GLI ANZIANI:
LE RADICI DA PRESERVARE

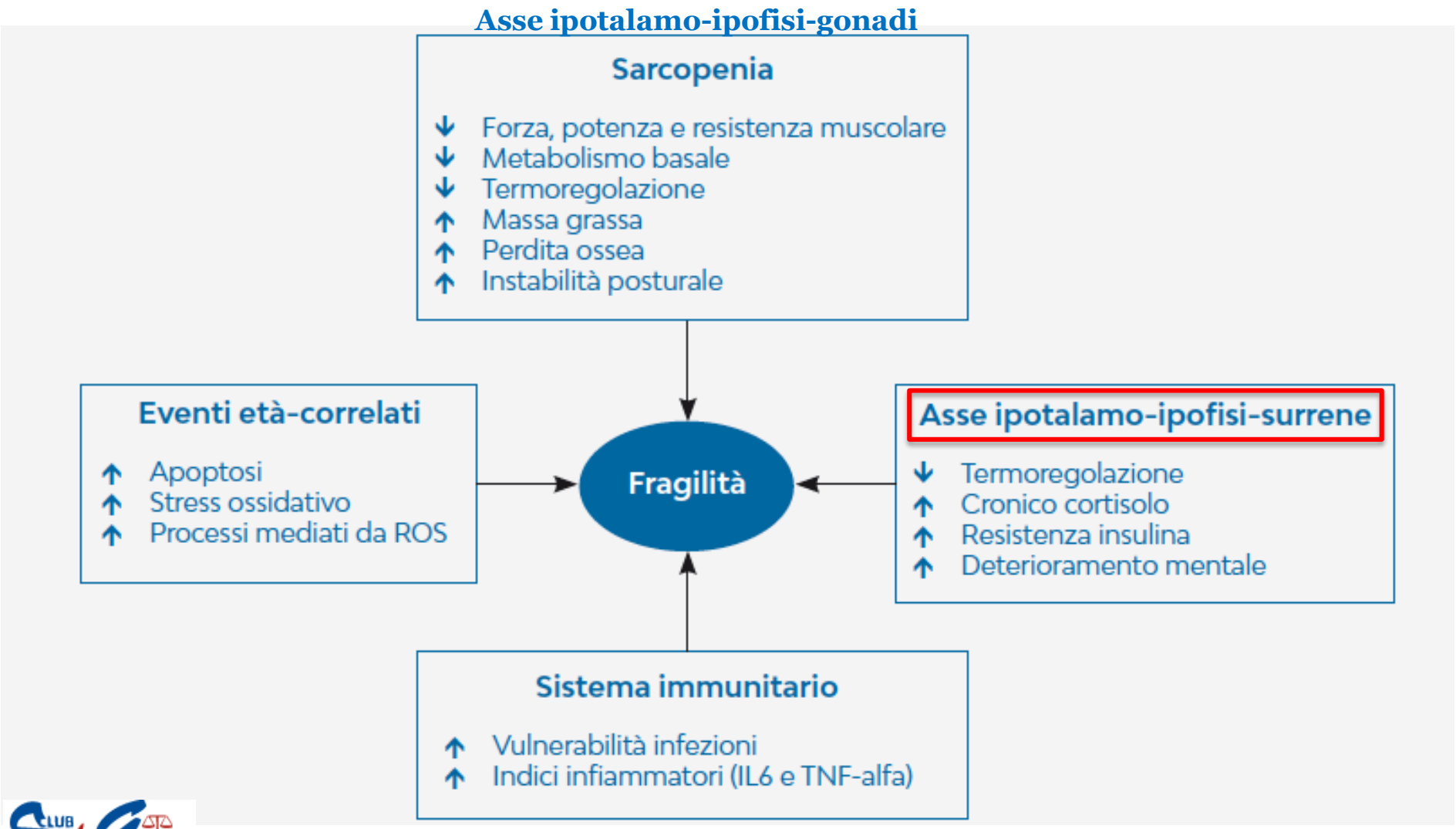
ROMA 28 novembre 01 dicembre 2018 Auditorium della Tecnica, Roma

Profilo ormonale tiroideo e fragilità: non solo bassa T3

Fabio Monzani

Dipartimento di Medicina Clinica & Sperimentale, Università di Pisa

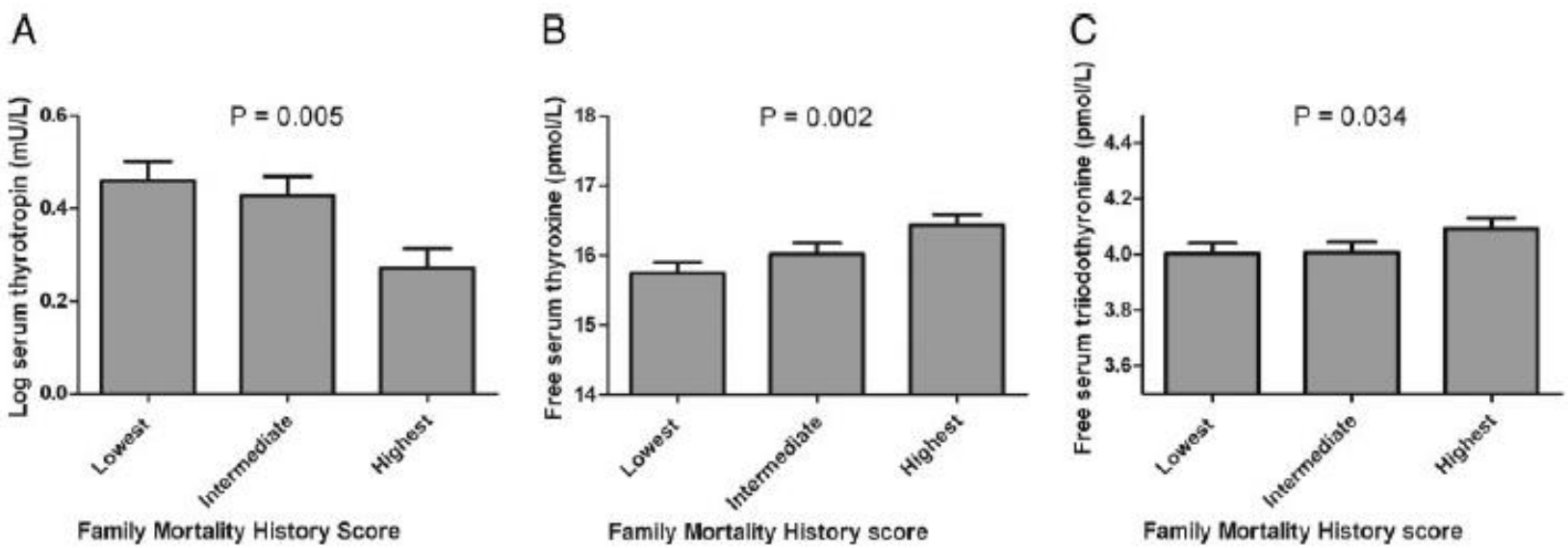
Determinanti di Fragilità



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)

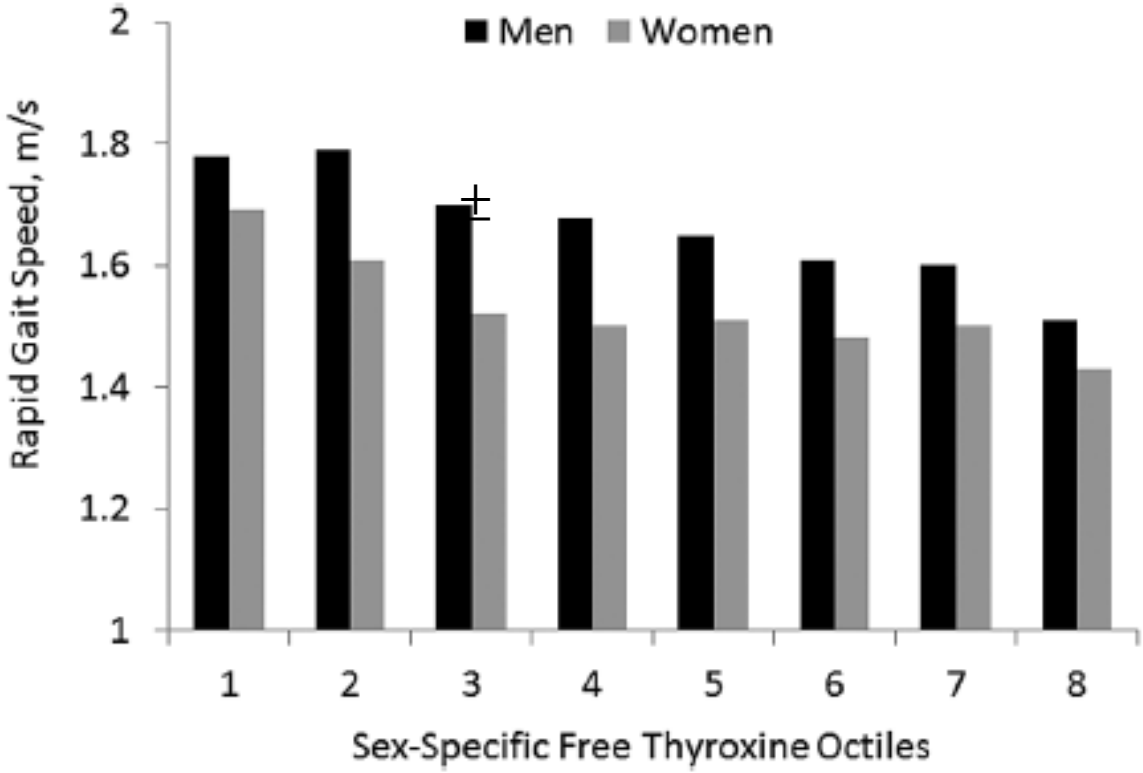
Mortalità familiare relativa ai soggetti con profilo tiroideo nella norma



Rozing MP et al. JCEM 2010

Free Thyroxine and 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)



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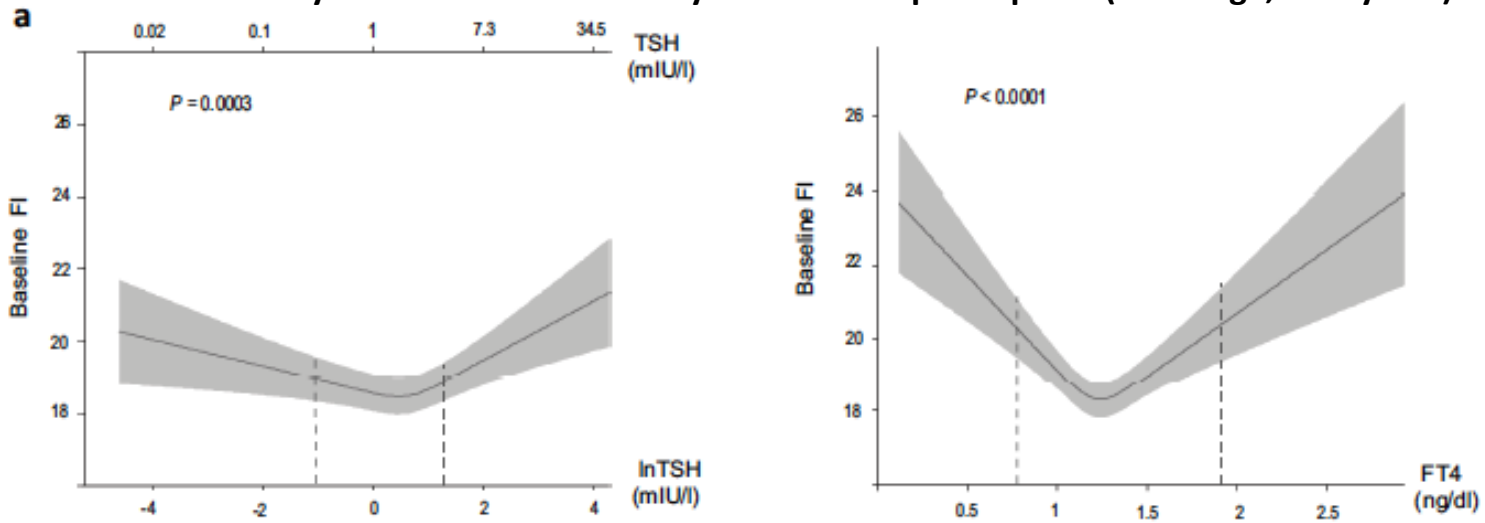
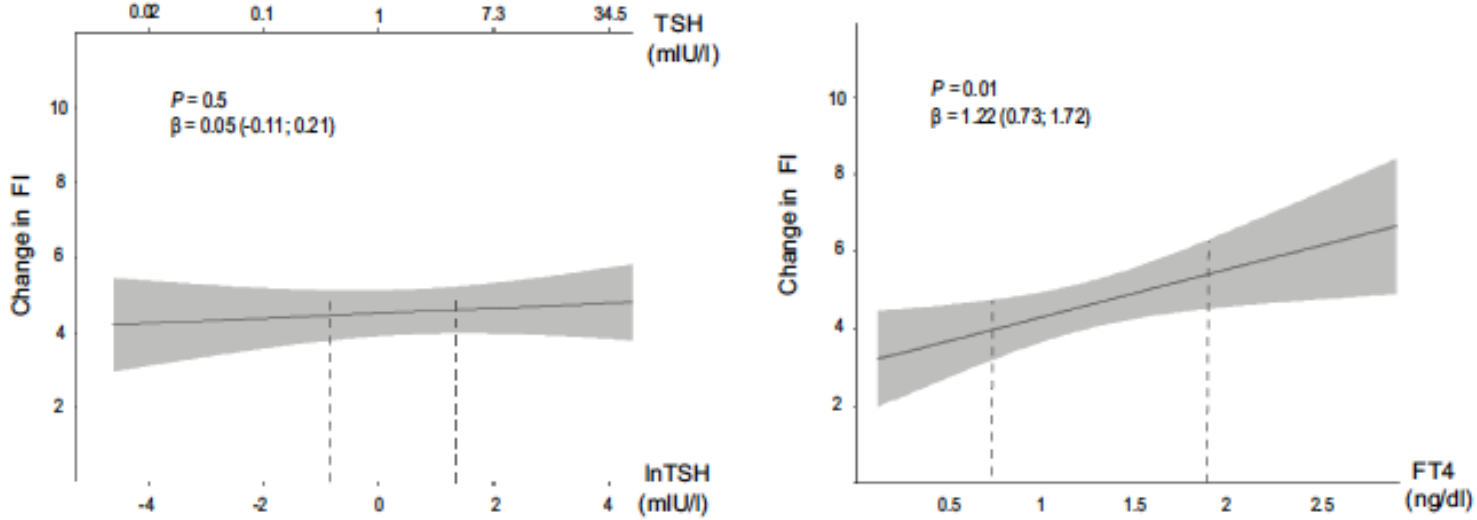
Simonsick EM et al. Journals of Gerontology 2016

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

Association of thyroid function with frailty index - 9640 participants (mean age, 64.9 years).

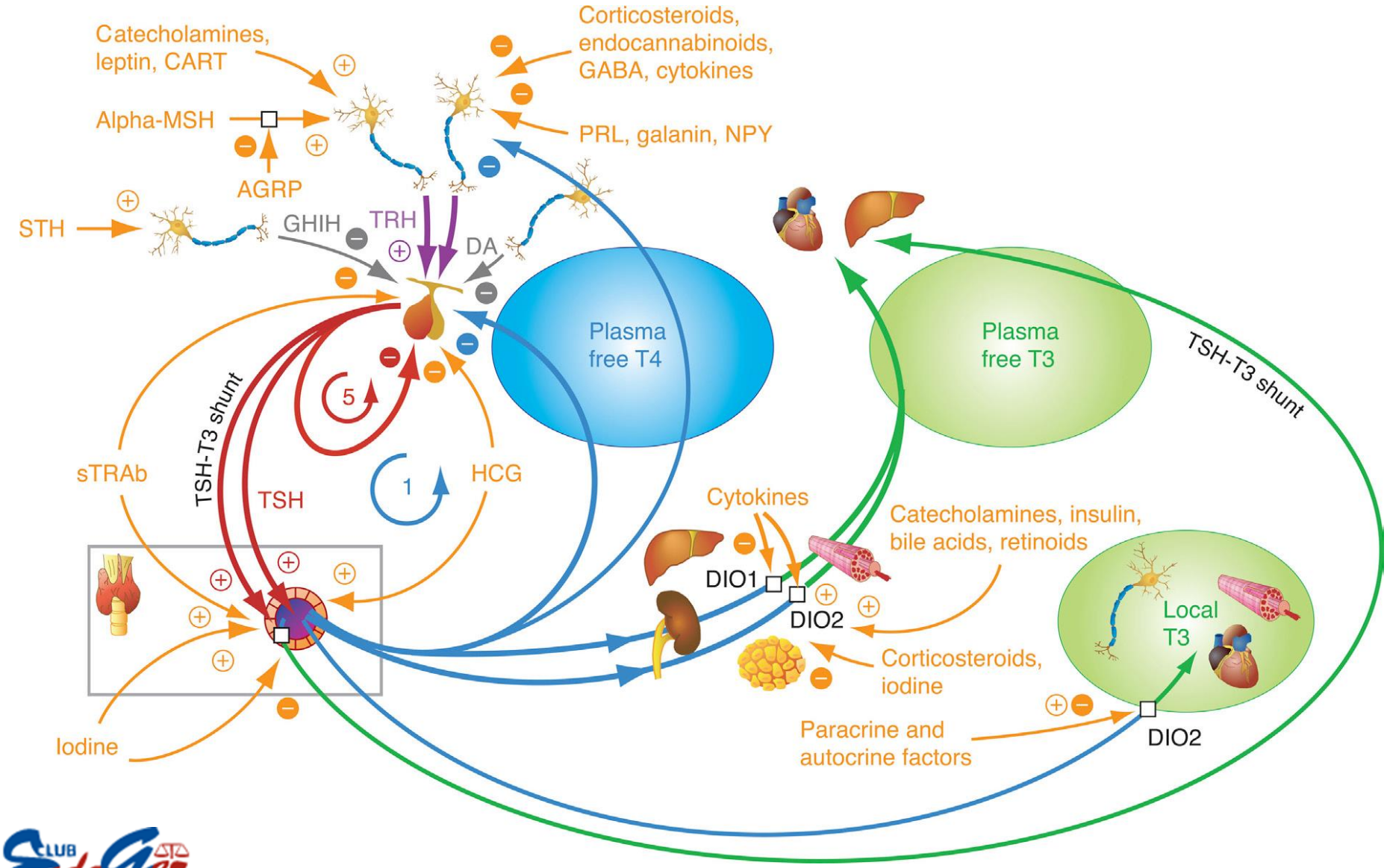


Variation of thyroid function and frailty index in euthyroid subjects. (median follow-up 10.1 years (range 5.7 to 10.8)



Bano A et al. JCEM 2018

Homeostatic Control of the Thyroid–Pituitary Axis: Perspectives for Diagnosis and Treatment



Hoermann R et al. Frontiers Endocrinol 2015

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.

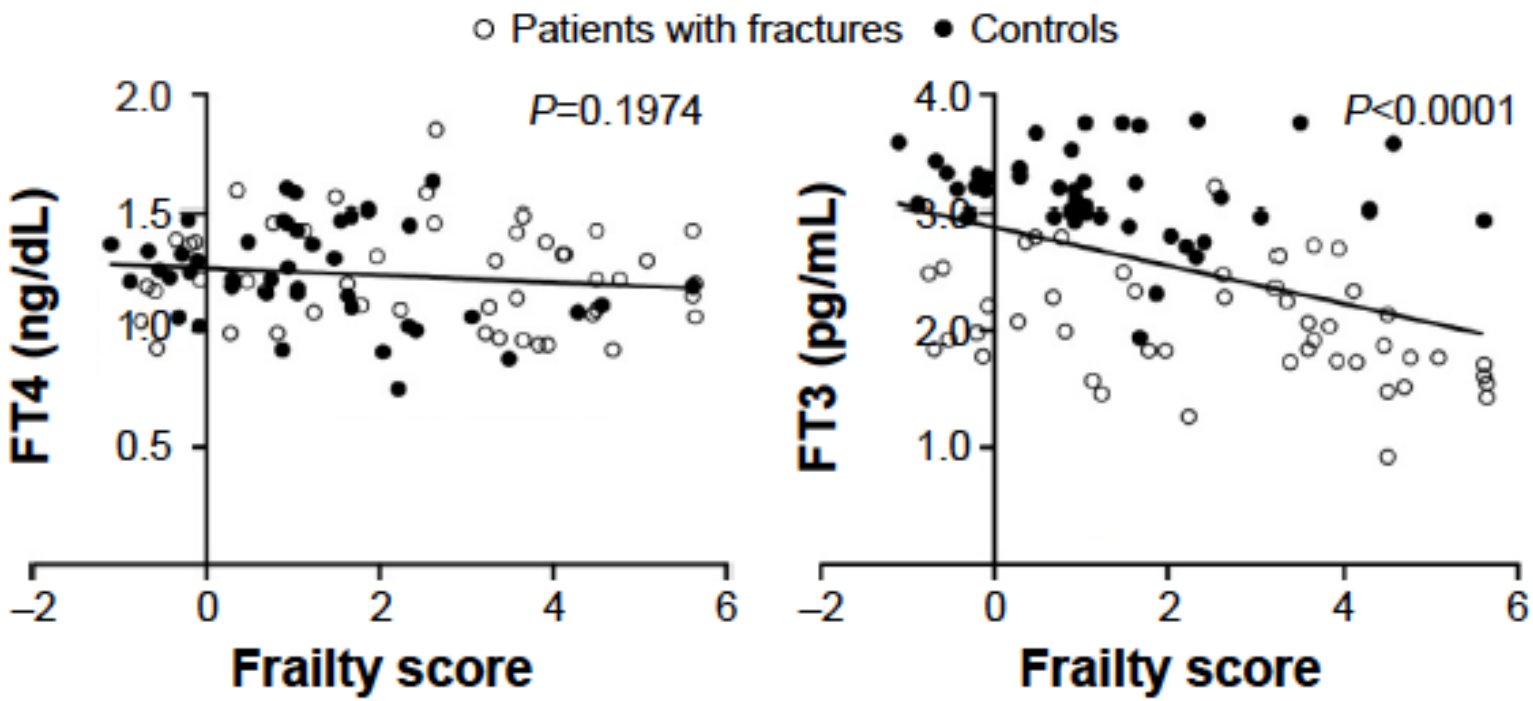
Disease	Patients (n)	Gender (%women)	Age (years)	NTIS (%)	P
NYHA IV HF	42	47.6	82.9 ± 6.9	52.4	0.003
NYHA II–III HF	20	30.0	80.6 ± 7.0	20.0	0.37
COPD	42	26.8	81.6 ± 6.8	38.1	0.42
Pneumonia	39	33.3	80.8 ± 7.4	25.6	0.44
Non-controlled DM	19	44.4	75.9 ± 7.1	22.2	0.44
Non-metastatic cancer	27	48.0	85.1 ± 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

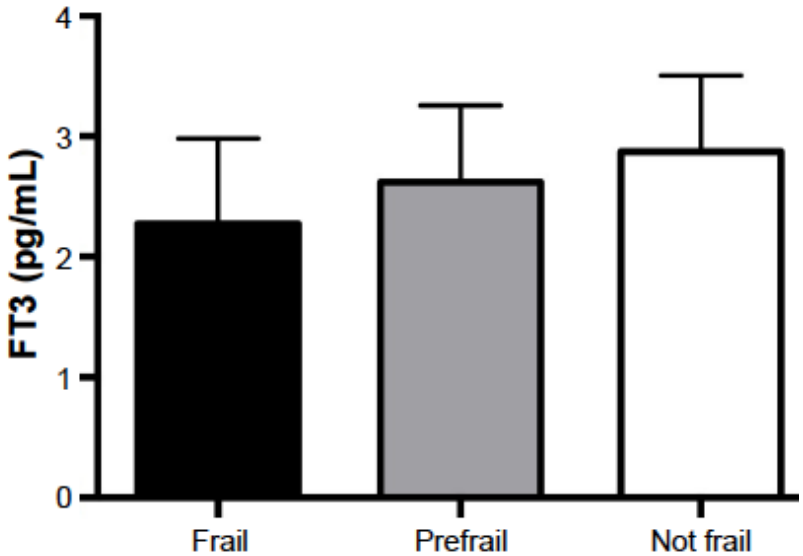
HF, heart failure; COPD, chronic obstructive pulmonary disease (level II–III exacerbation); DM, diabetes mellitus (we assumed for non-controlled DM HbA1c level >8.5%).

NTIS is very common in hospitalized elderly (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

Low FT3: possible marker of frailty in the elderly





Bertoli A. et al. Clinical Interventions in Aging 2017

Physical performance across the thyroid function values within the normal range in adult and older persons

Relationship between SPPB and FT3 in older subjects - Multivariate analysis

	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

CESD, Center for Epidemiologic Studies-Depression score

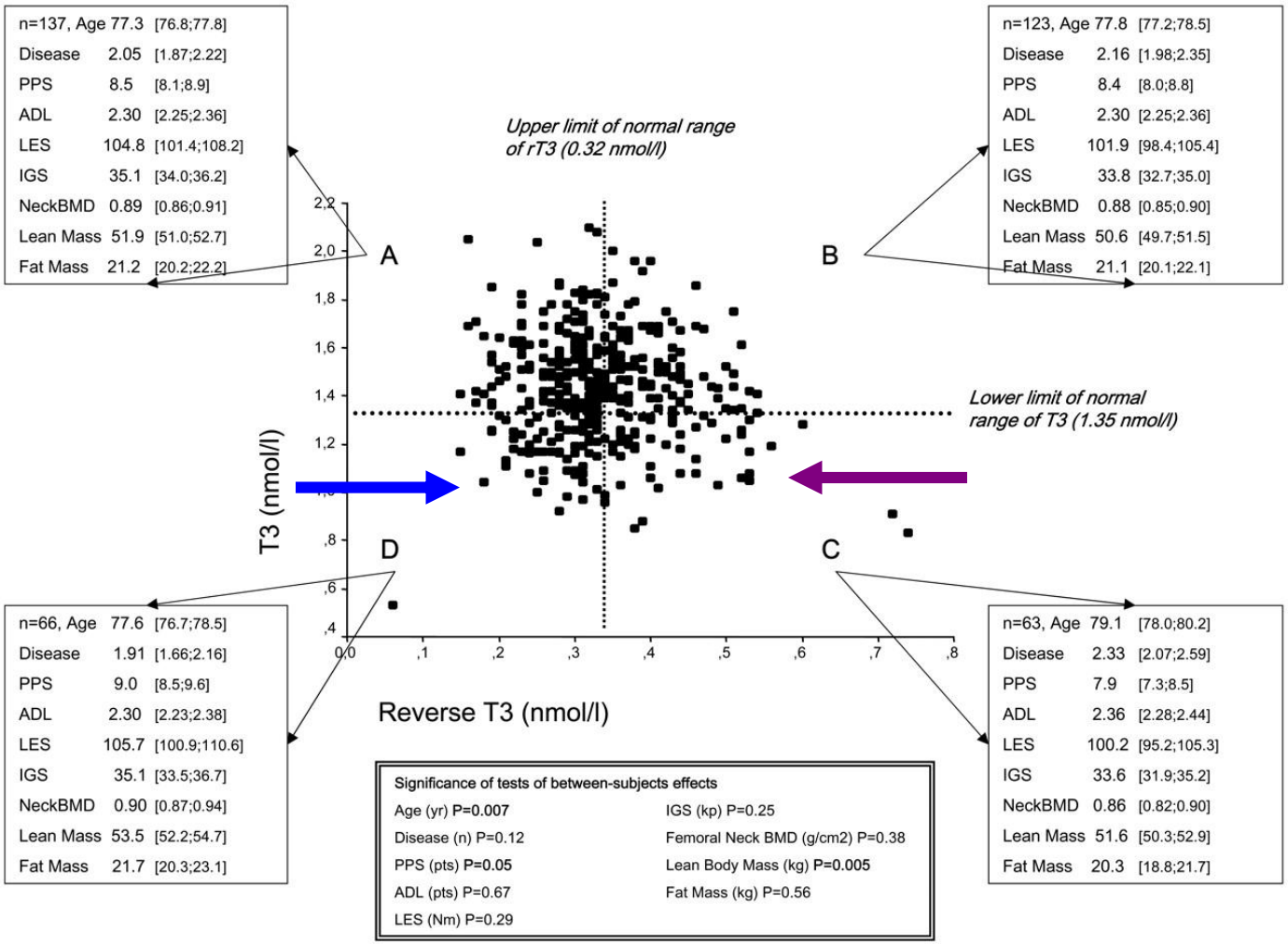
CSMA, cross sectional muscle area

NCV, Nerve Conduction Velocity

In Chianti study

Ceresini G et al, Aging Clin Exp Res, 2018

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): Reduced survival, lower physical performance

van den Beld et al. JCEM 2005

Degree of Peripheral ThyroxinDeiodination, Frailty,and Long-Term Survival in Hospitalized Older Patients

1156 pazienti ricoverati per patologia acuta sono stati arruolati nello studio

356 pazienti sono stati esclusi per malattie tiroidee note e/o terapie interferenti con la funzione tiroidea

157 pazienti sono stati esclusi per valori di TSH fuori dai limiti di riferimento (0,4-4,0 mU/l)

24 pazienti persi durante il follow-up

619 pazienti erano disponibili per le analisi di follow-up

Pasqualetti et al JCEM 2018

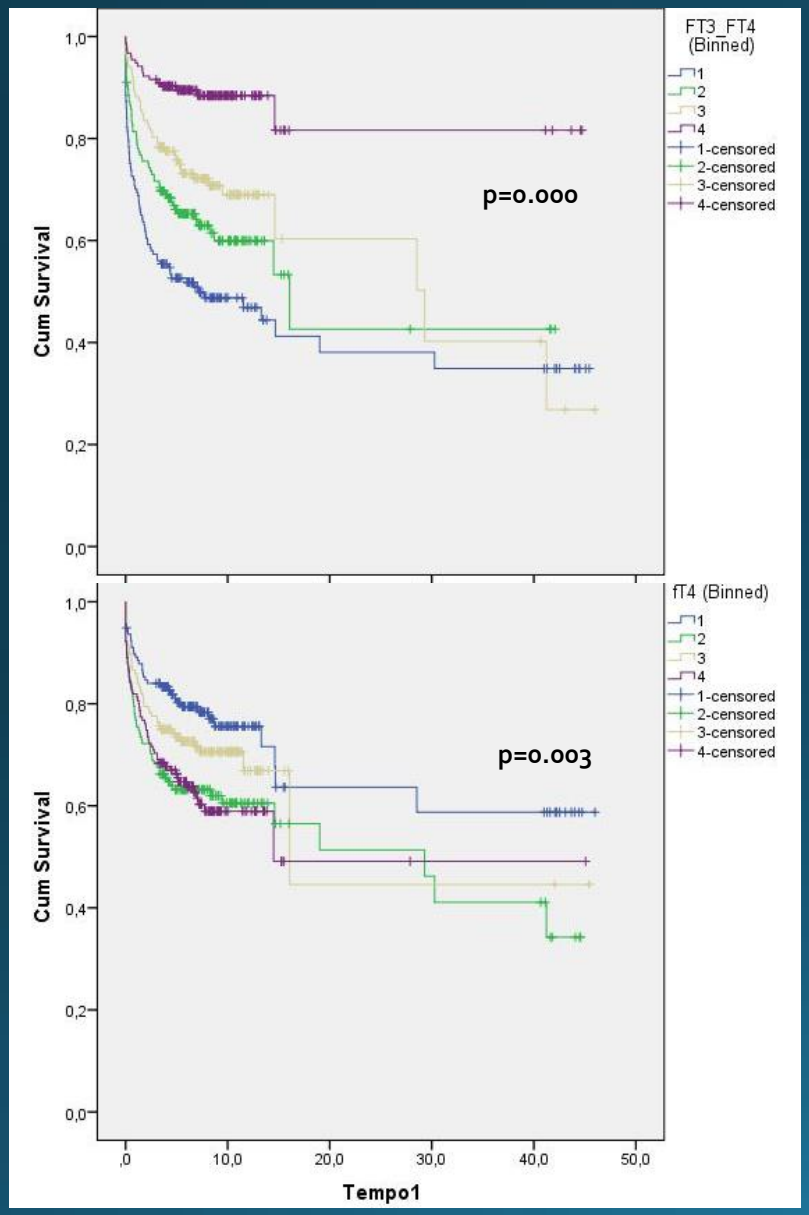
Degree of Peripheral ThyroxinDeiodination, Frailty,and Long-Term Survival in Hospitalized Older Patients

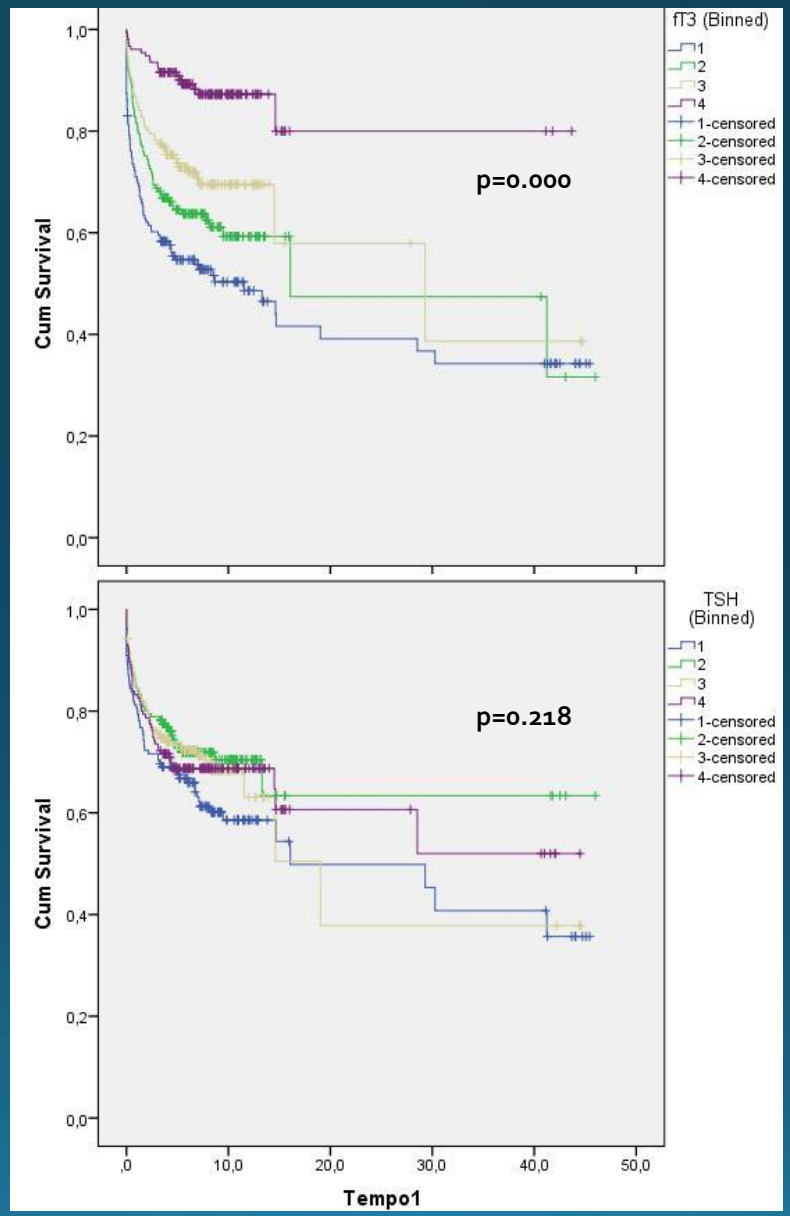
Quartili FT_3/FT_4	Q1 Mediana (range), % media±DS	Q2 Mediana (range), % media±DS	Q3 Mediana (range), % media±DS	Q4 Mediana (range), % media±DS	*p*
Sesso % (F)*	55.6%	62.3%	50.3%	43.8%	0.008
Età (anni)	86 (65-97)	84 (66-100)	85 (65-101)	82 (65-100)	0.008
CIRS_S	2.3±0.4	2.1±0.4	2.1±0.4	2.0±0.4	0.000
CIRS_C	5.5±1.8	5.1±1.8	4.8±1.9	4.5±1.9	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
MPI	0.72±0.27	0.63±0.28	0.52±0.30	0.42±0.26	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 2018

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





Follow-up disponibile per 619 paz.

mediana 30.3 mesi

206 decessi (33.3%)

Pasqualetti et al JCEM 2018

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

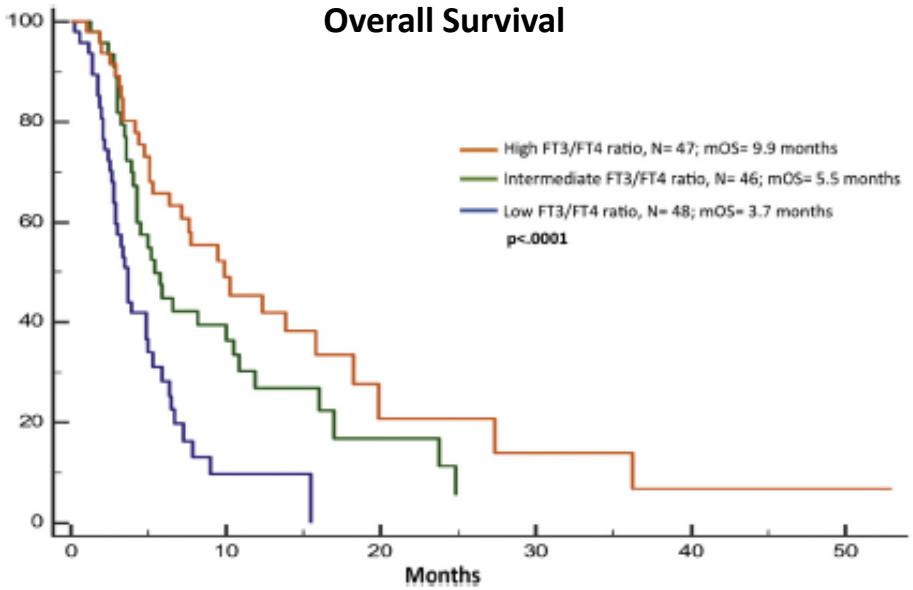
Cox regression multivariate analysis of FT3/FT4 quartiles (4th FT_3/FT_4 quartile as the reference)

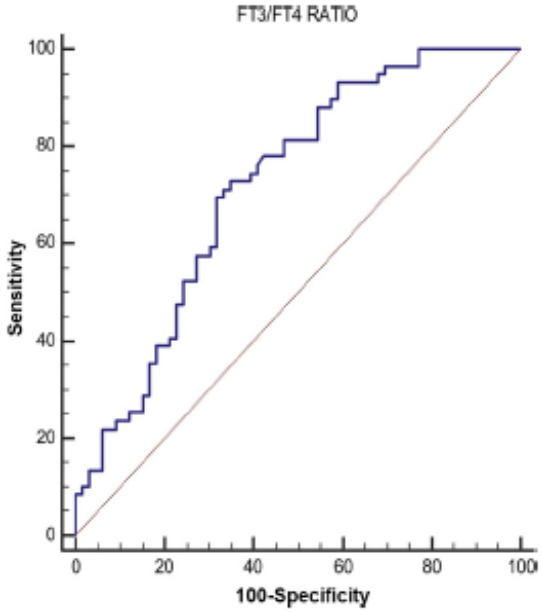
	Model 1				Model 2					Model 3		
	p	HR	95.0% CI		p	HR	95.0% CI		p	HR	95.0% CI	
			Lower	Upper			Lower	Upper			Lower	Upper
Q4 (FT3/FT4 >2.60)		1				1				1		
Q 1 (FT3/FT4<1.51)	0.000	5.73	3.43	9.55	0.000	5.37	3.21	8.89	0.005	2.49	1.31	4.73
Q2 (1.51<FT3/FT4<2.02)	0.000	3.85	2.27	6.53	0.000	3.77	2.22	6.41	0.008	2.22	1.23	4.97
Q3 (2.02<FT3/FT4<2.6)	0.000	2.84	1.64	4.89	0.000	2.63	1.52	4.55	0.018	2.01	1.12	3.59

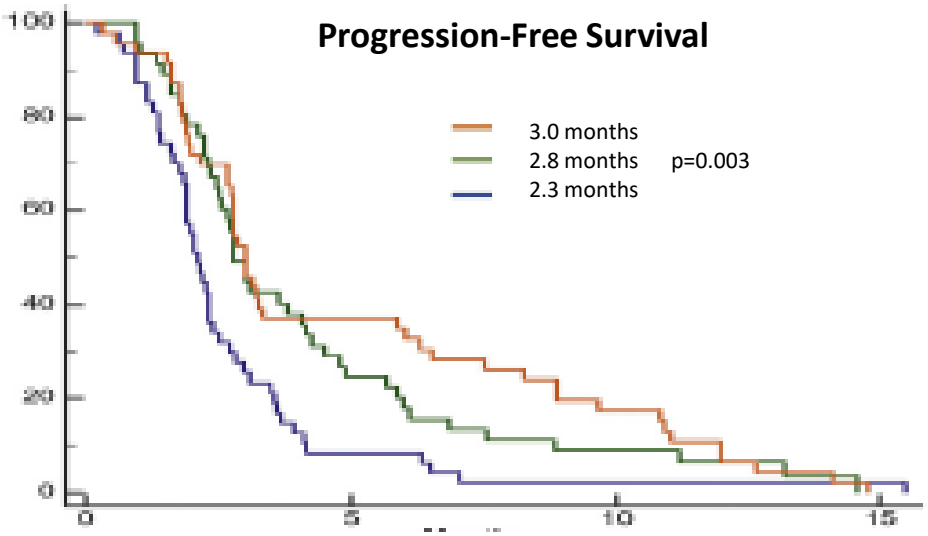
Model 1: not adjusted;
Model 2: age and sex adjusted;
Model 3: age, sex, LDH, Hb, CRP, albumin, MPI and FT3 adjusted

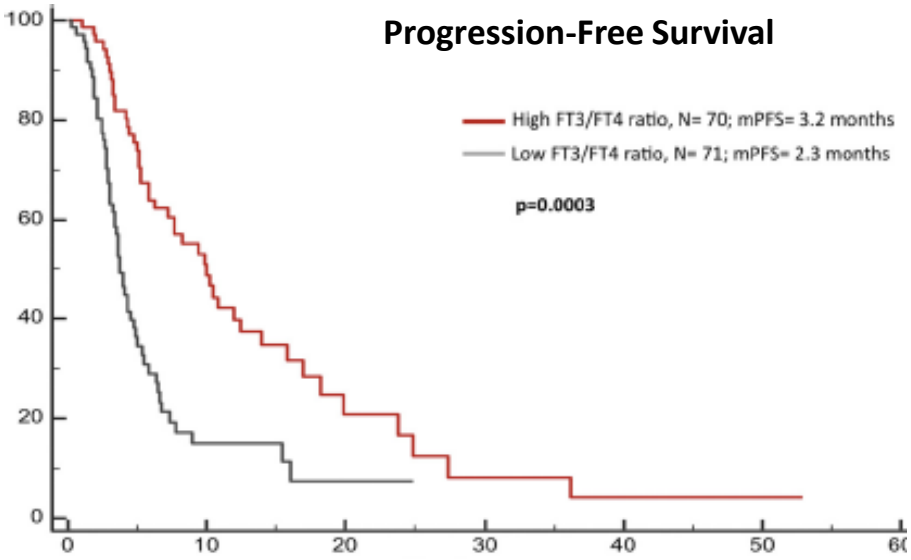
Pasqualetti et al JCEM 2018

Prognostic Value of FT3/FT4 Ratio in Patients With Advanced Metastatic Colorectal Cancer Treated With Regorafenib: The TOREADOR Study









Schirripa M. et al. Clinical Colorectal Cancer 2018

Prognostic Value of FT3/FT4 Ratio in Patients With Advanced Metastatic Colorectal Cancer Treated With Regorafenib: The TOREADOR Study

Multivariate for OS	HR	95% CI	P
Resection of primary tumor Y/N	0.37	0.14 – 1.00	0.0521
Number of previous lines 3/>3	0.90	0.43 – 1.87	0.7738
Time from diagnosis and rego start 18 months/ >18 months	0.17	0.06 – 0.51	0.0016
Terzile_Ratio_Modified	0.36	0.21 – 0.62	0.0002

Multivariate for PFS	HR	95% CI	P
Resection of primary tumor Y/N	0.33	0.14 - 0.78	0.0119
Time from diagnosis and rego start 18 months/ >18 months	0.61	0.27 – 1.36	0.2293
Terzile_Ratio _Modified	0.59	0.40 – 0.86	0.0070

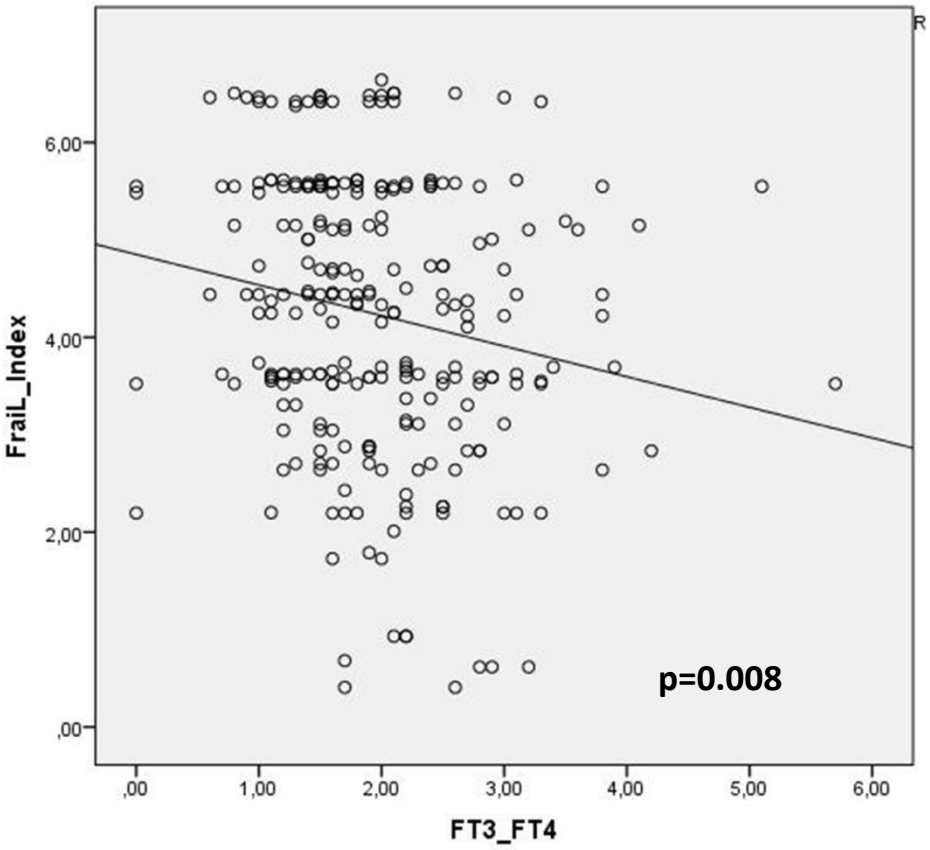
ESMO Designated Centers of Integrated Oncology and Palliative Care

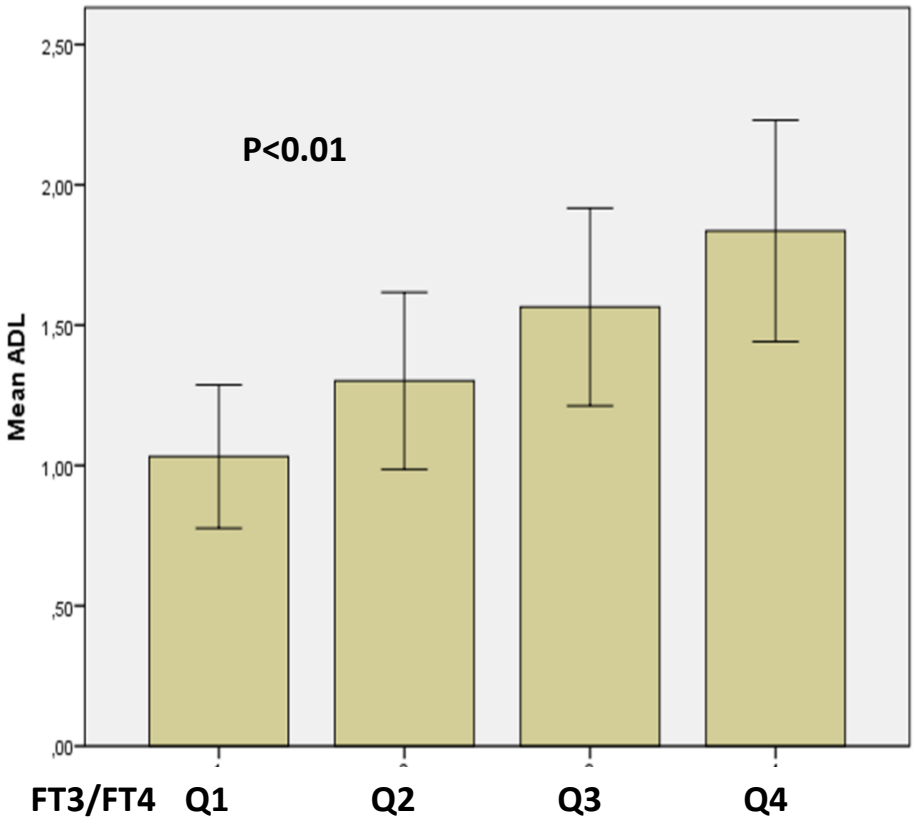
Schirripa M. et al. Clinical Colorectal Cancer 2018

OECI COMPREHENSIVE Cancer Centre

Correlazione tra rapporto FT3/FT4 e grado di fragilità in una popolazione di soggetti anziani residenti in RSA

250 soggetti (66.4% F), età media 85.0±7.2 aa

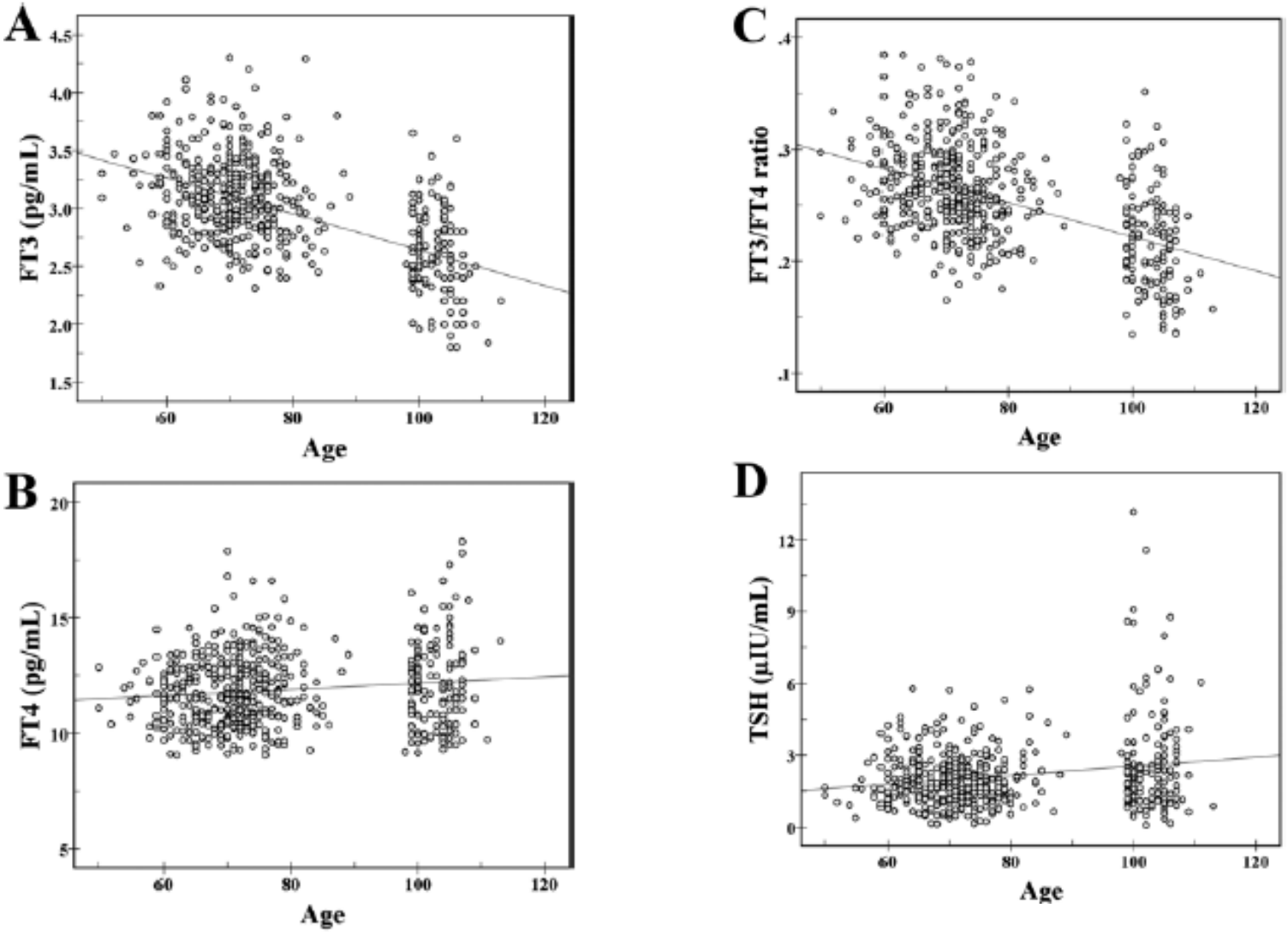




Malara A et al. Poster#216

Heterogeneity of Thyroid Function and Impact of Peripheral Thyroxine Deiodination in Centenarians and Semi-Supercentenarians: Association With Functional Status and Mortality

Age-dependent variations of circulating hormones



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672 Italian subjects (age range: 52–113 years)

Ostan R et al. Journals of Gerontology 2018

Heterogeneity of Thyroid Function and Impact of Peripheral Thyroxine Deiodination in Centenarians and Semi-Supercentenarians: Association With Functional Status and Mortality

A	ADL score		Handgrip strength[a]	
	B coefficient (95% CI)	*p*	B coefficient (95% CI)	*p*
FT3	0.6 (−0.2 to 1.6)	.160	3.6 (0.4–6.8)	**.026**
FT4	−0.3 (−0.5 to −0.1)	**<.001**	−1.3 (−1.8 to −0.7)	**<.001**
FT3/FT4	14.5 (7.2–21.9)	**<.001**	64.1 (38.9–89.2)	**<.001**
TSH	0.1 (0.0–0.3)	.088	0.3 (−0.2 to 0.9)	.208
B	**SMMSE score[b]**		**GDS score[c]**	
	B coefficient (95% CI)	*p*	B coefficient (95% CI)	*p*
FT3	2.1 (−2.5 to 6.8)	.368	−0.5 (−2.9 to 1.9)	.696
FT4	−1.2 (−2.0 to −0.4)	**.005**	0.2 (−0.2 to 0.6)	.332
FT3/FT4	26.2 (−1.9 to 54.4)	.067	−9.1 (−27.6 to 9.4)	.331
TSH	1.0 (0.3–1.8)	**.006**	0.7 (−0.3 to 0.4)	.489

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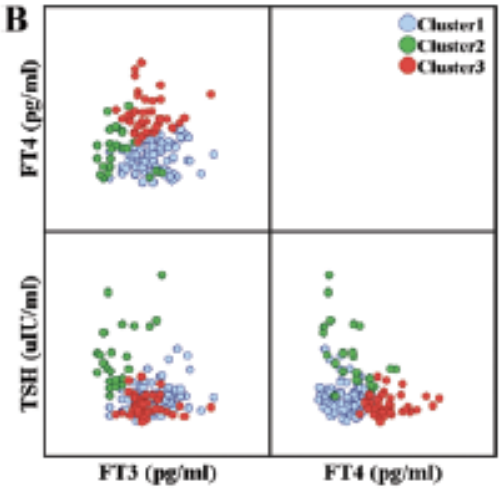
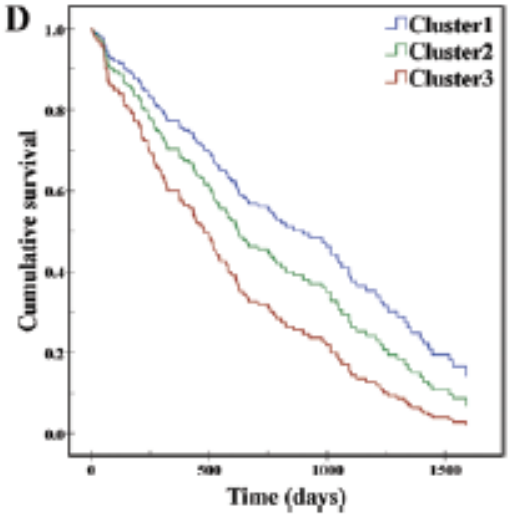
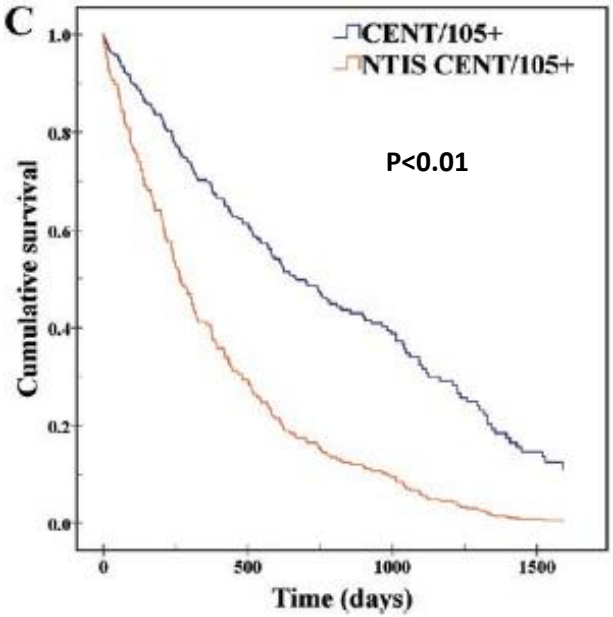
Heterogeneity of Thyroid Function and Impact of Peripheral Thyroxine Deiodination in Centenarians and Semi-Supercentenarians: Association With Functional Status and Mortality



C

	Hazard ratio		
	B coefficient	Exp(B) (95% C.I.)	p
Cluster1	-	-	-
Cluster2	0.353	1.4 (0.8-2.4)	.204
Cluster3	0.709	2.0 (1.3-3.1)	.001





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TAKE HOME MESSAGES

- Recentemente è stato documentato come nei soggetti anziani sia la fragilità che la mortalità aumentino con l'aumentare dei livelli di tiroxina circolante
- E' noto da tempo come la "Sindrome da bassa T3 o Sindrome del malato eutiroideo" (NTIS) si associ ad una riduzione della sopravvivenza a breve termine
- Nei pazienti anziani la prevalenza di NTIS è elevata e si associa a fragilità oltre che a ridotta sopravvivenza
- Dati recenti documentano come la desiodazione periferica di T_4 si riduca progressivamente in relazione al grado di fragilità
- Il rapporto FT_3/FT_4 risulta un marker di fragilità, disabilità e mortalità molto accurato (più dei livelli di FT_3 e FT_4 considerati singolarmente)
- Il rapporto FT_3/FT_4 potrebbe rappresentare un efficace biomarker quantitativo di fragilità


GRAZIE
Un ringraziamento particolare a tutti i miei collaboratori