Minicorso 7: "Aspetti endocrino-metabolici nell'anziano"

Bari,
7-10 novembre 2013

12° Congresso Nazionale AME
6th Joint Meeting with AACE

Update in Endocrinologia Clinica

"Tireopatie subcliniche: Trattamento dell'ipotiroidismo subclinico nell'anziano: utile o dannoso?"

Giovanna Spiazzi
U.O.C. di Endocrinologia e Malattie Metaboliche
Azienda Ospedaliera Universitaria Integrata Verona

Ipotiroidismo subclinico (SCH)

Bari,
7-10 novembre 2013

- Prevalenza
- Evoluzione nel tempo
- Modificazioni morfofunzionali dell'asse HPT nell'invecchiamento
- SCH e insufficenza cardiaca (HF)
- SCH e patologia cardiovascolare
- SCH e i "centenari"
- Trattamento dell'SCH benefici o danni?

Serum TSH, T_4, and Thyroid Antibodies in the United States Population (1988 to 1994): National Health and Nutrition Examination Survey (NHANES III)

JOSEPH G. HOLLOWELL, NORMAN W. STAEHLING, W. DANA FLANDERS, W. HARRY HANNON, ELAINE W. GUNTER, CAROLE A. SPENCER, AND LEWIS E. BRAVERMAN

Centers for Disease Control, National Center for Environmental Health, Division of Emergency and Environmental Services (J.G.H.), Division of Environmental Hazards and Health Effects (N.W.S.), Division of Environmental Laboratory Sciences (W.H.H., E.W.G.), Atlanta, Georgia 30341; Emory University School of Public Health (W.D.F.), Atlanta, Georgia 30324; University of Southern California Medical Center (C.A.S.), Los Angeles, California 90032; and Boston M (L.E.B.), Boston, Massachusetts 02116

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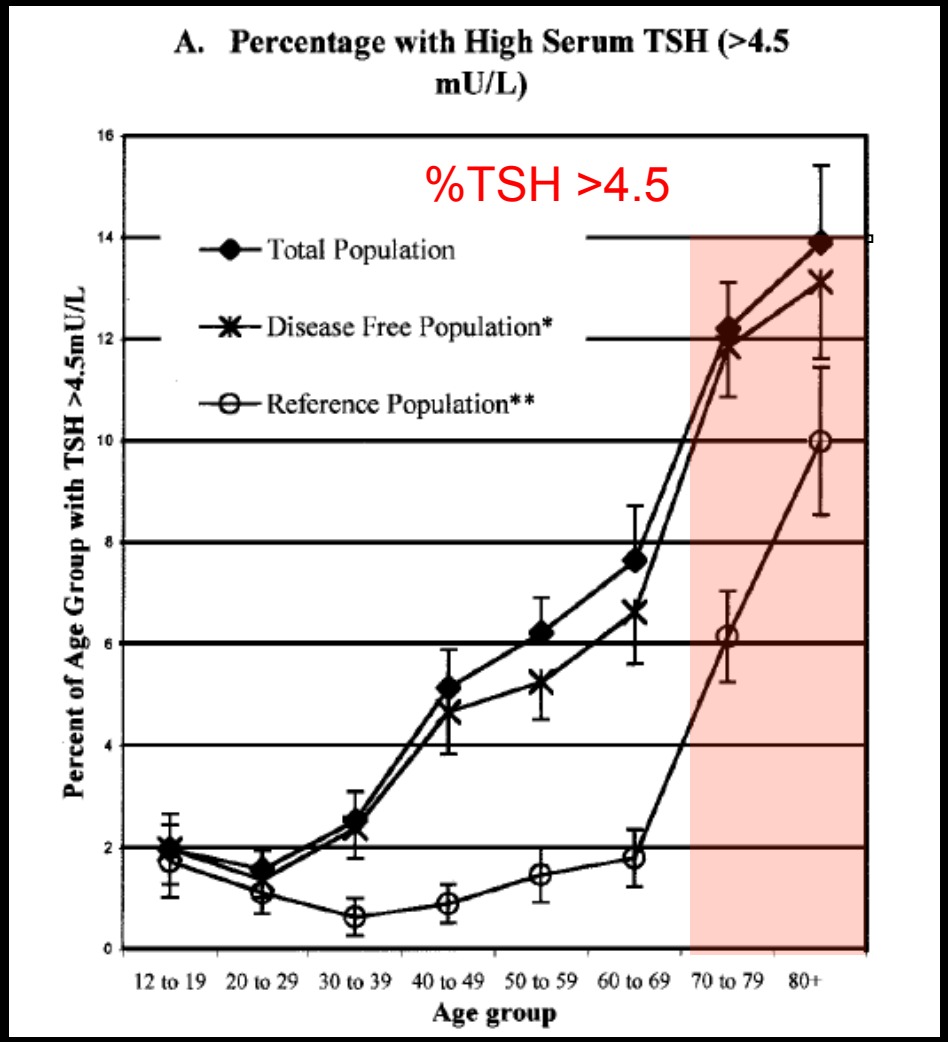
J Clin Endocrinol Metab, February 2002, 87(2):489–499



- N 17353
- 16533 disease free = non riferiscono patologia tiroidea
  13344 popolazione riferimento: no gravide, no estrogeni, androgeni, litio, no alterazioni ormoni tiroidei o Ab +
  TSH 0.45-4.12 mUI/L

- **Prevalenza SCH : 4.3 %**
- 3.9% nella popolazione di riferimento
- I valori di TSH sono più elevati nelle femmine, nei bianchi e aumentano con età.

Bari,
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ORIGINAL INVESTIGATION

The Colorado Thyroid Disease Prevalence Study

Gay J. Canaris, MD, MSPH; Neil R. Manowitz, PhD; Gilbert Mayor, MD; E. Chester Ridgway, MD

Arch Intern Med. 2000;160:526-534

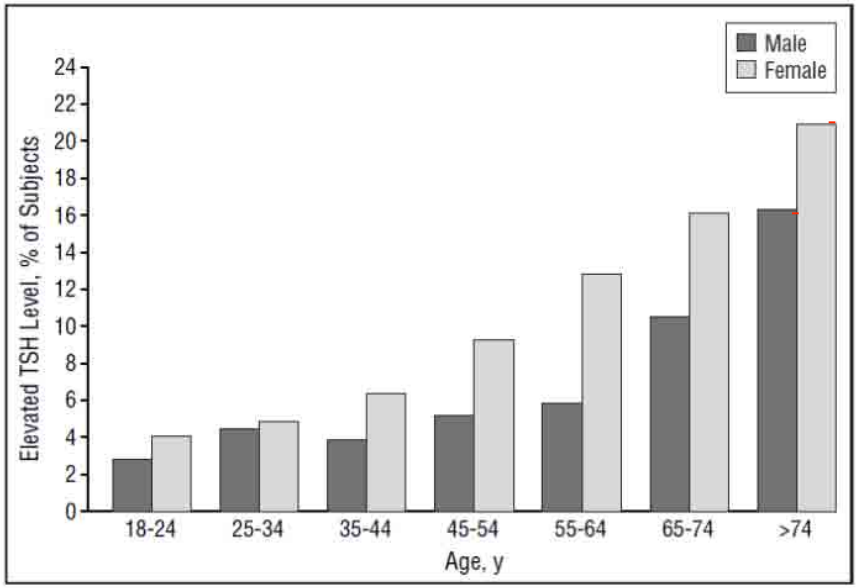
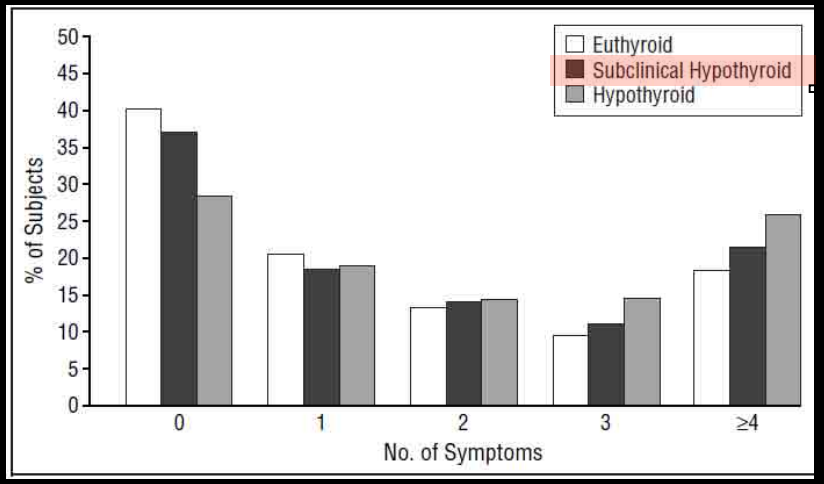


Figure 1. *The percentage of subjects with an elevated thyrotropin (thyroid-stimulating hormone [TSH]) level by sex and decade of age. Percentages of hypothyroidism ranged from 4% to 21% in women and from 3% to 16% in men.*

N=25.862, TSH>5.1 mIU/L
Prevalenza SCH **9.5%**
Oltre 90 anni prev SCH 15-20%, F>M



The Natural History of Subclinical Hypothyroidism in the Elderly: The Cardiovascular Health Study

Lily L. Somwaru, Chevon M. Rariy, Alice M. Arnold, and Anne R. Cappola

Department of Medicine (C.M.R.) and Division of Endocrinology, Diabetes, and Metabolism (L.L.S., A.R.C.), Perelman School of Medicine at the University of Pennsylvania, Philadelphia, Pennsylvania, 19104; and Department of Biostatistics (A.M.A.), University of Washington, Seattle, Washington 98155

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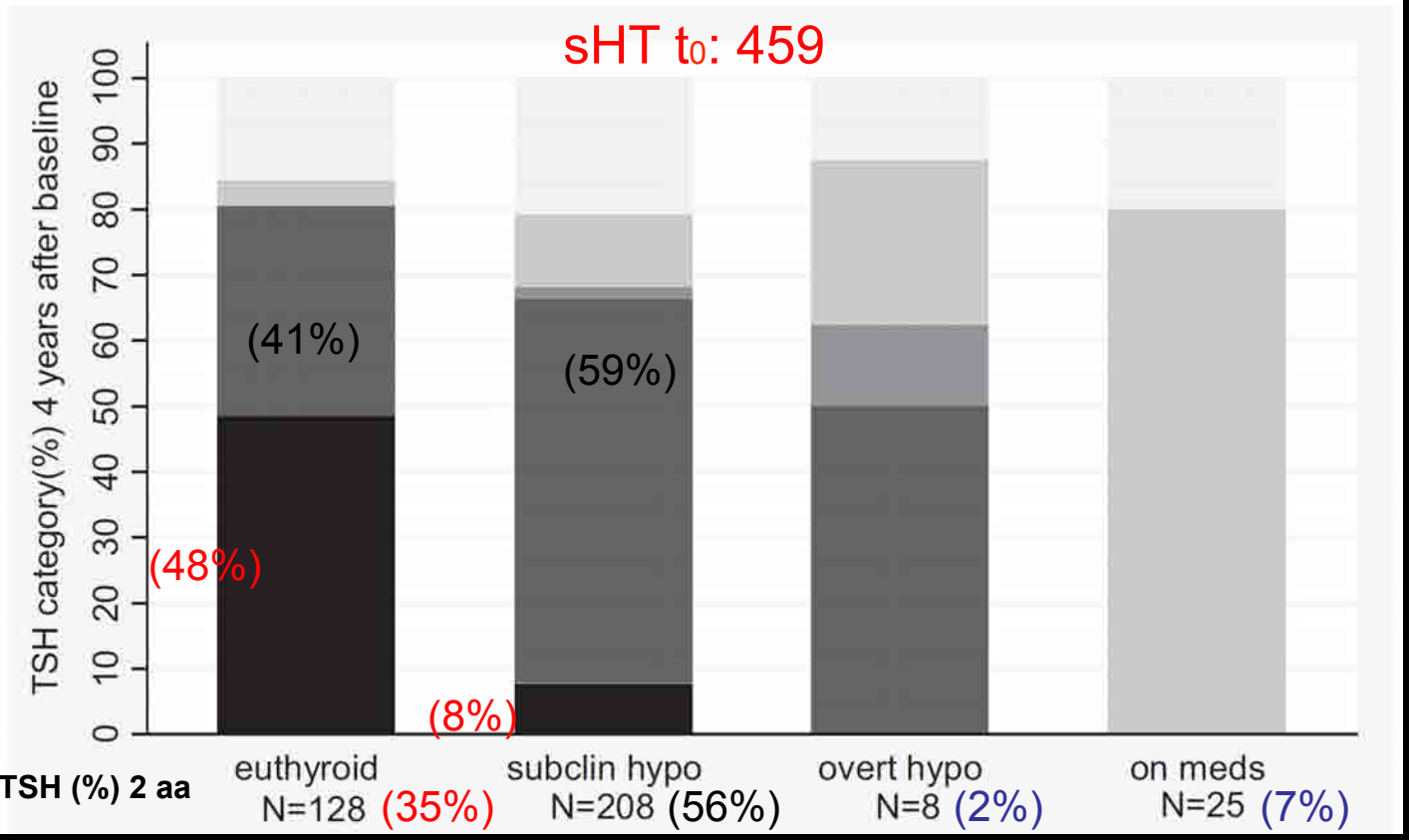
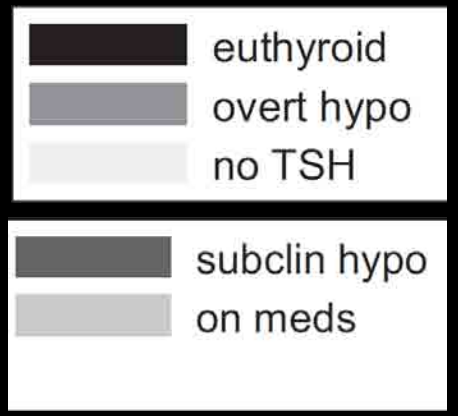
J Clin Endocrinol Metab, June 2012, 97(6):1962–1969



N: 3996, >65 aa



Conclusions: Subclinical hypothyroidism persists for 4 yr in just over half of older individuals, with high rates of reversion to euthyroidism in individuals with lower TSH concentrations and TPOAb negativity.

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Farmaci e Tiroide

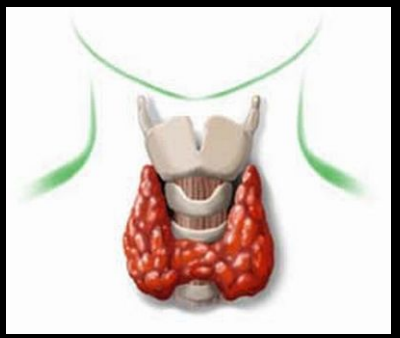

Table 10. Agents and Conditions Having an Impact on L-thyroxine Therapy and Interpretation of Thyroid Tests

10.1. *Interference with absorption*		
Bile acid sequestrants (cholestyramine, colestipol, colesevelam) Sucralfate Cation exchange resins (Kayexelate) Oral bisphosphonates Proton pump inhibitors Raloxifene[a] Multivitamins (containing ferrous sulfate or calcium carbonate) Ferrous sulfate Phosphate binders (sevelamer, aluminum hydroxide)	Calcium salts (carbonate, citrate, acetate) Chromium picolinate Charcoal Orlistat[b] Ciprofloxacin H2 receptor antagonists[a] Malabsorption syndromes • Celiac disease • Jejunoileal bypass surgery • Cirrhosis (biliary) • Achlorhydria	Diet • Ingestion with a meal • Grapefruit juice[a] • Espresso coffee • High fiber diet • Soybean formula (infants) • Soy
10.2. *Thyroid gland hormone production and secretion*		
Direct and indirect effects on the thyroid gland • Iodine uptake ◦ Iodine (including kelp supplements) ◦ Amiodarone ◦ Ethionamide ◦ Iodinated contrast (ipodate,[c] iopanoic acid[c]) ◦ Perchlorate[c] • Hormone production ◦ Iodine (including kelp supplements) ◦ Amiodarone ◦ Thionamides (carbimazole, methimazole, propylthiouracil) ◦ Iodinated contrast (ipodate,[c] iopanoic acid[c])	◦ Sulfonylureas ◦ Sulfonamides ◦ Ethionamide • Secretion ◦ Lithium ◦ Iodine (including kelp supplements) ◦ Amiodarone ◦ Iodinated contrast (ipodate,[c] iopanoic acid[c]) • Thyroiditis ◦ Induces - Amiodarone - Tyrosine kinase inhibitors (sunitinib, sorafenib) - Interferon alpha - Interleukins	- Antiangiogenic (lenalidomide, thalidomide) - Lithium - Alemtuzumab - Denileukin diftitoxin ◦ Ameliorates (if autoimmune) - Glucocorticoids • Development of Graves' ◦ Interferon alpha ◦ HAART (highly active antiretroviral therapy) ◦ Alemtuzumab • Amelioration of Graves' ◦ Glucocorticoids
10.3. *Direct and indirect effects on the hypothalamic–pituitary–thyroid axis*		
TSH secretion • Decrease ◦ Bexarotene ◦ Dopamine ◦ Dopaminergic agonists (bromocriptine, cabergoline) ◦ Glucorticoids ◦ Thyroid hormone analogues	◦ Somatostatin analogues (octreotide, lanreotide) ◦ Metformin ◦ Opiates (e.g., heroin) ◦ Interleukin-6 • Increase ◦ Dopamine receptor blockers (metoclopramide)	◦ Hypoadrenalism ◦ Interleukin 2 ◦ Amphetamine ◦ Ritonavir[b] ◦ St. John's Wort[a] Hypophysitis • Ipilimumab
10.4. *Increased clearance*		**10.5. *Peripheral metabolism***
Phenobarbital Primidone Phenytoin Carbamazepine Oxacarbazepine[b] Rifampin Growth hormone	Sertraline[b] Tyrosine kinase inhibitors (imatinib,[b] sunitinib) Quetiapine[b] Stavudine[b] Nevirapine[a,b]	Glucocorticoids Amiodarone Propylthiouracil Beta blockers (e.g., propranolol, nadolol) Iodinated contrast (ipodate,[c] iopanoic acid[c]) Interleukin-6 Clomipramine

Modificazioni morfofunzionali della tiroide con l'invecchiamento

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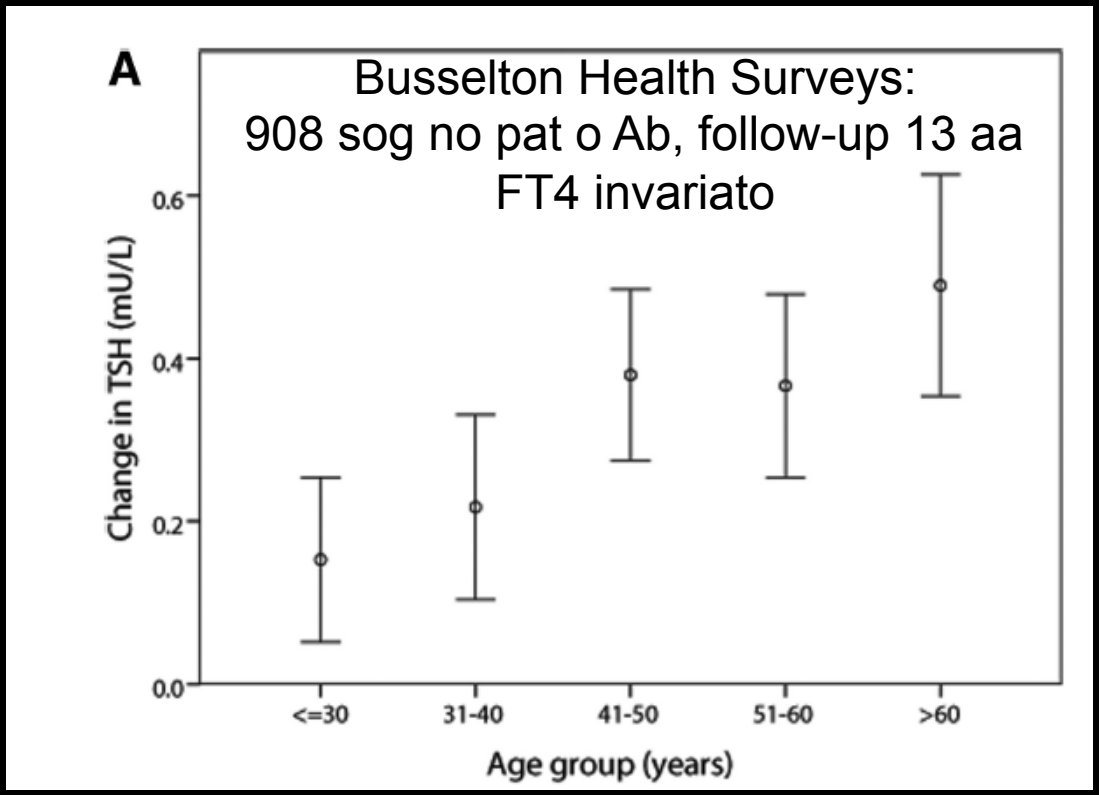

Resettato set point del TSH?
Ridotta bioattività del TSH?
Down-regulation dell'asse HPTP?

Riduzione dell'omeostasi metabolica correlata all'età

Age-Related Changes in Thyroid Function: A Longitudinal Study of a Community-Based Cohort

Alexandra P. Bremner, Peter Feddema, Peter J. Leedman, Suzanne J. Brown, John P. Beilby, Ee Mun Lim, Scott G. Wilson, Peter C. O'Leary, and John P. Walsh

TABLE 2. Age-related reference ranges for TSH derived from the cross-sectional reference group (n = 1751)

Age (yr)	n	TSH reference range (mU/liter) Lower limit	Mean	Upper limit
<30	304	0.51	1.34	3.54
30–40	299	0.48	1.25	3.21
40–50	269	0.44	1.32	3.92
50–60	321	0.42	1.31	4.09
60–70	334	0.38	1.34	4.70
>70	224	0.52	1.66	5.28
All	1751	0.44	1.35	4.10

Reference ranges were calculated as mean ± 2 SD of log-transformed serum TSH concentrations for each age stratum.

J Clin Endocrinol Metab, May 2012, 97(5):1554–1562

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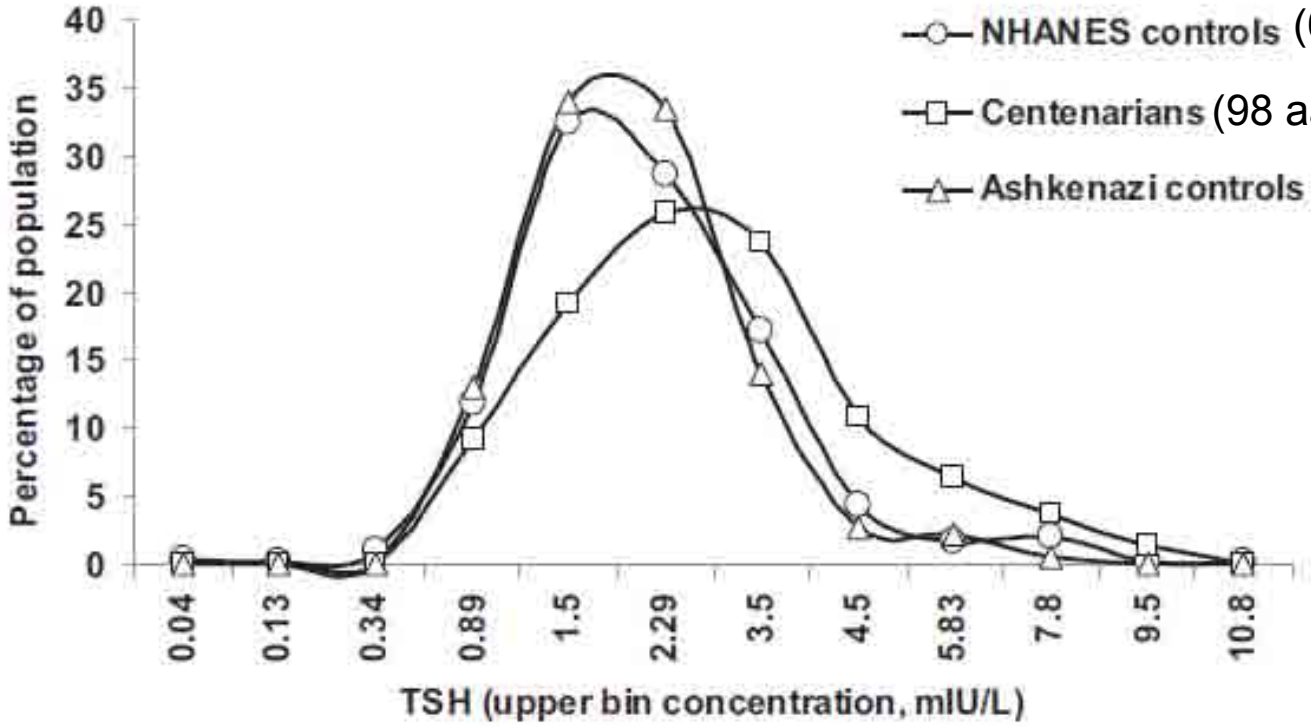
Extreme Longevity Is Associated with Increased Serum Thyrotropin

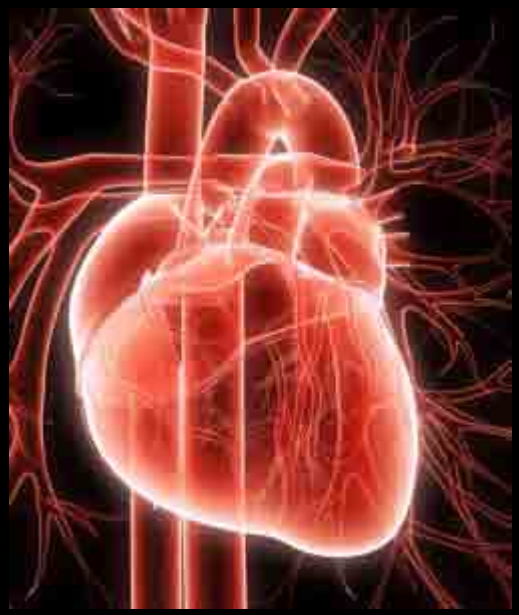
Gil Atzmon, Nir Barzilai, Joseph G. Hollowell, Martin I. Surks, and Ilan Gabriely

Distribuzione TSH nei centenari Ashkenazi vs controlli A. e del NHANES III



J Clin Endocrinol Metab 94: 1251–1254, 2009

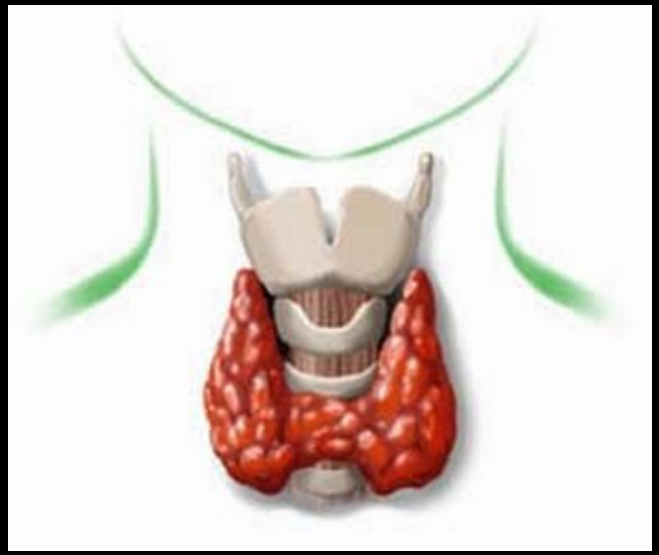
Tiroide e Apparato CardioVascolare



-Contrattilità miocardica
-Funzione endoteliale
-Resistenze vascolari
-PA

-Metabolismo lipidico

Cluster di fattori di rischio CV



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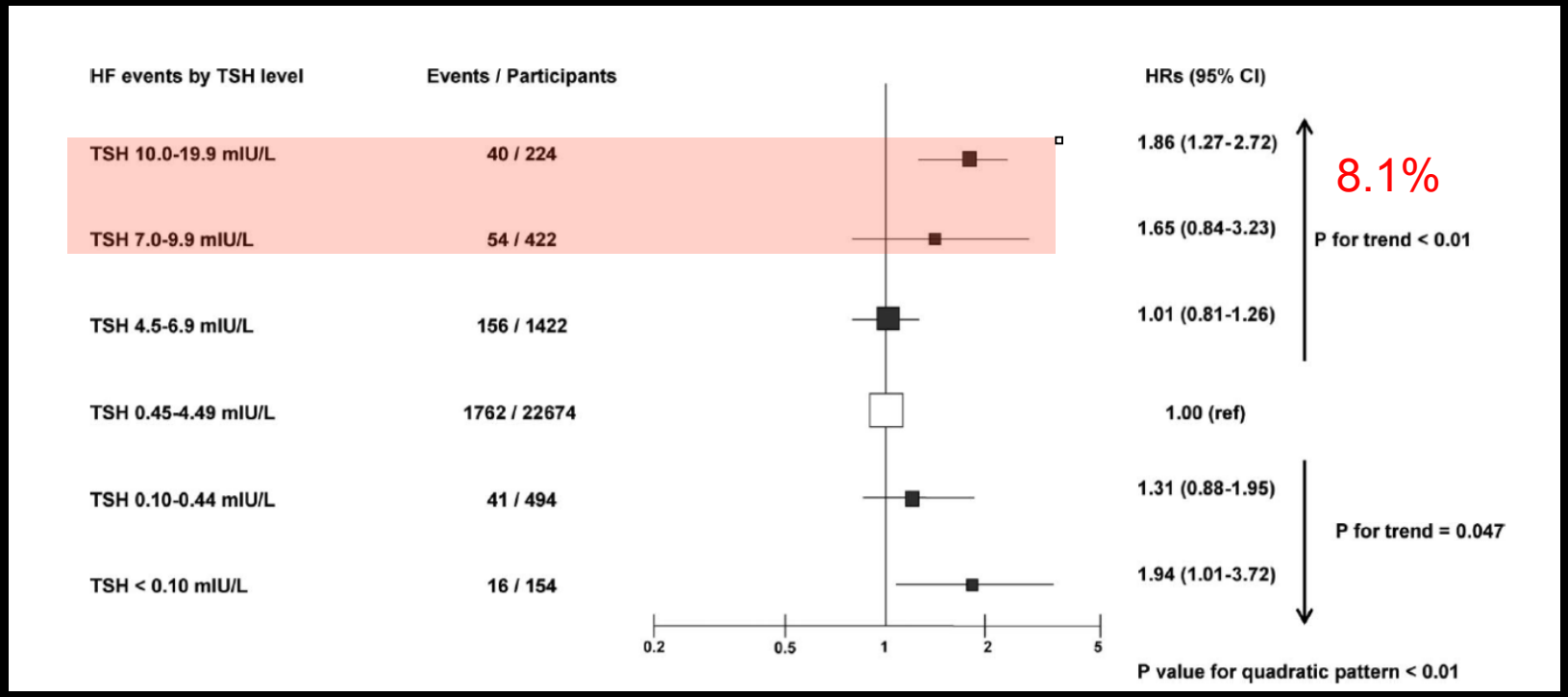
Subclinical Thyroid Dysfunction and the Risk of Heart Failure Events

An Individual Participant Data Analysis From 6 Prospective Cohorts

Baris Gencer, MD; Tinh-Hai Collet, MD; Vanessa Virgini, MD; Douglas C. Bauer, MD; Jacobijn Gussekloo, MD, PhD; Anne R. Cappola, MD, ScM; David Nanchen, MD; Wendy P.J. den Elzen, PhD; Philippe Balmer, BSc; Robert N. Luben, PhD; Massimo Iacoviello, MD; Vincenzo Triggiani, MD; Jacques Cornuz, MD, MPH; Anne B. Newman, MD, MPH; Kay-Tee Khaw, MD; J. Wouter Jukema, MD, PhD; Rudi G.J. Westendorp, MD, PhD; Eric Vittinghoff, PhD; Drahomir Aujesky, MD, MSc; Nicolas Rodondi, MD, MAS; for the Thyroid Studies Collaboration

(*Circulation*. 2012;126:1040-1049.)

- 6 coorti prospettiche, N: 25390, età media 70 aa
- TSH > 10 mUI/L, aumento HF indipendentemente da età



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

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

Bari,
7-10 novembre 2013

J Clin Endocrinol Metab, August 2008, 93(8):2998–3007

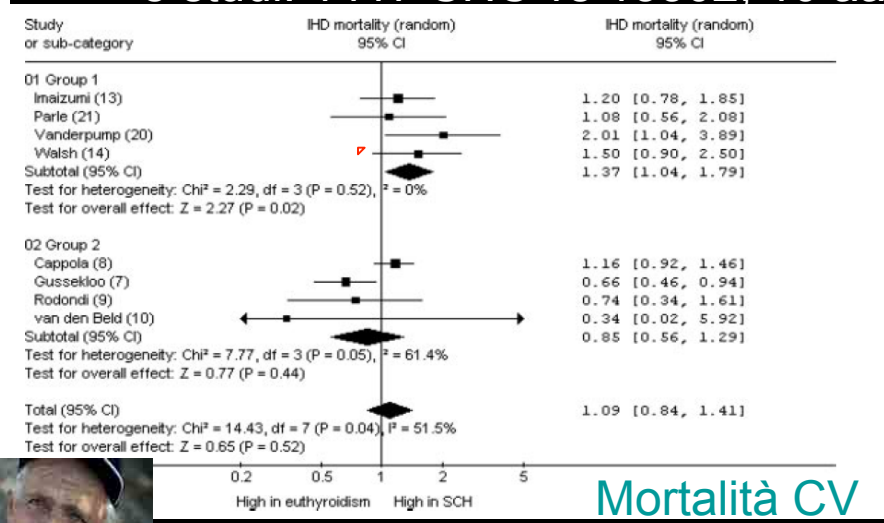
12 studi: 2399 SHC vs 24868

<65 aa

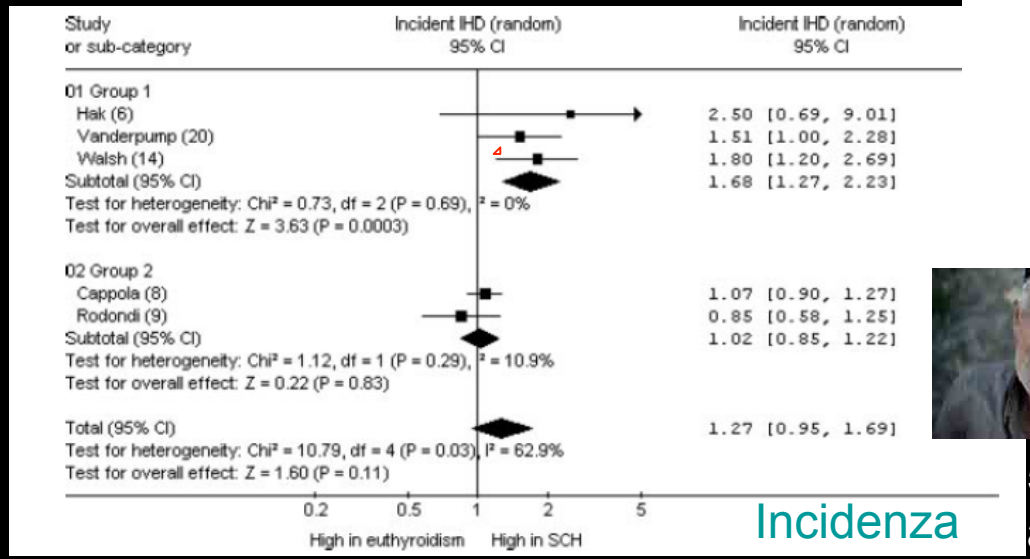
>65 aa

Prevalenza

8 studi: 1417 SHC vs 13302, 10 aa



Mortalità CV



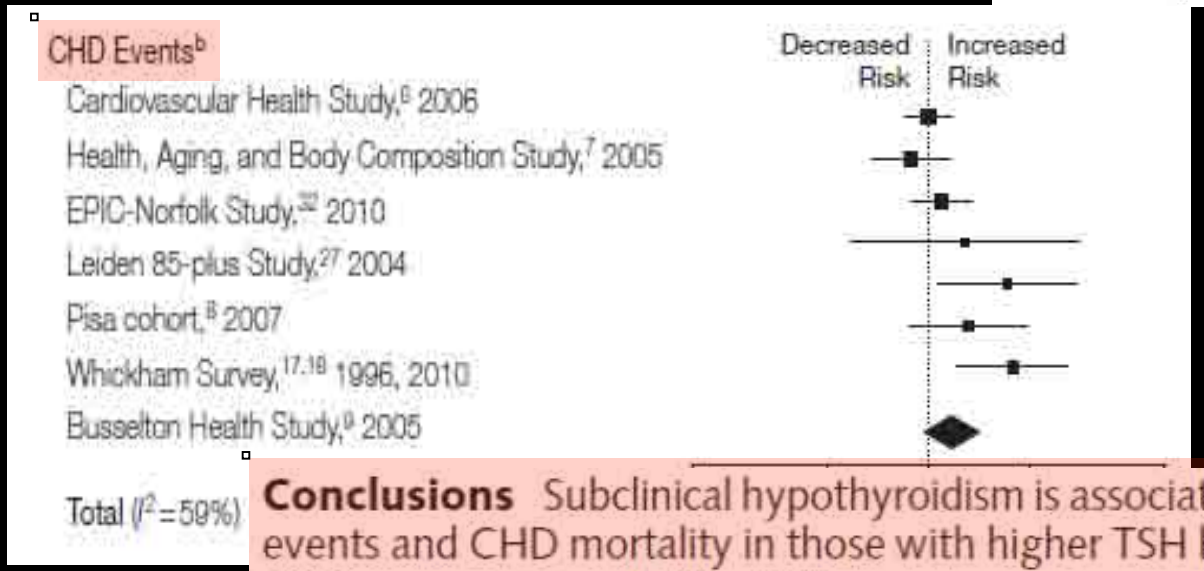
Incidenza

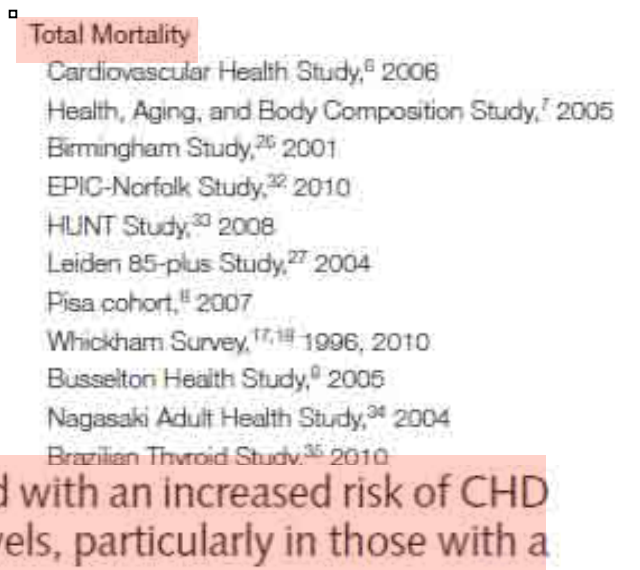
5 studi: 954 SHC vs 8673, 8.6 aa
anche per TSH < 10

Subclinical Hypothyroidism and the Risk of Coronary Heart Disease and Mortality

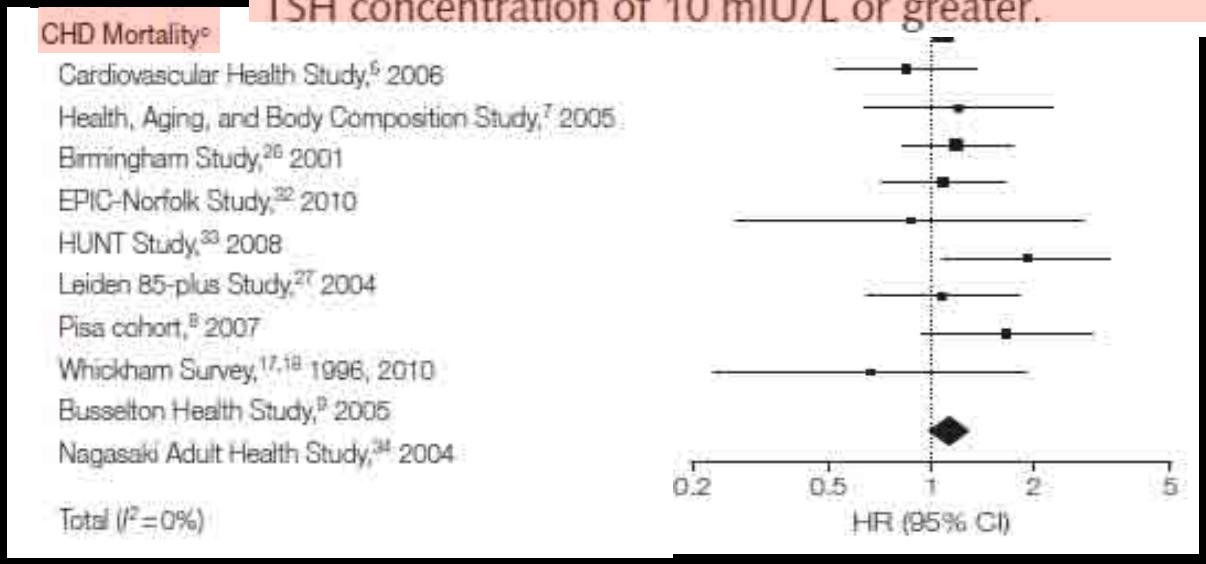
Bari,
7-10 novembre 2013

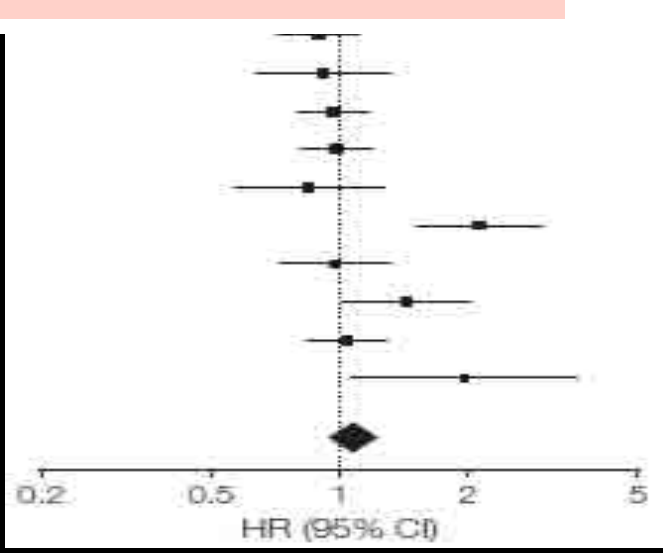
JAMA, September 22/29, 2010—Vol 304, No. 12





Conclusions Subclinical hypothyroidism is associated with an increased risk of CHD events and CHD mortality in those with higher TSH levels, particularly in those with a TSH concentration of 10 mIU/L or greater.





Nicolas Rodondi, MD, MAS

Thyroid Status, Disability and Cognitive Function, and Survival in Old Age

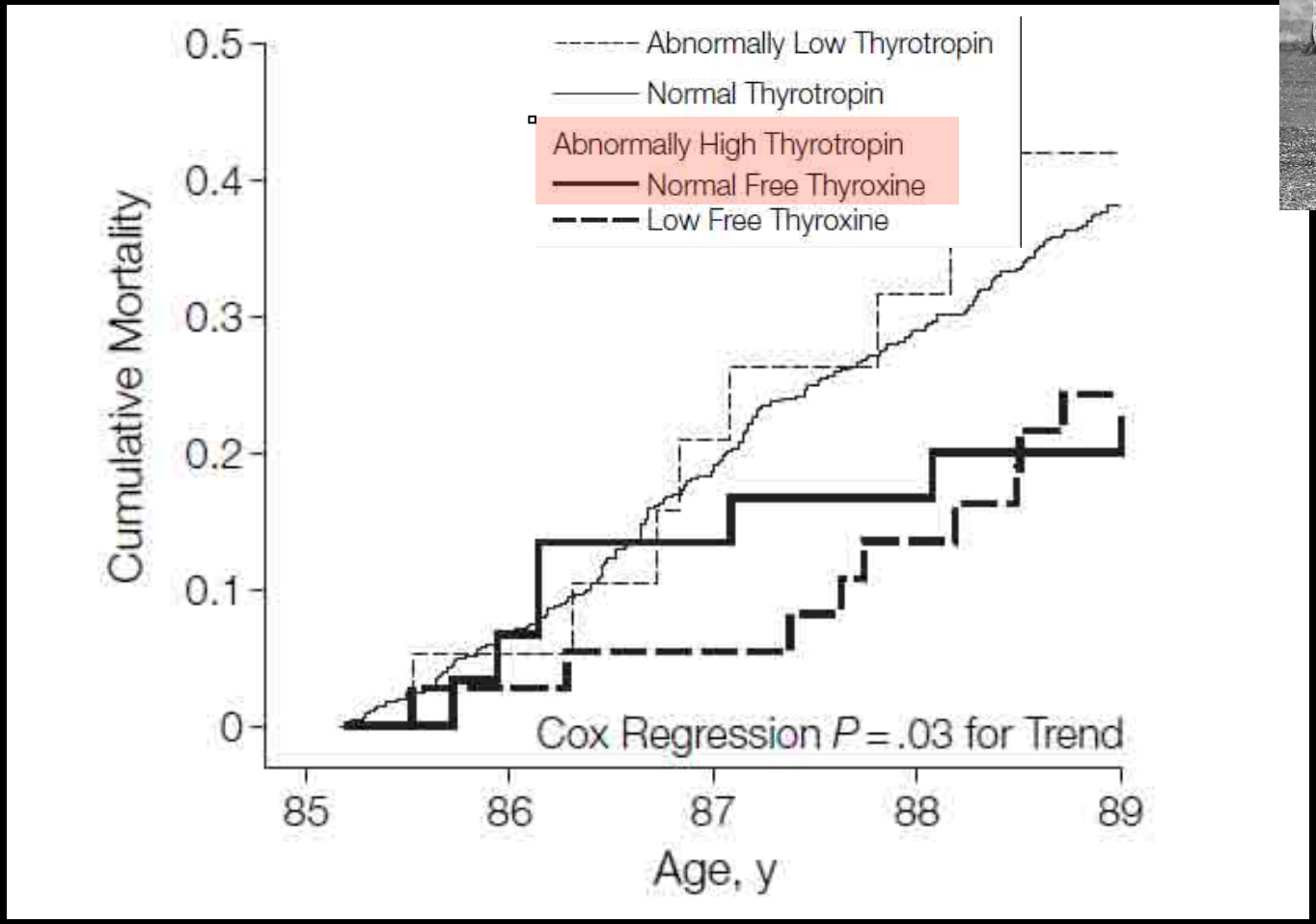
Bari,
7-10 novembre 2013

Jacobijn Gussekloo, MD, PhD

JAMA, December 1, 2004—Vol 292, No. 21

Leiden 85-Plus Study

N: 599
85-89 aa



Studi di intervento

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- Migliorano indici di performance cardiaca
- Migliora il profilo lipidico
- Migliora la funzione endoteliale
- Migliora lo spessore intima-media

Thyroid hormone replacement for subclinical hypothyroidism

Heloisa Cerqueira Cesar Esteves Villar[1], Humberto Saconato[2], Orsine Valente[3], Álvaro N Atallah[4]

Bari,
7-10 novembre 2013

THE COCHRANE COLLABORATION®

Authors' conclusions

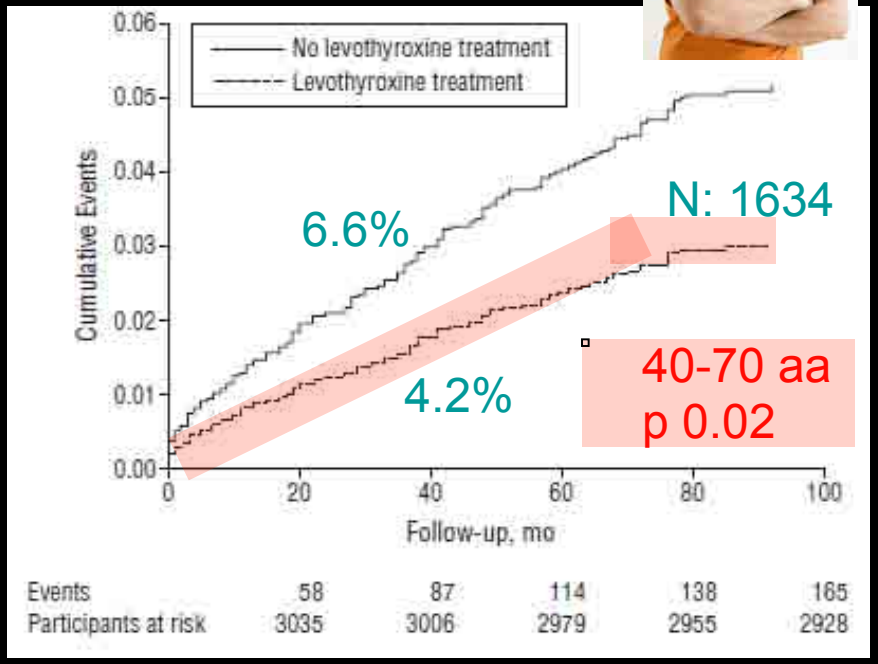
In current RCTs, levothyroxine replacement therapy for subclinical hypothyroidism did not result in improved survival or decreased cardiovascular morbidity. Data on health-related quality of life and symptoms did not demonstrate significant differences between intervention groups. Some evidence indicates that levothyroxine replacement improves some parameters of lipid profiles and left ventricular function.

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

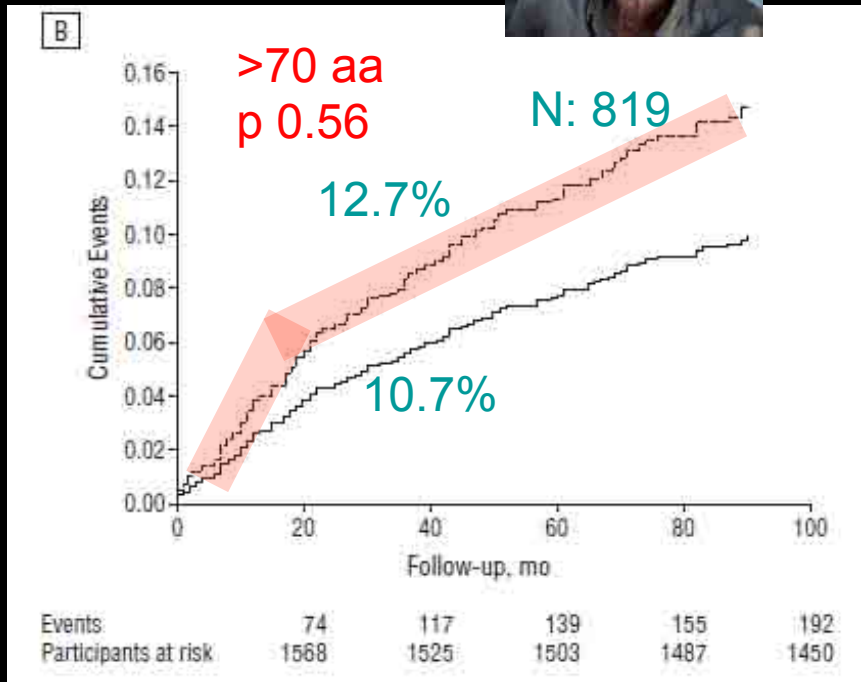
Salman Razvi, MD, FRCP; Jolanta U. Weaver, PhD, FRCP; Timothy J. Butler, MRCGP; Simon H. S. Pearce, MD, FRCP

Bari,
7-10 novembre 2013

ARCH INTERN MED/VOL 172 (NO. 10), MAY 28, 2012



Studio retrospettivo
Follow up
(0-8 aa,media 5.2 aa)



Follow up
(0-8 aa,media 7.6 aa)

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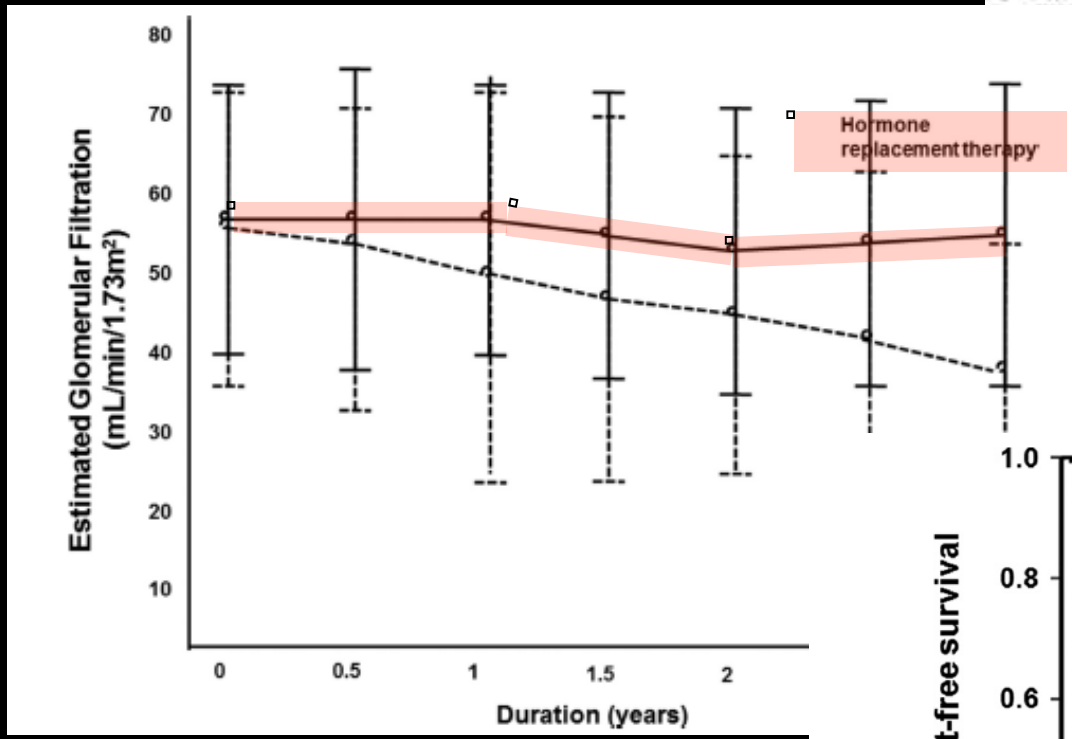
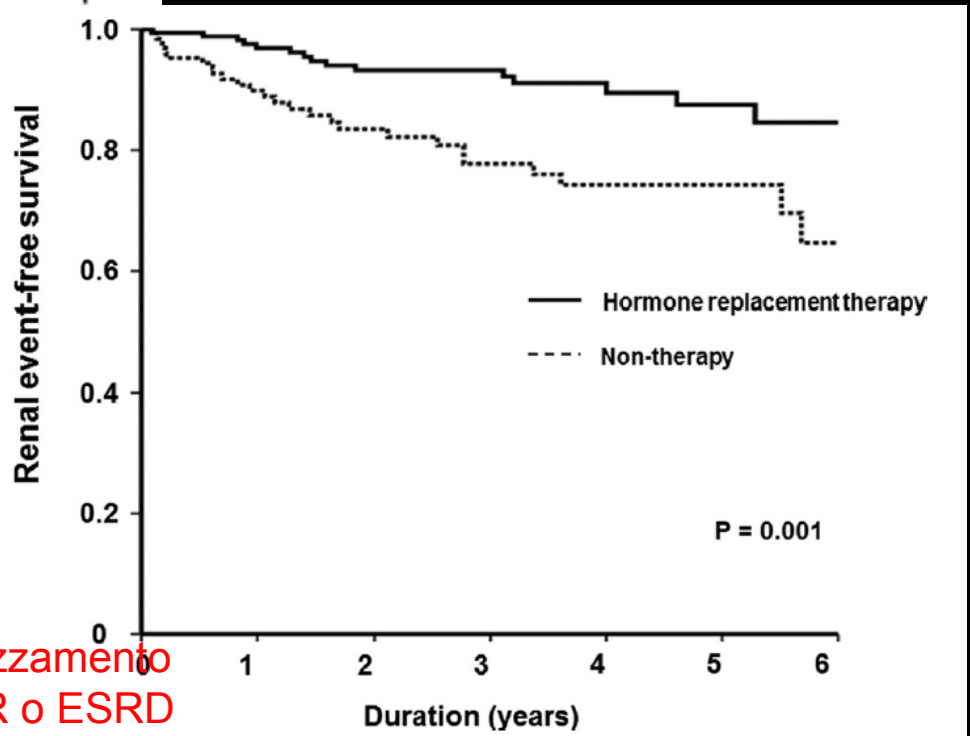
Preservation of Renal Function by Thyroid Hormone Replacement Therapy in Chronic Kidney Disease Patients with Subclinical Hypothyroidism

Dong Ho Shin, MI Jung Lee, Seung Jun Kim, Hyung Jung Oh, Hyoung Rae Kim, Jae Hyun Han, Hyang Mo Koo, Fa Mee Doh, Jung Tak Park, Seung Hyeok Han, Tae-Hyun Yoo, and Shin-Wook Kang

J Clin Endocrinol Metab, August 2012, 97(8):2732–2740



N:309 pz (180 vs 129)
Età media 63 aa



Dimezzamento eGFR o ESRD

Terapia con Levotiroxina

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Table 2. Prevalence of Thyroid Abnormalities

Thyroid Status*	No. of Subjects (%)
Total subjects	(N = 25 862)
Euthyroid	22 842 (88.3)
Hypothyroid	114 (0.4)
Subclinical hypothyroid	2336 (9.0)
Hyperthyroid	35 (0.1)
Subclinical hyperthyroid	535 (2.1)
Subjects taking thyroid medication	(n = 1525)
Euthyroid	916 (60.1)
Hypothyroid	11 (0.7)
Subclinical hypothyroid	269 (17.6)
Hyperthyroid	13 (0.9)
Subclinical hyperthyroid	316 (20.7)
Subjects not taking thyroid medication	(n = 24 337)
Euthyroid	21 926 (90.1)
Hypothyroid	103 (0.4)
Subclinical hypothyroid	2067 (8.5)
Hyperthyroid	22 (0.1)
Subclinical hyperthyroid	219 (0.9)

Arch Intern Med. 2000;160:526-534

WHAT THIS STUDY ADDS

BMJ 2011;342:d2238

Before this study the effect of levothyroxine dose on fracture outcomes was not known, particularly in the at risk population of older people (≥70 years)

In this population, higher doses of levothyroxine treatment were associated with a twofold to threefold increased risk of fracture compared with lower doses

Conclusioni:

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- L'sHT nell'anziano non costituisce una condizione unica (fasce di TSH e di età)
- I soggetti con età >80 aa devono essere monitorizzati e spesso non richiedono terapia sostitutiva
- La decisione di trattare l'sHT in un anziano deve essere ponderata considerando:
le possibili cause di danno tiroideo,
il rischio CV pre-esistente,
la presenza di HF e di IR,
le comorbidità e le possibili interferenze farmacologiche

- Sono necessari studi randomizzati controllati che valutino endpoint CV: (Thyroid Hormone Replacement for Untreated older adults with Subclinical hypothyroidism Trial:
the TRUST trial 2012)

Grazie per l'attenzione