- Treatment of subclinical hypothyroidism in older people: further results from the TRUST trial

- David J Stott
  - Professor of Geriatric Medicine, University of Glasgow, UK
  - On behalf of the TRUST Study Group

Thyroid hormone Replacement for Untreated older adults with Subclinical hypothyroidism; a randomised placebo-controlled Trial

TRUST
THYROID TRIAL

University of Glasgow

LUMC Leiden University Medical Center

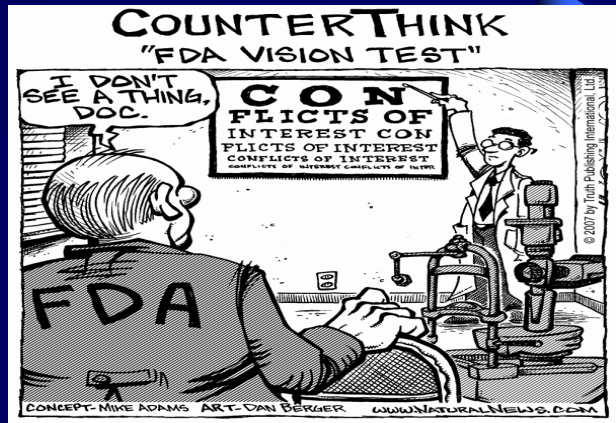
u^b UNIVERSITÄT BERN

UCC Coláiste na hOllscoile Corcaigh, Éire University College Cork, Ireland

Leyden Academy ON VITALITY AND AGEING

Disclosure of interests

- Main Grant funding - European Commission - Research: The Seventh Framework Programme FP7 (agreement number 278148)
- Medicines from Merck KGaA
- Above had no role in the design, analysis or reporting of the study

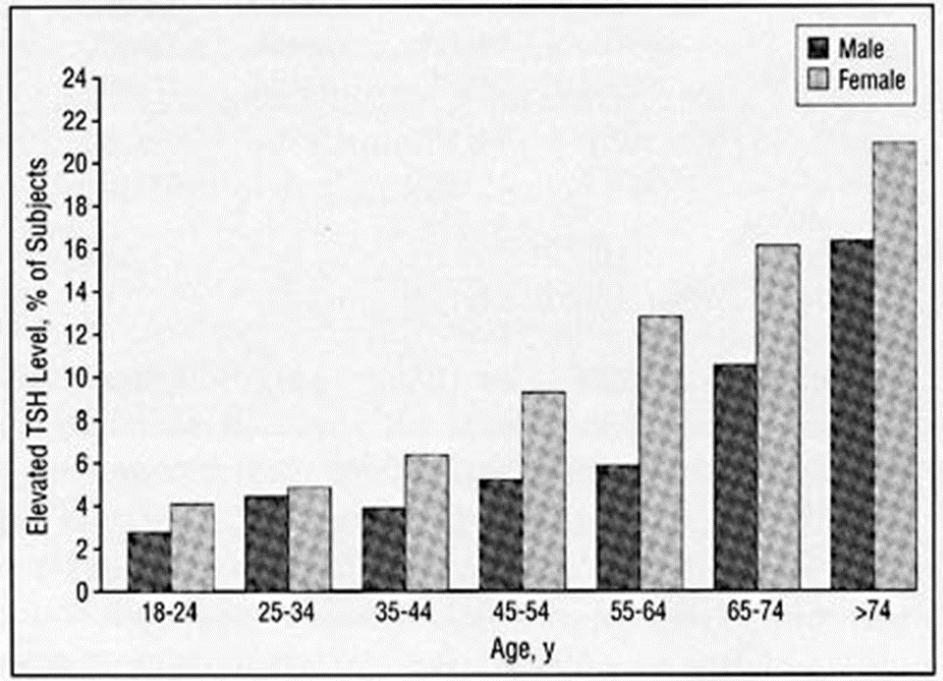


Definition – subclinical hypothyroidism

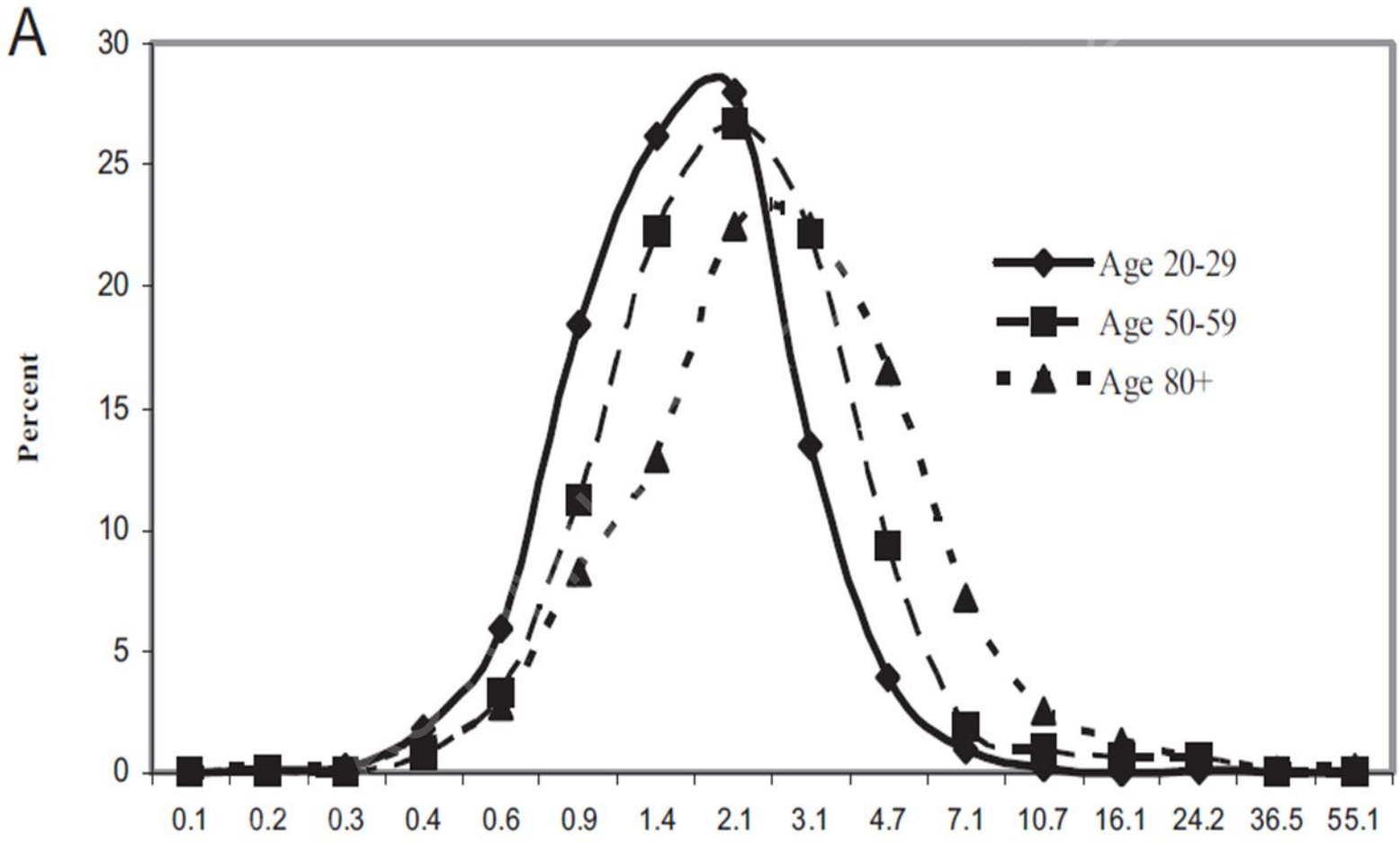
- Few / no symptoms or signs of thyroid dysfunction
- TSH > 4.5 IU/L
- Serum free thyroxine (fT4) in reference range
- Not on thyroxine
- Rugge et al, U.S. Preventive Services Task Force
  - Ann Intern Med 2015;162:35-45

Epidemiology of subclinical hypothyroidism (SCH)

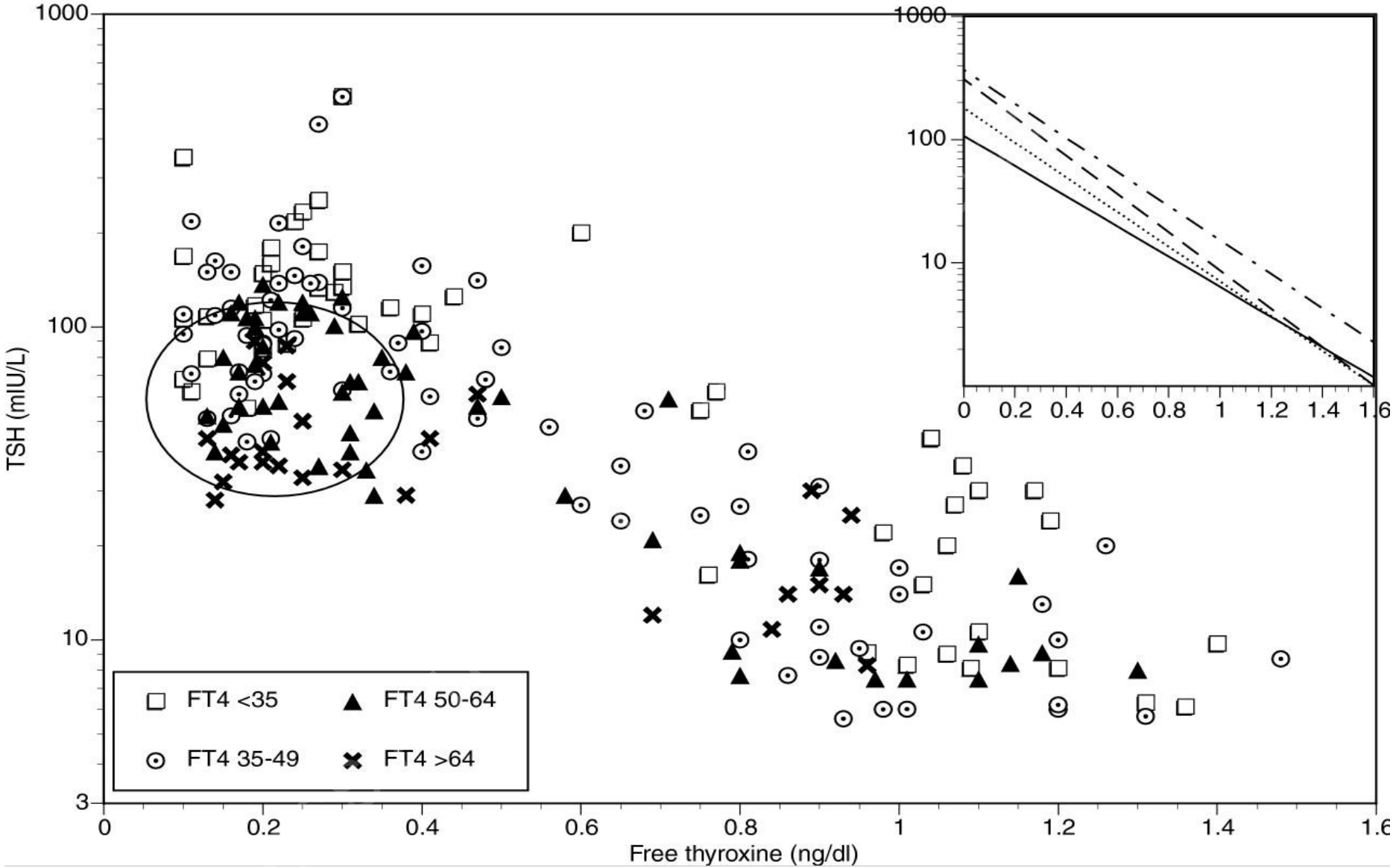
- Older age is associated with higher TSH
- SCH is common in older age
  - Canaris et al, Colorado Thyroid Disease Prevalence Study, Arch Intern Med 2000;160:526-534
- Possible harms
  - Fatigue, low mood
  - Ischaemic heart disease, heart failure
- Possible benefits
  - Reduced risk atrial fibrillation
  - Reduced risk osteoporosis / fractures
  - Prolonged survival very elderly



Surks and Hollowell JCEM 2007

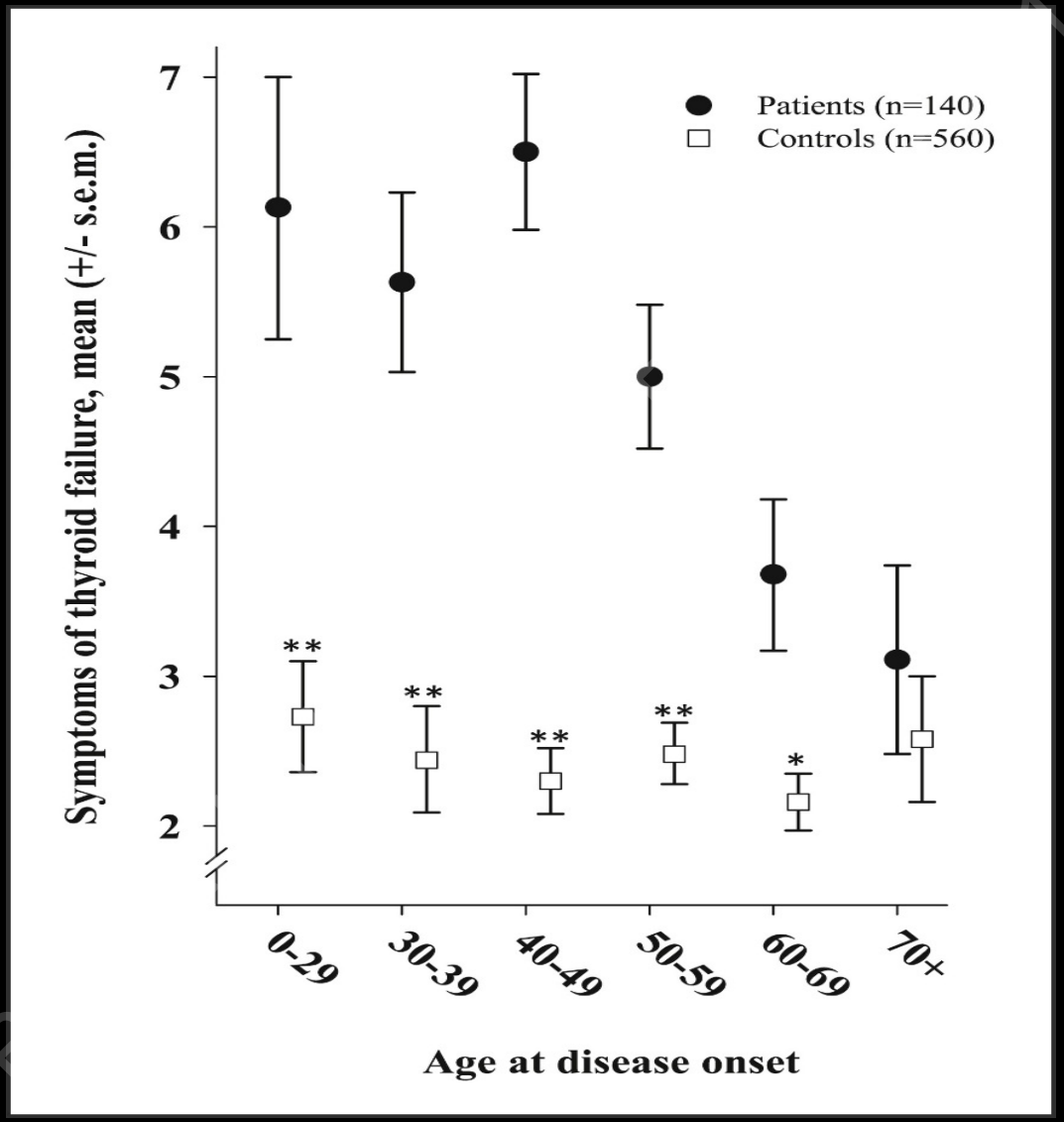


TSH level mU/L



Over at al JCEM 2010

Symptoms of thyroid failure by age of onset



The American Journal of Medicine 2016 129, 1082-1092DOI: (10.1016/j.amjmed.2016.06.013)

- For subclinical hypothyroidism (SCH)
  - No evidence thyroid hormone treatment associated with improved quality of life, cognitive function, BP or BMI
  - Cohort study - treatment associated with decreased coronary heart disease events
  - Treatment harms ‘poorly studied and sparsely reported’

Stott *et al. BMC Endocrine Disorders* (2017) 17:6
DOI 10.1186/s12902-017-0156-8

BMC Endocrine Disorders

STUDY PROTOCOL Open Access

Study protocol; Thyroid hormone Replacement for Untreated older adults with Subclinical hypothyroidism - a randomised placebo controlled Trial (TRUST)

David J. Stott[1,21*], Jacobijn Gussekloo[2], Patricia M. Kearney[3], Nicolas Rodondi[4,5], Rudi G. J. Westendorp[6,7], Simon Mooijaart[8], Sharon Kean[9], Terence J. Quinn[1], Naveed Sattar[10], Kirsty Hendry[1], Robert Du Puy[2], Wendy P. J. Den Elzen[11], Rosalinde K. E. Poortvliet[2], Jan W. A. Smit[12], J. Wouter Jukema[13], Olaf M. Dekkers[8], Manuel Blum[14], Tinh-Hai Collet[15], Vera McCarthy[16], Caroline Hurley[17], Stephen Byrne[18], John Browne[3], Torquil Watt[19], Douglas Bauer[20] and Ian Ford[9]

clinicaltrials.gov number NCT01660126

Study aims and objectives

- To determine if there are clinical benefits from levothyroxine for older people with SCH
  - across wide range of outcomes, including health-related quality of life, cardiovascular disease, muscle function, cognition, BP, BMI, waist circumference
- Specific subgroups of older people
  - Women, very elderly, subgroups of TSH
- Are benefits offset by adverse effects?
- To establish a study biobank for future research

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Thyroid Hormone Therapy for Older Adults with Subclinical Hypothyroidism

D.J. Stott, N. Rodondi, P.M. Kearney, I. Ford, R.G.J. Westendorp, S.P. Mooijaart, N. Sattar, C.E. Aubert, D. Aujesky, D.C. Bauer, C. Baumgartner, M.R. Blum, J.P. Browne, S. Byrne, T.-H. Collet, O.M. Dekkers, W.P.J. den Elzen, R.S. Du Puy, G. Ellis, M. Feller, C. Floriani, K. Hendry, C. Hurley, J.W. Jukema, S. Kean, M. Kelly, D. Krebs, P. Langhorne, G. McCarthy, V. McCarthy, A. McConnachie, M. McDade, M. Messow, A. O'Flynn, D. O'Riordan, R.K.E. Poortvliet, T.J Quinn, A. Russell, C. Sinnott, J.W.A. Smit, H.A. Van Dorland, K.A. Walsh, E.K. Walsh, T. Watt, R. Wilson, and J. Gussekloo, for the TRUST Study Group*

ABSTRACT

BACKGROUND

The use of levothyroxine to treat subclinical hypothyroidism is controversial. We aimed to determine whether levothyroxine provided clinical benefits in older persons with this condition.

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Address reprint requests to Dr. Stott at the Glasgow Royal Infirmary, Rm.

TRUST trial – entry criteria

- Age ≥65 years, community dwelling
- TSH 4.6 – 19.9 mU/L persisting on repeat measurement
- fT4 in reference range
- Not on thyroxine / antithyroid drugs
- Minimum 4 weeks after major non-thyroidal illness
- No dementia

TRUST trial – intervention / control

- Randomised double-blind placebo controlled trial
- Levothyroxine
  - Starting dose 50µg
    - reduced to 25µg if weight <50Kg or coronary heart disease
  - Dose titration according to TSH, target 0.40-4.59mU/L
  - 25µg adjustments at 6-8 weeks, then annually
- Matching placebo with mock titration
- Minimum 12 months duration

TRUST trial - outcomes

Primary

- Thyroid-specific quality of life (ThyPRO) at 12months
  - Tiredness
  - Hypothyroid symptoms

*demoted –
initially planned as co-primary outcome

Secondary

- ThyPRO Tiredness and Hypothyroid symptoms at 6-8 weeks and on extended follow-up
- Euroqol 5-D / VAS
- ThyPRO39 (end of study only)
- Handgrip strength
- Digit-symbol substitution test
- Cardiovascular events*
- Total and CVS mortality
- Blood pressure
- BMI, weight, waist circumference
- Barthel index
- IADL

Power calculations for effect of levothyroxine – sample size

- Co-primary outcomes
  - ThyPRO Fatigue and Hypothyroid scores (0-100) at 12m (adjusted for baseline)
  - SDs 13.3 and 18.3
  - 80% power at p=0.025 (0.05/2)
  - 540 (750) participants
  - Difference of 3.5 (3.0) on the Hypothyroid scale
  - Difference of 4.9 (4.1) on the Tiredness scale

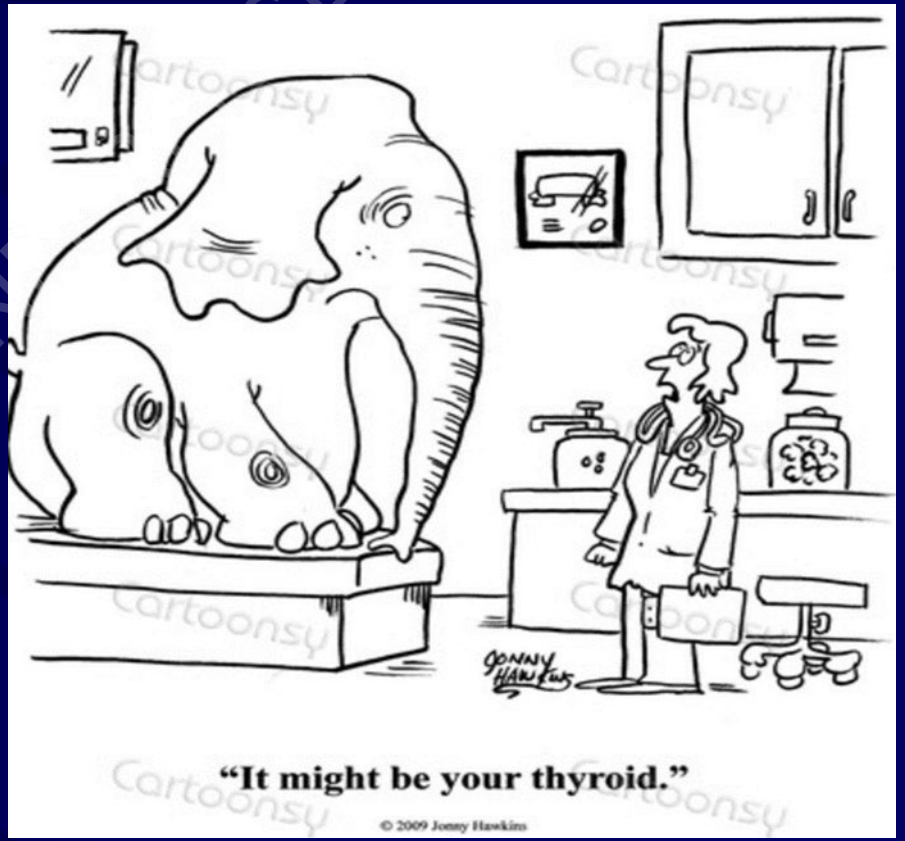
ThyPRO Fatigue domain

- Fatigue
  - During the past four weeks have you:
    - been tired?
    - been exhausted?
    - had difficulty getting motivated to do anything at all?
    - felt worn out?
- Vitality
  - During the past four weeks have you:
    - Felt full of life?
    - Felt energetic?
    - Been able to cope with the demands of your life?

5 response options: Not at all; A little; Some; Quite a bit; Very much

ThyPRO Hypothyroid symptoms

- Hypothyroid symptoms
  - During the past four weeks have you:
    - Been sensitive to cold?
    - Had swollen hands or feet?
    - Had dry skin?
    - Had itchy skin?

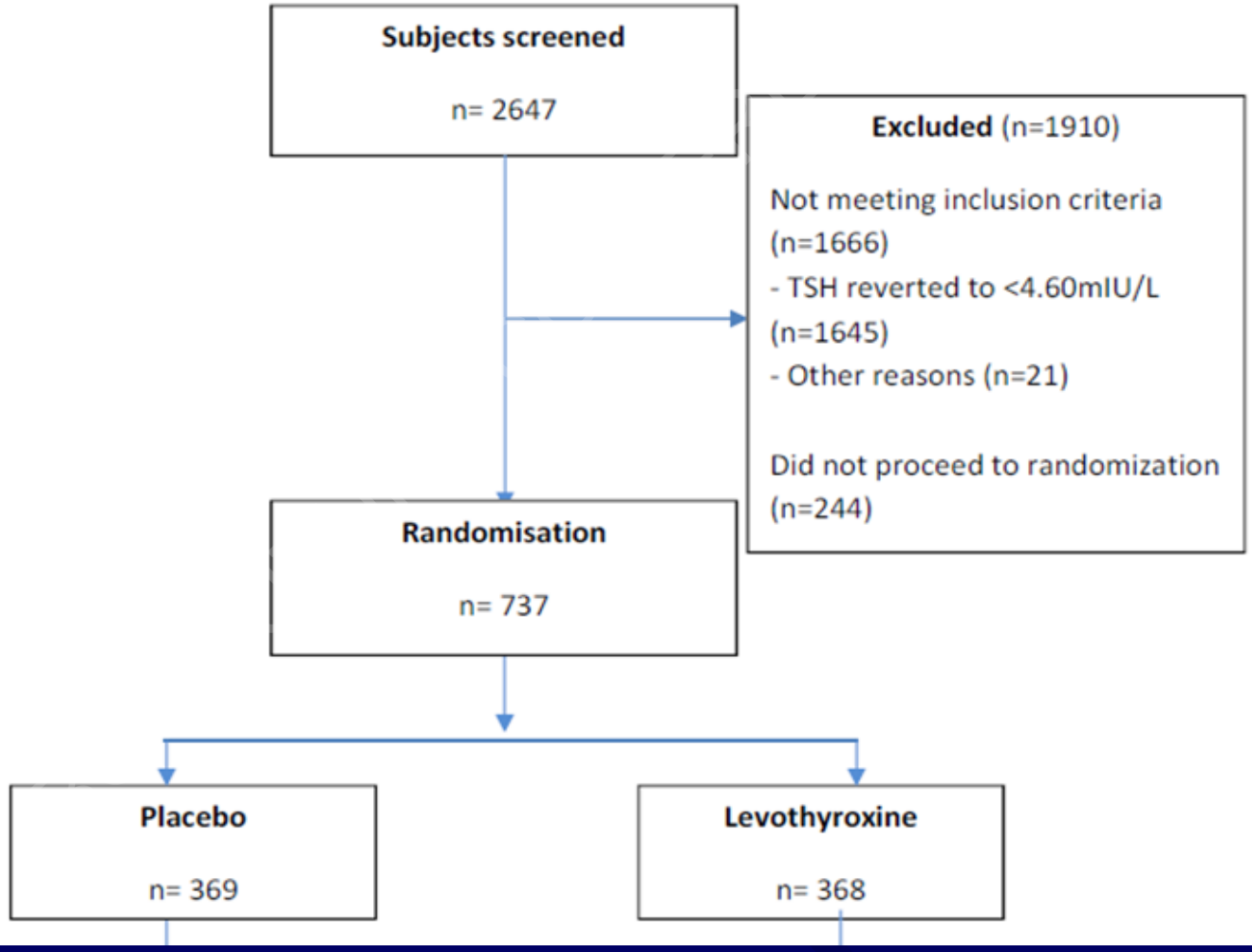


5 response options: Not at all; A little; Some; Quite a bit; Very much

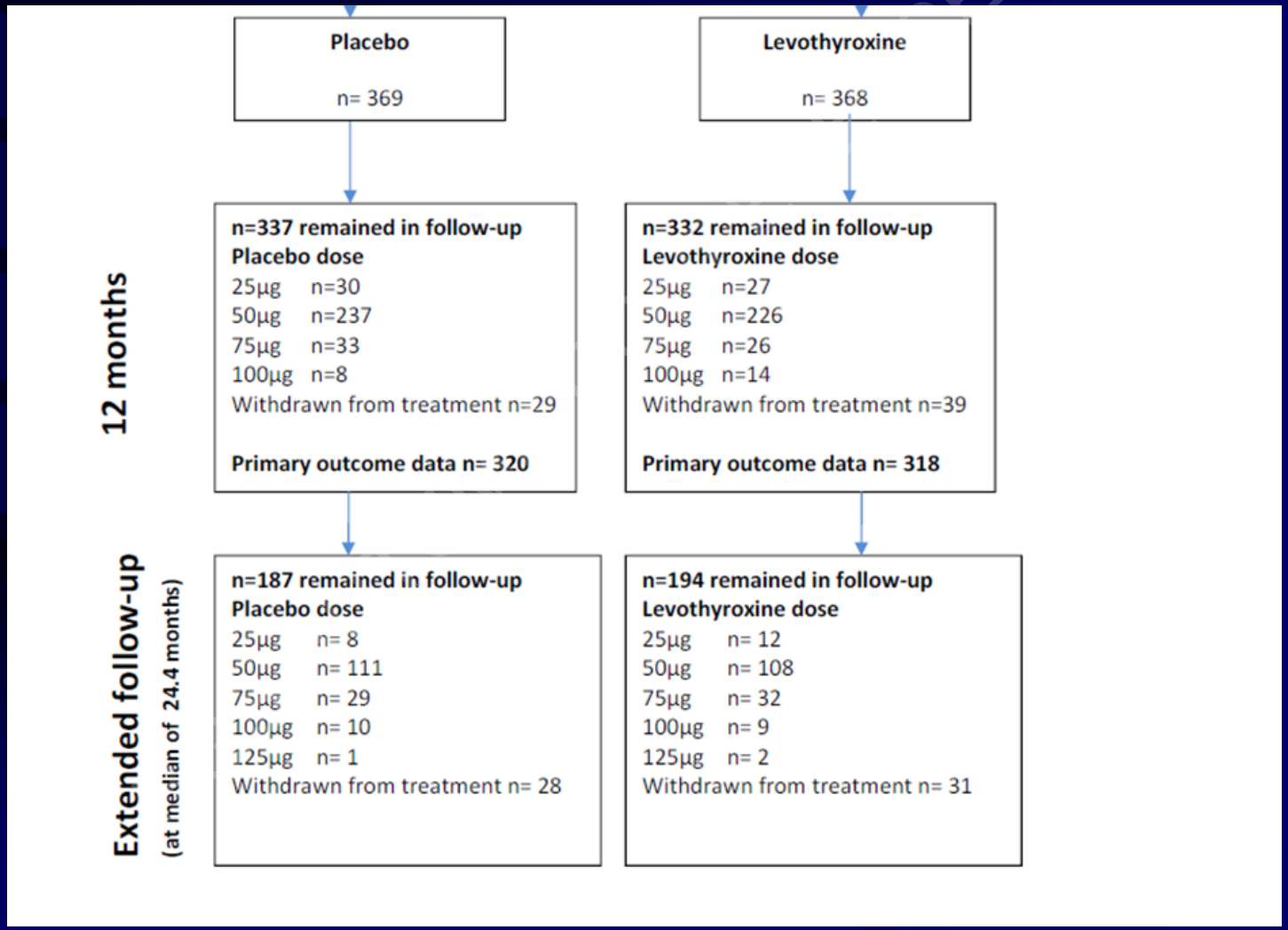
Adverse effects

- Adverse events of special interest
  - New atrial fibrillation (AF)
  - Heart failure
  - New diagnosis osteoporosis
  - Fracture
- Serious Adverse Events
- ThyPRO Hyperthyroid symptoms

Screening and recruitment



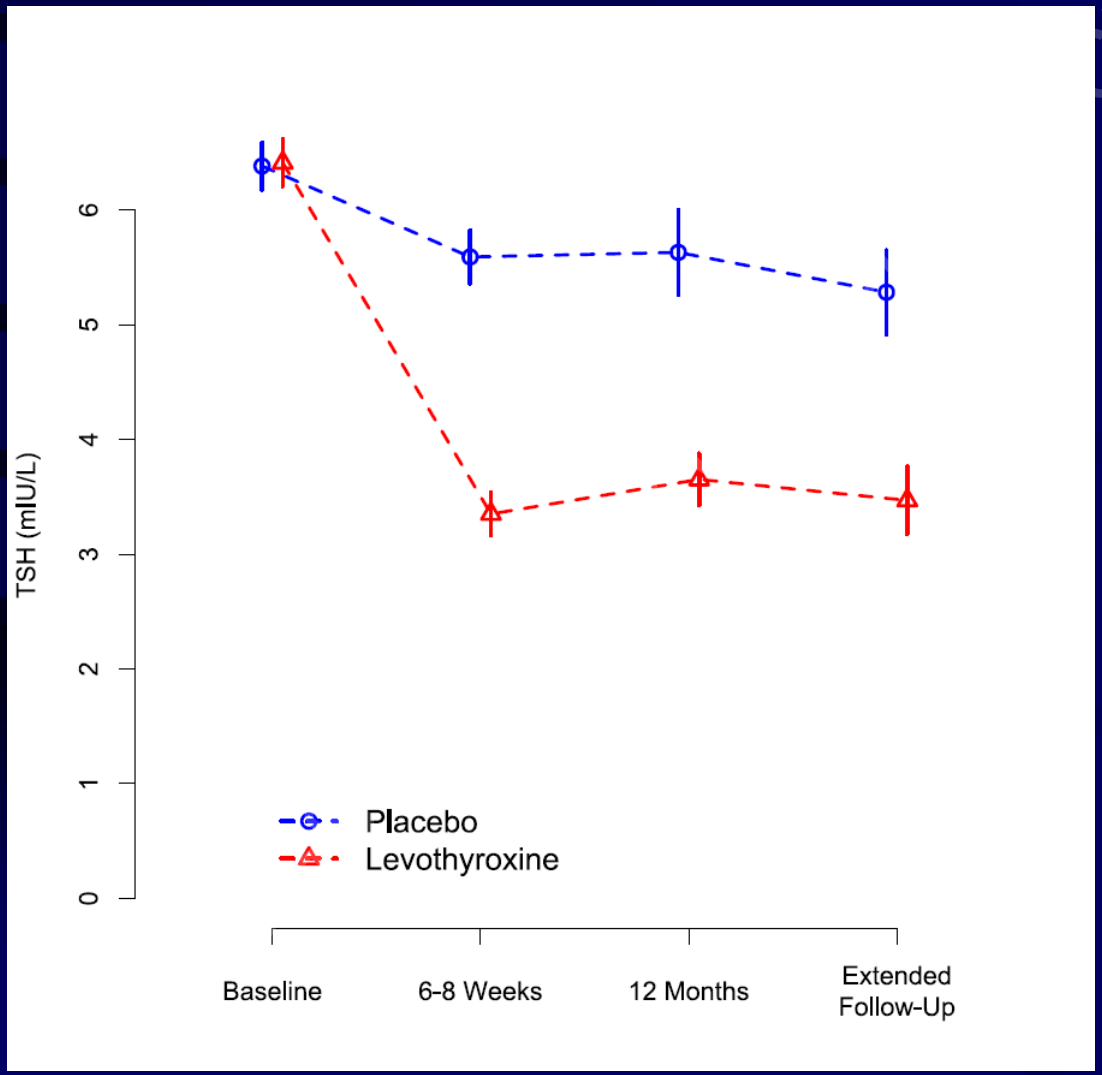
Progress through the study



Baseline characteristics

	Placebo (n=369)	Levothyroxine (n=368)
Age (years); mean, range	74.8 (65.1-93.4)	74.0 (65.2-93.0)
Female sex	198 (53.7%)	198 (53.8%)
Standard housing	356 (96.5%)	358 (97.3%)
TSH (mIU/L); mean, range	6.38 (4.6-17.6)	6.41 (4.6-17.6)
fT4 (pmol/L); mean, SD	13.3 (1.9)	13.4 (2.1)

TSH in placebo and levothyroxine groups



Mean and 95% CI

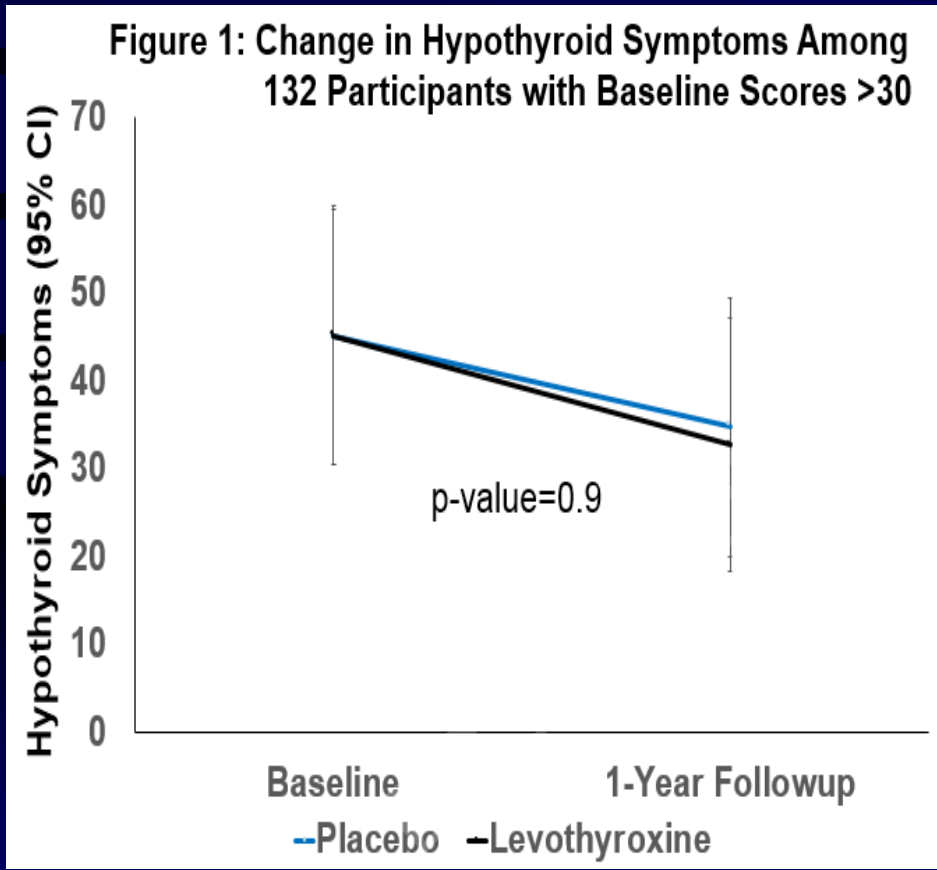
$p<0.001$ for all in-study time points

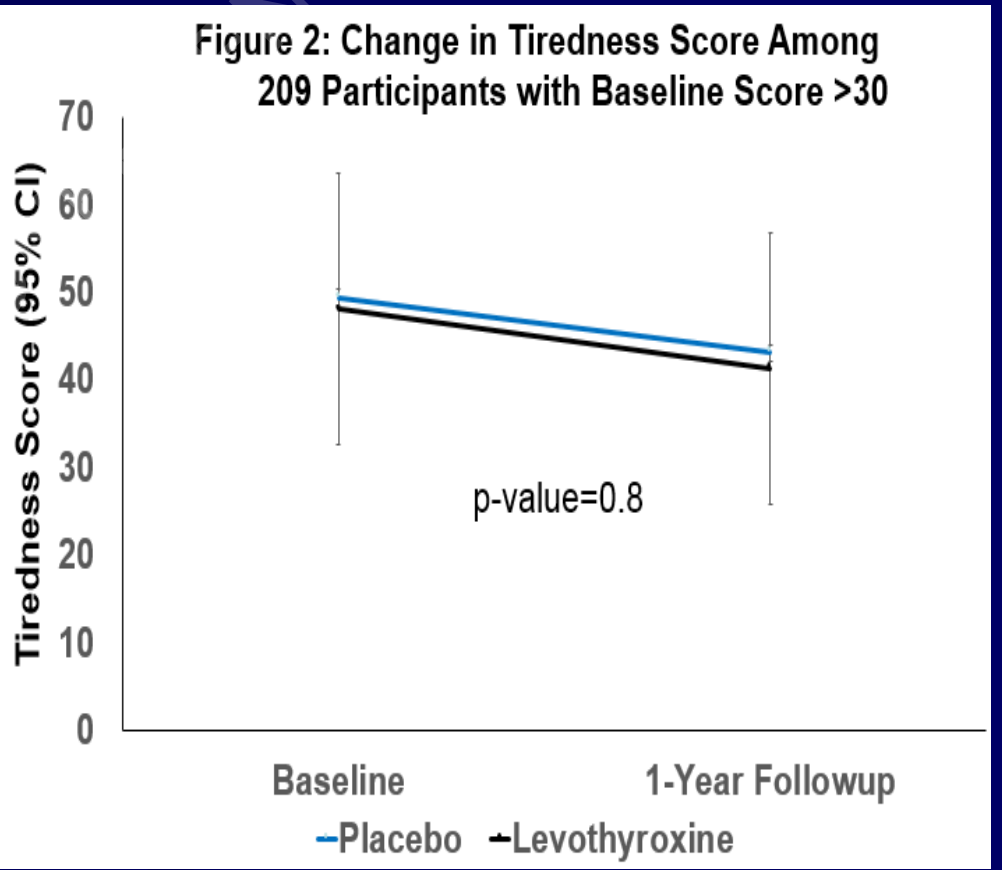
Primary outcomes – hypothyroid symptoms and tiredness (12 months)

	Placebo (mean, SD)	Levothyroxine (mean, SD)	Levothyroxine-placebo difference (mean, 95% CI)
ThyPRO Hypothyroid Symptoms (0-100)	16.7 (17.5) n=320	16.6 (16.9) n=318	0.0 (-2.0, 2.1)
ThyPRO Tiredness (0-100)	28.6 (19.5) n=320	28.7 (20.2) n=318	0.4 (-2.1, 2.9)

Modified intention to treat analysis; results adjusted for stratification variables and baseline levels of the same variable using linear regression

Post-hoc subgroup analyses – subjects with highest level of baseline symptoms





Subgroup baseline TSH ≥10 mIU/L

	Baseline Placebo n=17	Baseline Levothyroxine n=18	12 months Placebo n=17	12 months Levothyroxine n=18	Between group difference (95% CI)
TSH mIU/L	12.48 (2.35)	12.78 (2.43)	10.06 (5.15)	6.10 (3.94)	-4.19 (-5.95, -2.43)
ThyPRO Hypothyroid symptoms	20.2 (22.5)	12.2 (18.2)	19.1 (23.4)	14.2 (16.4)	0.6 (-8.3, 9.6)
ThyPRO Tiredness	25.0 (15.8)	25.7 (24.8)	28.8 (20.3)	25.4 (24.3)	-2.8 (-13.6, 8.0)

ThyPRO results at 12 months are adjusted for stratification variables (country, sex and starting dose of levothyroxine) and baseline levels of the same variable using linear regression

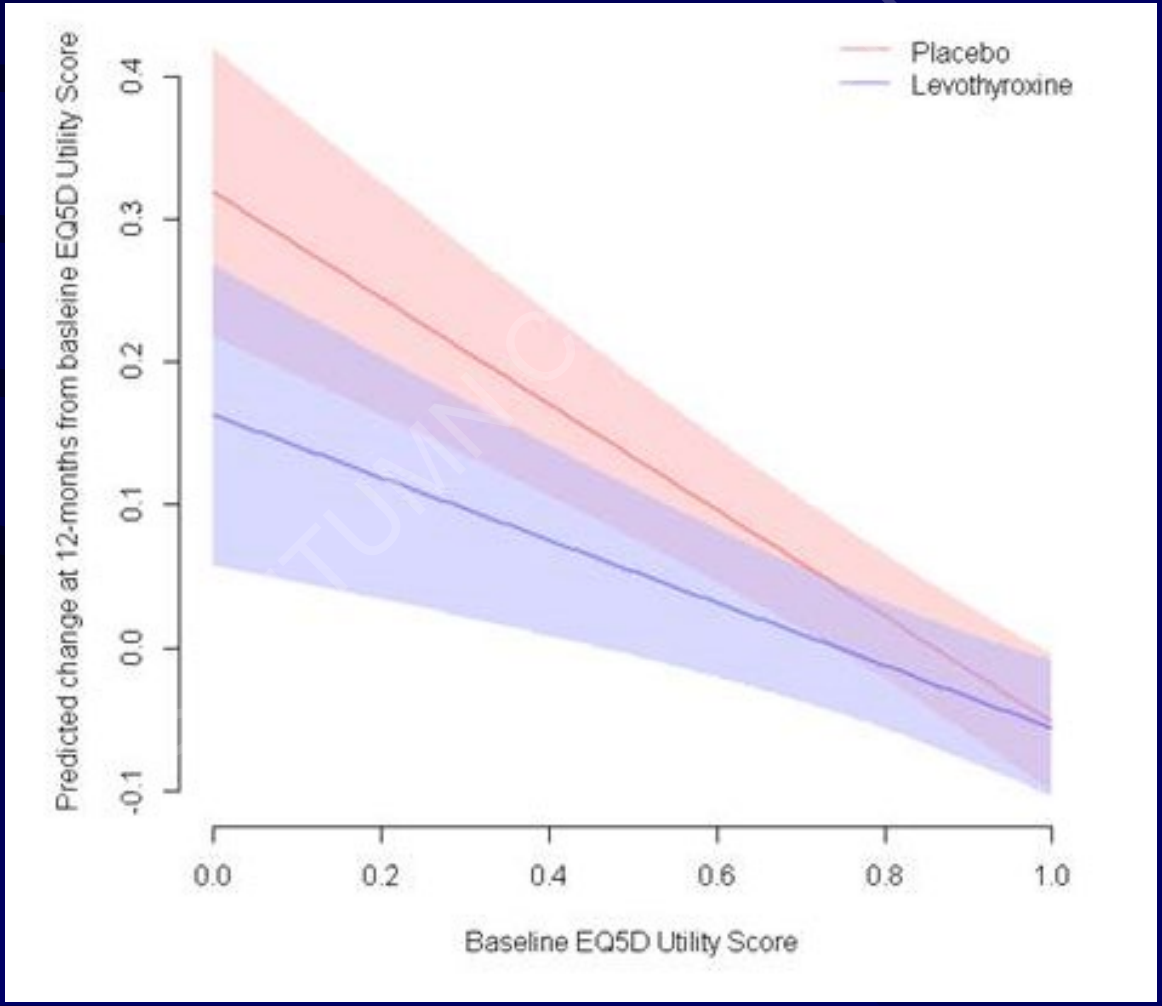
Secondary outcomes – generic health-related quality of life (EuroQol)

	Placebo at 12 months	Levo-thyroxine at 12 months	Difference at 12 months (95% CI)	Placebo at extended follow-up	Levo-thyroxine at extended follow-up	Difference at extended follow-up (95% CI)
EuroQol 5D	0.853 (0.191) n=320	0.833 (0.212) n=318	-0.025* (-0.050,0.000)	0.829 (0.209) n=187	0.864 (0.188) n=193	0.040** (0.005,0.075)
EuroQol visual analogue scale	77.4 (13.7) n=319	77.3 (15.65) n=318	-1.3 (-3.2, 0.6)	77.2 (13.5) n=187	76.8 (14.2) n=193	-0.8 (-3.2, 1.7)

*p=0.05, **p=0.03

Modified intention to treat analysis; data adjusted for stratification variables and baseline levels of the same variable using linear regression; extended follow-up visit additionally adjusted for time to visit.

Post-hoc analysis change in EQ5D by baseline EQ5D

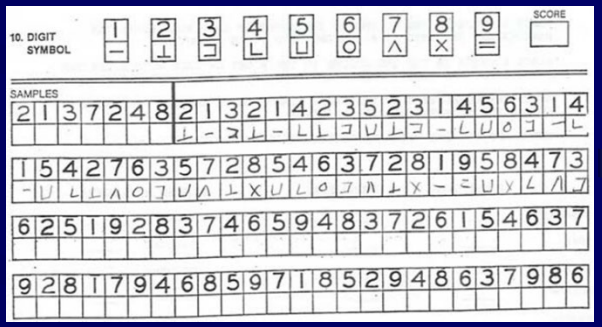


Interpretation – Effect of levothyroxine on EuroQol in older people with subclinical hypothyroidism

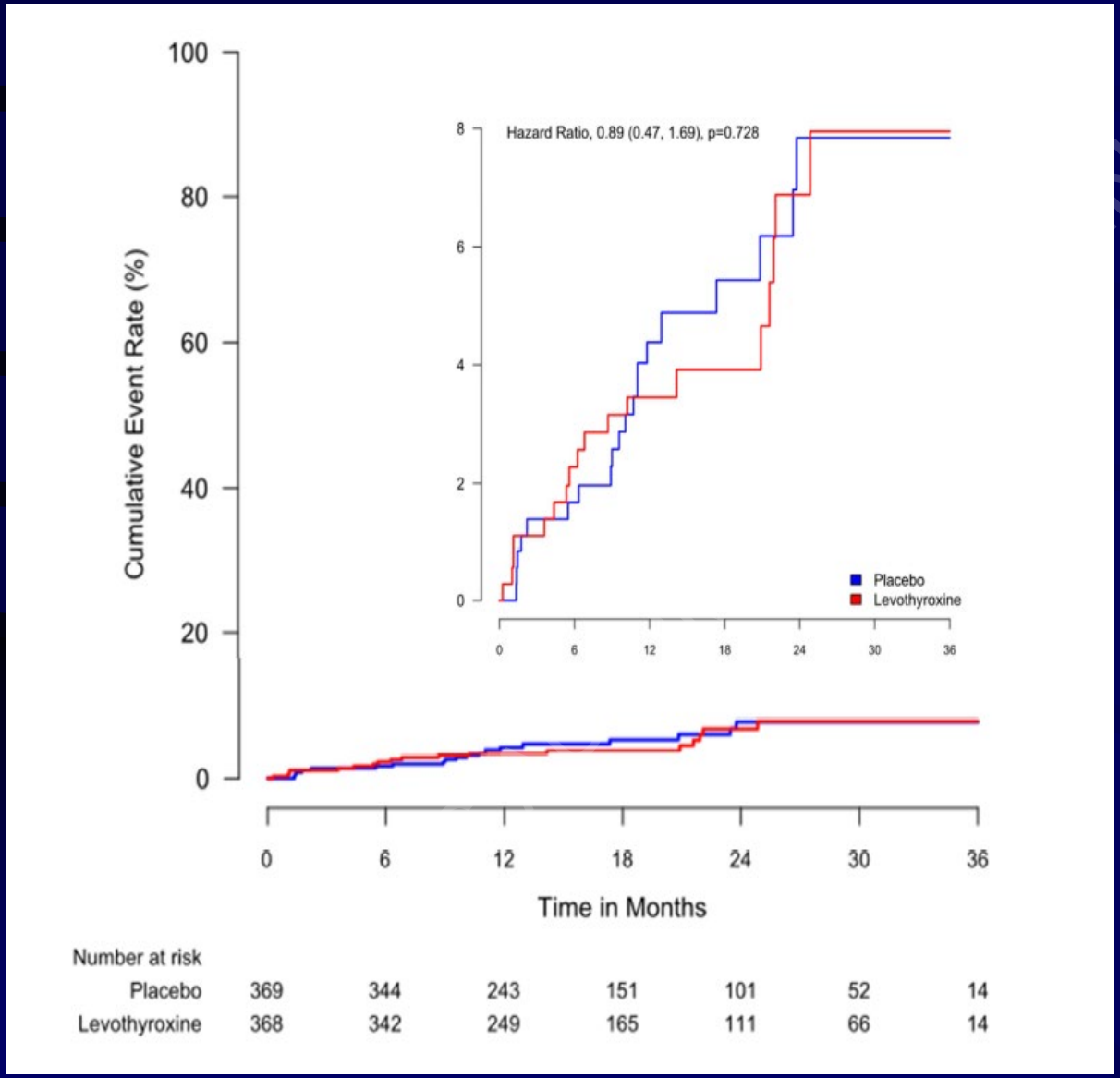
- Statistically significant deterioration with levothyroxine in EQ5D at 12 months
  - Those with worse EQ5D at baseline appear to do worst with levothyroxine
- Statistically significant improvement with levothyroxine in EQ5D at extended follow-up (24.4 months)
- May be chance findings
- Magnitude of effect very small - clinically not relevant

No effects of levothyroxine observed on the following measures

- Secondary outcomes
  - ThyPRO39
  - Handgrip strength
  - Digit-symbol substitution
  - Cardiovascular events
  - Total and CVS mortality
  - Blood pressure
  - BMI, weight, waist circumference
  - Barthel index
  - IADL



Incident cardiovascular events



- Levothyroxine vs placebo
- HR 0.89
- 95%CI 0.47-1.69
- p=0.728

Adverse events of special interest

	Placebo n=369	Levothyroxine n=368	Treatment effect HR (95% CI)
New AF	13 (3.5%)	11 (3.0%)	0.80 (0.35, 1.80)
Heart failure	6 (1.6%)	3 (0.8%)	-
Fracture	8 (2.1%)	9 (2.4%)	1.06 (0.41, 2.76)
New osteoporosis	4 (1.1%)	3 (0.8%)	-

Modified intention to treat analysis

Summary of findings – RCT of levothyroxine versus placebo

- We recruited a large cohort of older patients with SCH
- Mean baseline TSH 6.40 (SD 2.01) mIU/L
- Levothyroxine (median dose 50μg) reduced TSH by approximately 2 mIU/ L
- No effect of levothyroxine on co-primary outcomes – ThyPRO Hypothyroid symptoms and Fatigue scores at 12m
- No consistent effect on generic HR-Qol (EuroQol5D/VAS)
- No effect on ThyPRO39, handgrip strength, digit symbol substitution, BP, weight, BMI, waist circumference
- No evidence of effect on cardiovascular events, ADL (Barthel) or Instrumental ADL
- No excess of adverse events of special interest, no increase in Hyperthyroid symptoms (ThyPRO)

DAILY RECORD 4/4/17

THYROID HORMONE 'USELESS'

Scots prof slams drug

THE third most prescribed drug in the UK is ineffective and should not be routinely issued, according to new research.

» MARK WAGHORN
reporters@dailyrecord.co.uk

Levothyroxine is a hormone tablet which replaces thyroxine – the chemical produced by the thyroid gland.

It is taken by thousands of older people suffering from underactive thyroid – known medically as hypothyroidism.

The condition can lead to constant tiredness, unexplained weight gain, lack of energy, depression, puffy face and feeling cold.

Hypothyroidism is badly under-diagnosed and when the gland functions below par or stops working completely, the symptoms can blight sufferers' lives.

But scientists now say treatment guidelines for a mildly underactive thyroid – which affects up to one in 10 older men and women – are outdated.

The drug levothyroxine is prescribed to nine in 10 women with the condition.

And a five-year European study, published in The New England Journal of Medicine, found that while levothyroxine did effectively restore a normal balance of thyroid function, it did not relieve symptoms.

Professor David Stott, of Glasgow University, said: "Treatment with levothyroxine is common in clinical practice, but controversial.

"Our study concludes this treatment provides no apparent benefits for older adults and should therefore no longer be started routinely for this condition."

Daily Record

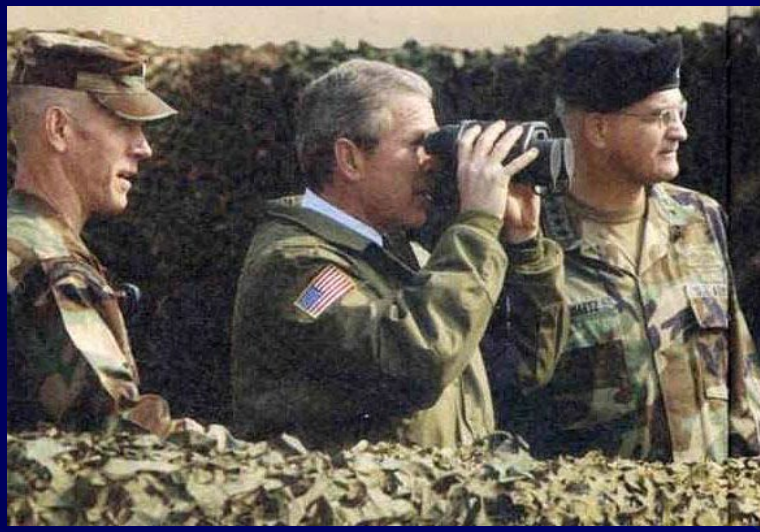
Conclusions

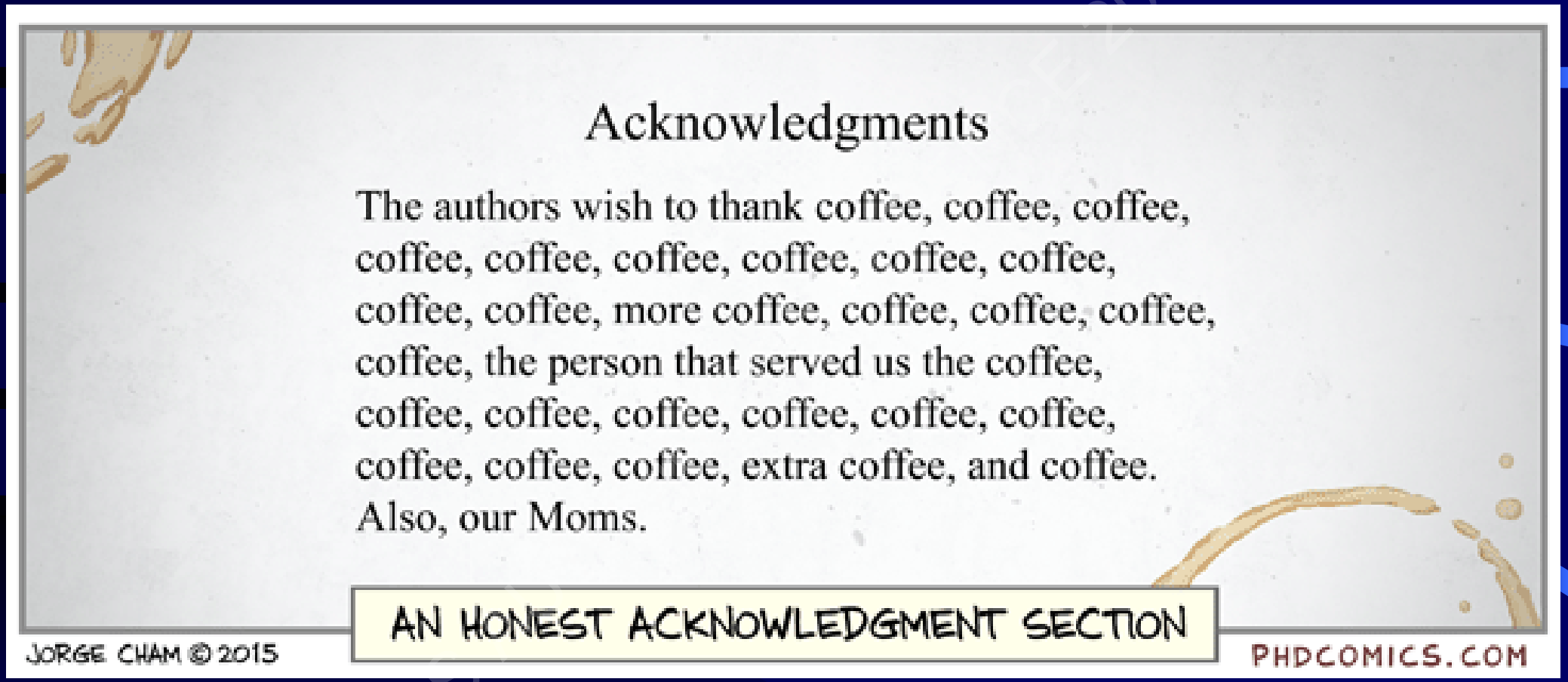
- Levothyroxine provided no symptomatic benefits for elderly patients with SCH
- Good statistical power to exclude benefit
- Range of secondary outcomes of clinical relevance

- Limitations
  - Few participants with baseline TSH >10mIU/L
  - Symptom levels low; cannot exclude possible benefit in persons with more marked complaints
  - Underpowered to detect effect on cardiovascular events or mortality

TRUST - looking to the future

- Collaboration with IEMO RCT over 80s
  - PI Simon Mooijaart
- Exploratory analyses
- Biobank studies
  - Thyroid autoantibodies
  - Lipids
  - Markers of bone turnover




Acknowledgments
The authors wish to thank coffee, coffee, coffee,
coffee, coffee, coffee, coffee, coffee, coffee,
coffee, coffee, more coffee, coffee, coffee, coffee,
coffee, the person that served us the coffee,
coffee, coffee, coffee, coffee, coffee, coffee,
coffee, coffee, coffee, extra coffee, and coffee.
Also, our Moms.
AN HONEST ACKNOWLEDGMENT SECTION
JORGE CHAM © 2015
PHDCOMICS.COM

Acknowledgements - PIs

TRUST THYROID TRIAL

- Principal investigators
  - David J Stott (CI)
  - Ian Ford
  - Jacobijn Gussekloo
  - Patricia Kearney
  - Nicolas Rodondi
  - Rudi GJ Westendorp
- IEMO 80+
  - Simon Mooijaart

University of Glasgow

LUMC Leiden University Medical Center

u b UNIVERSITÄT BERN

UCC Coláiste na hOllscoile Corcaigh, Éire University College Cork, Ireland

Leyden Academy ON VITALITY AND AGEING

Acknowledgements – TRUST Study Group

TRUST THYROID TRIAL

- Principal investigators
  - David J Stott (CI), Ian Ford, Jacobijn Gussekloo, Patricia Kearney, Nicolas Rodondi, Rudi Westendorp
- Co-investigators
  - Simon Mooijaart, Naveed Sattar, Carole Aubert, Draho Aujesky, Doug Bauer, Christine Baumgartner, Manuel Blum, John Browne, Stephen Byrne, Tinh-Hai Collet, Olaf Dekkers, Wendy den Elzen, Robert du Puy, Graham Ellis, Martin Feller, Carmen Floriani, Kirsty Hendry, Caroline Hurley, Wouter Jukema, Sharon Kean, Maria Kelly, Danielle Krebs, Peter Langhorne, Gemma McCarthy, Vera McCarthy, Alex McConnachie, Mairi McDade, Martina Messow, Anne-Marie O'Flynn, David O'Riordan, Rosalinde Poortvliet, Terry Quinn, Audrey Russell, Carol Sinnott, Jan Smit, Anette Van Dorland, Kieran Walsh, Elaine Walsh, Torquil Watt, Robbie Wilson
- Thyroid Federation International
  - Yvonne Andersson Lakwijk
- Data Monitoring Committee
  - Gary Ford (chair), Tom Robinson, Colin Dayan, Kathleen Bennett
- Endpoints Committee
  - Peter Langhorne (chair), Wouter Jukema, Tinh-Hai Collet, Olaf Dekkers, Anne Marie O'Flynn, Eleanor Dinnett
- Research Pharmacy
  - Elizabeth Douglas
- Other supporting staff
  - Lorna Gillespie, Paula McSkimming, Alan Stevenson, Charlotte Syme

University of Glasgow

LUMC Leiden University Medical Center

u b UNIVERSITÄT BERN

UCC Coláiste na hOllscoile Corcaigh, Éire University College Cork, Ireland

Leyden Academy ON VITALITY AND AGEING

Pre-planned secondary analyses

- Subgroups
  - Sex (female / male)
  - TSH
    - <10, ≥10 mIU/L
    - <7, 7-9.99, >10 mIU/L
- Exploratory and sensitivity analyses
  - Per-protocol analyses
  - Mixed effects models with multiple imputations for missing data

No significant effects of levothyroxine vs placebo were seen in any of these secondary analyses