percentile	Median	97.5th percentile
12–19§,¶	1.35	4.07	0.41	1.30	3.78	0.51	1.34	3.54			
20–29	1.26	3.56	0.40	1.30	3.60						
30–39**	1.29	3.68	0.38	1.25	3.60	0.48	1.25	3.21			
40–49††	1.40	3.82	0.41	1.40	3.90	0.44	1.32	3.92			
50–59‡‡	1.50	4.03	0.49	1.50	4.20	0.42	1.31	4.08			
60–69§§	1.61	4.35	0.46	1.60	4.70	0.38	1.34	4.30			
70–79¶¶	1.76	5.90	0.47	1.74	5.60	0.52	1.66	5.28	0.71	1.56	2.67
80–84***	1.90	7.49	0.44	1.90	6.30				0.60	2.20	6.16
85–89									0.51	2.59	6.41
≥ 90									0.20	2.53	7.96

*2.5th percentile not reported. †Study included only an elderly population. ‡Mean ± 2 SD of log-transformed serum TSH concentrations. §13–19 for Boucai et al. ¶< 30 for Bremner et al. **30–40 for Bremner et al. ††40–50 for Bremner et al. ‡‡50–60 for Bremner et al. §§60–70 for Bremner et al. ¶¶> 70 for Bremner et al.; 75–79 for Waring et al. ***≥ 80 for Surks and Hollowell and Boucai et al. TSH, thyroid-stimulating hormone.

It is currently difficult to ascertain the true prevalence of sHT in older people and to correctly label and treat sHT patients

Hennessey JV & Espaillat R 2015

CHD mortality in longitudinal studies of people with sHT according to age



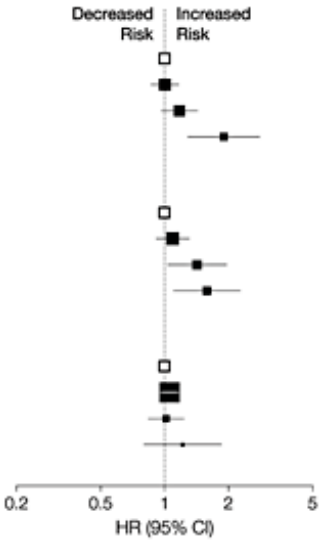
Group 1: aged < 65 yrs
Group 2: aged > 65yrs

Dividing the studies according to age group substantially reduced the heterogeneity in both of the groups and shows that the increased IHD/cardiovascular mortality is confined to the group 1 studies.

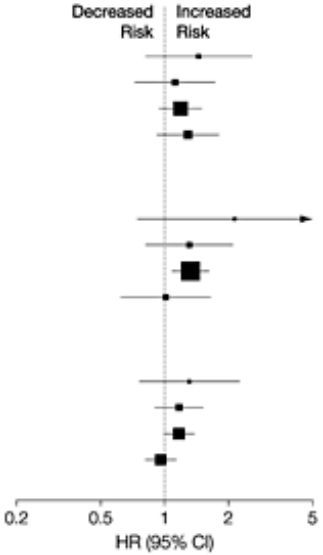
Razvi et al. JCEM 2008

HR for CHD Events, CHD and Total Mortality According to Elevated TSH Categories and sHT Stratified by Age

CHD Events by TSH Level, mIU/L[b]	No. of Events	No. of Participants	HR Ratio (95% CI)
0.5-4.49	4040	23957	1 [Reference]
4.5-6.9	264	1344	1.00 (0.86-1.18)
7.0-9.9	96	441	1.17 (0.96-1.43)
10-19.9	70	235	1.89 (1.28-2.80)
			P<.001 for trend
CHD Mortality by TSH Level, mIU/L[c]			
0.5-4.49	1958	50953	1 [Reference]
4.5-6.9	132	2363	1.09 (0.91-1.30)
7.0-9.9	50	652	1.42 (1.03-1.95)
10-19.9	28	333	1.58 (1.10-2.27)
			P = .005 for trend
Total Mortality by TSH Level, mIU/L[d]			
0.5-4.49	8749	51837	1 [Reference]
4.5-6.9	640	2431	1.06 (0.96-1.17)
7.0-9.9	170	672	1.02 (0.84-1.24)
10-19.9	105	347	1.22 (0.80-1.87)
			P = .39 for trend



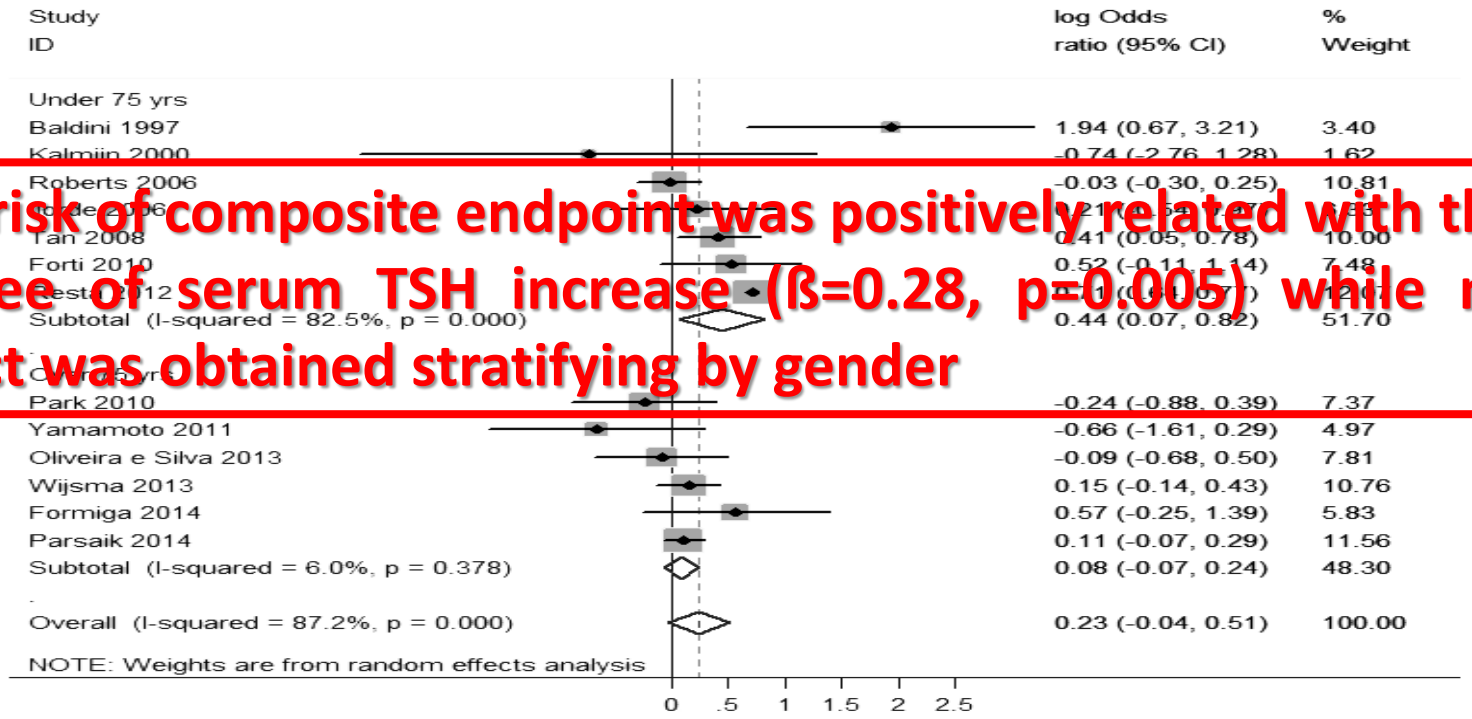
	Subclinical Hypothyroidism		Euthyroidism		
CHD Events, by Age, y[b]	No. of Events	No. of Participants	No. of Events	No. of Participants	HR Ratio (95% CI)
18-49	12	221	272	5405	1.46 (0.82-2.62)
50-64	54	517	997	7876	1.13 (0.73-1.77)
65-79	322	1158	2511	9668	1.20 (0.95-1.51)
≥80	42	124	260	1008	1.30 (0.93-1.82)
					P = .78 for trend
CHD Mortality, by Age, y[c]					
18-49	2	444	54	13560	2.13 (0.74-6.14)
50-64	16	1072	316	18513	1.30 (0.81-2.08)
65-79	163	1608	1288	16567	1.32 (1.08-1.62)
≥80	29	224	300	2313	1.01 (0.62-1.63)
					P = .22 for trend
Total Mortality, by Age, y[d]					
18-49	14	465	340	13832	1.31 (0.76-2.26)
50-64	108	1121	1492	18875	1.17 (0.90-1.51)
65-79	623	1636	5316	16785	1.17 (0.99-1.39)
≥80	170	228	1601	2345	0.96 (0.81-1.12)
					P = .29 for trend



Rodondi, N. et al. JAMA 2010

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

Risk of Composite Endpoint stratified by age



The risk of composite endpoint was positively related with the degree of serum TSH increase (ß=0.28, p=0.005) while no effect was obtained stratifying by gender

Composite endpoint: Incidence or prevalence of dementia, MMSE score, miscellaneous cognitive function scales, WMS Revised score and total memory quotient

Pasqualetti G et al JCEM 2015

Subclinical Hypothyroidism and the Risk of Stroke Events and Fatal Stroke: An Individual Participant Data Analysis

SPECIAL FEATURE

Review

Data Extraction and Synthesis: We collected individual participant data on 47 573 adults (3451 subclinical hypothyroidism) from 17 cohorts and followed up from 1972–2014 (489 192 person-years). Age- and sex-adjusted pooled hazard ratios (HRs) for participants with subclinical hypothyroidism compared to euthyroidism were 1.05 (95% confidence interval [CI], 0.91–1.21) for stroke events (combined fatal and nonfatal stroke) and 1.07 (95% CI, 0.80–1.42) for fatal stroke. Stratified by age, the HR for stroke events was 3.32 (95% CI, 1.25–8.80) for individuals aged 18–49 years. There was an increased risk of fatal stroke in the age groups 18–49 and 50–64 years, with a HR of 4.22 (95% CI, 1.08–16.55) and 2.86 (95% CI, 1.31–6.26), respectively (p trend 0.04). We found no increased risk for those 65–79 years old (HR, 1.00; 95% CI, 0.86–1.18) or ≥80 years old (HR, 1.31; 95% CI, 0.79–2.18). There was a pattern of increased risk of fatal stroke with higher TSH concentrations.

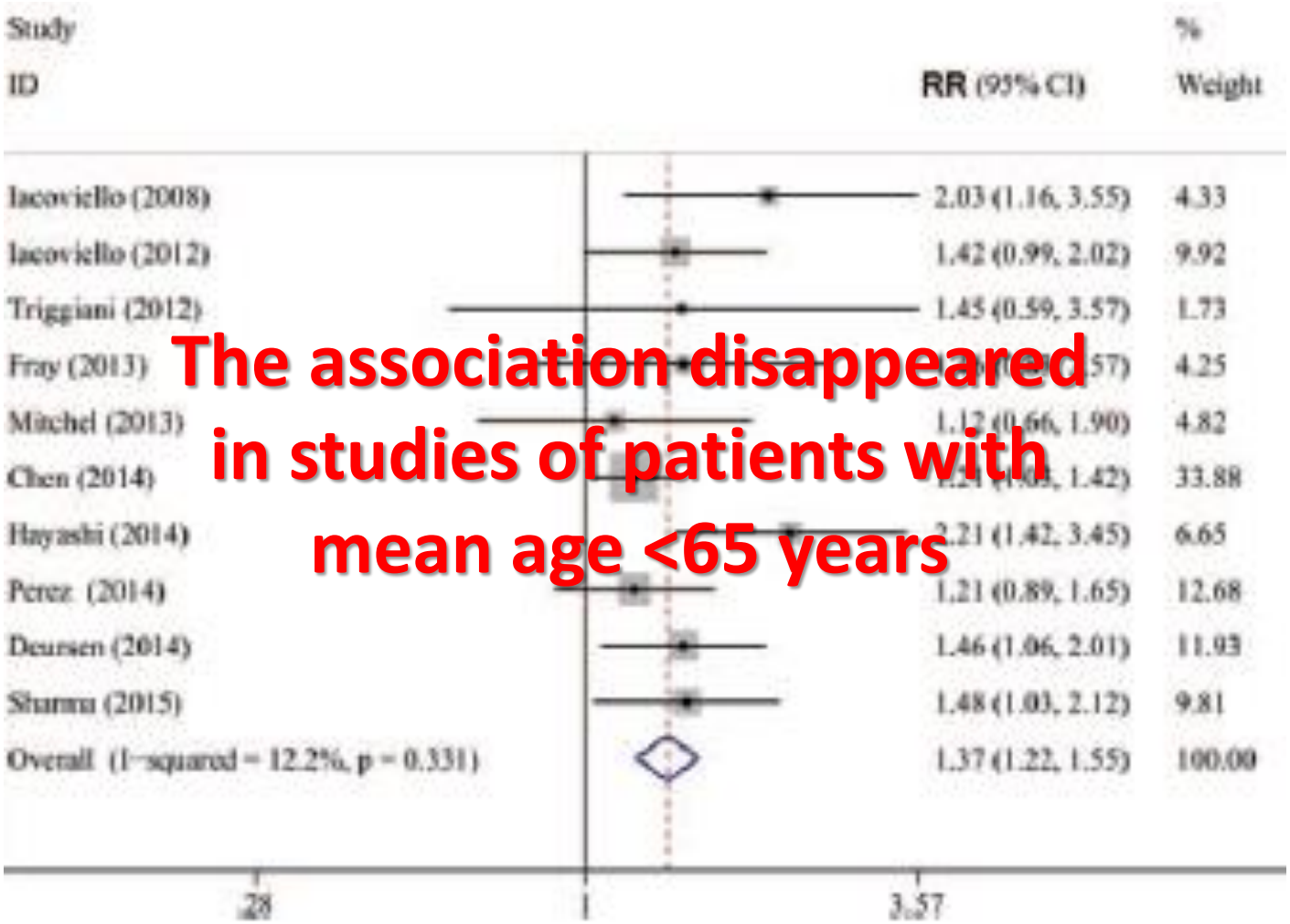
Conclusions: Although no overall effect of subclinical hypothyroidism on stroke could be demonstrated, an increased risk in subjects younger than 65 years and those with higher TSH concentrations was observed. (*J Clin Endocrinol Metab* 100: 2181–2191, 2015)

Chaker L. et al. JCEM 2015

The lack of utilization of age related serum TSH reference ranges and consequent potential misdiagnosis of sHT in older people may account for the peculiar scenario of the elderly

Prognostic Role of Hypothyroidism in Heart Failure

A meta-analysis



The association disappeared in studies of patients with mean age <65 years

Forest plot of RR for hypothyroidism and cardiac death and/or hospitalization in patients with heart failure

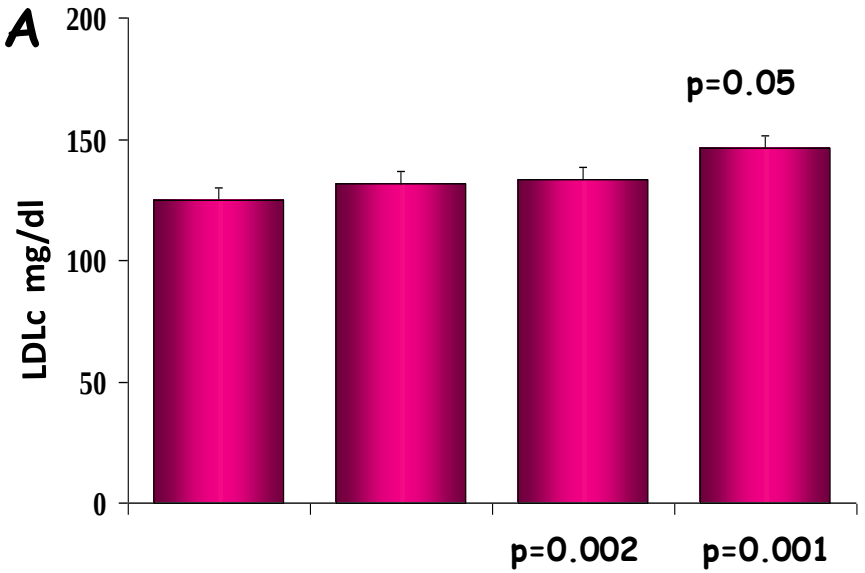
Dengfeng Gao et al Medicine 2015

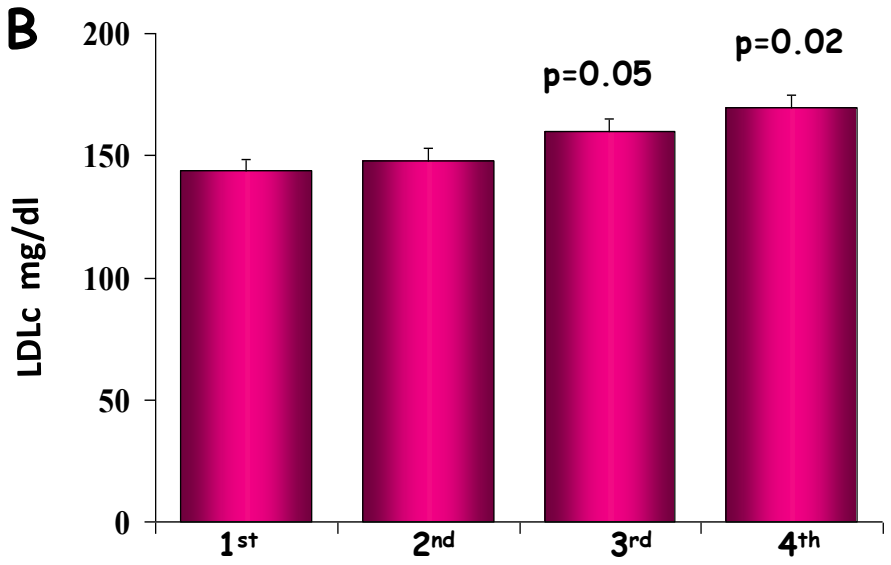
Age and gender substantially influence the relationship between thyroid status and the lipoprotein profile

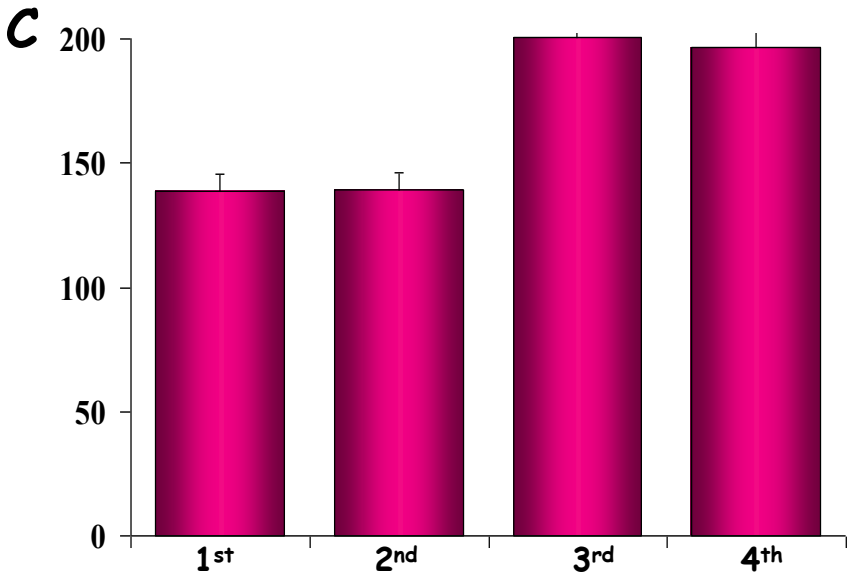
2308 consecutive outpatients with suspected or diagnosed thyroid disease

Age Groups
A: 30-49 years
B: 50-64 years
C: >65 years

1st quartile: TSH <0.36 mUI/L
2nd quartile: TSH >0.36 <3.60 mUI/L
3rd quartile: TSH >3.60 <10 mUI/L
4th quartile: TSH >10 mUI/L

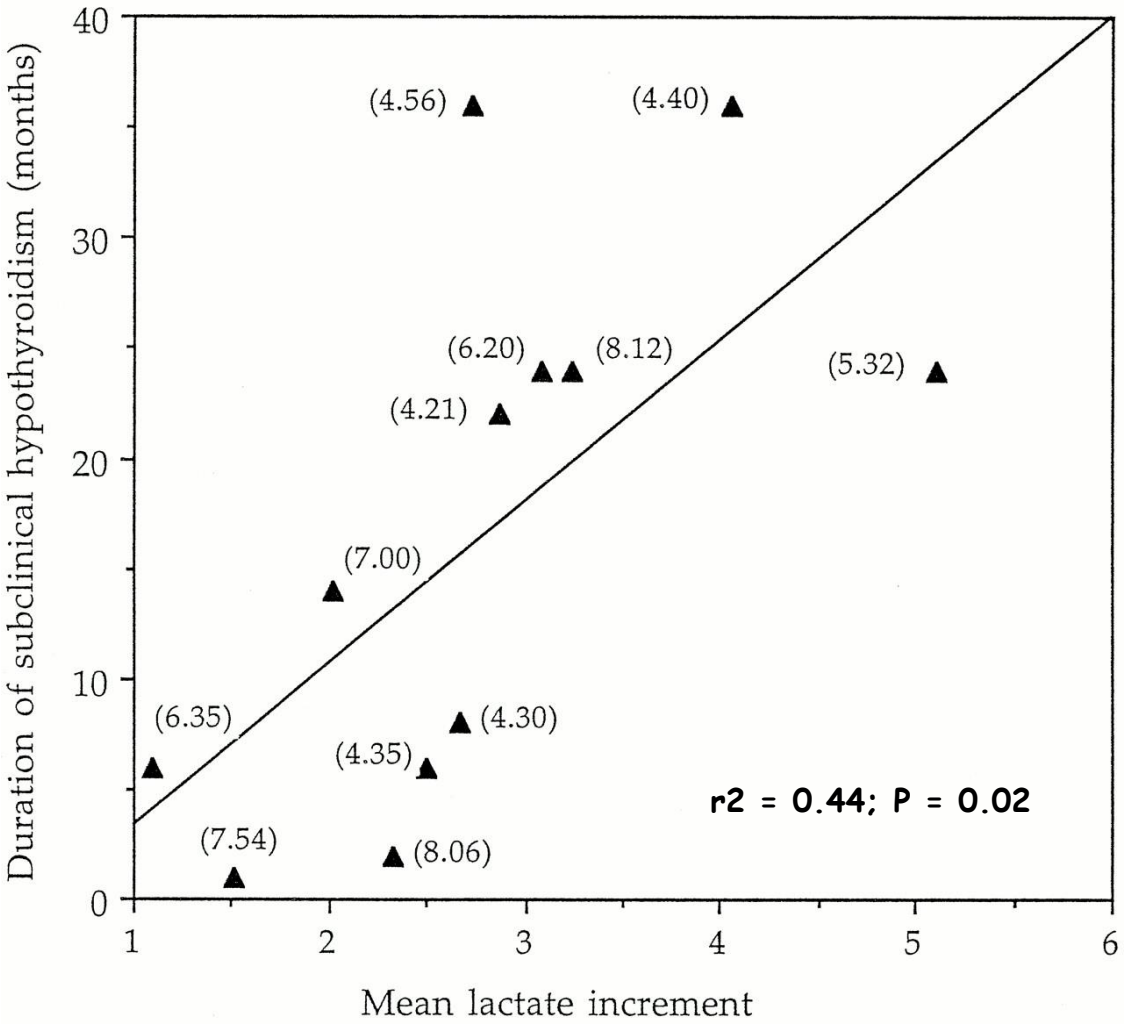






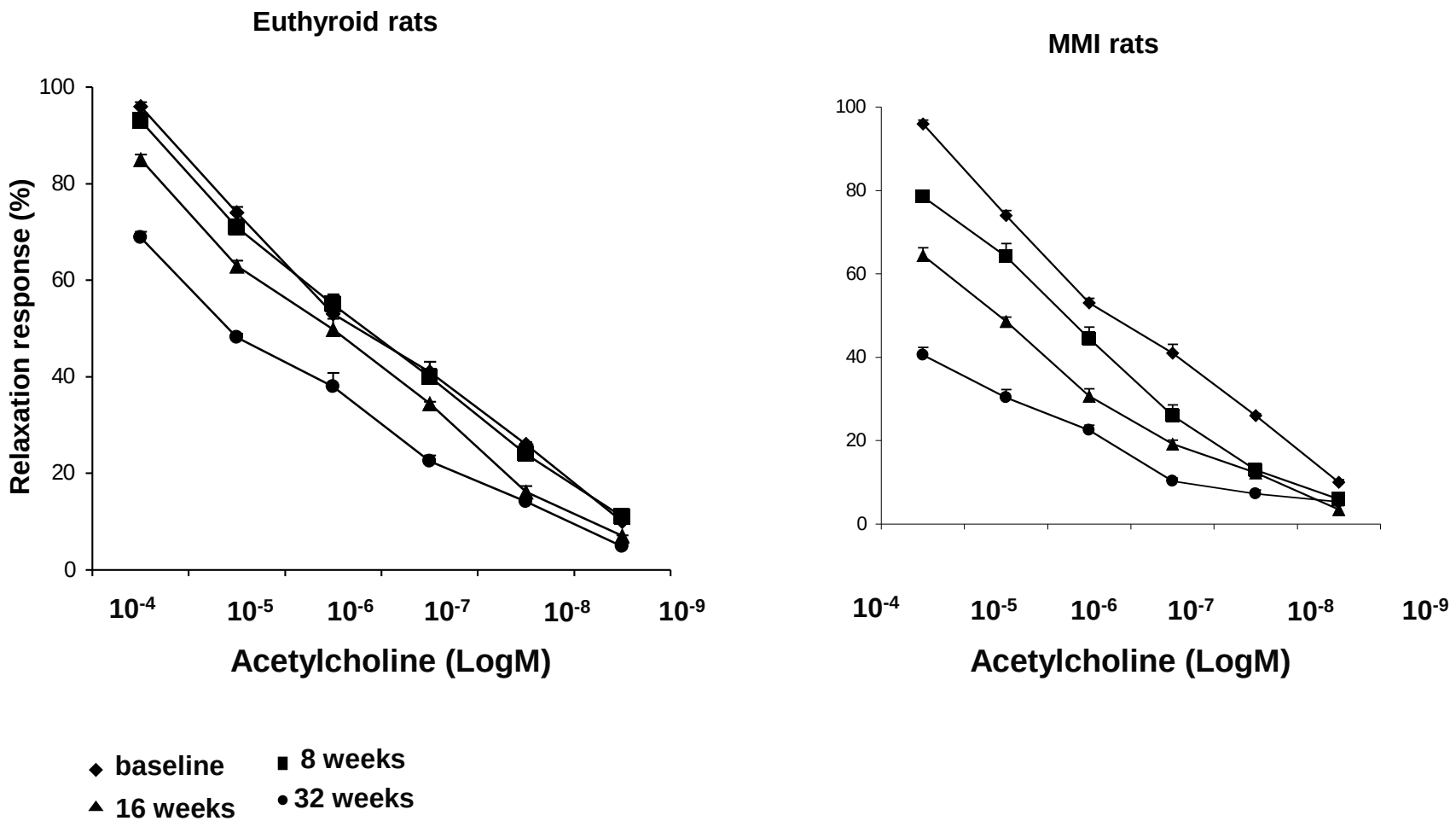
Modified from Tognini S et al. Thyroid 2012

Mild hypothyroidism and mitochondrial dysfunction: effect of disease duration



Monzani F et al. JCEM 1997

Endothelium dependent dilation in mesenteric arteries from euthyroid and MMI-treated rats



Virdis A et al. Endocrinology 2009 & Unpublished data

TAKE HOME MESSAGES

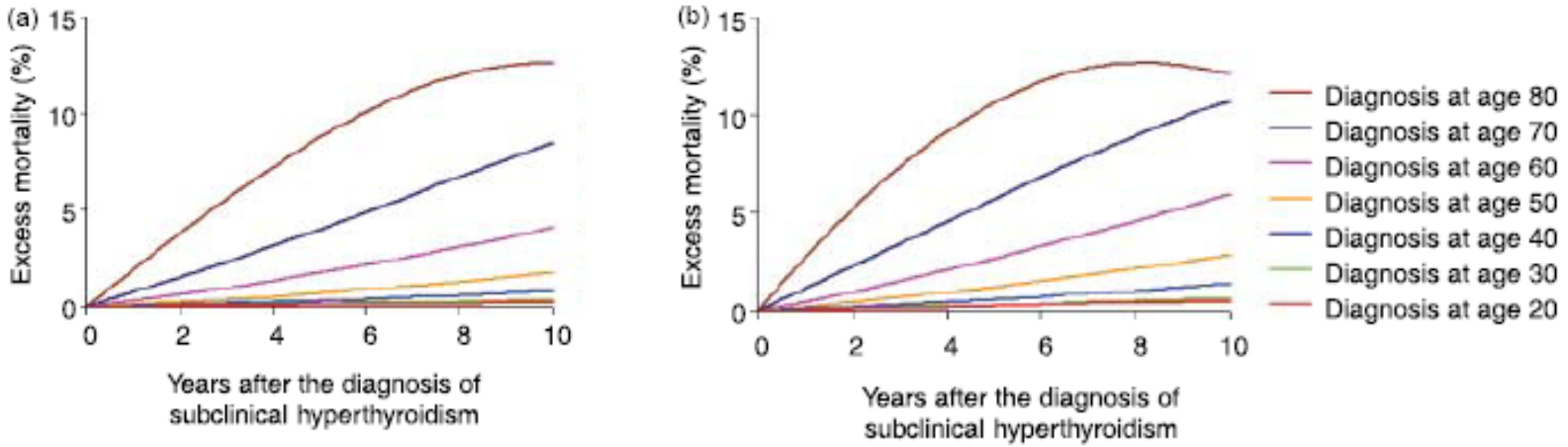
- Ageing is characterized by complex alterations of thyroid economy
- The prevalence of mild thyroid dysfunction increases with increasing age, especially subclinical hypothyroidism in women.
- The lack of age specific serum TSH reference ranges may result in over diagnosis of subclinical hypothyroidism in older people, especially the oldest old.
- The effect of subclinical hypothyroidism on cognition as well as cardiovascular and cerebrovascular morbidity and mortality could be depicted with two faces as the ancient Roman myth of “Janus Bifrons”.
- Besides the lack of age specific TSH reference ranges, the presence of organ specific effects of TH, the time of exposition to mild thyroid failure as well as the narrow individual normal variation of TSH and TH may account for the peculiar clinical scenario
- The possible presence of NTIS and the potential role of drugs should be not overlooked
- Physicians should be particularly cautious in treating subclinical hypothyroidism in older people (>75-80 years) with serum TSH levels lower than 10 mIU/L (without thyroid disease), also for the risk of iatrogenic hyperthyroidism with its detrimental clinical effects.

GRAZIE PER L'ATTENZIONE

GRAZIE A TUTTI I MIEI COLLABORATORI

Excess mortality from all causes after the diagnosis of subclinical hyperthyroidism (subjects living in US)

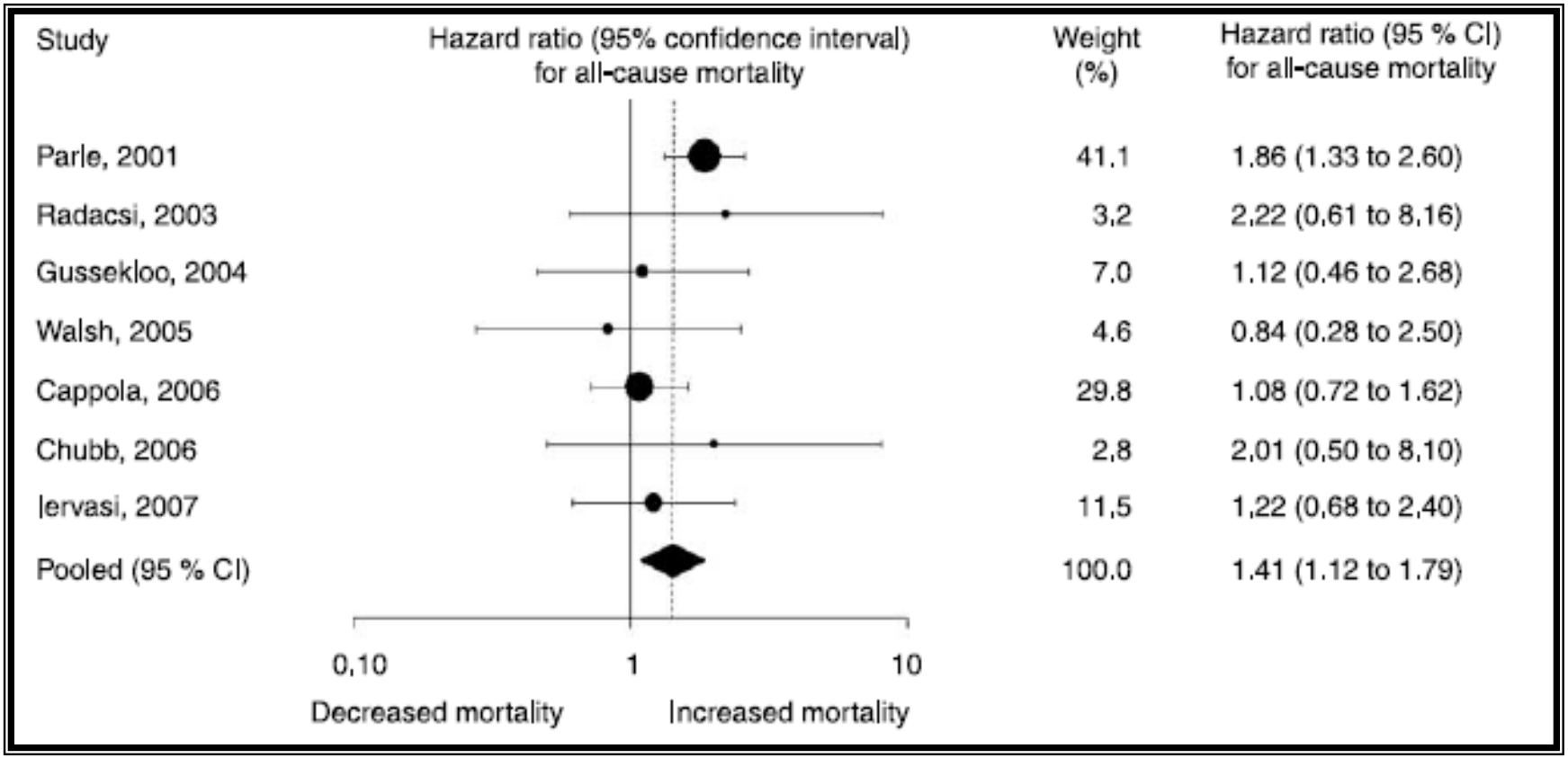
Women **Men**



From aggregated data reported in original cohort studies and life-tables

Haentjens et al. Eur J Endocrinol 2008

All-cause mortality in patients with subclinical hyperthyroidism: a meta-analysis



Haentjens et al. Eur J Endocrinol 2008

Thyroid Function Abnormalities and Cognitive Impairment in Elderly People: Results of the Invecchiare in Chianti Study

The study population consisted of men and women, aged 23 to 102 who participated in the InCHIANTI Study, conducted in two small towns in Tuscany, Italy. The final study population included 1,171 subjects (652 women and 519 men).

Table 3. Multivariate Regression Analysis* Relating Subclinical Hyperthyroidism to the Risk of Having Low Mini-Mental State Examination Score (<24)

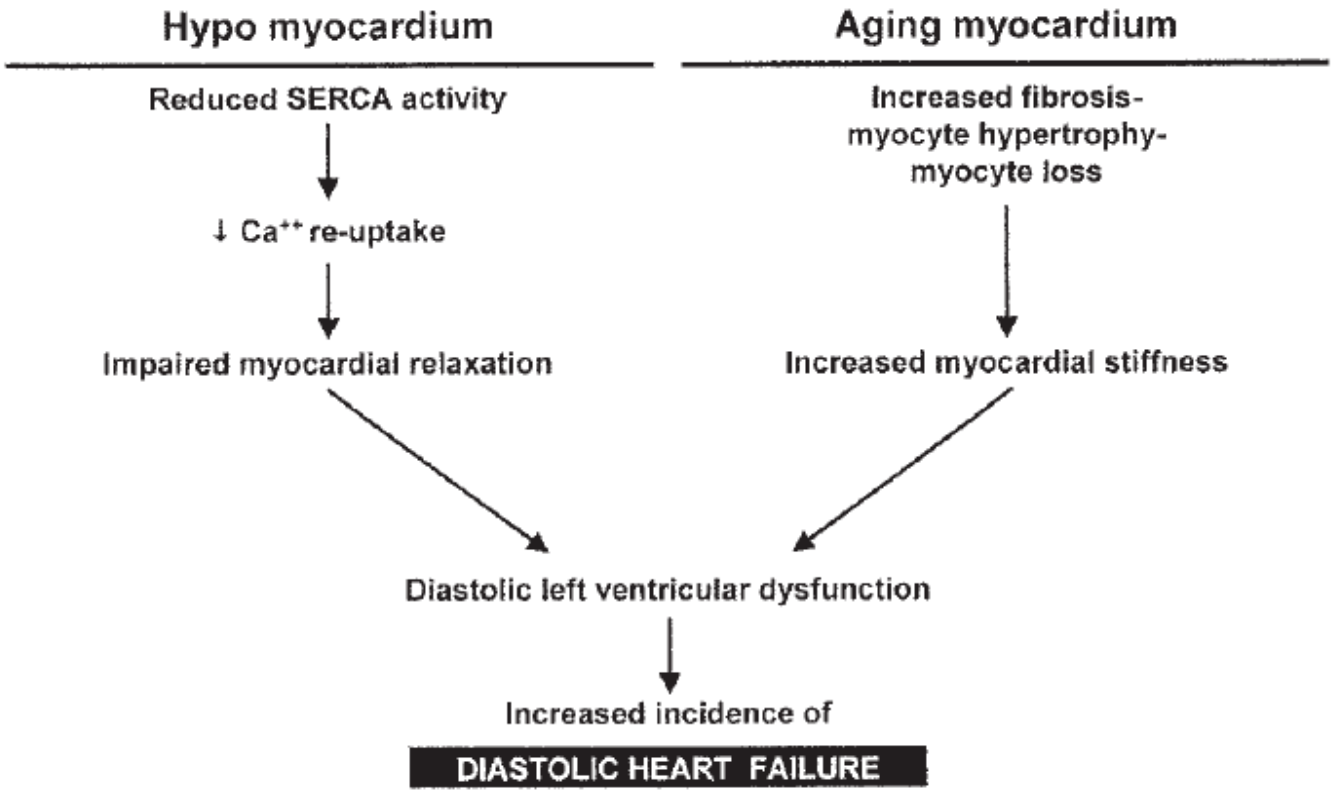
Characteristic	Hazard Ratio (95% Confidence Interval)	*P*-Value
Subclinical hyperthyroidism	2.26 (1.32–3.91)	.003
Age	1.12 (1.09–1.14)	<.001
Sex	1.62 (1.15–2.30)	.006
Physical activity	0.64 (0.45–0.91)	.01
Stroke	1.38 (0.99–1.90)	.05
Parkinson's disease	2.11 (1.06–4.19)	.03
Diabetes mellitus	1.06 (0.99–1.13)	.06

* Also adjusted for smoking, hypertension, and chronic heart failure (using backward selection analysis).

Subclinical hypo- and hyperthyroidism were more prevalent in older than in younger participants (subclinical hypo: 3.5 vs 0.4% subclinical hyper: 7.8 vs 1.9%). In euthyroid participants, TSH and FT3 declined with age, whereas FT4 increased.

Ceresini G et al. JAGS 2008

Thyroid hormone deficiency and the aging myocardium



Biondi & Klein, Endocrine 2004

Guidance in Subclinical Hyperthyroidism and Subclinical Hypothyroidism: Are We Making Progress?

Wilmar M. Wiersinga

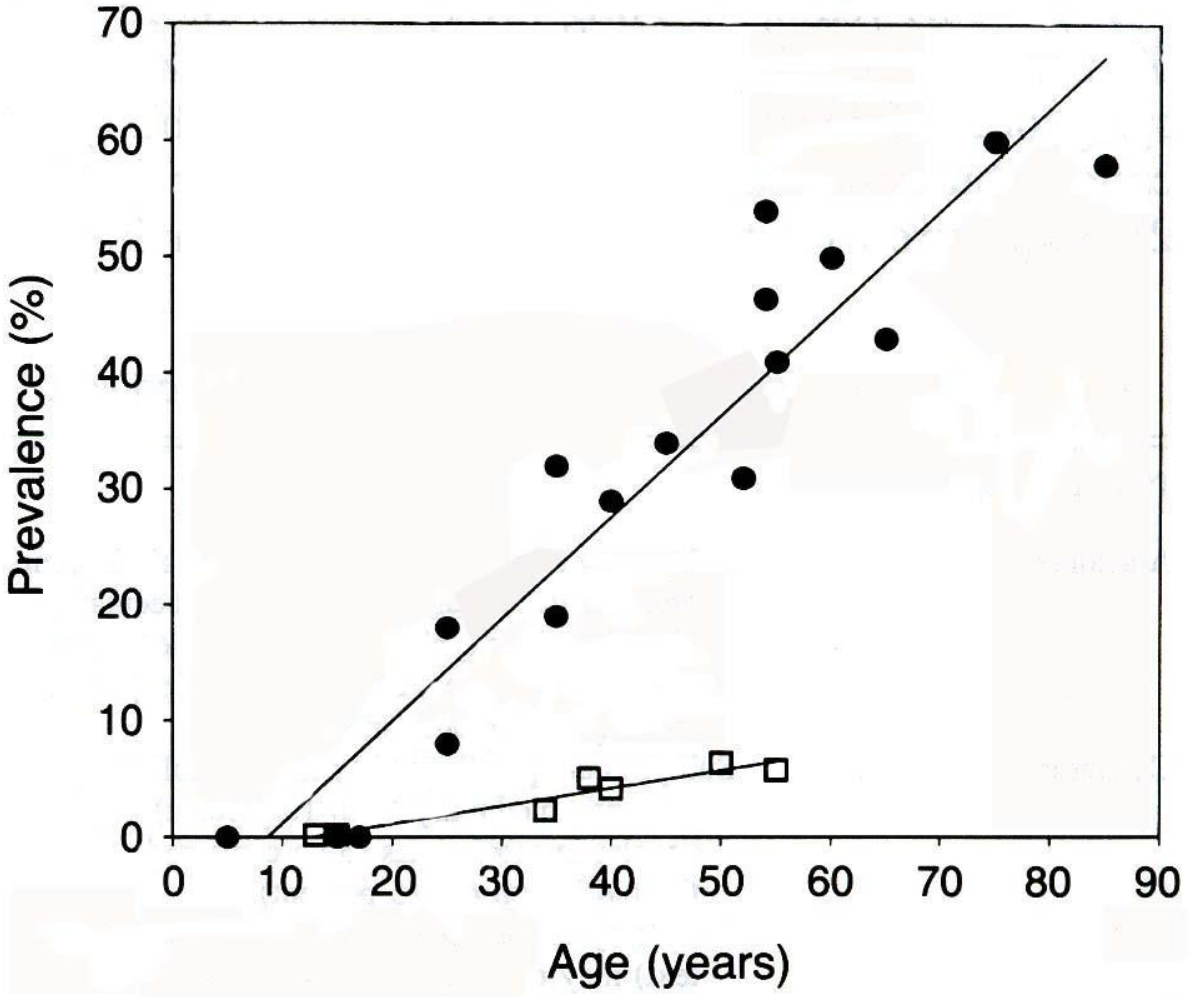
Editorial

'Subclinical' Is a Misnomer and Should Be Replaced by a Grading System

	TSH	FT_4	FT_3
Hypothyroidism grade IA	increased, >4.0 to <10 mU/l	normal	normal
Hypothyroidism grade IB	increased, ≥10 mU/l	normal	normal
Hypothyroidism grade II	increased	decreased	normal
Hypothyroidism grade III	increased	decreased	decreased
Hyperthyroidism grade IA	decreased, >0.1 to <4.0 mU/l	normal	normal
Hyperthyroidism grade IB	decreased, ≤0.1 mU/l	normal	normal
Hyperthyroidism grade II	decreased	normal	increased
Hyperthyroidism grade III	decreased	increased	increased

Eur Thyroid J 2015

Prevalence of palpable thyroid nodules detected at autopsy or by US (●) or by palpation (□) in subjects without radiation exposure or known thyroid disease.



Mazzaferri EL, N Engl J Med, 1993