INVECCHIAMENTO SCENARIO 2.0

NAPOLI

29 Novembre - 2 Dicembre 2017

RUOLO DEI DISTIROIDISMI NEL DEFICIT COGNITIVO

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Dipartimento di Medicina Clinica & Sperimentale

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AGENDA

- Azione degli OT sul SNC
- Funzione tiroidea e invecchiamento
- Ipertiroidismo e funzione cognitiva
- Ipotiroidismo e funzione cognitiva
- Fisiopatologia del peculiare scenario clinico

frontiers in ENDOCRINOLOGY

MINI REVIEW ARTICLE
published: 28 April 2014
doi: 10.3389/fendo.2014.00062

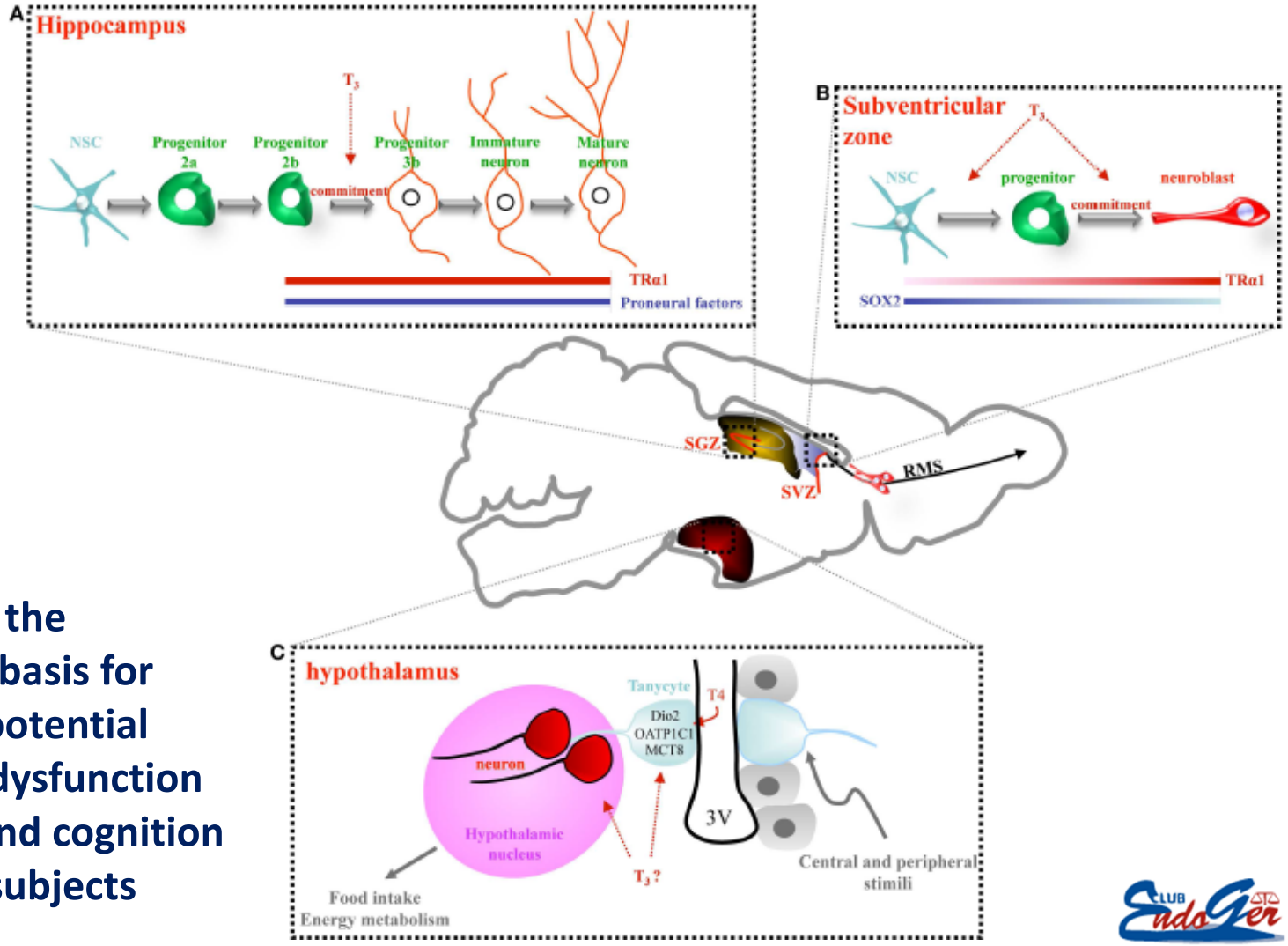
Thyroid hormone signaling and adult neurogenesis in mammals

*Sylvie Remaud, Jean-David Gothié, Ghislaine Morvan-Dubois and Barbara A. Demeneix**

UMR CNRS 7221, Evolution des Régulations Endocriniennes, Département Régulations, Développement et Diversité Moléculaire, Muséum National d'Histoire Naturelle, Paris, France

TH signaling regulates adult neurogenesis in the hippocampus, the sub ventricular zone and the hypothalamus, resulting one of the few endocrine signals that exerts marked effects on neurogenesis in adult mammalian brain

This represents the physio-pathological basis for understanding the potential association of thyroid dysfunction with changes in mood and cognition of adult and older subjects

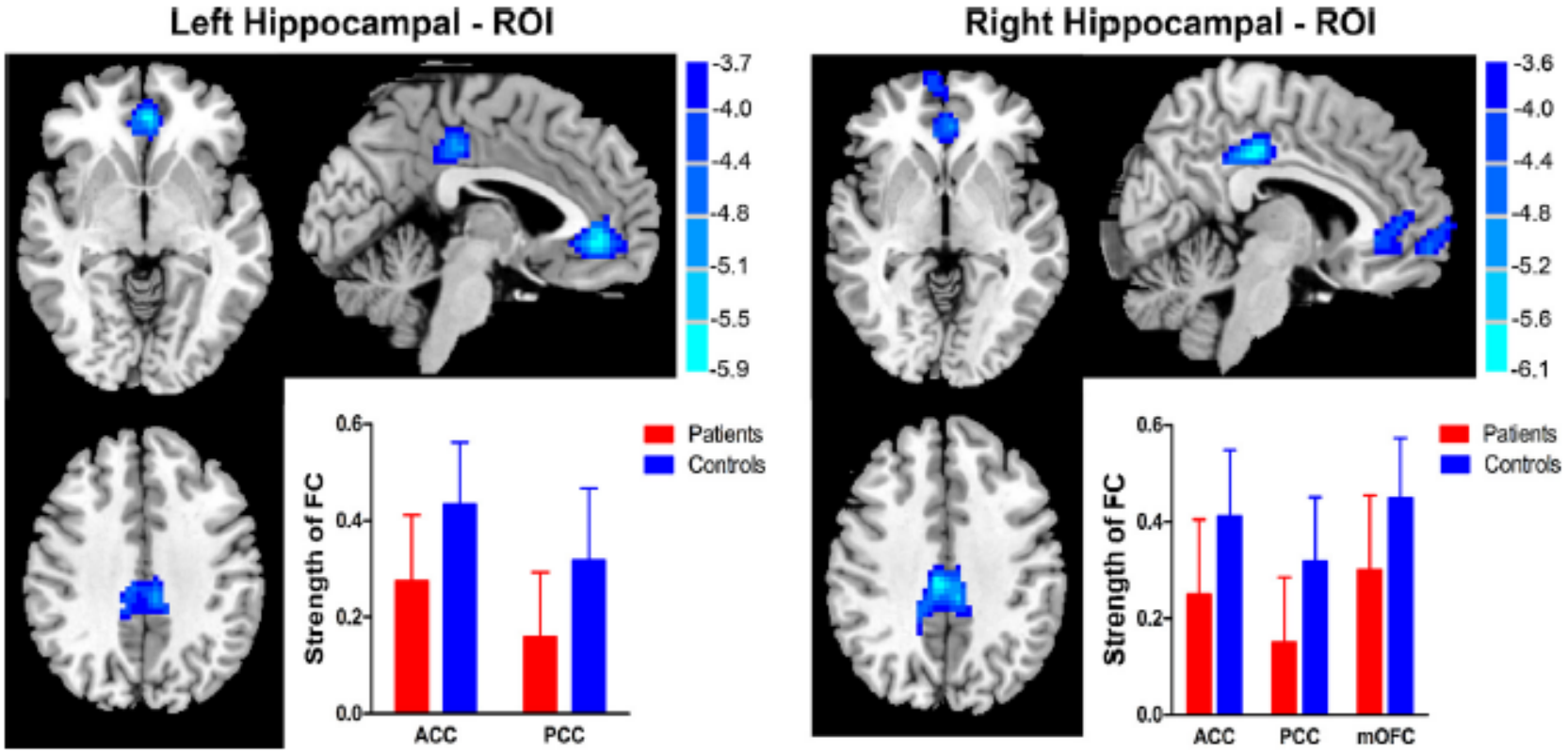


Contents lists available at ScienceDirect

European Journal of Radiology

journal homepage: www.elsevier.com/locate/ejrad

Disrupted functional connectivity of the hippocampus in patients with hyperthyroidism: Evidence from resting-state fMRI



Decreased functional connectivity between the hippocampus, anterior and posterior cingulate cortex, and right medial orbitofrontal cortex

Zhang W et al. 2014

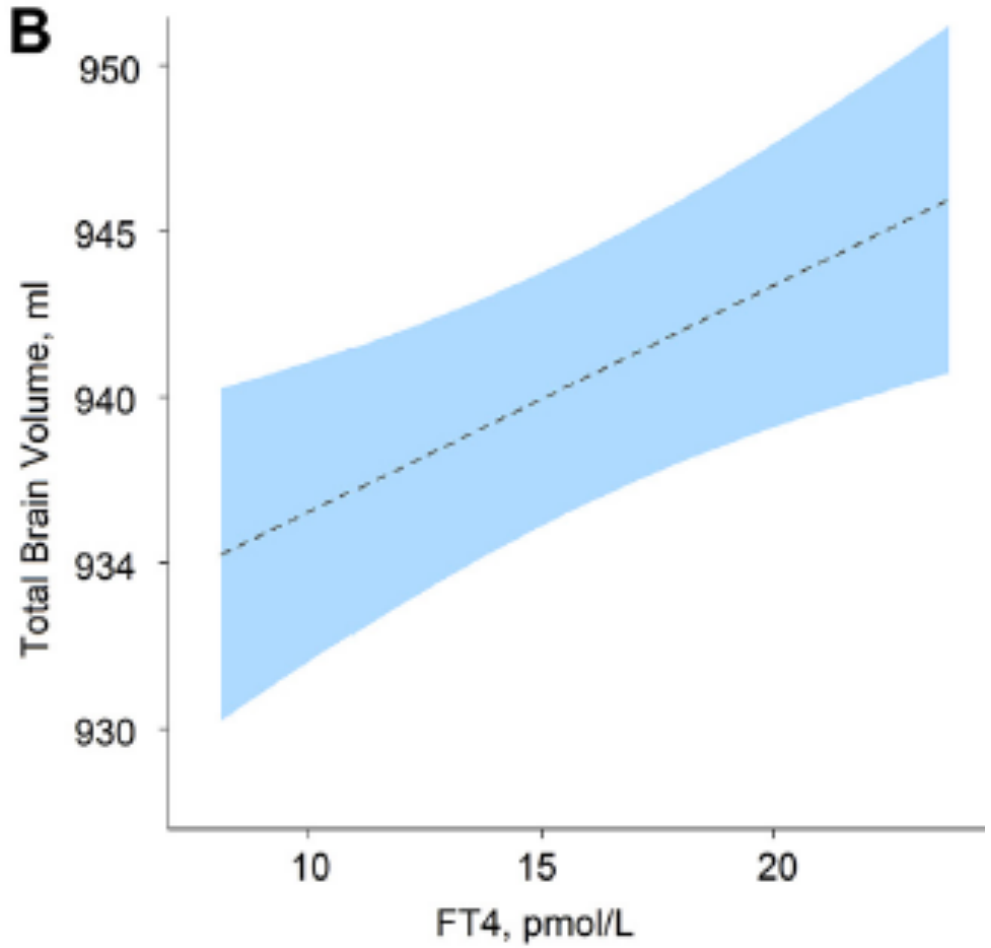
Age-dependent association of thyroid function with brain morphology and microstructural organization Evidence from brain imaging

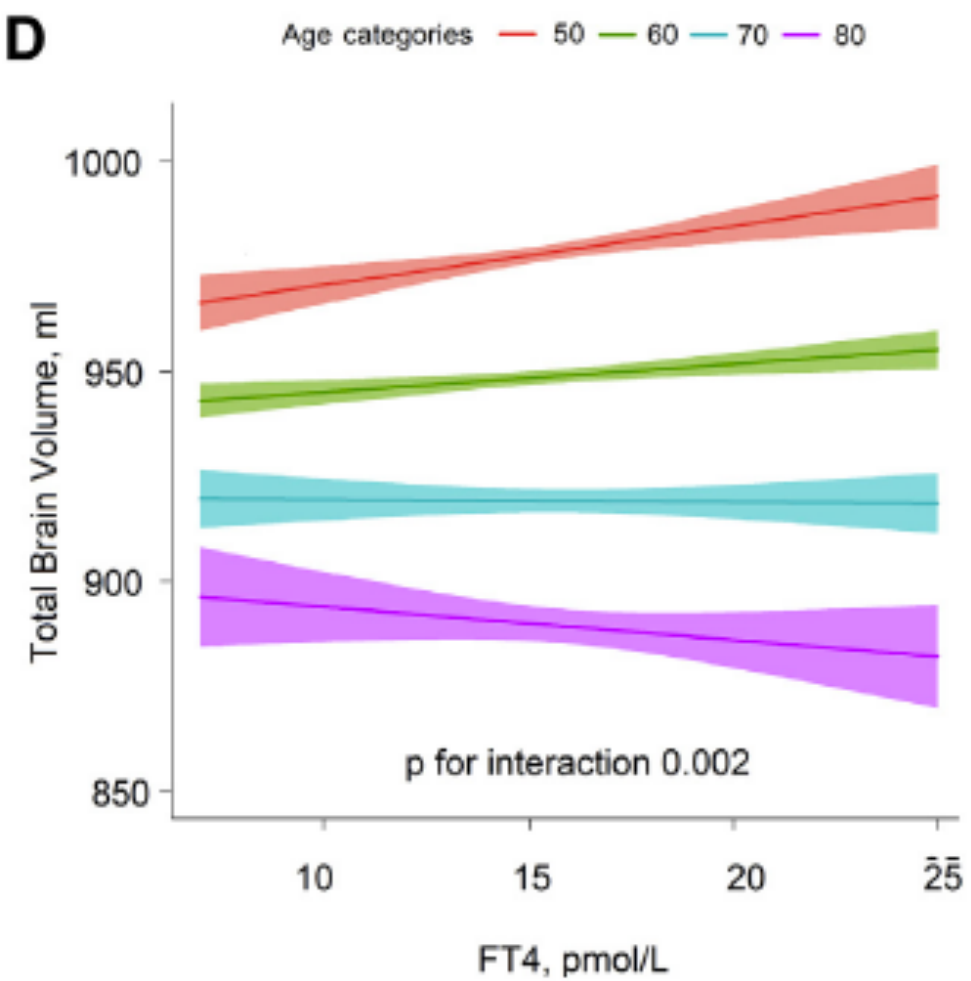
Characteristics of the study partecipants (4683)

Age, y	60.2 (7.3)
Female sex n, %	2571 (54.9)
TSH, mIU/L median (IQR)	1.97 (1.36–2.78)
FT4, pmol/L	15.5 (2.1)
Intracranial volume, mL	1140.0 (115.5)
Gray matter volume, mL	529.4 (53.6)
White matter volume, mL	409.2 (59.1)
White matter lesion volume, mL, median, IQR	2.9 (1.7–6.0)
Mean fractional anisotropy	0.34 (0.02)
Mean diffusivity, 10^{-3} mm^2/s	0.74 (0.03)
BMI, kg/m^2	27.1 (4.0)
Total cholesterol, mmol/L	5.70 (1.02)
HDL cholesterol, mmol/L	1.42 (0.41)
Systolic blood pressure, mmHg	134.8 (19.3)
Diastolic blood pressure, mmHg	79.9 (10.9)
Prevalent diabetes n, %	399 (8.5)
Smoking	
Current n, %	1029 (22.0)
Past n, %	2211 (47.2)
Never n, %	1443 (30.8)
Alcohol use, grams per day, median, IQR	15.0 (6.3–21.4)
Time between thyroid function measurement and scan (in y) median, IQR	0.21 (0.06–10.16)

Chaker et al. Neurobiology of Aging 2017

Age-dependent association of thyroid function with brain morphology and microstructural organization Evidence from brain imaging



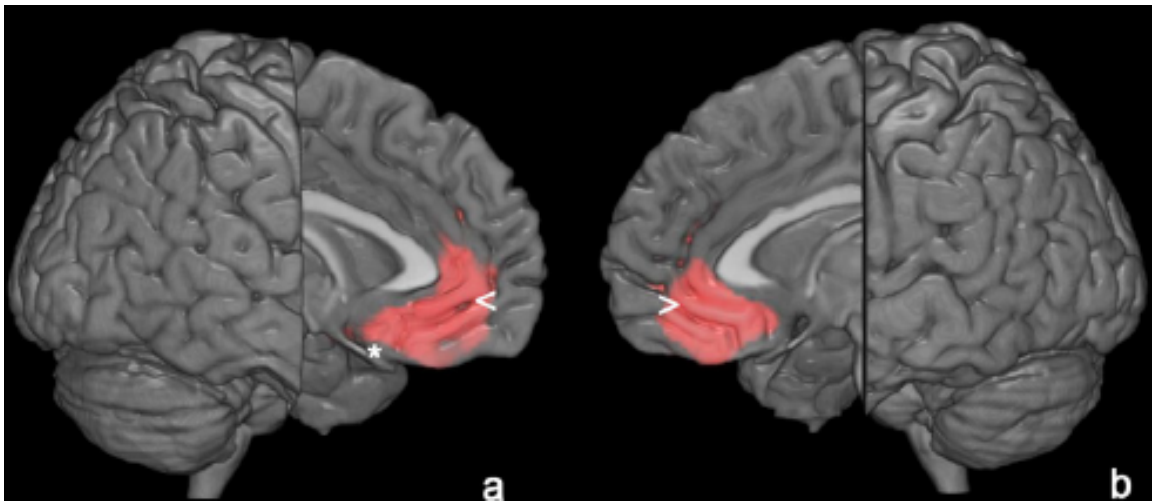


Adjusted for age, sex, cohort, intracranial volume and time between laboratory measurements and MRI scan

Chaker et al. Neurobiology of Aging 2017

Functional correlates of TSH, FT3 and FT4 in Alzheimer disease: a F-18 FDG PET/CT study

Correlation between TSH and brain glucose consumption in left anterior cingulate cortex (<) and medial frontal gyrus (*) and in the right anterior cingulate cortex (>)



No significant relationships were found between cortical F-18 FDG uptake and T3 and T4 serum levels

General overview of the AD population examined, including socio-demographic variables

	AD (n = 87)	CG (n = 13)	*p*-value
Age	70 ± 6	71 ± 6	0.28
Male sex	37	41	ns
Education: BUL	68	59	ns
Education: ULoA	19	21	
Occupation: M	70	65	ns
Occupation: S	17	15	
MMSE	18.9 ± 7.2	28.4 ± 1.5	<0.0001
$A\beta_{1-42}$ (pg/ml)	344.28 ± 134.31	818 ± 202.7	<0.0001
p-Tau (pg/ml)	96.7 ± 76.9	40.3 ± 10.9	<0.0001
t-Tau (pg/ml)	679.15 ± 330.5	272 ± 84.2	<0.0001
TSH (uU/ml)	1.38 ± 0.84	1.58 ± 0.73	0.10
FT3 (pg/ml)	3.04 ± 0.33	3.18 ± 0.27	0.004
FT4 (ng/ml)	1.16 ± 0.17	1.22 ± 0.21	0.08

BUL: below university level; ULoA: university level or above; M: manual; S: skilled.

Chiaravallotti A et al. Scientific Reports 2017

EFNS guidelines for the diagnosis and management of Alzheimer's disease

Recommendations for diagnosis

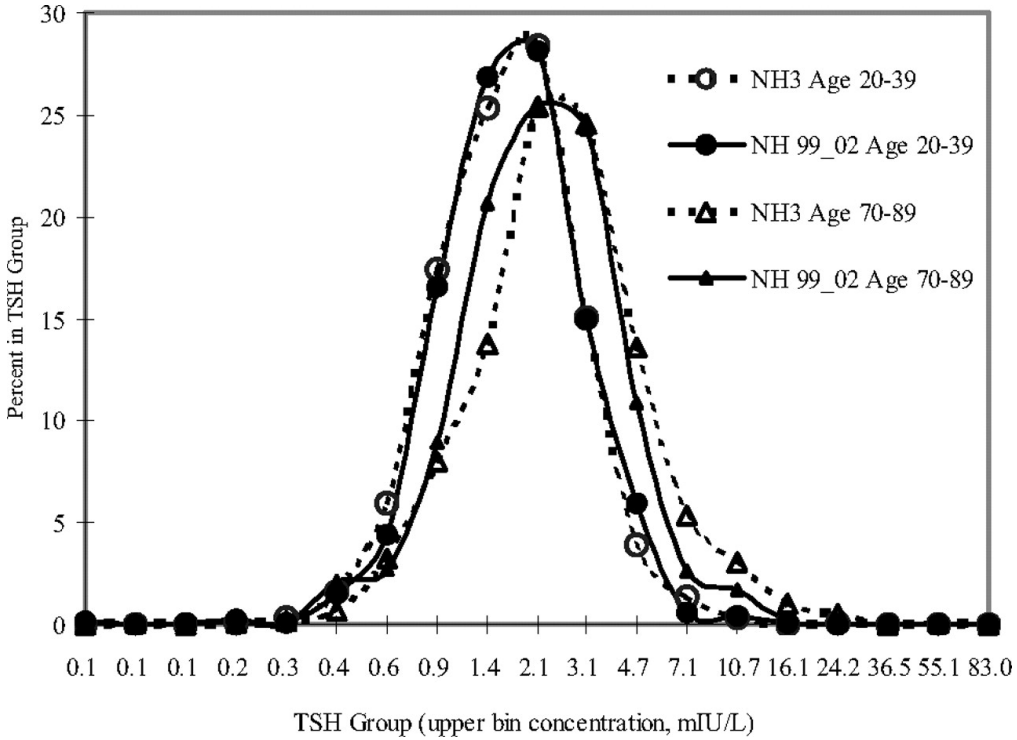
Assessment of co-morbidity is important in AD patients, both at the time of diagnosis and throughout the course of the illness (good practice point) and should always be considered as a possible cause of BPSD (Level C). Blood levels of folate, vitamin B12, thyroid stimulating hormone, calcium, glucose, complete blood cell count, renal and liver function tests should be evaluated at the time of diagnosis and serological tests for syphilis, Borelia and HIV might also be needed in cases with atypical presentation or clinical features suggestive of these disorders (good practice point).

EFNS Task Force European Journal of Neurology 2010

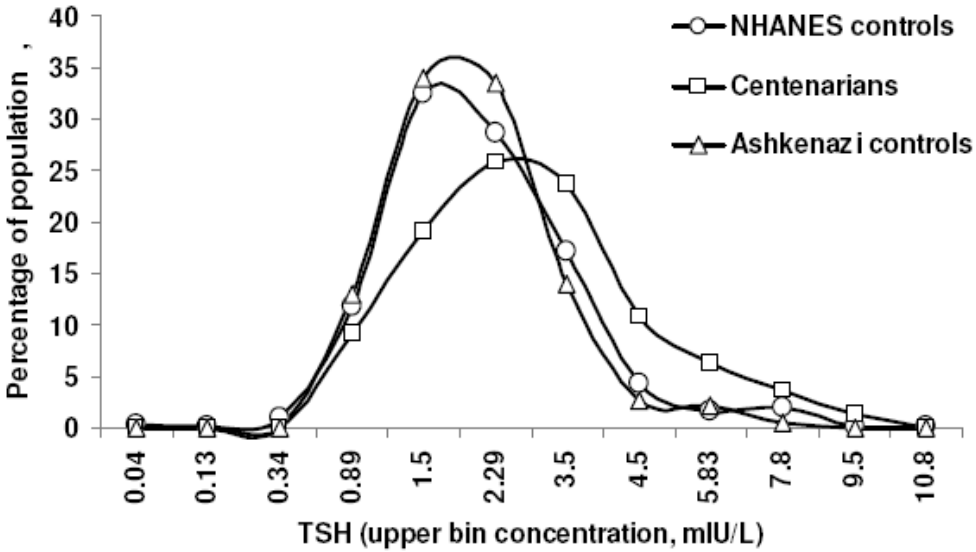
THE EFFECT OF AGING ON THYROID ECONOMY

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

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

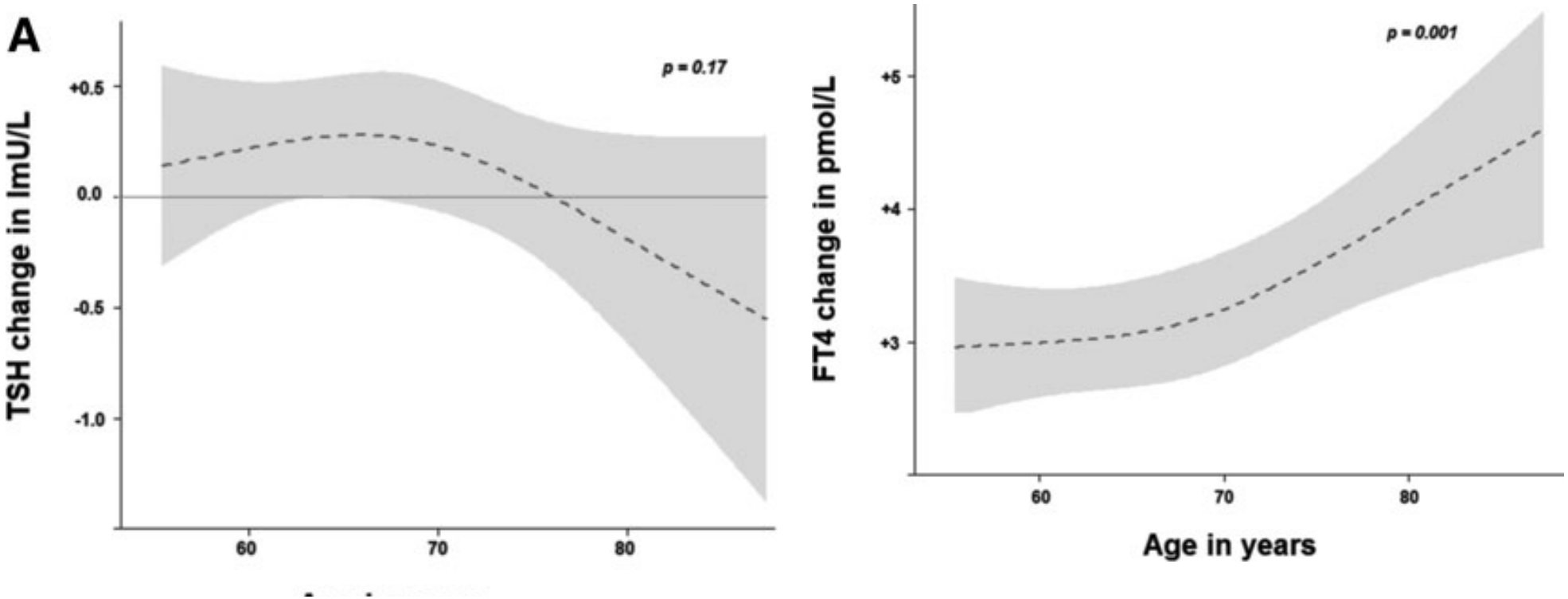
	TSH Concentration, mIU/l											
	Surks and Hollowell, 2007* (26)		Boucai et al., 2011 (28)			Bremner et al., 2012 (67)			Waring et al., 2012† (68)		
Age range, years	Median	97.5th percentile	2.5th percentile	Median	97.5th percentile	Lower limit‡	Mean	Upper limit‡	2.5th percentile	Median	97.5th percentile
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	4.09			
60–69§§	1.61	4.35	0.58	1.60	4.50	0.38	1.34	4.34			
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

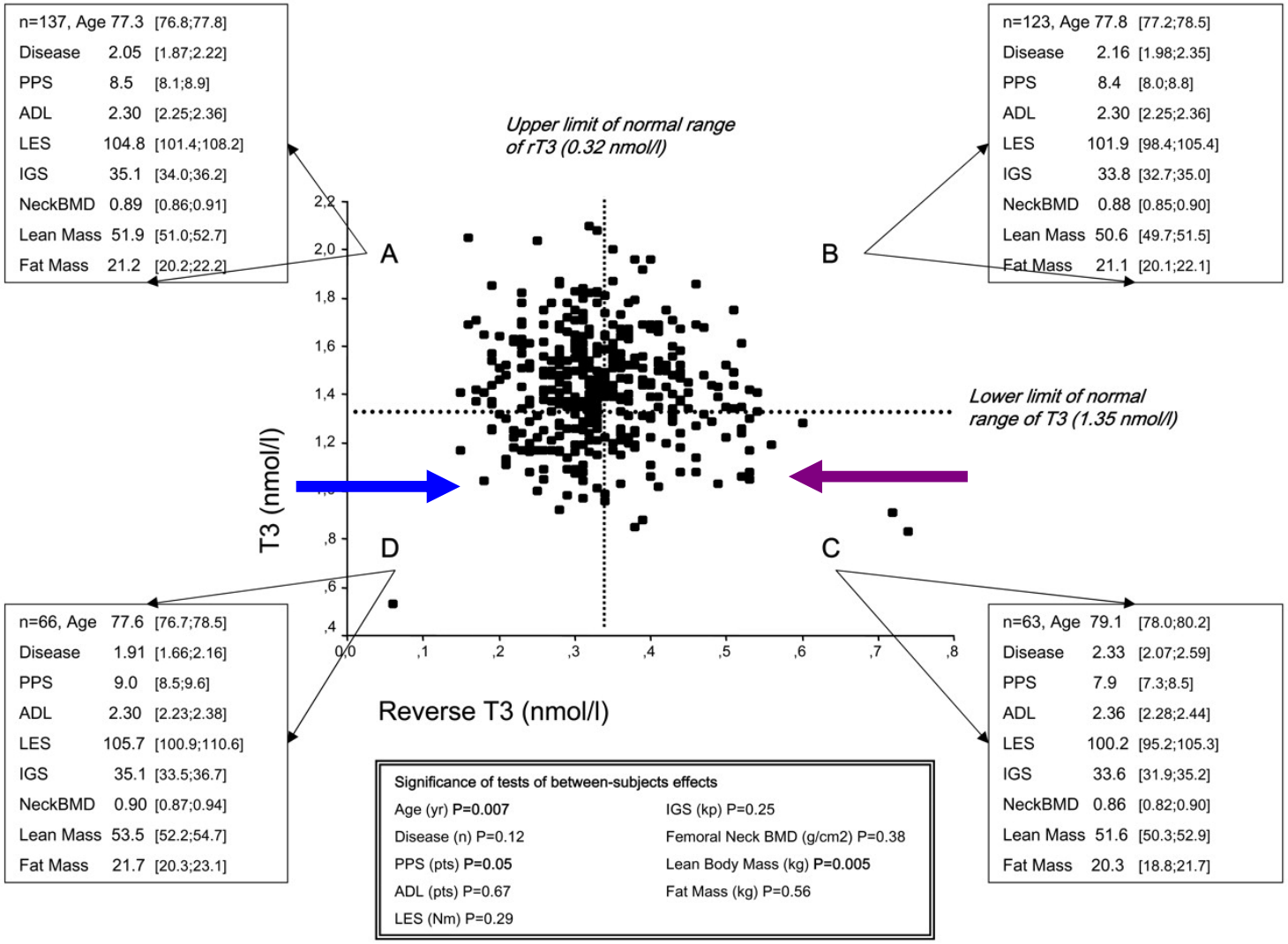
Thyroid Function Characteristics and Determinants: The Rotterdam Study



Repeated measurements (6.5-year interval) were available for 1225 participants

Chaker et al. Thyroid 2016

Overview of the values of T3 and rT3 within a population of 403 elderly men



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

THE GERIATRIC CLINICAL SCENARIO
Subclinical Thyroid Dysfunction & Cognition

Caratteristiche cliniche pazienti ambulatorio Demenze AUSL 6 Livorno

	Pazienti (n=127)	Femmine (n=76)	Maschi (n=51)
Età	78,2±7,1	78,5±7,1	77,6±7,2
MMSE	20,6±5,1	20,2±4,9	21,0±5,4
IA	53,1%	54,2%	51,4%
Diabete mellito	34,7%	35,6%	33,3%
IFG	7,9%	10,2%	4,8%
Dislipidemia	79,1%	88,5%	64,7%
CVI	53,1%	48,8%	57,9%
IRC	24,0%	48,6%	30,9%
Ipo-subclin.	12%	16%	6%
Iper-subclin.	6%	8%	3%
↑ Indici di flogosi	41,7%	48,6%	30,4%

Unpublished data

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

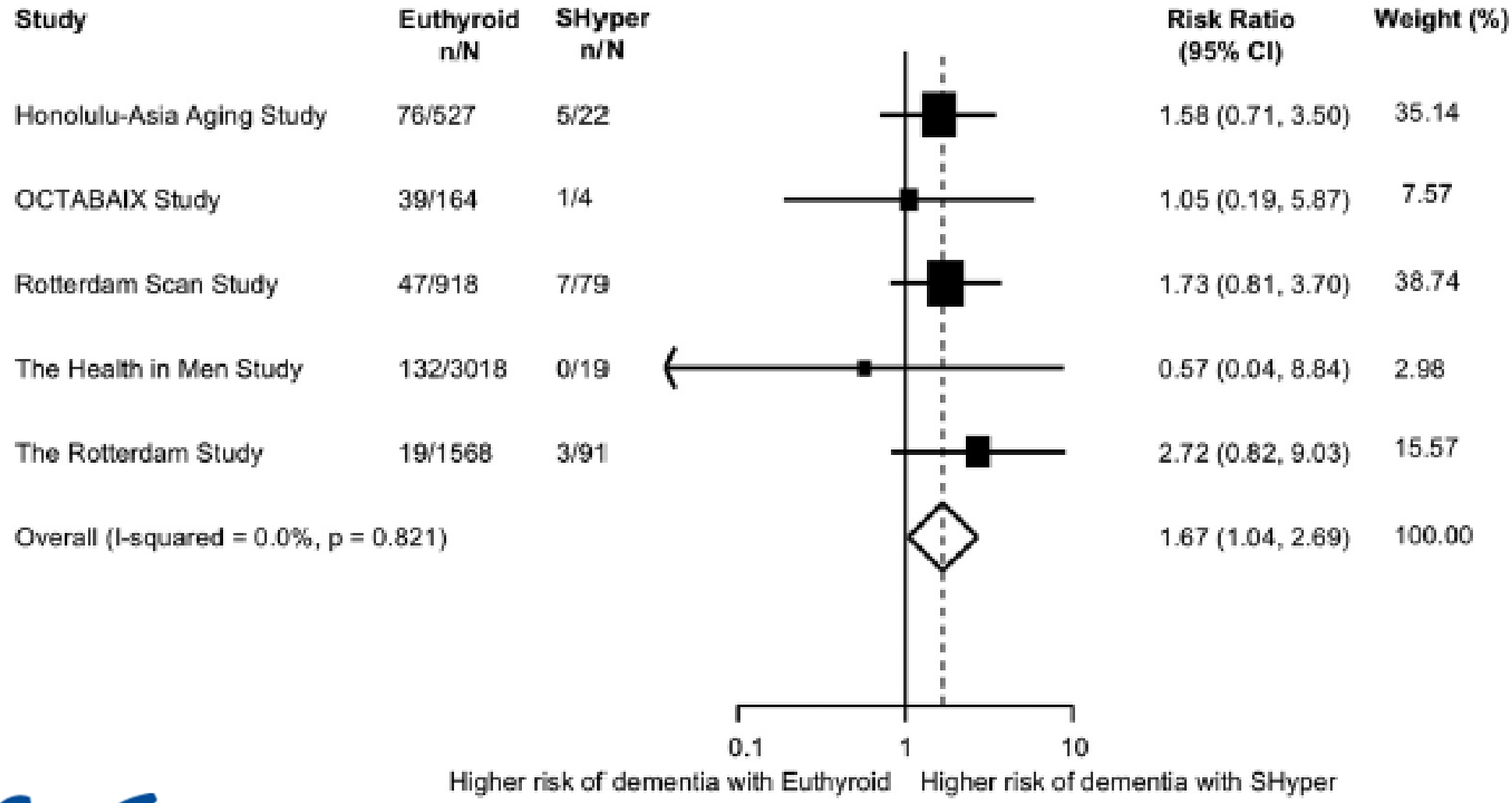
Subclinical Thyroid Dysfunction and the Risk of Cognitive Decline: a Meta-Analysis of Prospective Cohort Studies

Eleven prospective cohorts followed 16,805 participants during a median follow-up of 44.4 months. Five studies analyzed the risk of dementia in subclinical hyperthyroidism (n=6410), six in subclinical hypothyroidism (n=7401)

Study, Year of publication	Population	Women	Mean age; [scap]sd	Follow-up time	Age	TSH cutoff level (mU/liter)		fT4 measured	Thyroid
	N	%	years	months	min-max. years	SHypo	SHyper		
Rotterdam,[31] 2000[§]	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[†]; 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	<0.3	yes	yes
Framingham,[34] 2008[‡]	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[§]	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[†]	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	307	54.6	85.0; 0.0	36.0	85	> 5	<0.25	yes	yes

Rieben C et al JCEM 2016

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



Rieben C et al JCEM 2016

Lower-But-Normal Serum TSH level Is Associated With the Development or Progression of Cognitive Impairment in Elderly: Korean Longitudinal Study on Health and Aging (KLoSHA)

313 euthyroid participants (mean age 72.5 6.9 yr at baseline) completed cognitive function tests at 5-year follow- up

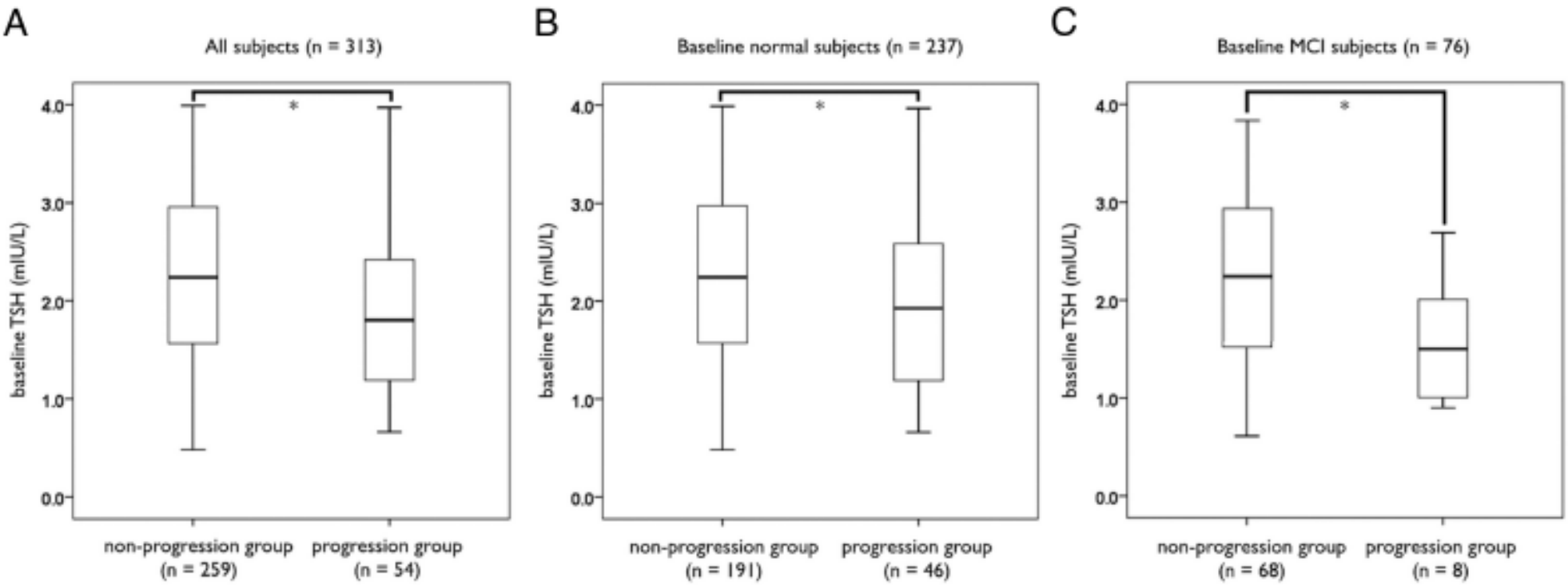


Figure 1. Baseline TSH levels according to the development or progression of cognitive impairment in all subjects (n = 313) (A), in subjects with baseline normal cognitive function (n = 237) (B), and in subjects with baseline MCI (n = 76) (C), *, $P < .05$ derived from Mann-Whitney *U* test.

Moon JH et al. JCEM 2014

OPEN ACCESS Freely available online

PLOS | ONE

Subclinical Thyroid Dysfunction and Cognitive Decline in Old Age

Prospective, longitudinal study of 5154 subjects, aged 70-82 yrs, with 3 yrs mean follow-up

Table 2. Association of subclinical thyroid status and various cognitive performance tests at baseline.

	Thyroid status			p-value for difference	
Cognitive test	Subclinical hyperthyroidism N = 65	Euthyroidism N = 4,928	Subclinical hypothyroidism N = 161	Subclinical hyperthyroidism vs. euthyroidism	Subclinical hypothyroidism vs. euthyroidism
MMSE, score	28.04 (0.19)	28.04 (0.03)	27.87 (0.12)	0.97	0.15
Stroop, seconds	65.61 (3.07)	65.34 (0.46)	65.90 (2.02)	0.93	0.78
LDCT, digits coded	24.31 (0.86)	23.63 (0.13)	23.51 (0.54)	0.42	0.79
PLTi, pictures remembered	9.29 (0.23)	9.45 (0.03)	9.72 (0.14)	0.50	0.06
PLTd, pictures remembered	10.31 (0.32)	10.30 (0.05)	10.65 (0.20)	0.97	0.09

Conclusion: We found no consistent evidence that subclinical hyper- or hypothyroidism contribute to cognitive impairment or decline in old age. Although our data are not in support of treatment of subclinical thyroid dysfunction to prevent cognitive dysfunction in later life, only large randomized controlled trials can provide definitive evidence.

CLUB EndoGer

Wijsman LW et al 2013

The Thyroid in Mind: Cognitive Function and Low Thyrotropin in Older People

Clinical Review

Earn H. Gan and Simon H. S. Pearce

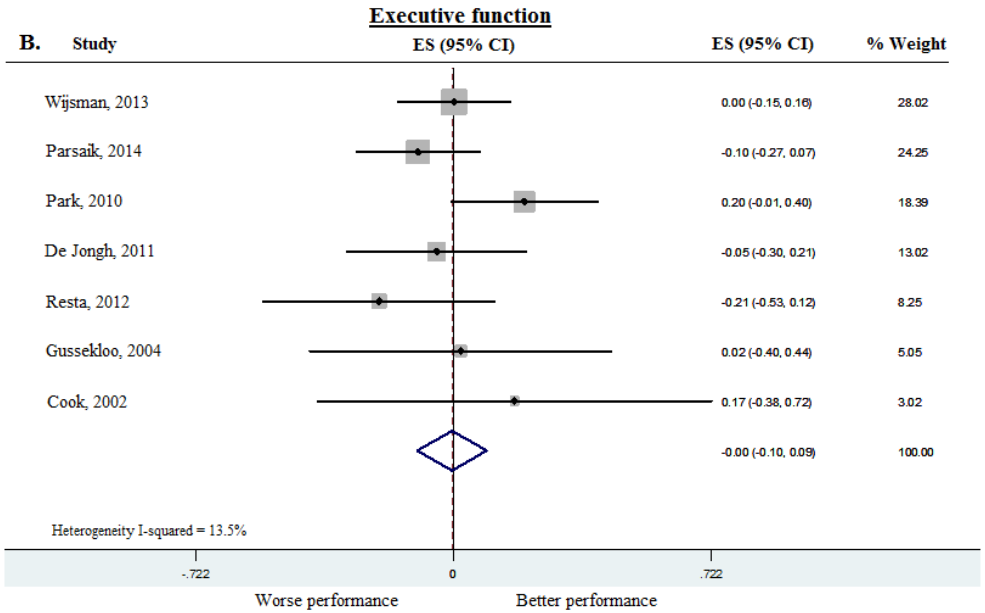
Results: This review examines the 23 studies that provide information about the association between SH or lower serum TSH within the reference range and cognition. Fourteen of these studies, including several well-designed and well-powered cross-sectional and longitudinal analyses, have shown a consistent finding of an association between SH with cognitive impairment or dementia.

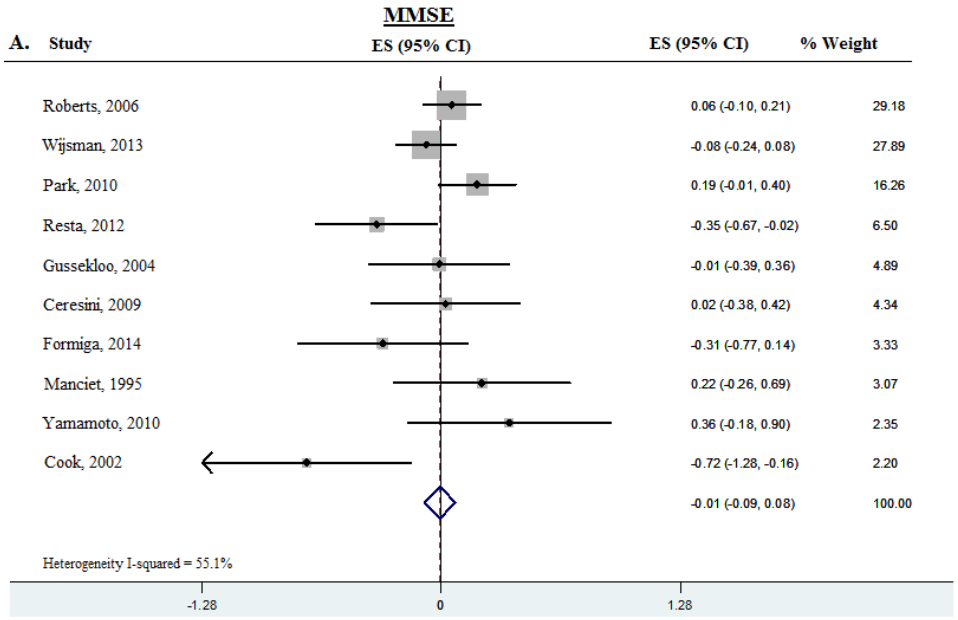
Conclusion: There is a substantial body of evidence to support the association between SH and cognitive impairment, but there is no clear mechanistic explanation for these associations. Nor is there an indication that antithyroid treatment might ameliorate dementia. Larger and more detailed prospective longitudinal or randomized controlled trials are required to inform these important questions.

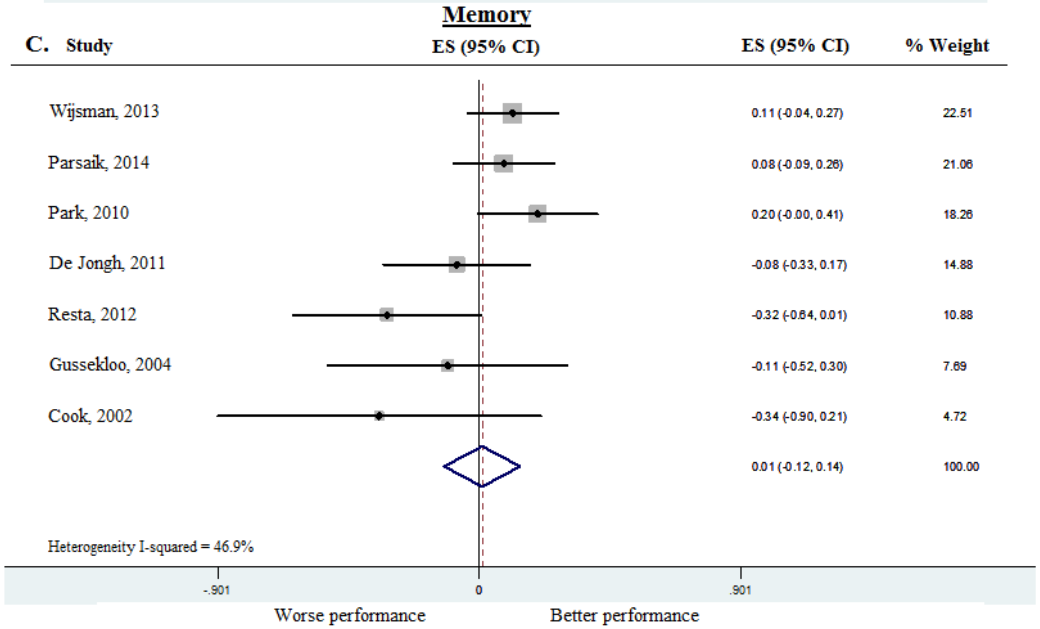
TABLE 3. Possible mechanism for association of cognitive impairment with SH or low serum TSH

A.	Excess circulating thyroid hormone resulting in neuronal loss.
B.	Primary neurodegeneration causes reduced central nervous system TRH secretion, hence lower TSH.
C.	SH and low TSH are biomarkers for age, and so are associated with other diseases of advanced age including dementias.
D.	Subjects with cognitive impairment have a high burden of comorbidity, and association is due to nonthyroidal illness and drug effects on serum TSH.

Subclinical hypothyroidism and cognitive function in people over 60 years: a systematic review and meta-analysis



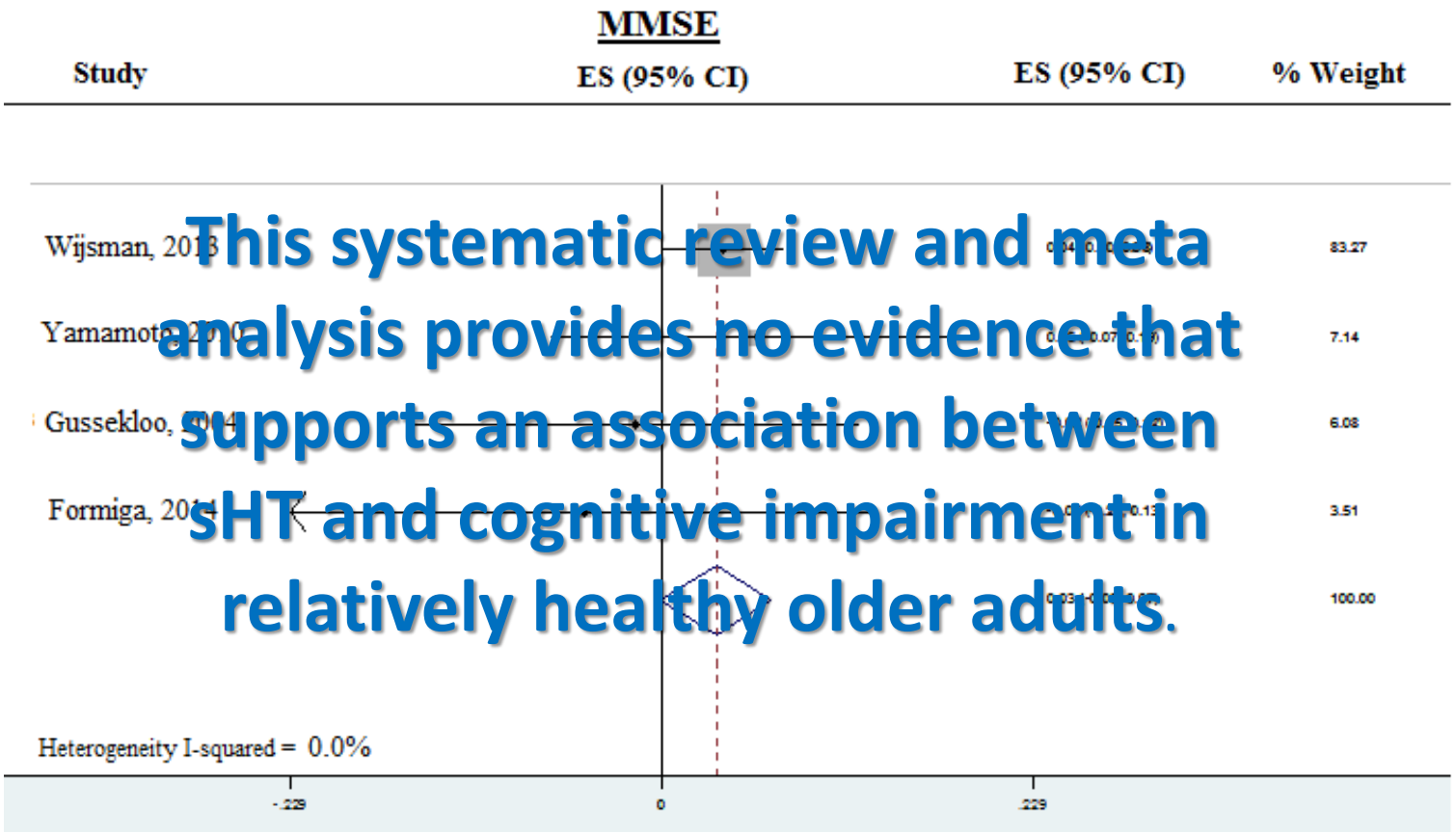




Forest plots depicting the cross-sectional associations observed between sHT and cognitive performance in 10 studies, arranged according to the weight of the studies.

Akintola AA et al. Frontiers in Aging Neuroscience 2015

Subclinical hypothyroidism and cognitive function in people over 60 years: a systematic review and meta-analysis

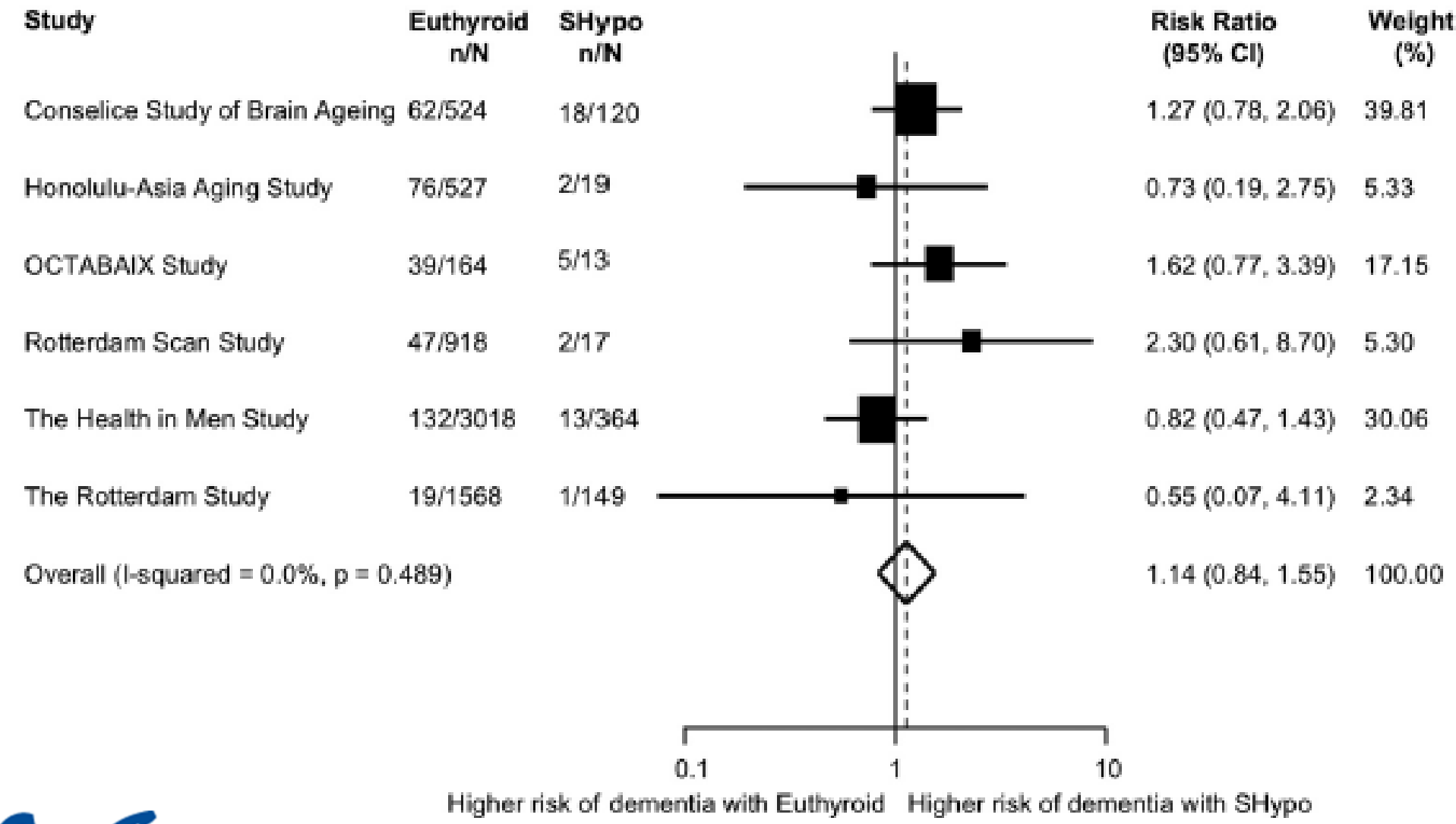


This systematic review and meta analysis provides no evidence that supports an association between sHT and cognitive impairment in relatively healthy older adults.

Forest plots depicting the prospective analysis of associations observed between sHT and decline in global cognition as measured by MMSE, arranged according to the weight of the studies

Akintola AA et al. Frontiers in Aging Neuroscience 2015

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



Rieben C et al JCEM 2016

Hypothyroidism and Risk of Mild Cognitive Impairment in Elderly Persons - A Population Based Study

Association of thyroid group with performance in cognitive domains

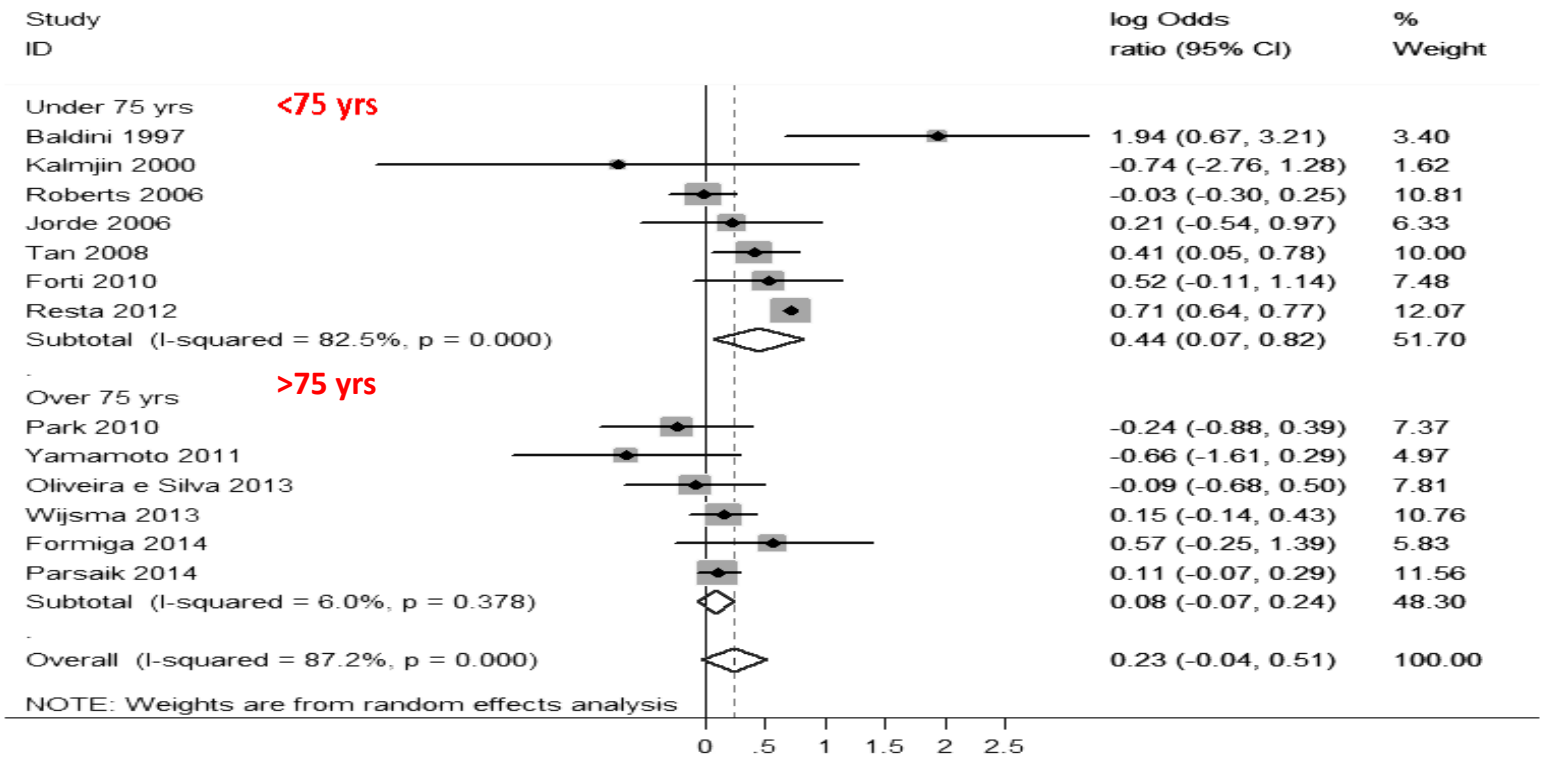
Cognitive domain	Thyroid groups				
	Normal Thyroid Function	Subclinical hypothyroidism		Clinical hypothyroidism	
		Beta (SE)	p-value	Beta (SE)	p-value
Memory	Reference	–0.03 (0.08)	0.67	0.06 (0.06)	0.34
Attention/executive function	Reference	0.01 (0.08)	0.85	0.05 (0.06)	0.36
Visual Spatial skills	Reference	–0.08 (0.08)	0.32	0.13 (0.06)	0.03
Language	Reference	0.02 (0.08)	0.82	0.06 (0.06)	0.33

Linear regression models, models are adjusted for age, sex, years of education, APOE e4 genotype. Cognitive measures are entered as continuous variables

JAMA Neurol. 2014

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

Risk of Composite Endpoint stratified by age

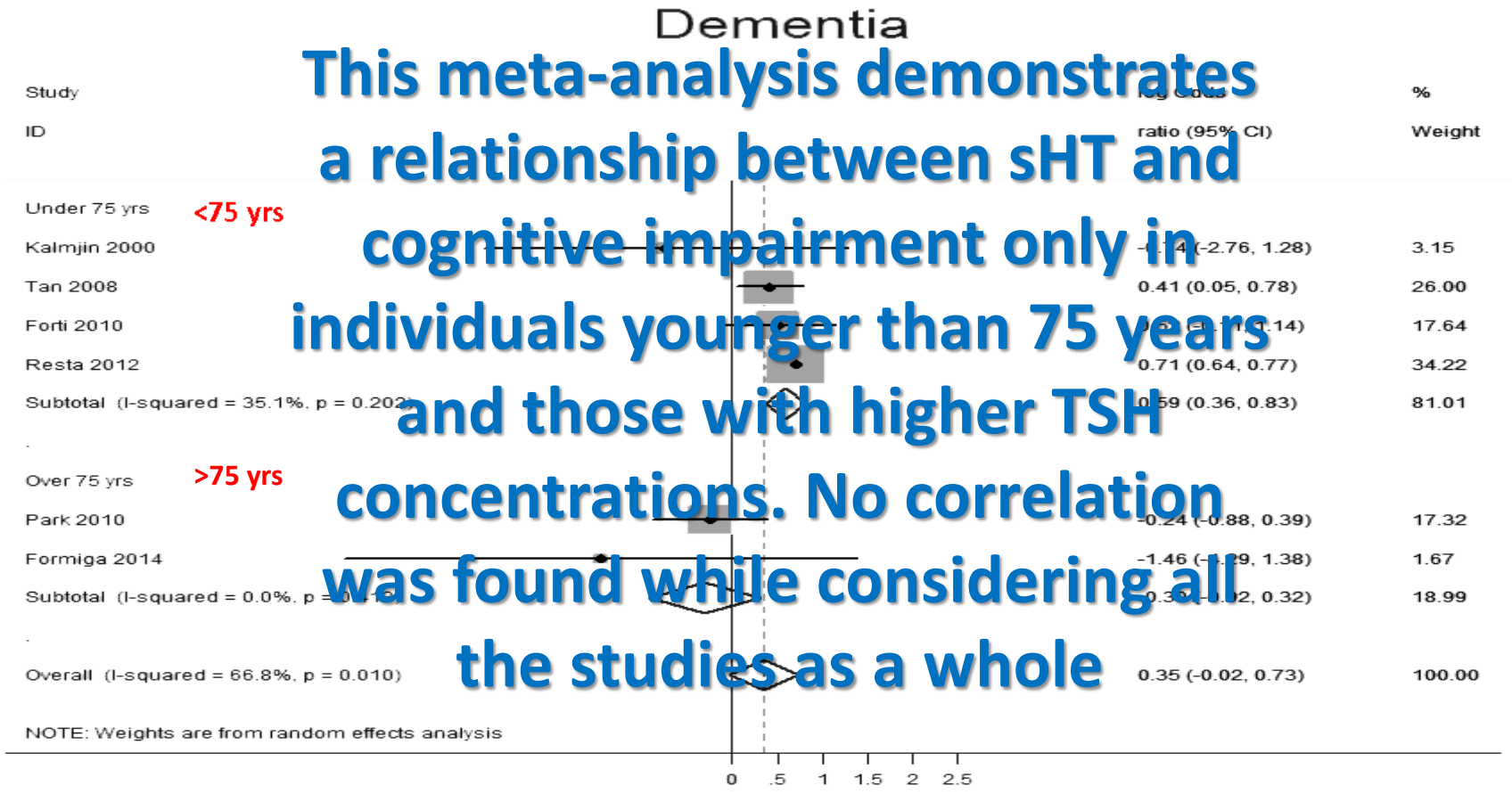


Incidence or prevalence of dementia, MMSE score, WMS Revised score and total memory quotient

The risk of composite endpoint was positively related with the degree of serum TSH increase (ß=0.28, p=0.005; data available for 5 studies) while no effect was obtained by stratifying for gender.

Pasqualetti G et al JCEM 2015

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



This meta-analysis demonstrates a relationship between sHT and cognitive impairment only in individuals younger than 75 years and those with higher TSH concentrations. No correlation was found while considering all the studies as a whole

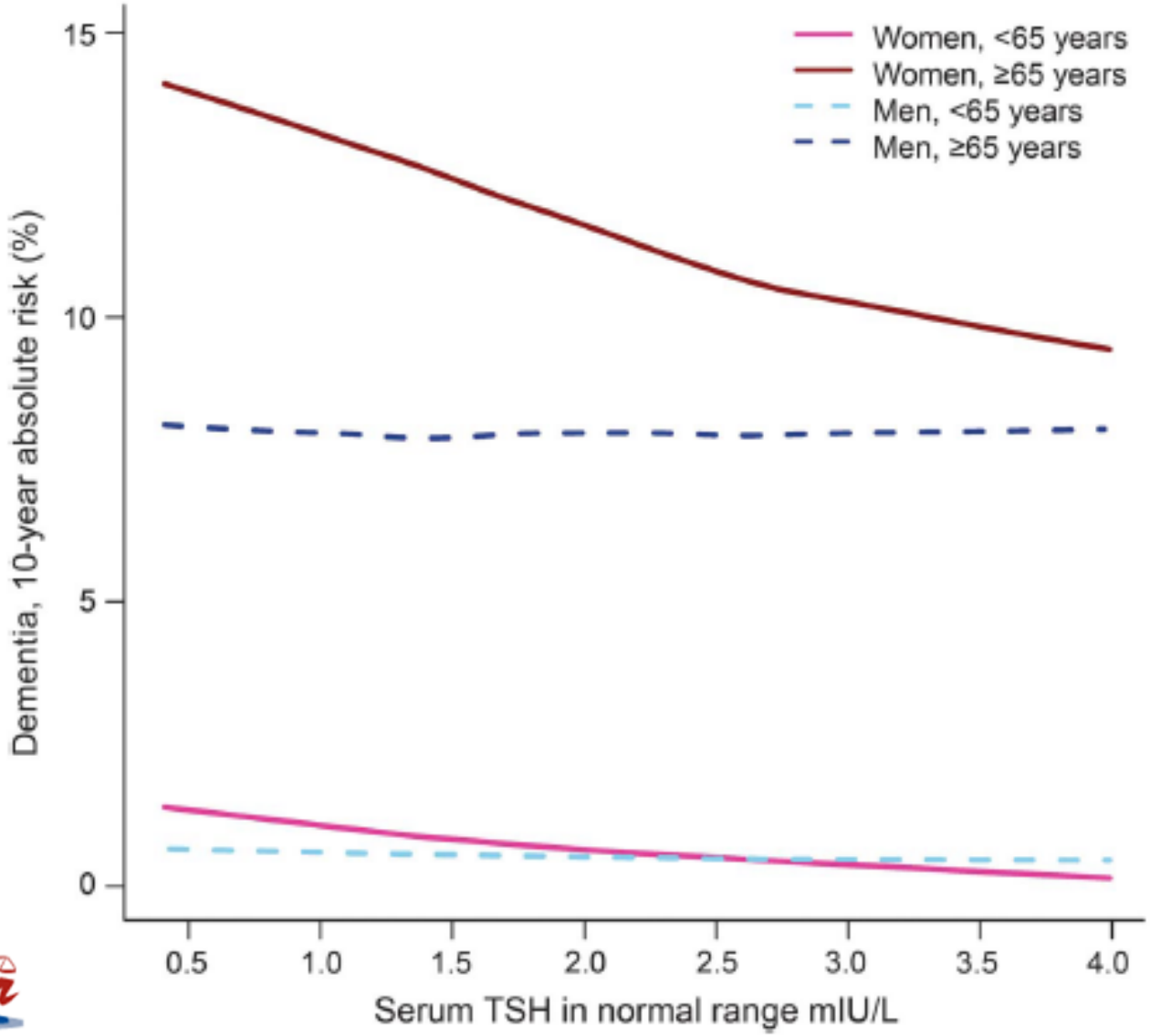
Pooled analyses (log of Odds Ratio) for incidence or prevalence of dementia. Data are stratified by age (above and below 75 years).

Pasqualetti G et al JCEM 2015

Thyroid function and the risk of dementia

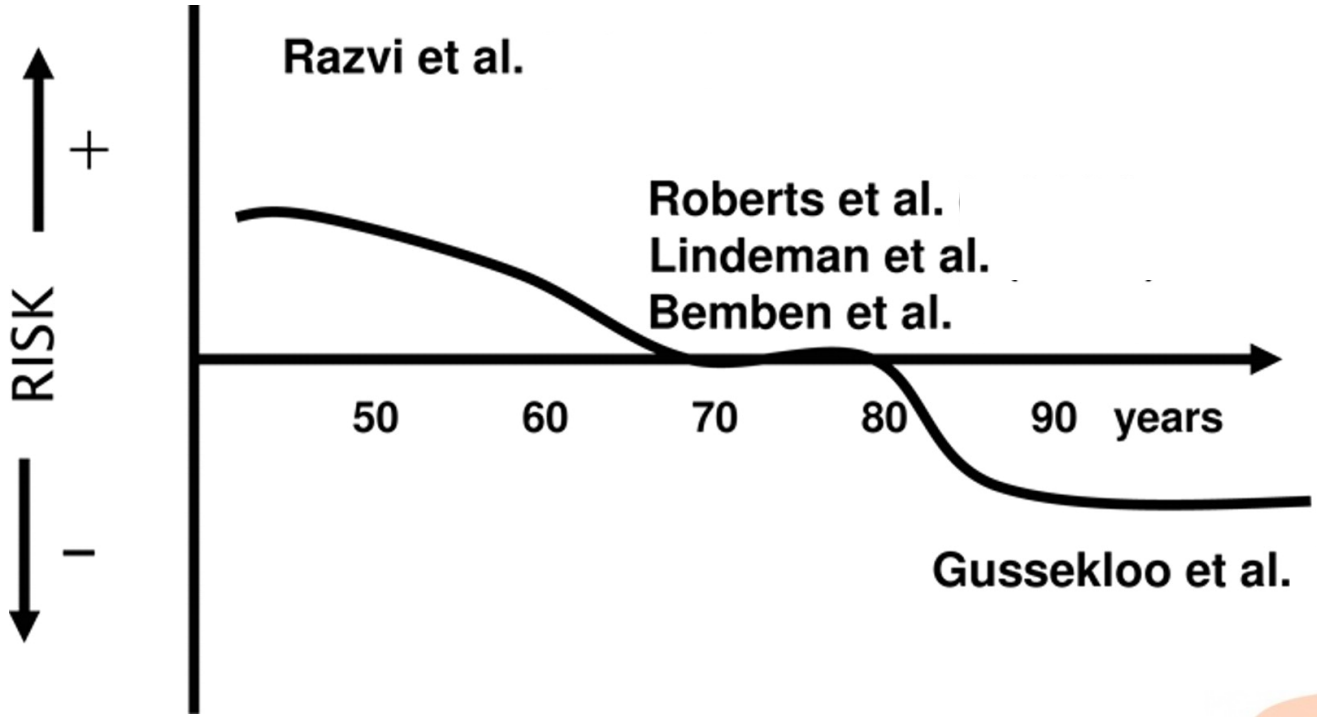
The Rotterdam Study

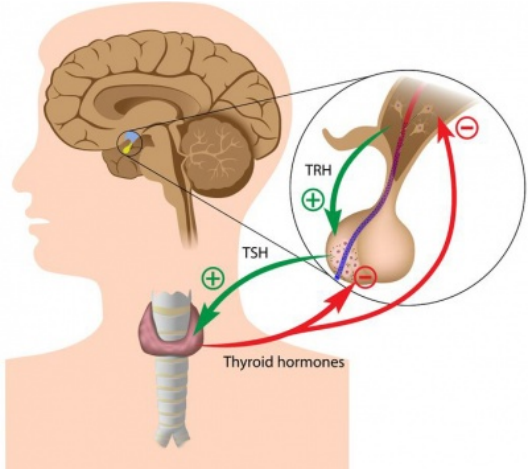
Absolute 10-year risk of dementia by TSH values within the normal range



Chaker et al. Neurology 2016

Hypothetical relationship between age and effect of sHT on symptoms, mood, and cognition





Biondi B et al. Endocr Rev 2008

Postgraduate Medicine

http://informahealthcare.com/pgm
ISSN: 0032-5481 (print), 1941-9260 (electronic)

Postgrad Med, 2015; Early Online: 78–
 DOI: 10.1080/00325481.2015.998158

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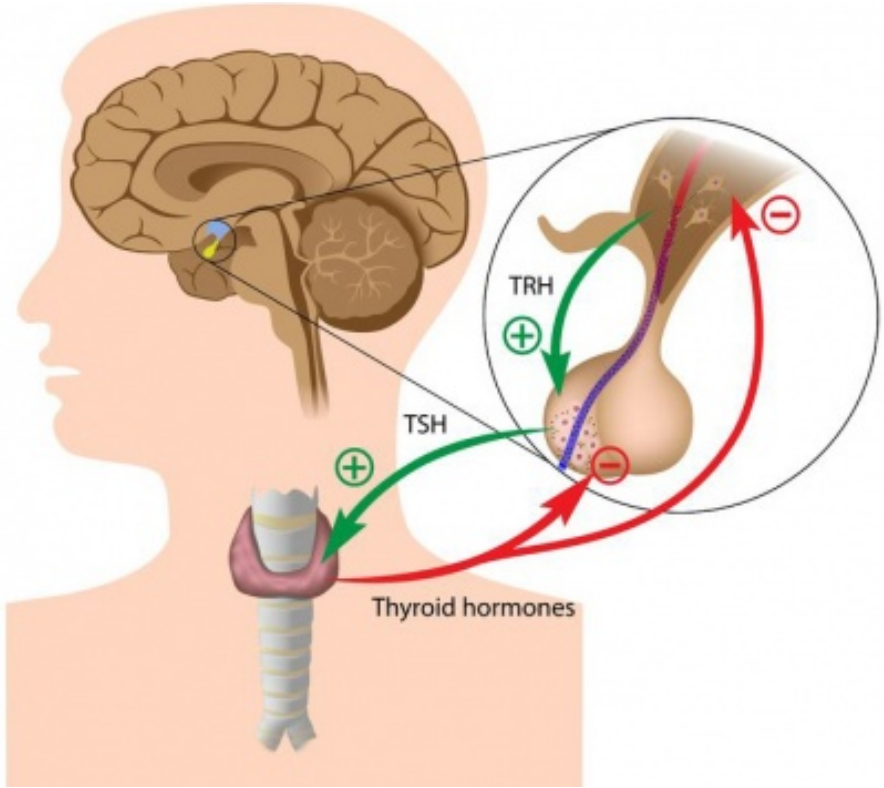
REVIEW

Reversible morbidity markers in subclinical hypothyroidism

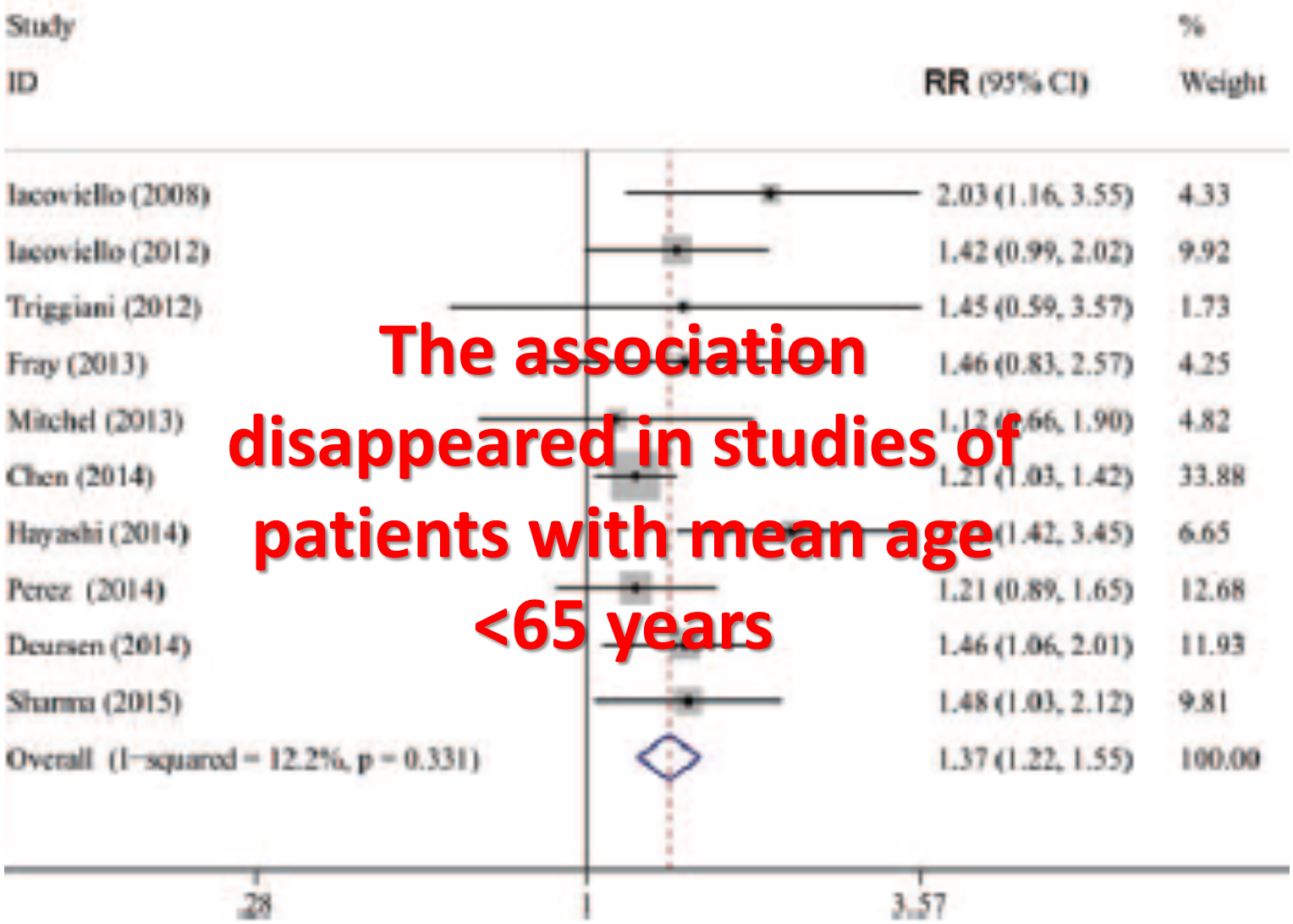
James V. Hennessey[1] & Ramon Espaillat[2]



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

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. Weights are from random-effects analysis

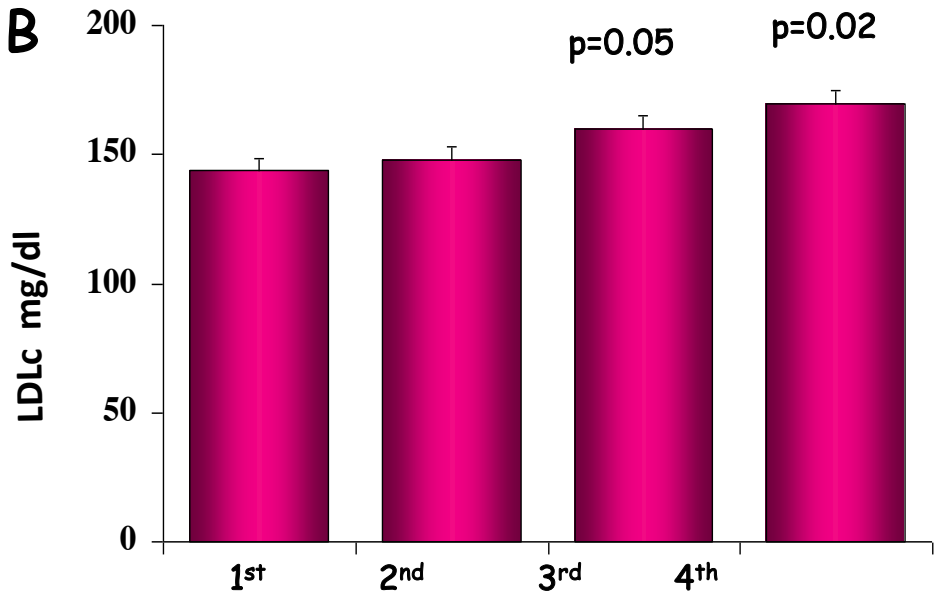
Dengfeng Gao et al Medicine 2015

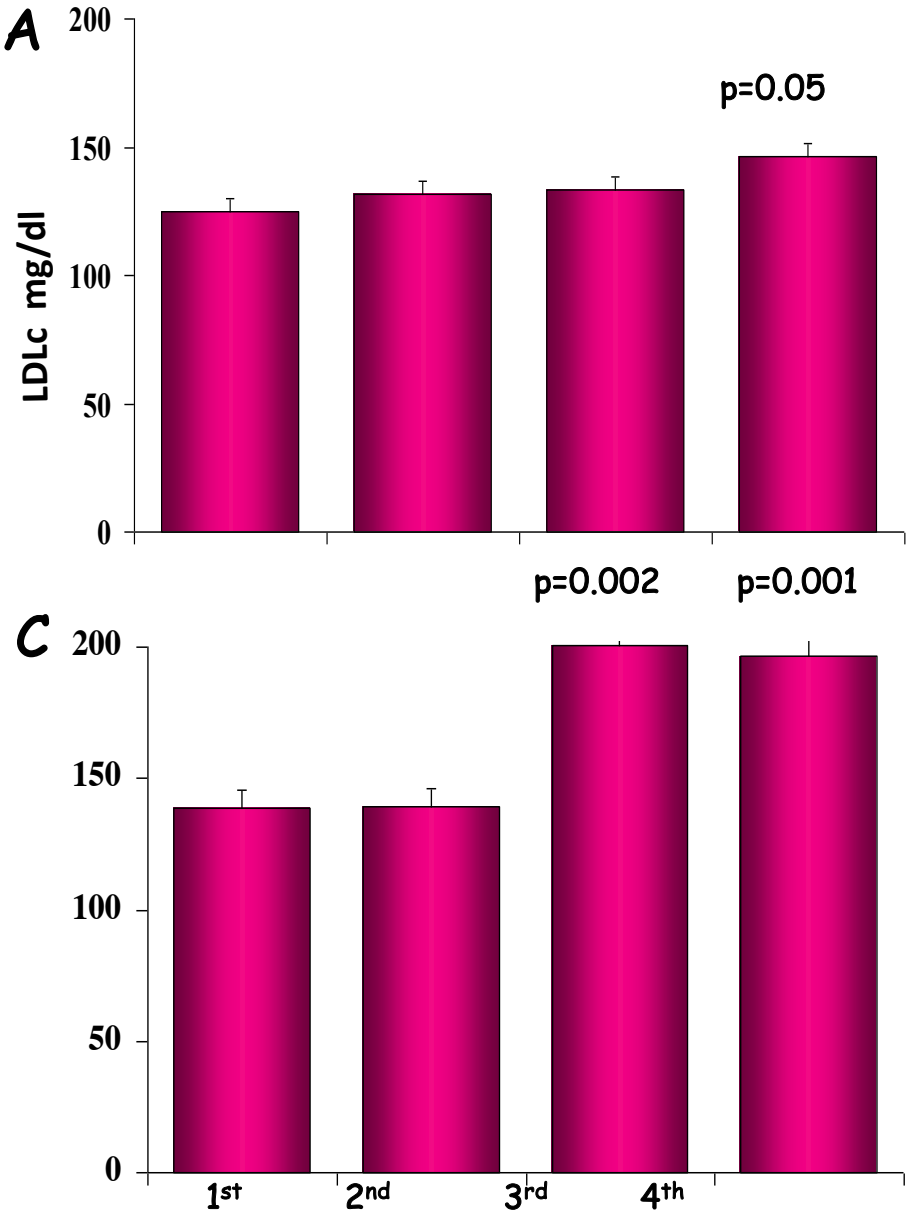
Age and gender substantially influence the relationship between thyroid status and the lipoprotein profile

2308 consecutive outpatients with suspected or diagnosed thyroid disease

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

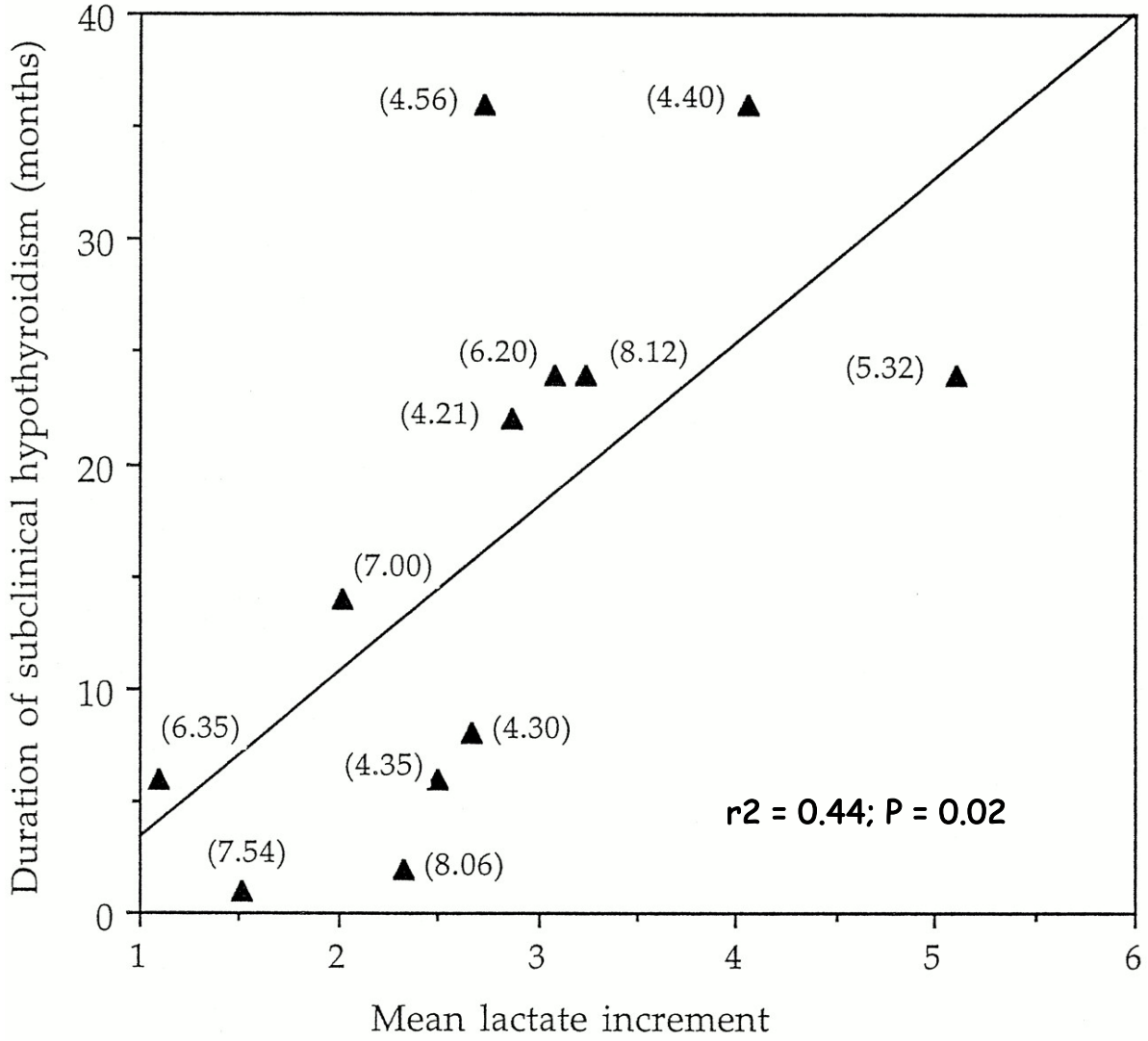
1st quartile: TSH <0.36 mUI/L
2nd quartile: TSH >0.36 <3.60 mUI/L
3rd quartile: TSH >3.60 <10 mUI/L
4th quartile: TSH >10 mUI/L





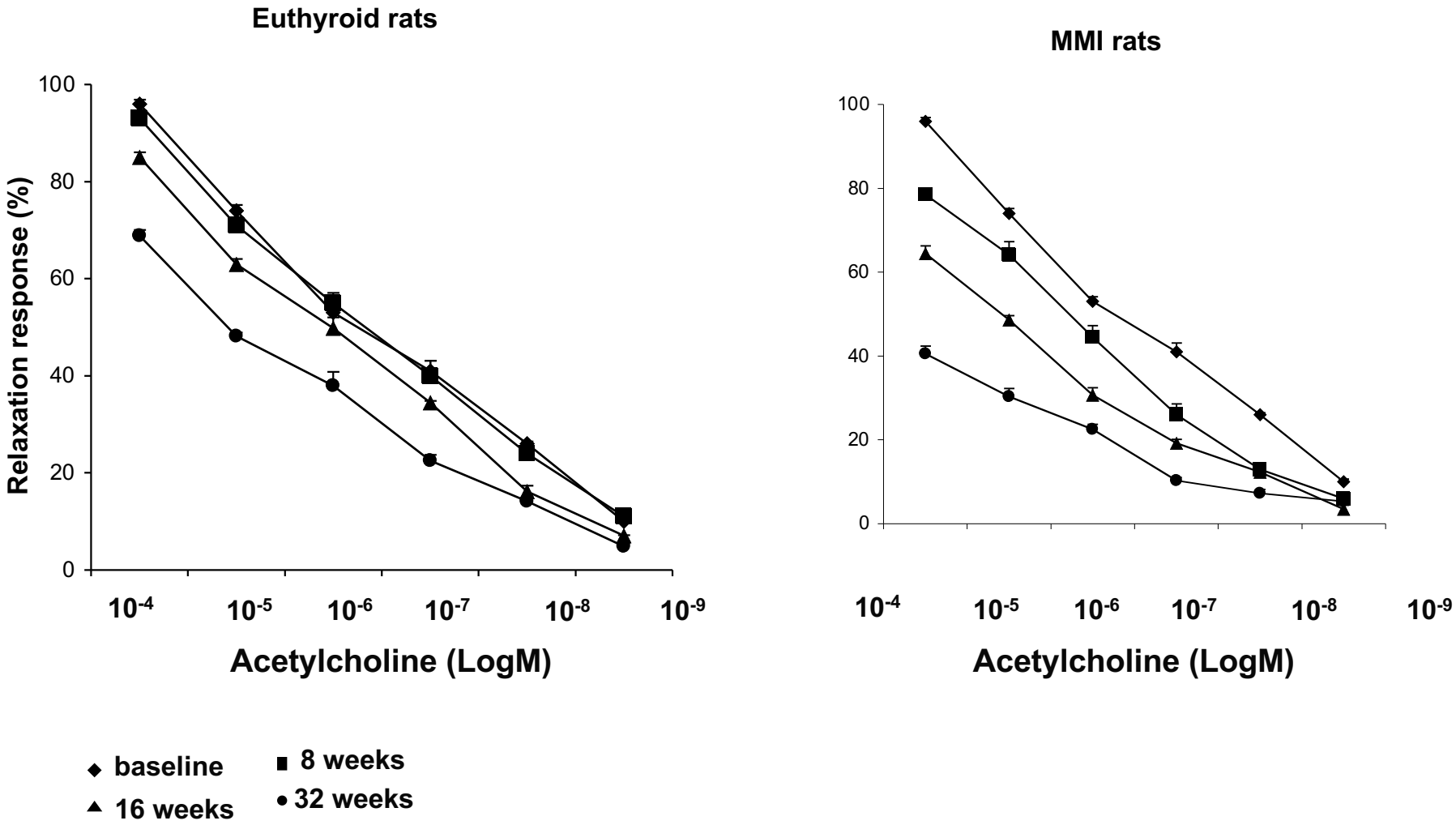
Modified from Tognini S et al. Thyroid 2012

Mild hypothyroidism and mitochondrial dysfunction: effect of disease duration



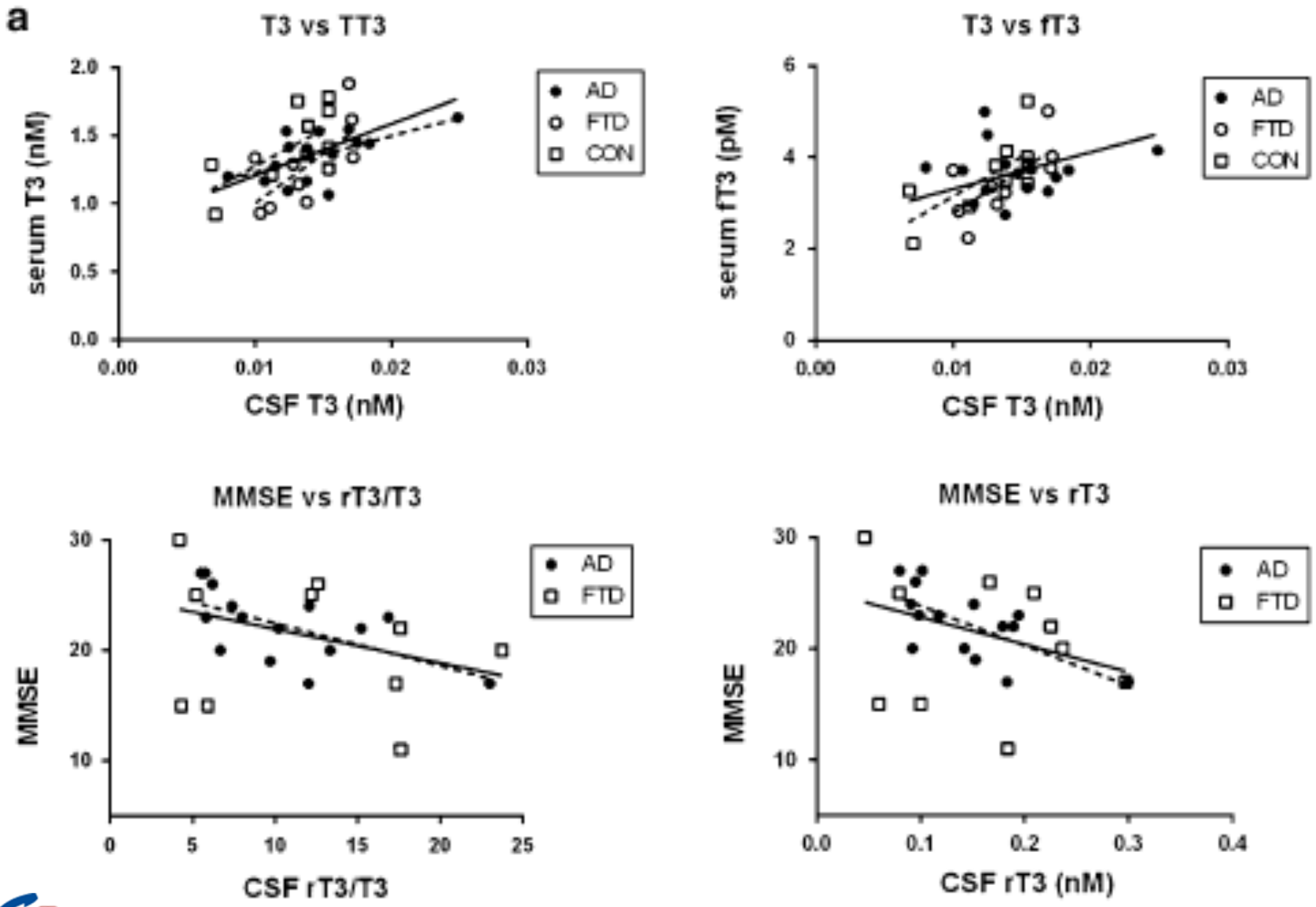
Monzani F et al. J Clin Endocrinol Metab 1997

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



Virdis A et al. Endocrinology 2009 & Unpublished data

Thyroid hormone levels in the cerebrospinal fluid correlate with disease severity in euthyroid patients with Alzheimer



Accorroni A et al. Endocrine 2017

Degree of peripheral T4 deiodination, frailty and long-term survival in hospitalized euthyroid older patients

	Q1 FT_3/FT_4<1.51pg Mediana (range) media±DS	Q2 1.51<FT_3/FT_4<2.02 Mediana (range) media±DS	Q3 2.02<FT_3/FT_4< 2.6 Mediana (range) media±DS	Q4 FT_3/FT_4>2.6 Mediana (range) media±DS	*p*
Sesso % (F)*	55.6%	62.3%	50.3%	43.8%	0.008
Età (anni)	86 (65-97)	84 (66-100)	85 (65-101)	82 (65-100)	0.008
CIRS_S	2.3±0.4	2.1±0.4	2.1±0.4	2.0±0.4	0.000
MPI	0.72±0.27	0.63±0.28	0.52±0.30	0.42±0.26	0.000
ADL**	2 (0-6)	2 (0-6)	4 (0-6)	6 (0-6)	0.000
IADL**	1 (0-8)	1 (0-8)	3 (0-8)	4 (0-8)	0.000
SPMSQ**	5 (0-10)	4 (0-10)	3 (0-10)	2 (0-10)	0.000
MNA positivo %*	55.0%	38.6%	26.8%	16.6%	0.000
CAM positivo %*	9.3%	20.4%	14.3%	7.1%	0.020
Durata degenza ospedaliera (giorni)**	6 (3-32)	5 (2-21)	5 (1-26)	5 (2-15)	0.000

DS: deviazione standard; CIRS: Cumulative Illness Rating Scale (severità e comorbidità); ADL: activities of daily living; IADL: instrumental activities of daily living; SPMSQ: Short Portable Mental Status Questionnaire; MNA: mini nutritional assessment; CAM: confusion assessment method;
** χ^2 test; **Test Kruskal-Wallis (per gli altri parametri one way ANOVA)*

Pasqualetti et al JCEM in press

TAKE HOME MESSAGES

- Most studies suggest an impact of subclinical hyperthyroidism on mood and cognition
- A relationship between sHT and cognition is only documented in individuals younger than 75 years and those with higher TSH concentrations
- The relationship between sHT and cognition as well as cerebrovascular diseases 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 may account for the peculiar clinical scenario of subclinical hypothyroidism in the elderly
- The possible presence of NTIS and the potential role of drugs should be not overlooked


GRAZIE
Un ringraziamento particolare a tutti i miei collaboratori