66° SIGG CONGRESSO NAZIONALE
ROMA, 1-4 DICEMBRE 2021
Geriatria e Rinascita
CLUB EndoGer
SOCIETÀ ITALIANA DI GERONTOLOGIA E GERIATRIA

KEYNOTE LECTURE
L'ENDOCRINOGERIATRIA

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ENDOCRINE FRAILTY IN THE ELDERLY

EDITED BY: Antonio Aversa, Sandro La Vignera and Fabio Monzani
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frontiers Research Topics

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ENDOCRINE FRAILTY IN THE ELDERLY

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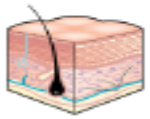
The physiology of endocrine system with ageing

Adrenal gland
ACTH remains relatively stable;
cortisol changes
- ↓ Negative feedback by glucocorticoids and mineralocorticoids
- Earlier morning cortisol maximum
- ↓ Circadian amplitude
- ↑ Late day and evening cortisol levels
- ↑ Irregular cortisol patterns

↓ DHEA and DHEAS
↓ Androstenedione


Adrenal gland

Skin
↑ Conversion of cortisone to cortisol
↓ Vitamin D

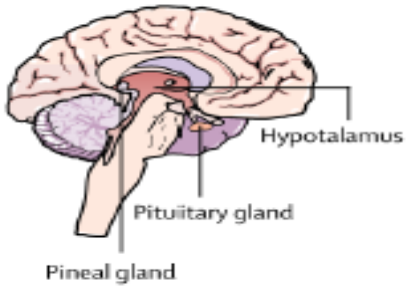

Skin

Bone
↑ Conversion of cortisone to cortisol
FGF23 (direction of change unknown)


Bone

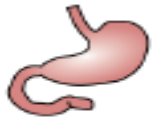
Gonadal system in women
Menopause
↓ Inhibin A and B, progesterone, testosterone, androstenedione, oestradiol, AMH
↑ LH and FSH pulse amplitude, loss of preovulatory gonadotropin surge
Post-menopause
↓ Gonadotropins
↓ Oestradiol, testosterone

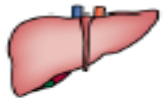

Ovaries




Testes

Gonadal system in men
↓ GnRH
↑ LH (with ↓ amplitude of LH pulses), FSH (modest)
↓ Serum inhibin B to FSH ratio
↓ Testosterone (with ↓ response to LH)
↑ SHBG
↓ Non-SHBG-bound testosterone
Blunted (free) testosterone circadian rhythmicity
↓ Dihydrotestosterone (free and total), androstenedione, androstanediol glucuronide


Stomach


Liver


Pancreas


Thyroid


Parathyroid

Stomach
↓ Acylated ghrelin
↓↔↑ Desacyl ghrelin (depending on body-weight and glycaemic control)

Somatotropic system
↓ GH
↓ IGF-1

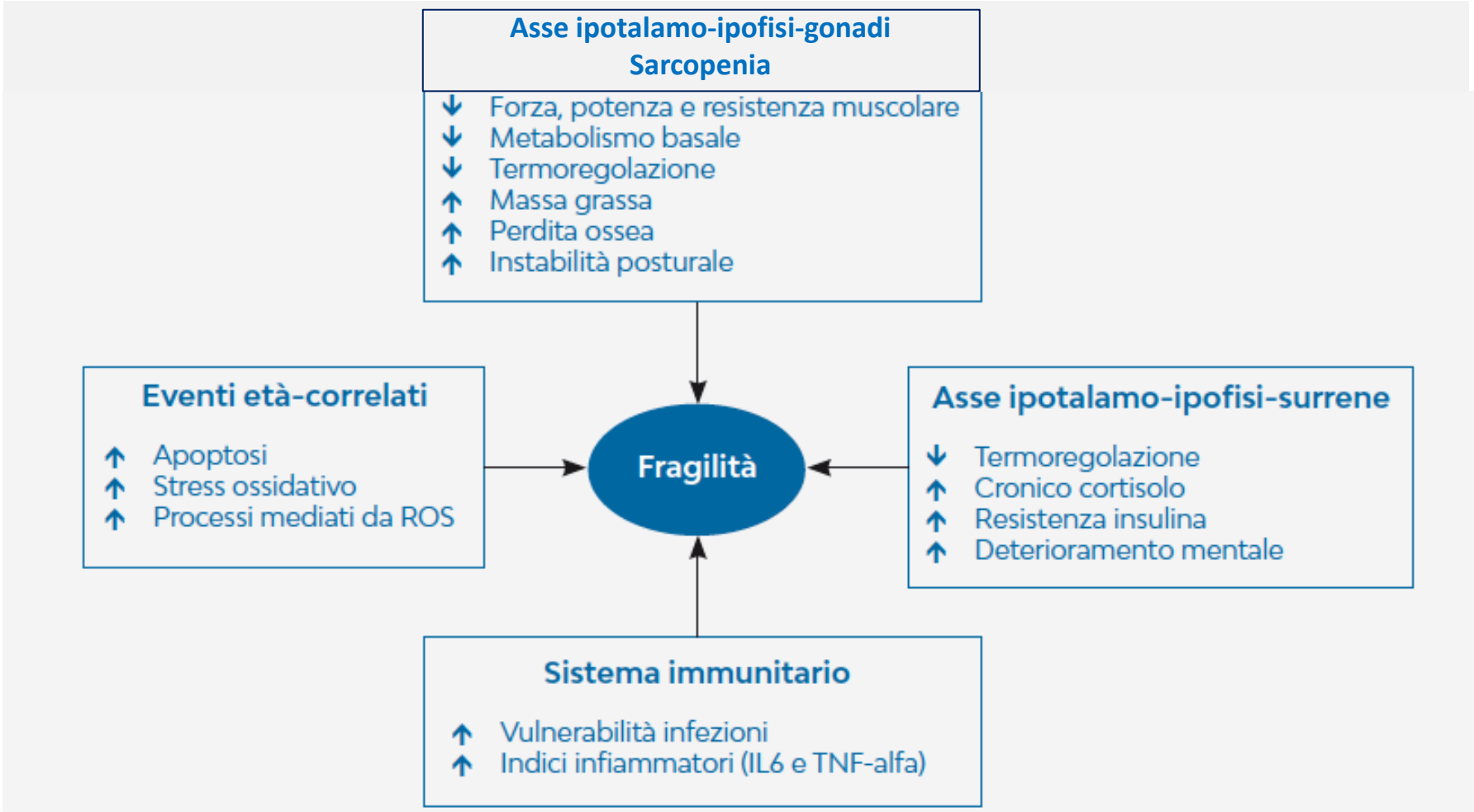
Glucose homoeostasis
↓ Amplitude and mass of high frequency insulin pulses
↓ Frequency of ultradian insulin pulses
↑ Insulin clearance

Thyrotropic system
↑ / = TSH
– / ↑ FT_4
↓ FT_3
↑ reverseT_3
↑ Thyroid antibodies

Parathyroid
↑ PTH

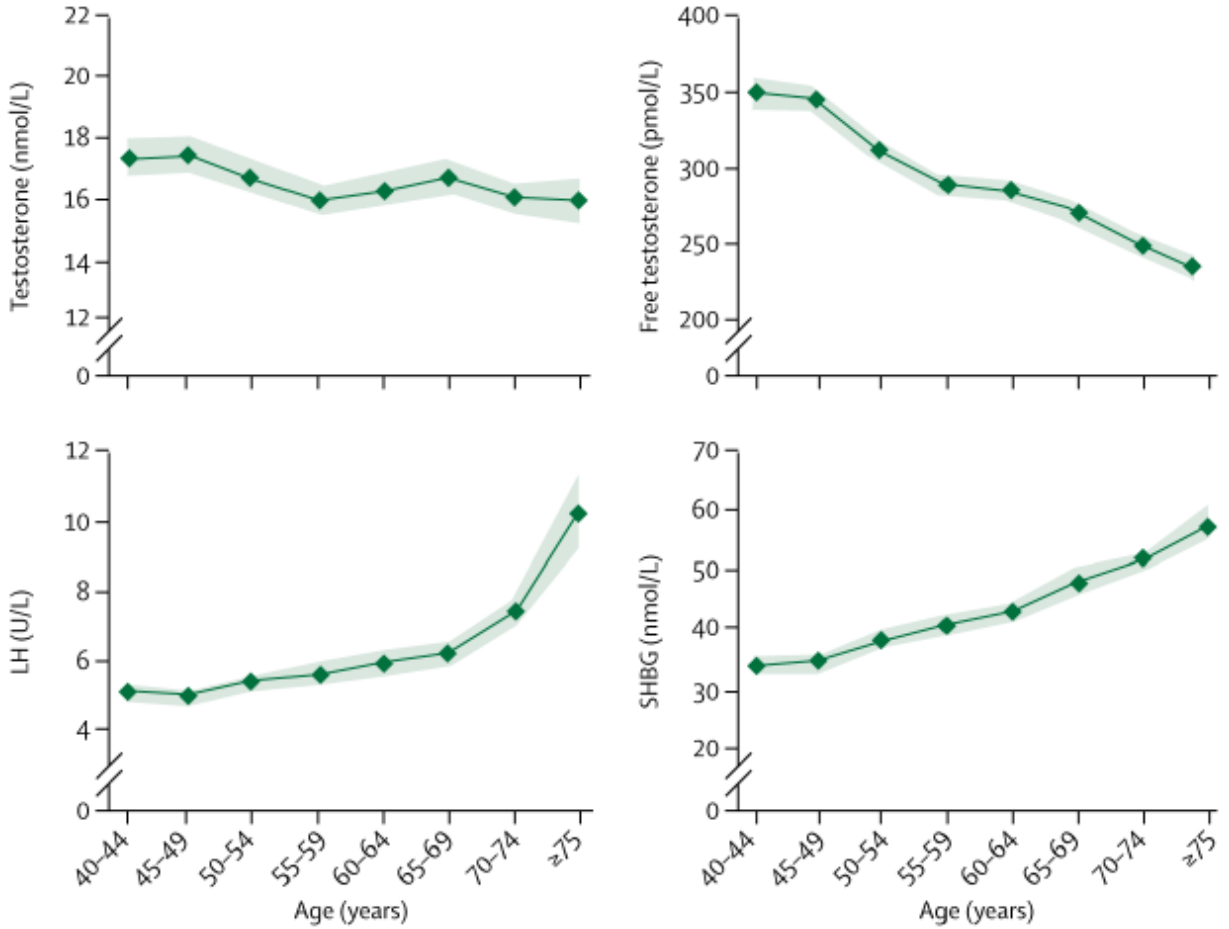
Most-reported changes in circulating hormone concentrations and hormone profiles with ageing

Determinanti di Fragilità



The physiology of endocrine systems with ageing

Mean hormone concentrations (95% CI) in 5 year age bands for a cohort of 3220 men living in Europe

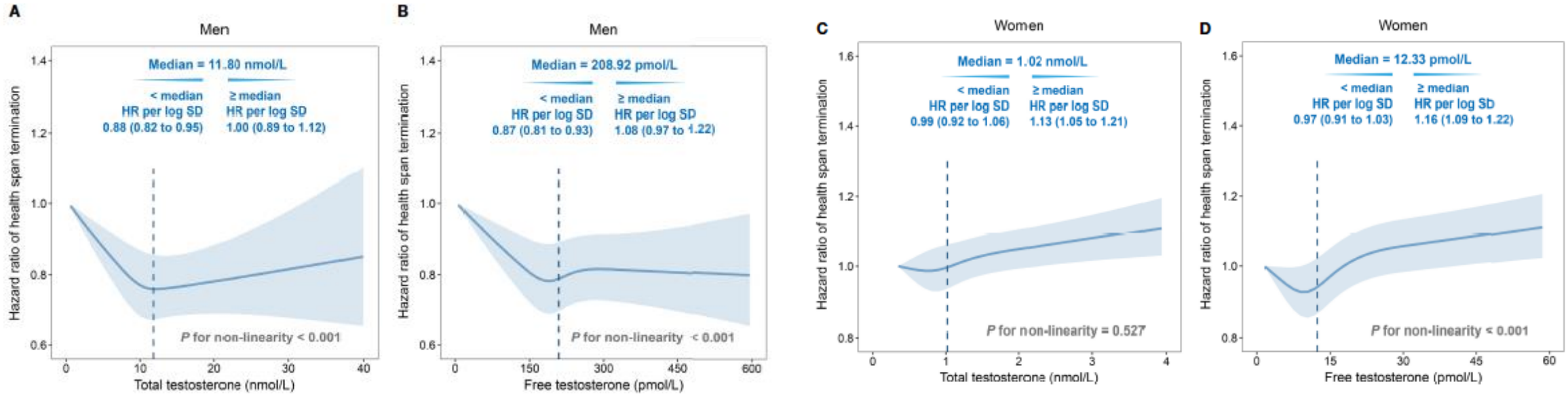


van den Beld AW Lancet Diabetes Endocrinol. 2018. doi:10.1016/S2213-8587(18)30026-3

frontiers in Endocrinology

Sex-Specific Associations of Testosterone and Genetic Factors With Health Span

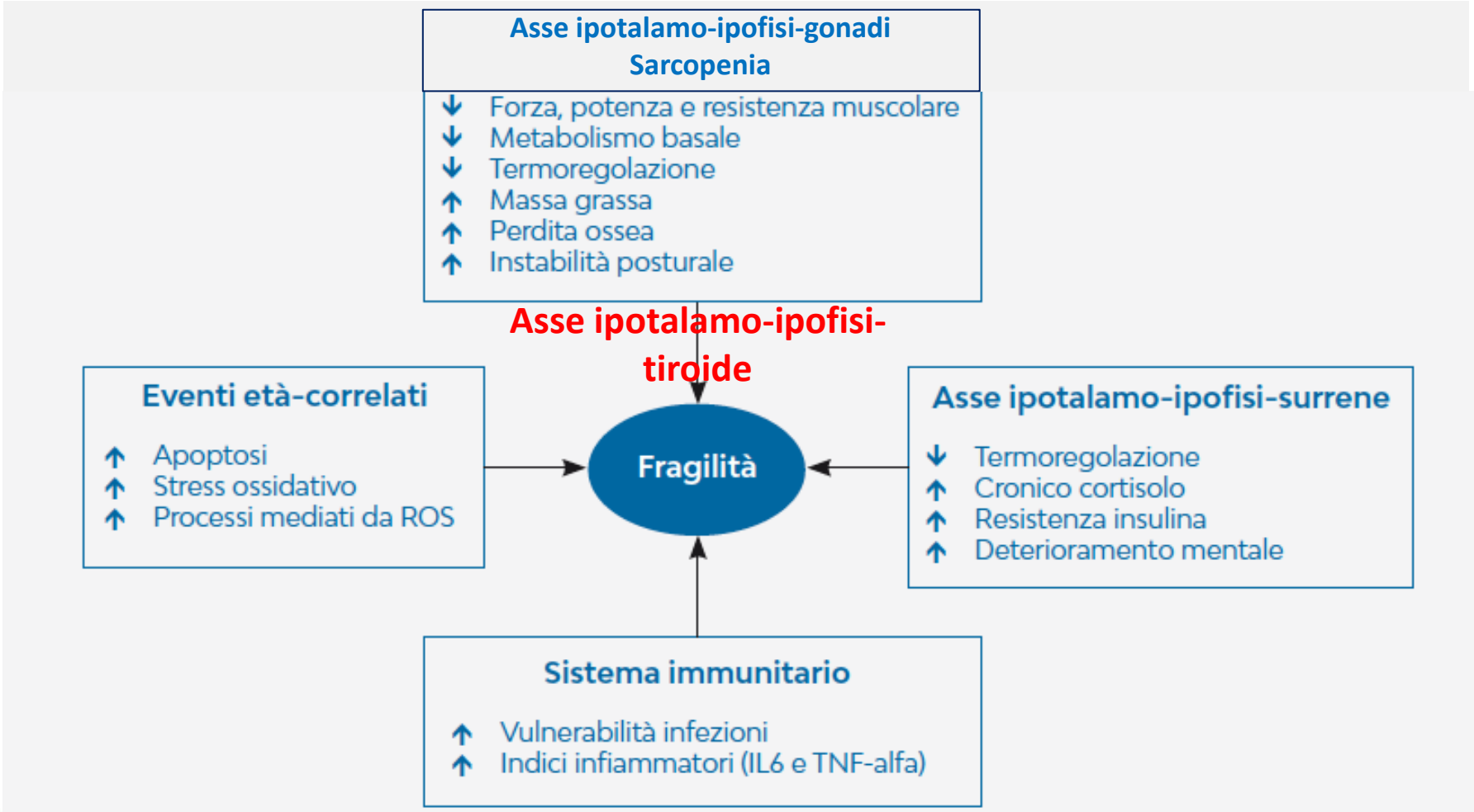
Non-linear associations of total testosterone/free testosterone (TT/FT) with risk of health span termination by multivariate cubic regression splines.
Fully adjusted model: age, menopause status (for women), college or university degree, deprivation index, BMI, smoking status, alcohol drinking, IPAQ group, healthy diet, family history of cardiac-cerebral vascular disease (CCVD) or cancer, use of aspirin/ibuprofen, hormone replacement therapy, SHBG

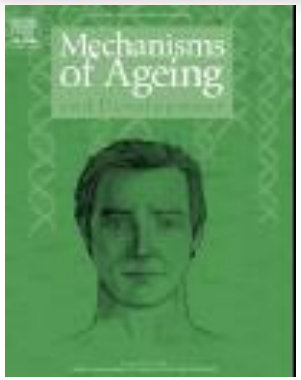


Testosterone was negatively associated with HST risk in men and positively associated with HST risk in women.
Genetic factors increased the HST risk, suggesting that participants with both high genetic risk and abnormal testosterone levels (high level in women or low level in men) should be the target for early intervention.

Zhao X et al 2021

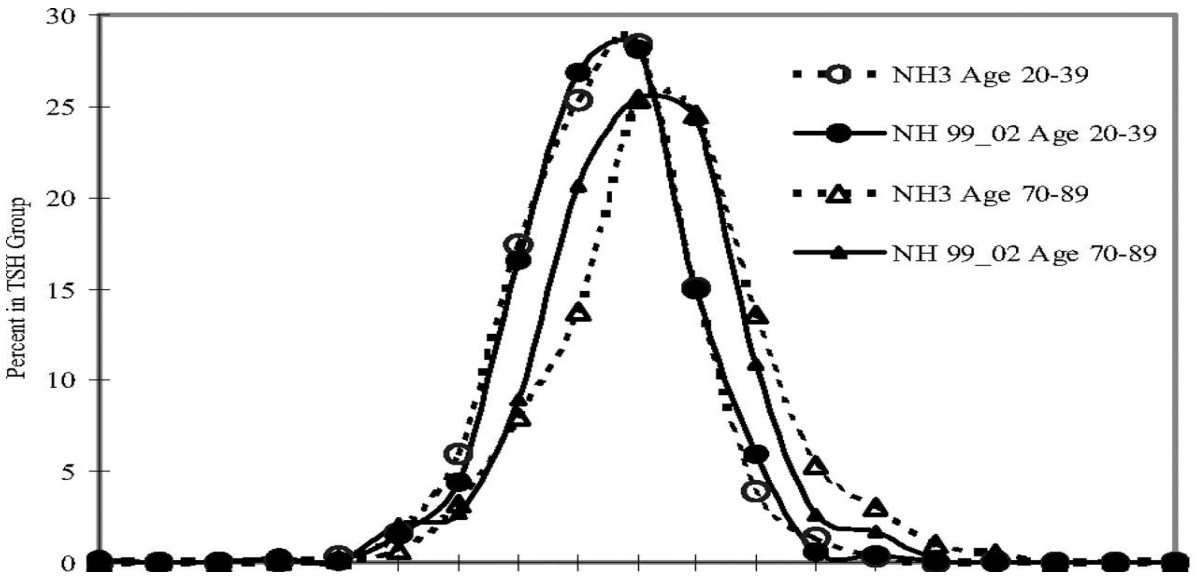
Determinanti di Fragilità



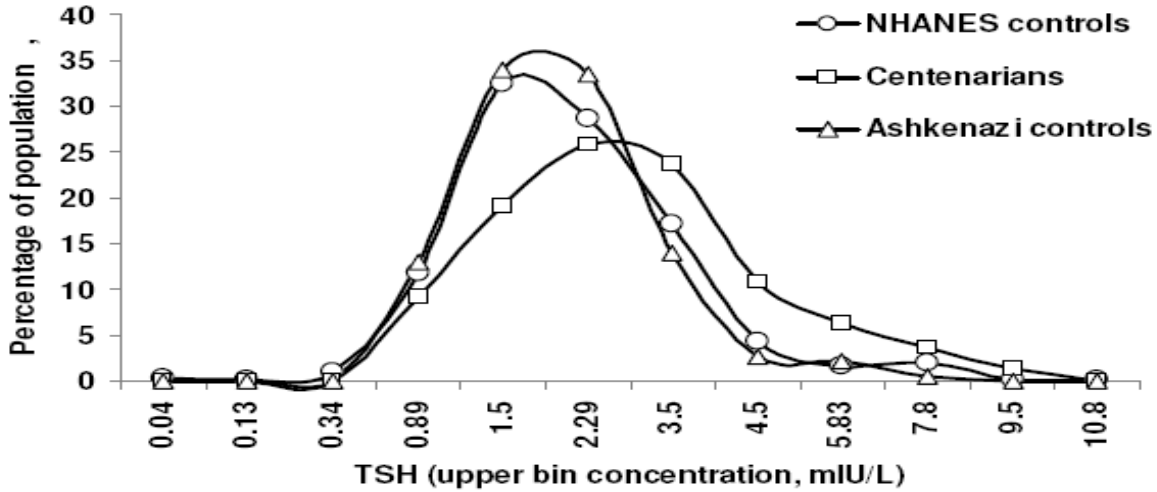


Thyroid hormones in extreme longevity

Home-dwelling, disease-free populations



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

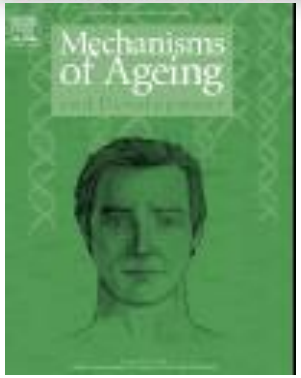


Ashkenazi centenarians (median age: 97.7 yrs)

Ashkenazi controls (median age: 71.0 yrs)

NHANES controls (age range 60-79 yrs)

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

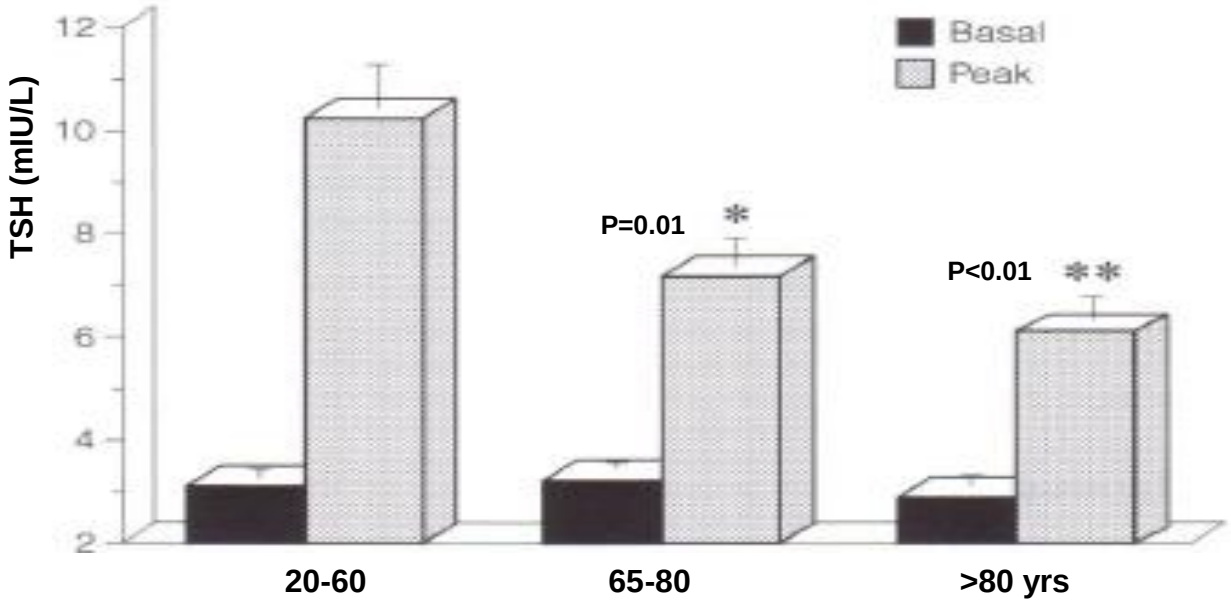


Age-Related Modifications in the Regulation of the Hypothalamic-Pituitary-Thyroid Axis

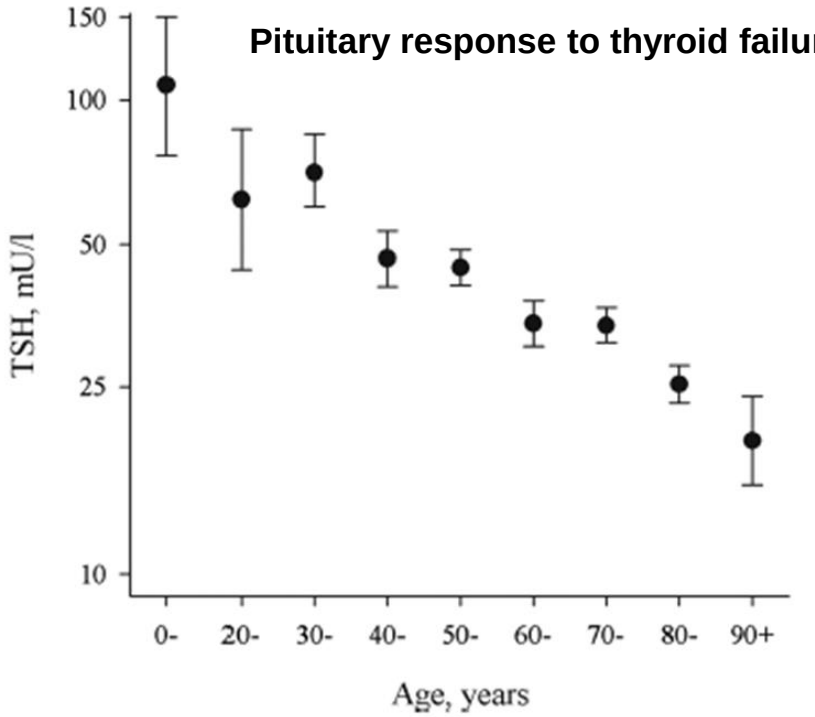
Original Paper

Horm Res 1996;46:107–112

TSH response to TRH injection

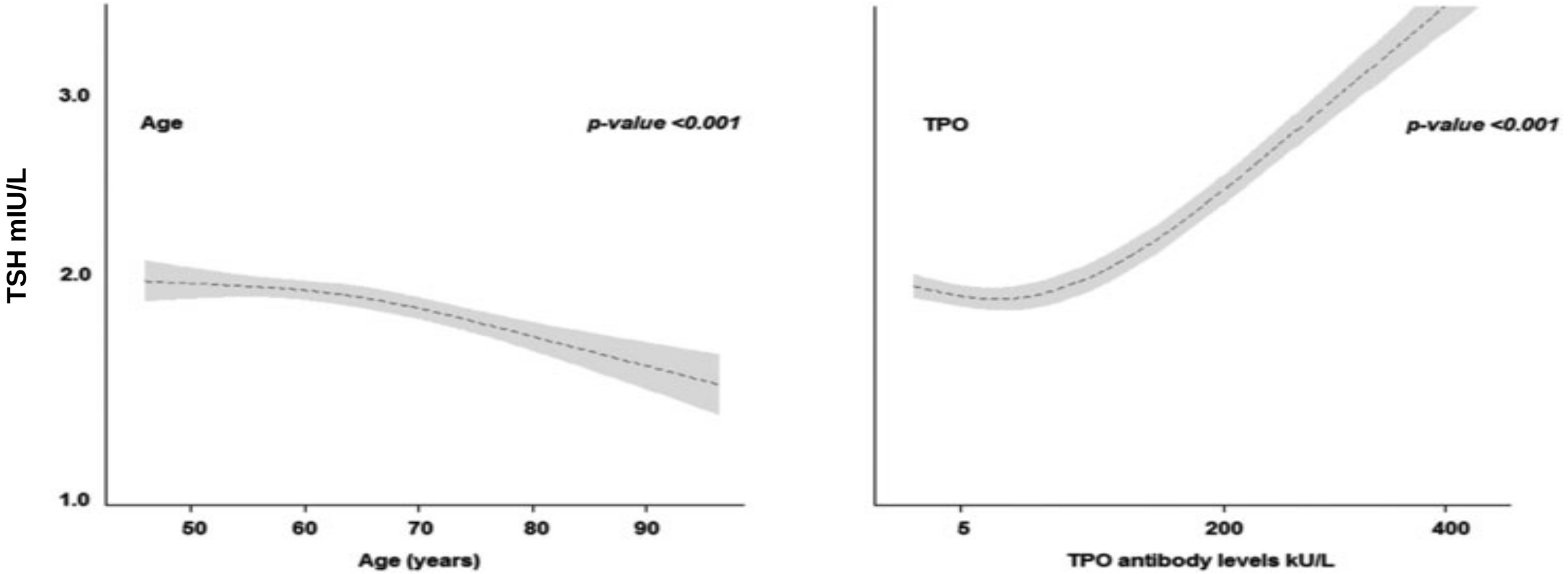


Pituitary response to thyroid failure



Garasto S et al. Mechanisms of Ageing and Development 2017 - Monzani F et al Horm Res 1996

Thyroid Function Changes with Ageing: The Rotterdam Study



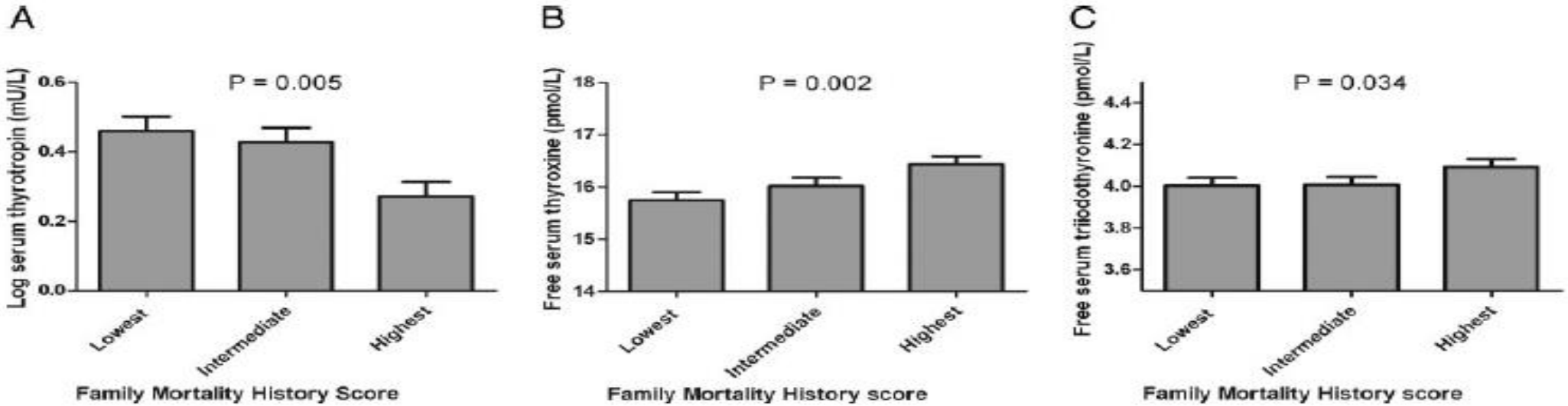
9402 participants from the Rotterdam Study not taking thyroid medication

Chaker et al. Thyroid 2016

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

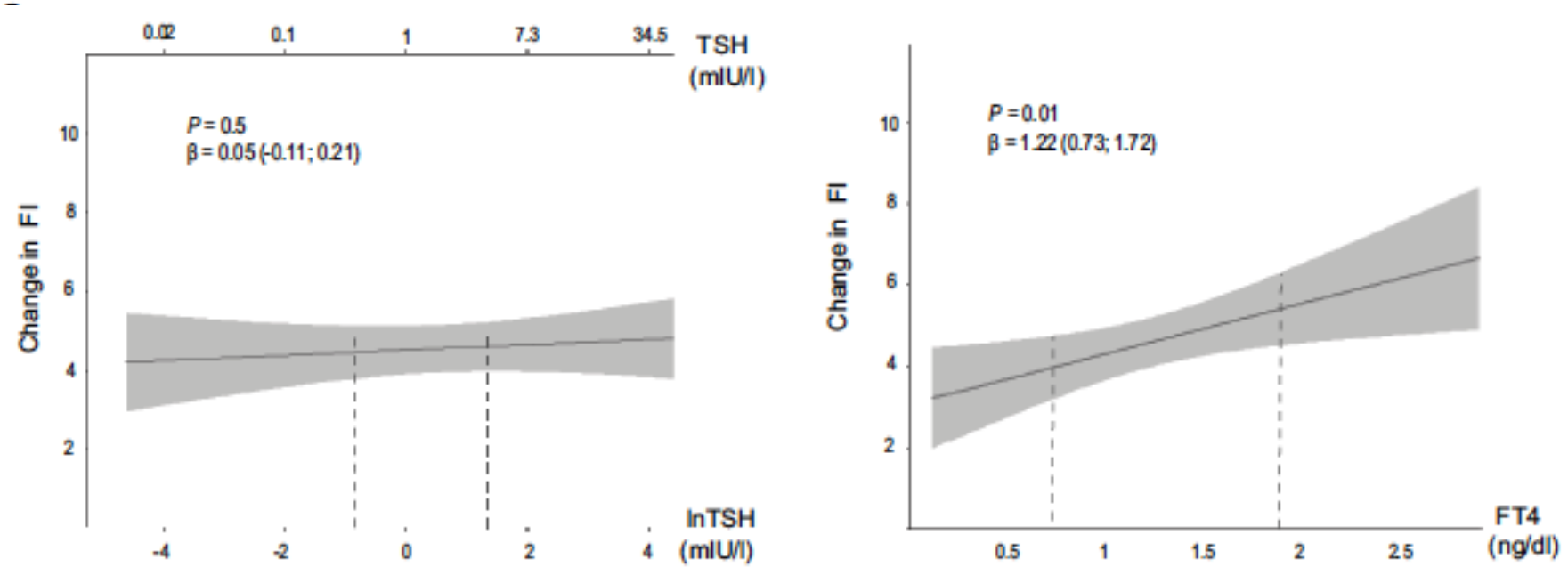


Rozing MP et al. JCEM 2010

High circulating free thyroxine levels may increase the risk of frailty: The Rotterdam Study

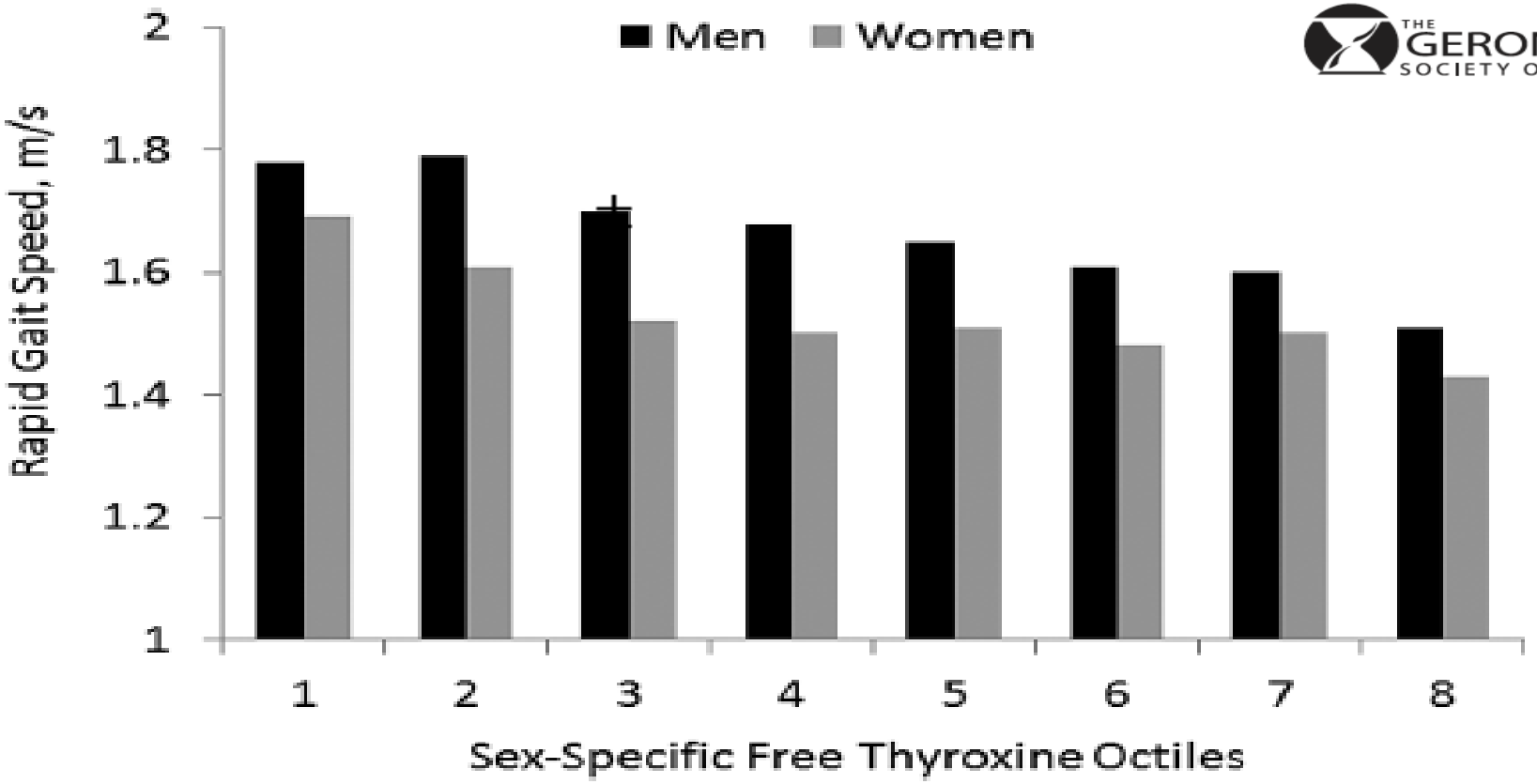
Variation of thyroid function and frailty index

Association of thyroid function and frailty index in euthyroid subjects



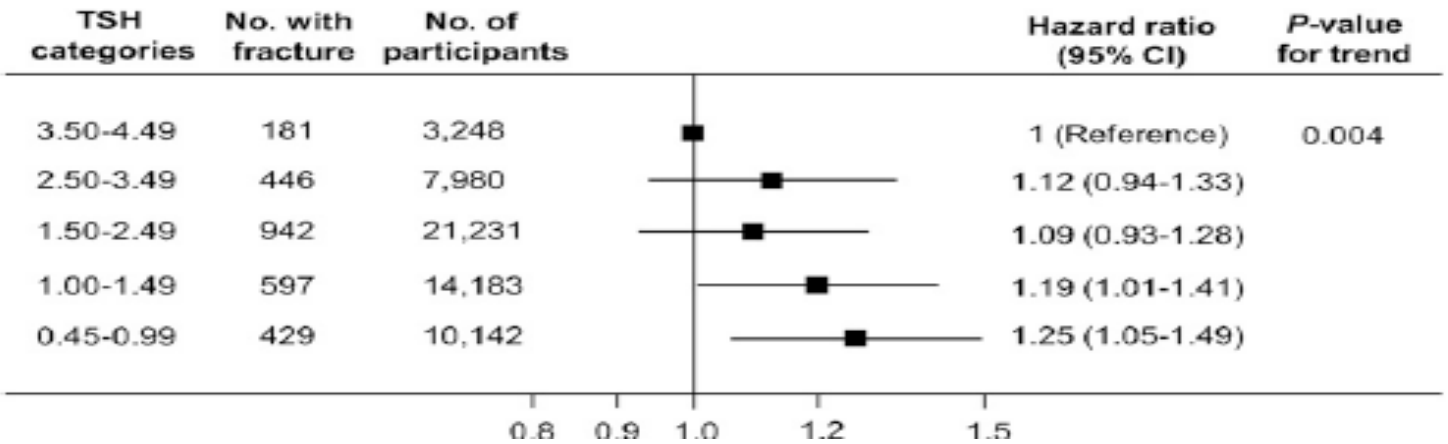
Bano A et al. JCEM 2017

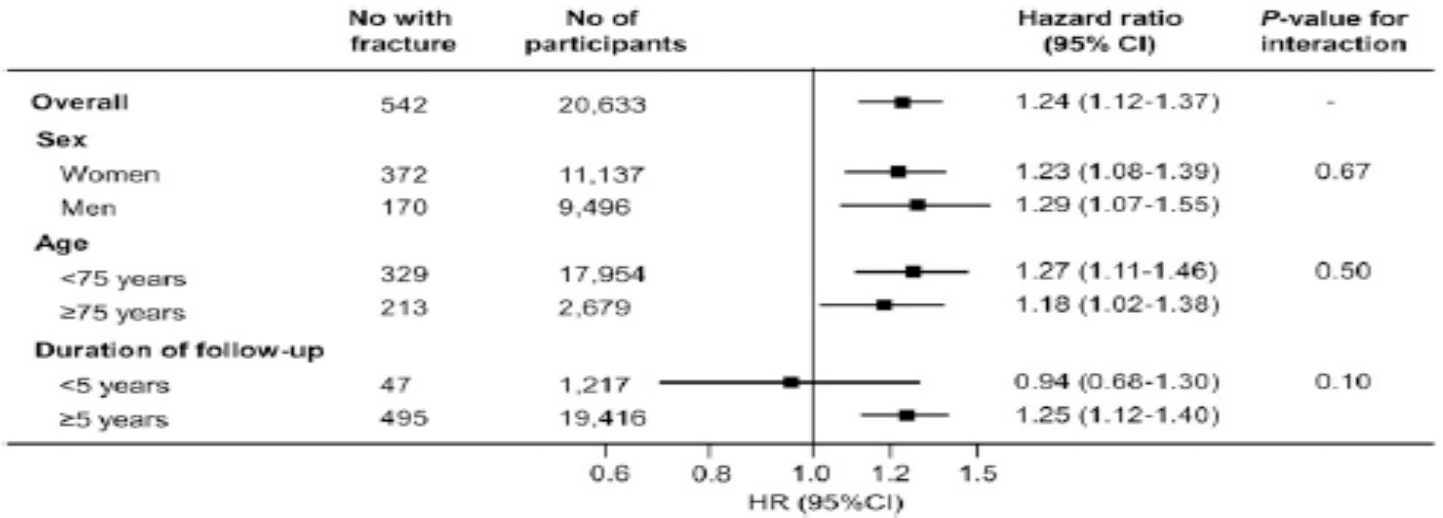
FT4 Functional Mobility, Fitness, and Fatigue in Euthyroid Older Men and Women in the Baltimore Longitudinal Study of Aging



335 men and 267 women (mean age 78.6±6.6 and 77.±6.7, respectively)

Thyroid Function Tests in the Reference Range and Fracture





Thirteen prospective cohort studies with baseline examinations between 1981 and 2002. During 659,059 person-years, 2,565 out of 56,835 participants had hip fracture (4.5%)

Risk of hip fracture according to TSH categories

HRs are for TSH 0.45 to 0.99 mIU/L, compared with the reference group TSH 3.50 to 4.99 mIU/L

Risk of hip fracture per one SD increase in FT4, overall and stratified by sex, age, and duration of follow-up

Aubert CE et al. J Clin Endocrinol Metab 2017

Changes in Serum Thyroid Function Predict Cognitive Decline in the Very Old: Longitudinal Findings from the Newcastle 85+ Study

	Odds ratio	p value	Participant number (n)
Entire cohort			
	1.60 (1.14-2.24)	0.006	250

TABLE 2. CHANGES IN THYROID HORMONES OVER TIME (BASELINE VS. YEAR 3) AS STRATIFIED BY SERUM THYROTROPIN TREND

Serum TSH trend	*Baseline fT4*	*Year 3 fT4*		*Baseline fT3*	*Year 3 fT3*	
	Mean (2.5–97.5 percentile)		*% change; p*	*Mean (2.5–97.5 percentile)*		*% change; p*
Falling ($n=221$)[a]	15.67 (12.00–20.00)	13.95 (10.60–18.35)	−11.0; < 0.001	4.63 (4.00–5.29)	4.48 (3.71–5.29)	−3.2; <0.01
Steady ($n=42$)[b]	15.37 (11.10–18.90)	14.12 (10.32–19.06)	−8.1; 0.005	4.51 (3.64–5.10)	4.31 (3.20–5.18)	−4.4; 0.045
Rising ($n=85$)[c]	15.01 (12.00–20.00)	14.96 (10.18–19.50)	−0.3; 0.590	4.54 (3.94–5.10)	4.38 (3.34–5.30)	−3.5; 0.030
All ($n=348$)[d]						

Odds Ratio, 95% confidence intervals

Decreasing TSH trajectory and the odds of incident cognitive impairment (MMSE <26) at 60 months, and cognitive decline (reduced score>3) over 5 years

Thyroid function values within the normal range and physical performance in the elderly

Relationship between SPPB and FT_3 in older subjects

The InCHIANTI study

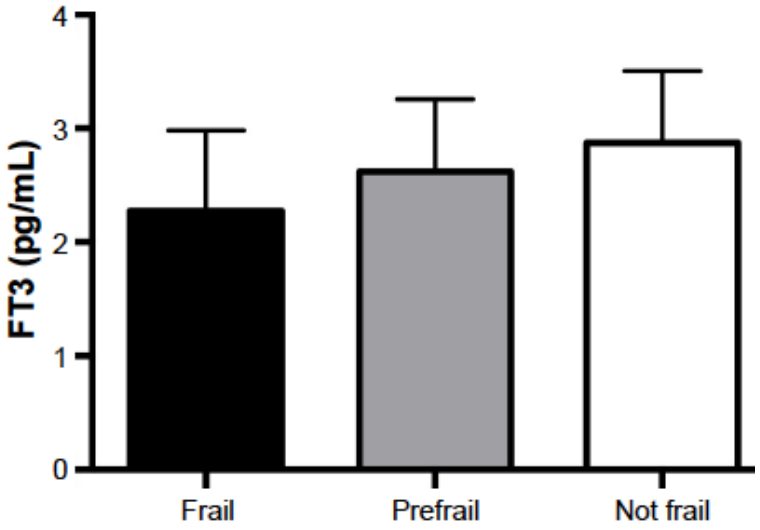
	Beta	SE	P
FT3	0.35	0.17	0.036
Age	-0.10	0.01	<.001
Sex	-0.006	0.21	0.97
Physical Activity	1.18	0.17	<.001
Il-6	-0.19	0.08	0.03
BMI	-0.07	0.02	0.009
Cancer	-0.35	0.29	0.23
Smoking	0.09	0.1	0.37
Renal Function	-0.14	0.07	0.83
CES-D	-0.03	0.008	0.002
CSMA	0.0003	0.00008	0.005
NCV	0.04	0.02	0.02
MMSE	0.039	0.02	0.09
Total Energy Intake	0.0001	0.0001	0.66
Stroke	-0.49	0.16	0.003
CHF	0.07	0.09	0.42

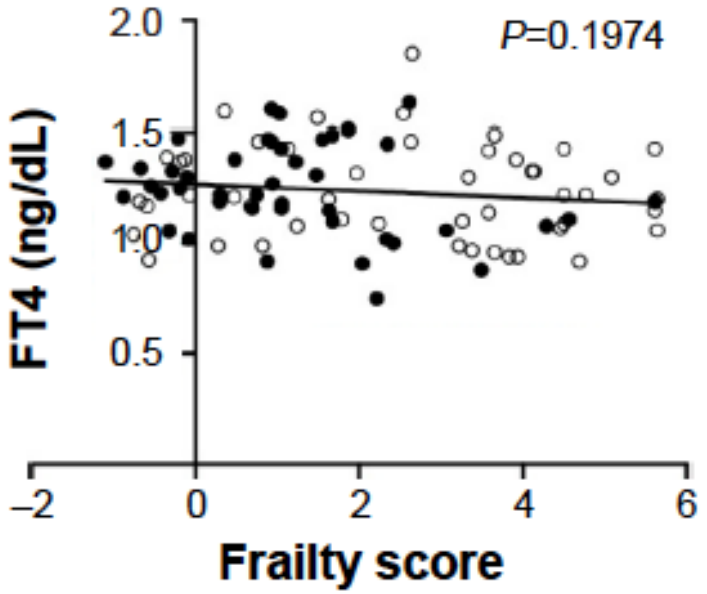
CHF chronic heart failure,
CES-D Center for Epidemiologic Studies-Depression score,
BZD benzodiazepine,
CSMA cross-sectional muscle area,
ACE-in ace-inhibitors,
NCV nerve conduction velocity

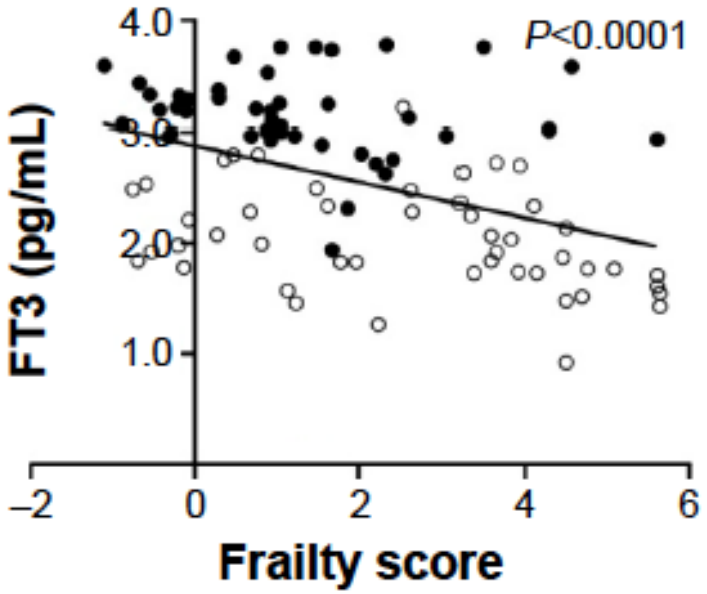
Multivariate analysis

Ceresini G et al, Aging Clin Exp Res, 2018

Low FT3: possible marker of frailty in the elderly







○ Patients with fractures ● Controls

Bertoli A. et al. Clinical Interventions in Aging 2017

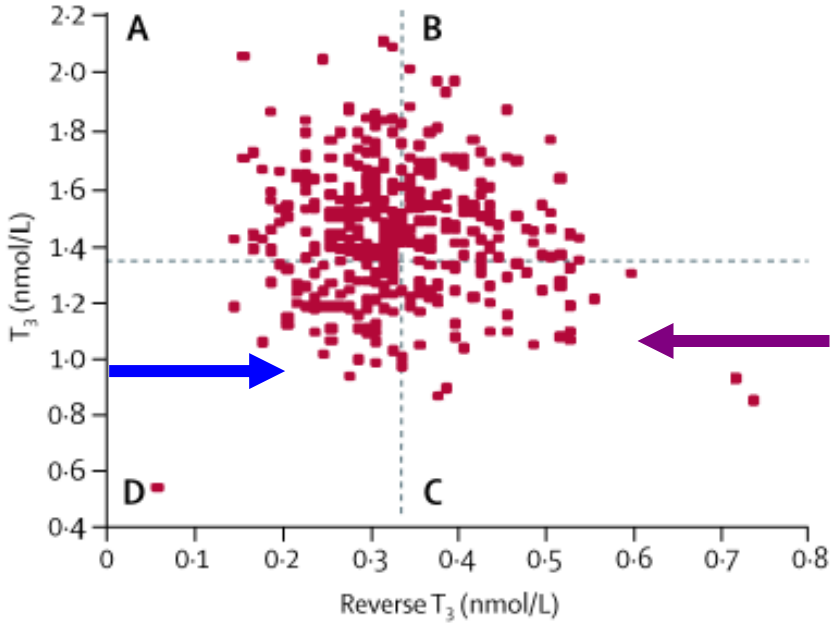
T3 value Physical Performance and Survival

A

n=137, age (years)	77·3 (76·8–77·8)
Diseases	2·05 (1·87–2·22)
PPS (points)	8·5 (8·1–8·9)
ADL (points)	2·30 (2·25–2·36)
LES (Nm)	104·8 (101·4–108·2)
IGS (kp)	35·1 (34·0–36·2)
Neck BMD (g/cm²)	0·89 (0·86–0·91)
Lean mass (kg)	51·9 (51·0–52·7)
Fat mass (kg)	21·2 (20·2–22·2)

D

n=66, age (years)	77·6 (76·7–78·5)
Diseases	1·91 (1·66–2·16)
PPS (points)	9·0 (8·5–9·6)
ADL (points)	2·30 (2·23–2·38)
LES (Nm)	105·7 (100·9–110·6)
IGS (kp)	35·1 (33·5–36·7)
Neck BMD (g/cm²)	0·90 (0·87–0·94)
Lean mass (kg)	53·5 (52·2–54·7)
Fat mass (kg)	21·7 (20·3–23·1)



Significance of tests of between-subjects effects

Age (years) p=0·007	IGS (kp) p=0·25
Disease (n) p=0·12	Femoral neck BMD (g/cm²) p=0·38
PPS (points) p=0·05	Lean mass (kg) p=0·005
ADL (points) p=0·67	Fat mass (kg) p=0·56
LES (Nm) p=0·29	

B

n=123, age (years)	77·8 (77·2–78·5)
Diseases	2·16 (1·98–2·35)
PPS (points)	8·4 (8·0–8·8)
ADL (points)	2·30 (2·25–2·36)
LES (Nm)	101·9 (98·4–105·4)
IGS (kp)	33·8 (32·7–35·0)
Neck BMD (g/cm²)	0·88 (0·85–0·90)
Lean mass (kg)	50·6 (49·7–51·5)
Fat mass (kg)	21·1 (20·1–22·1)

C

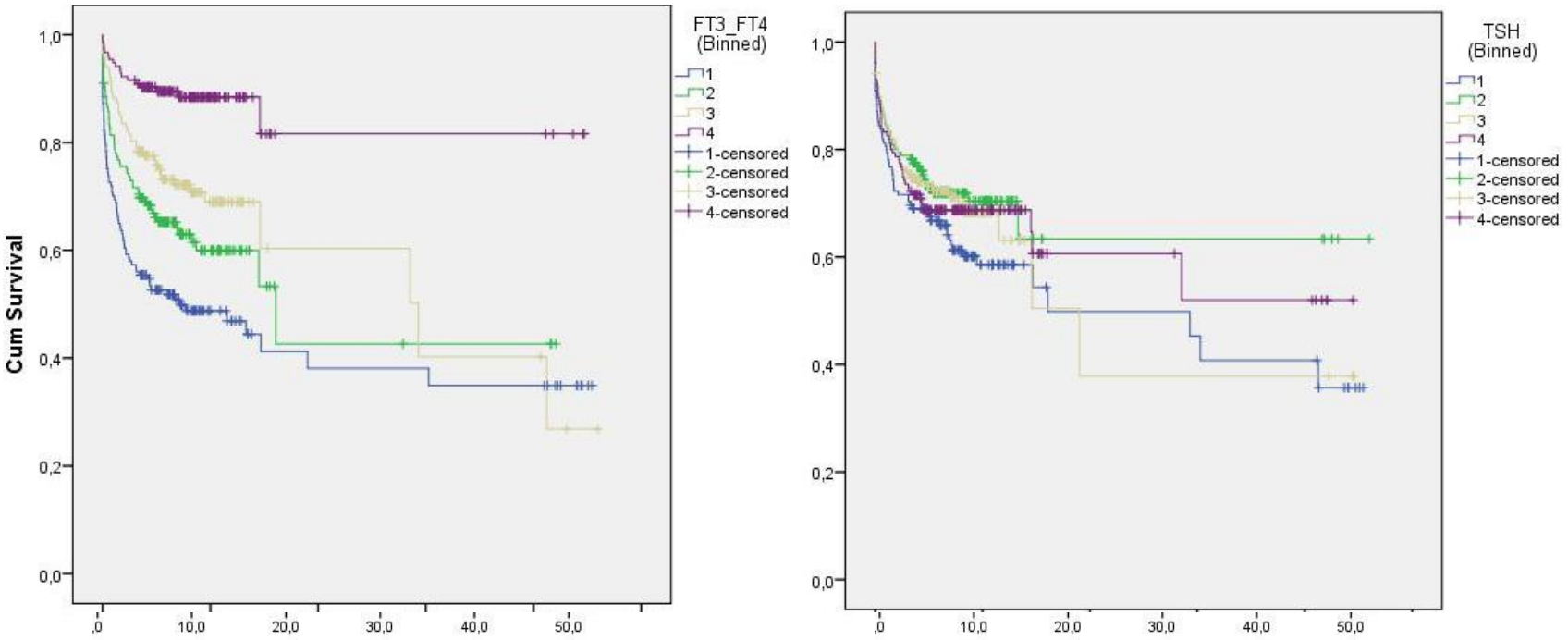
n=63, age (years)	79·1 (78·0–80·2)
Diseases	2·33 (2·07–2·59)
PPS (points)	7·9 (7·3–8·5)
ADL (points)	2·36 (2·28–2·44)
LES (Nm)	100·2 (95·2–105·3)
IGS (kp)	33·6 (31·9–35·2)
Neck BMD (g/cm²)	0·86 (0·82–0·90)
Lean mass (kg)	51·6 (50·3–52·9)
Fat mass (kg)	20·3 (18·8–21·7)

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 AW Lancet Diabetes Endocrinol. 2018. doi:10.1016/S2213-8587(18)30026-3

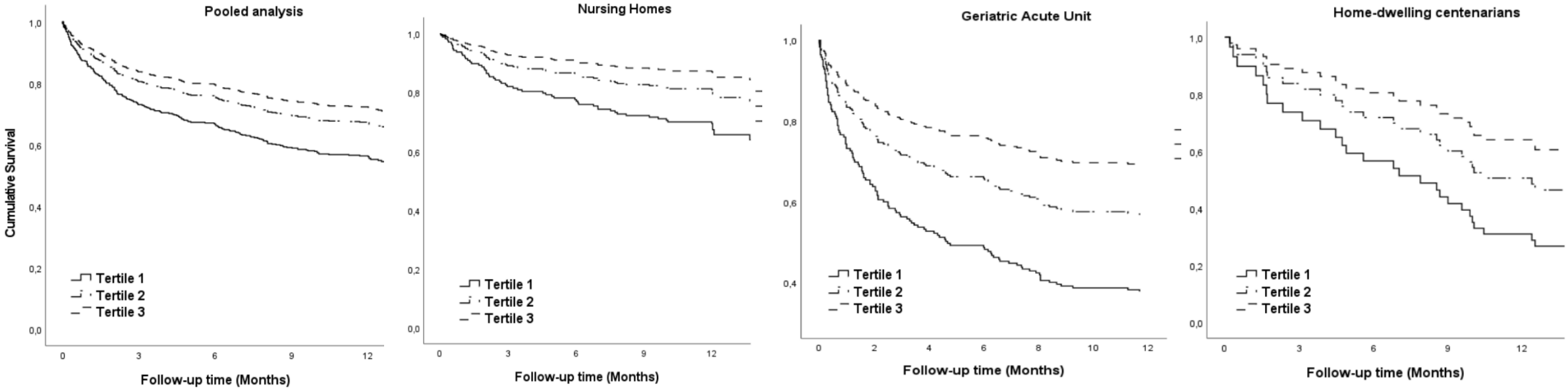
Degree of peripheral T4 deiodination, frailty and long-term survival in hospitalized euthyroid older patients



Mediana follow-up 30.3 mesi, 619 pazienti

Pasqualetti et al JCEM 2018

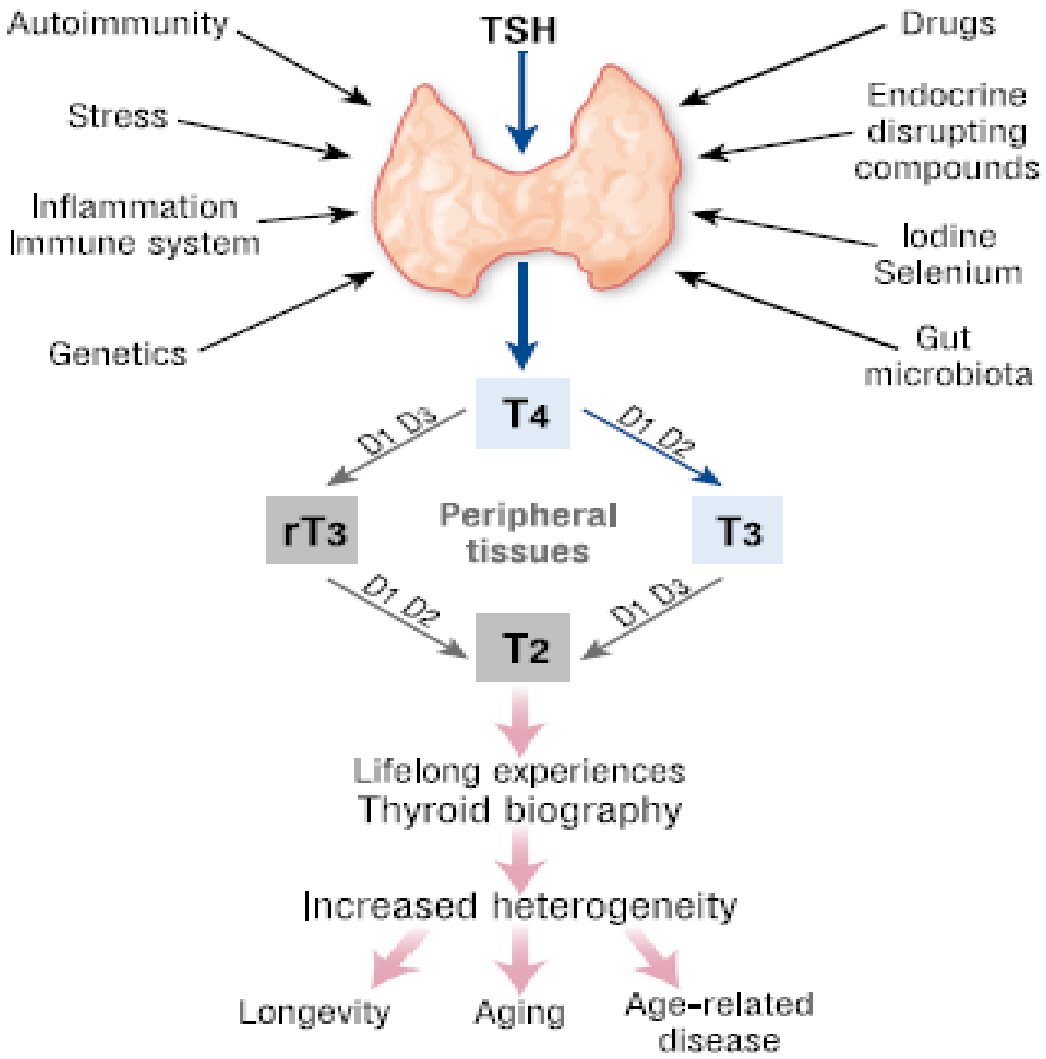
Relationship between fT_3/fT_4 ratio and frailty in the oldest adults: a longitudinal multicentre, multi-setting study

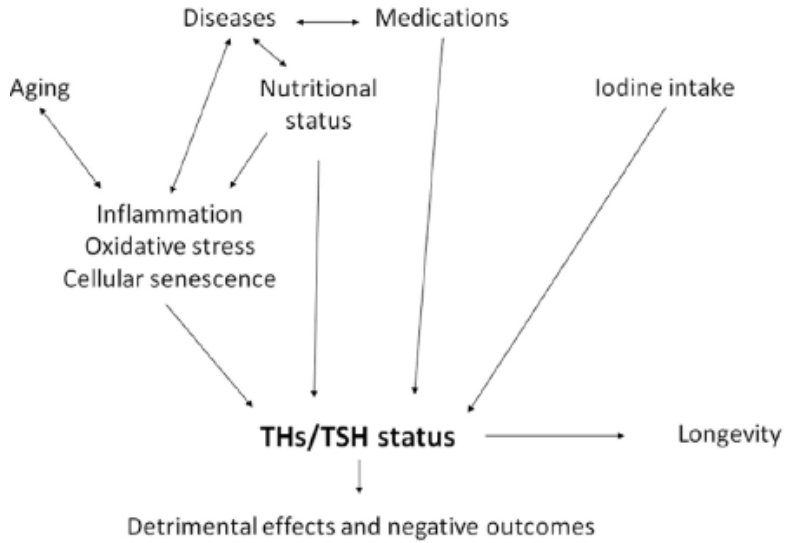


One-year all-cause mortality survival analysis: Kaplan Meier curves.

Monzani, Malara, Vitale Unpublished data

The Aging Thyroid: A Reappraisal Within the Geroscience Integrated Perspective





The new concept of "thyroid biography" is proposed to better understand the heterogeneity of thyroid aging in each individual or patient as a consequence of the unique combination of variables impinging lifelong on thyroid function

TAKE HOME MESSAGES

During ageing, the secretory patterns of the hormones produced by the hypothalamic–pituitary axis change, as does the sensitivity of the axis to negative feedback by end hormones. Glucose homoeostasis also tends towards disequilibrium with increasing age

Ageing-induced effects are difficult to disentangle from the influence of other factors that are common in older people, such as chronic diseases, inflammation, and low nutritional status, all of which can also affect endocrine systems

FT_3/FT_4 ratio is an effective marker of frailty, disability and reduced survival (more than each serum free thyroid hormone levels). Thus, FT_3/FT_4 ratio may represent a reliable biochemical marker of frailty in older individuals

Hormone replacement therapy is traditionally suggested as a therapeutic intervention to stop or reverse the decline of hormone activity during the ageing process. However, some of these changes are a beneficial adaptation to ageing, whereas hormonal intervention often causes important adverse effects

GRAZIE

Un ringraziamento particolare a tutti i miei collaboratori

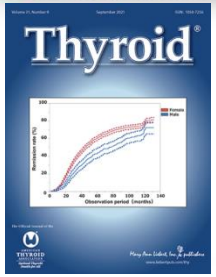
The Endocrinology of Ageing: A Mini-Review

Gerontology

Reported positive and negative health outcomes of female and male reproductive hormone replacement treatment

Organ system	Replacement hormone	Reported health outcome
Short-term outcomes		
Vascular	oestrogen	relief of vasomotor symptoms
Brain	oestrogen	improved mood and decreased depression in early menopause
Urogenital	testosterone and oestrogen	increased libido
	oestrogen	proliferative effect on the vaginal and vulval epithelium
	oestrogen	improved vaginal lubrication and reduced dyspareunia
	oestrogen	reduction in urinary frequency and urgency
	oestrogen	putative reduction in urinary tract infection incidence
Musculoskeletal	oestrogen and testosterone	protection against connective tissue loss
Long-term outcomes		
Musculoskeletal	oestrogen and testosterone	preserved bone mineral density
		reduced risk of osteoporosis-related fractures
Vascular	oestrogen (combined continuous regimes)	increased risk of coronary events
	oestrogen (combined and oestrogen only regimens)	increased risk of venous thromboembolism
	oestrogen (combined and oestrogen only regimens)	increased risk of stroke
Gastrointestinal	oestrogen	increased risk of gallbladder disease
		no significant impact on colorectal cancer
Cognition	oestrogen (combined regimens)	increased incidence of dementia
	oestrogen (single agent)	no significant change
Female reproductive system	oestrogen	increased risk of breast cancer
	oestrogen	conflicting reports regarding risk of ovarian cancer
	oestrogen (unopposed)	increased risk of endometrial cancer

Jones CM et al Gerontology 2015



Thyroid Hormone Therapy and Risk of Thyrotoxicosis in Community-Resident Older Adults: Findings from the Baltimore Longitudinal Study of Aging

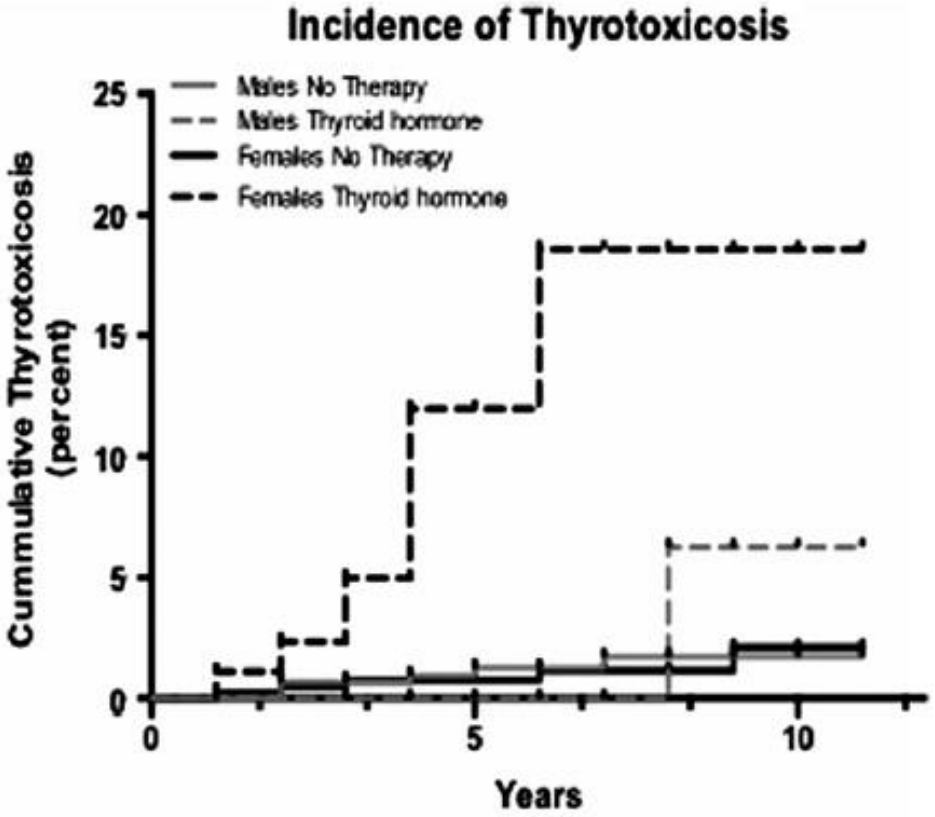


TABLE 1. COHORT CHARACTERISTICS

	Women	*Men*
Number (%)	718 (49.8)	725 (50.2)
Age (years), mean (*SD*)*	63.2 (14.2)	66 (14.5)
BMI (kg/m^2), mean (*SD*)[a]*	26.5 (5.2)	27.8 (4.1)
Never smoker, number (%)[b]*	441 (65)	377 (56)
Race/ethnicity, number (%)*		
Caucasian	458 (63.8)	537 (74.1)
African American	215 (30)	147 (20.3)
Other race/ethnicity	45 (6.2)	41 (5.6)
Year of first visit, median (min–max)	2005 (2003–2014)	2005 (2003–2014)
Years follow up, median (min–max)	4.7 (0–11)	4.3 (0–11)
Number of visits, median (min–max)	2.8 (1–11)	2.9 (1–11)

Cumulative incidence plot of thyrotoxicosis stratified by sex and the use of thyroid hormone

Mammen JS et al. Thyroid 2015