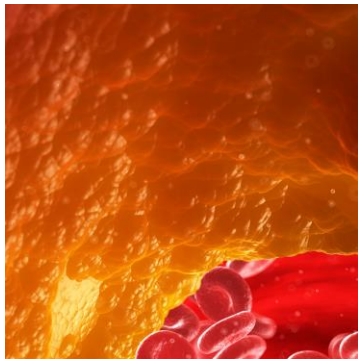
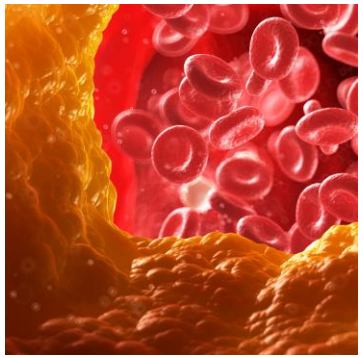
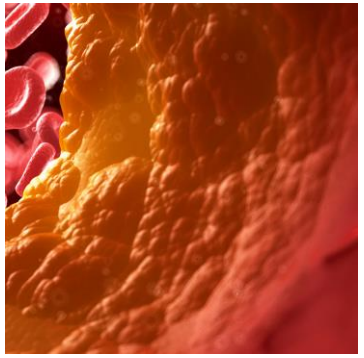
# The 2020 Digital learning journey on Thyroid disorders







SCIENTIFIC SEMINARS
INTERNATIONAL FOUNDATION

# Subclinical Hypothyroidism

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# Learning Objectives

1. Understand the definition and clinical implication of subclinical hypothyroidism

2. Apply a correct and personalized treatment approach to subclinical hypothyroidism

# Disclosure Statement

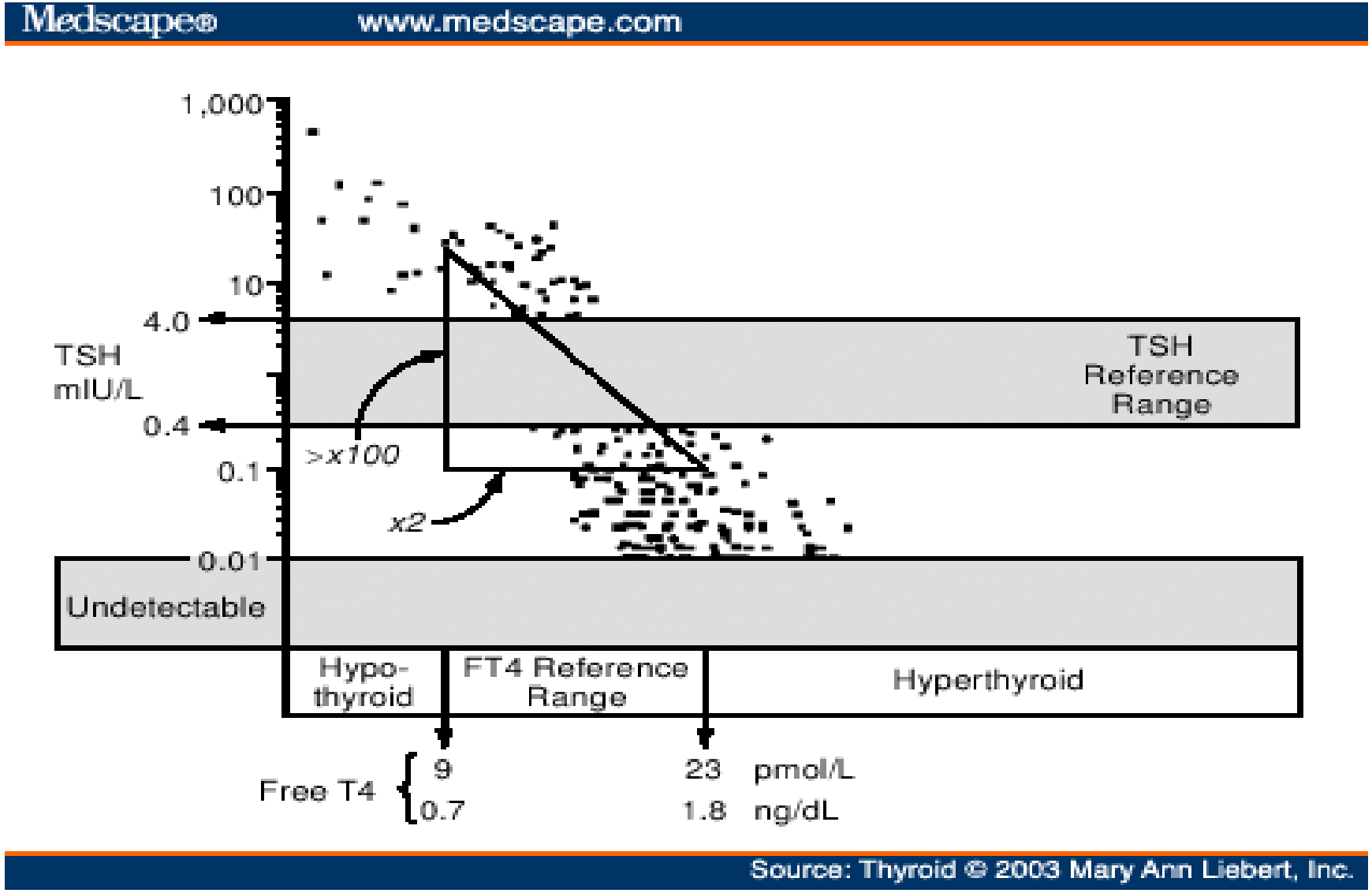
Dr Razvi has received speaker fees from Merck plc, Abbott Pharmaceuticals India Pvt. Ltd., and Berlin-Chemie plc, makers of thyroid hormone preparations.

# Definition of subclinical hypothyroidism

- Diagnosis is made purely on biochemical grounds with elevated serum thyrotropin (TSH) levels and normal thyroxine (T4) concentrations
- Levels of TSH are considered the best and most sensitive biomarker of an individual's thyroid status
- There exists an extremely sensitive relationship between TSH secretion and serum FT4 levels: for every 2-fold change in FT4 levels there is a 100-fold change in TSH secretion

Biondi B, et al. JAMA 2019;322(2):153–60.

# Log-linear relationship between TSH and T4

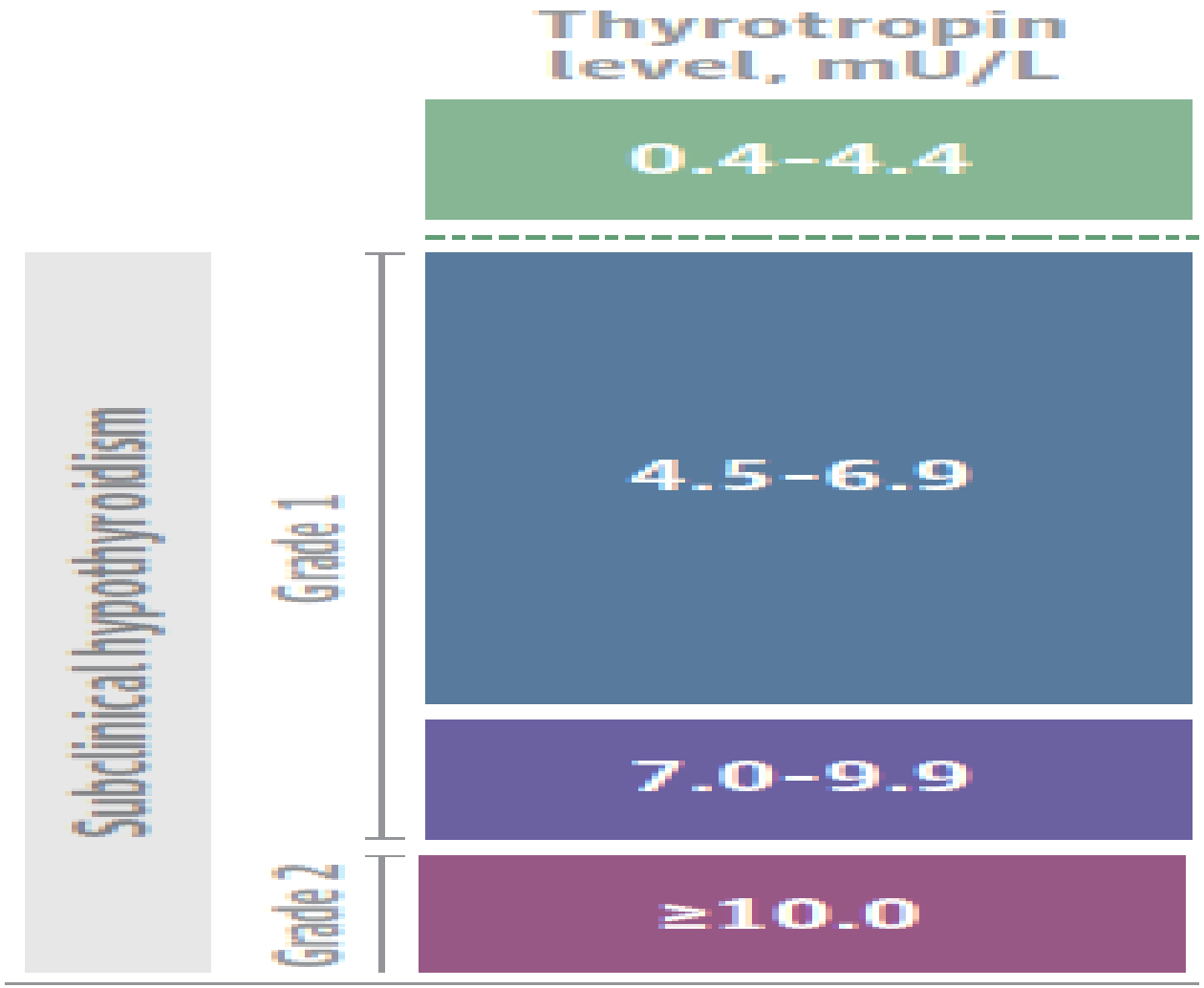


# Prevalence of subclinical hypothyroidism

- Affects approximately 10% of the population
- More common in:
  - Females
  - Older individuals
  - Those who are obese
  - Non-smokers
  - Those recovering from non-thyroidal illness
  - Those with iodine excess

Jonklaas J, Razvi S. Lancet Diabetes Endocrinol 2019;7(6):473–83.

# Grades of subclinical hypothyroidism



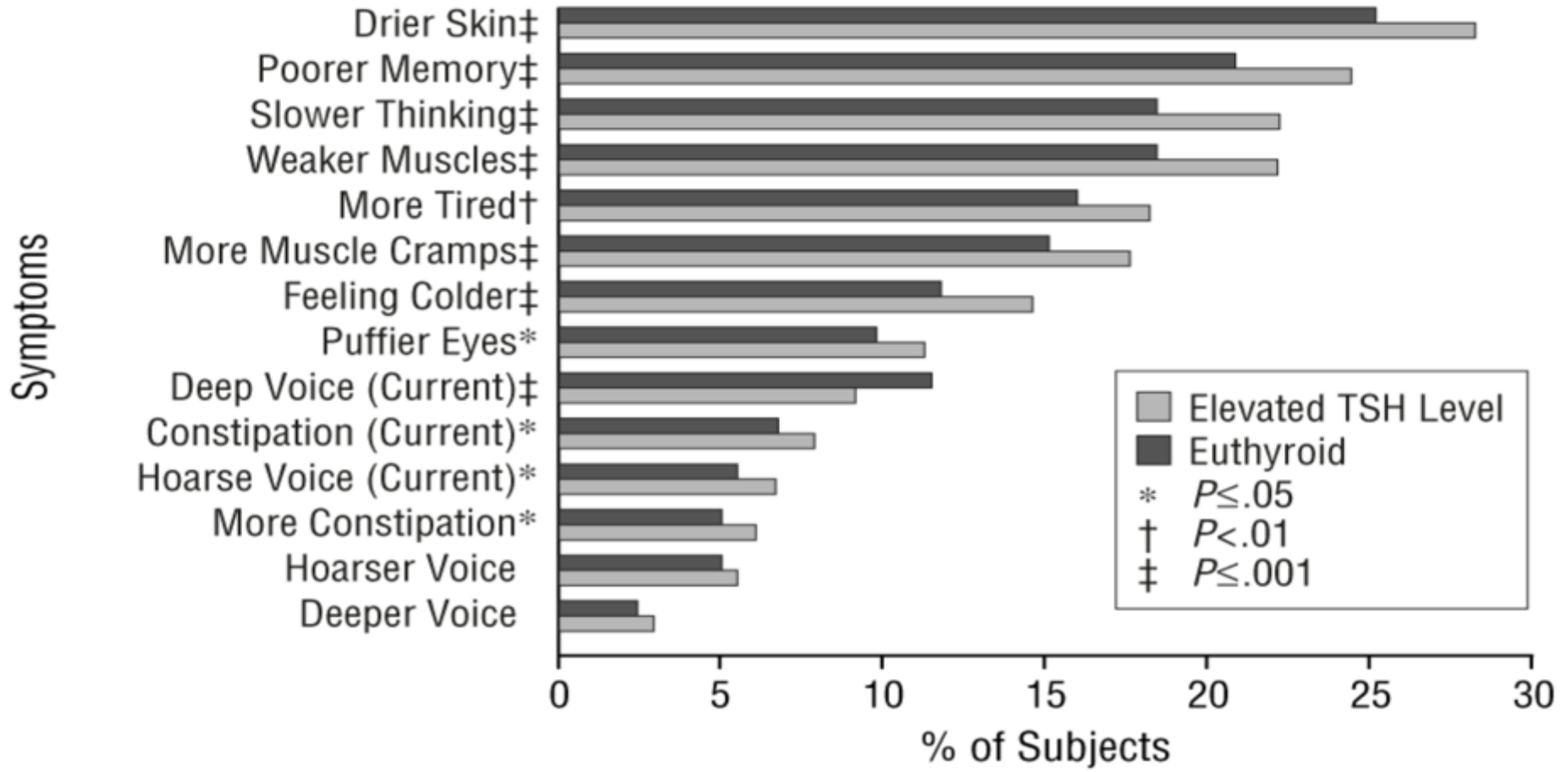

Peeters RP. N Engl J Med 2017;376(26):2556–65.

# Potential associations of subclinical hypothyroidism

- Symptoms of hypothyroidism
- Cognition and dementia
- Higher cardiovascular disease burden
- Progression to overt hypothyroidism
- Miscarriage and offspring’s IQ

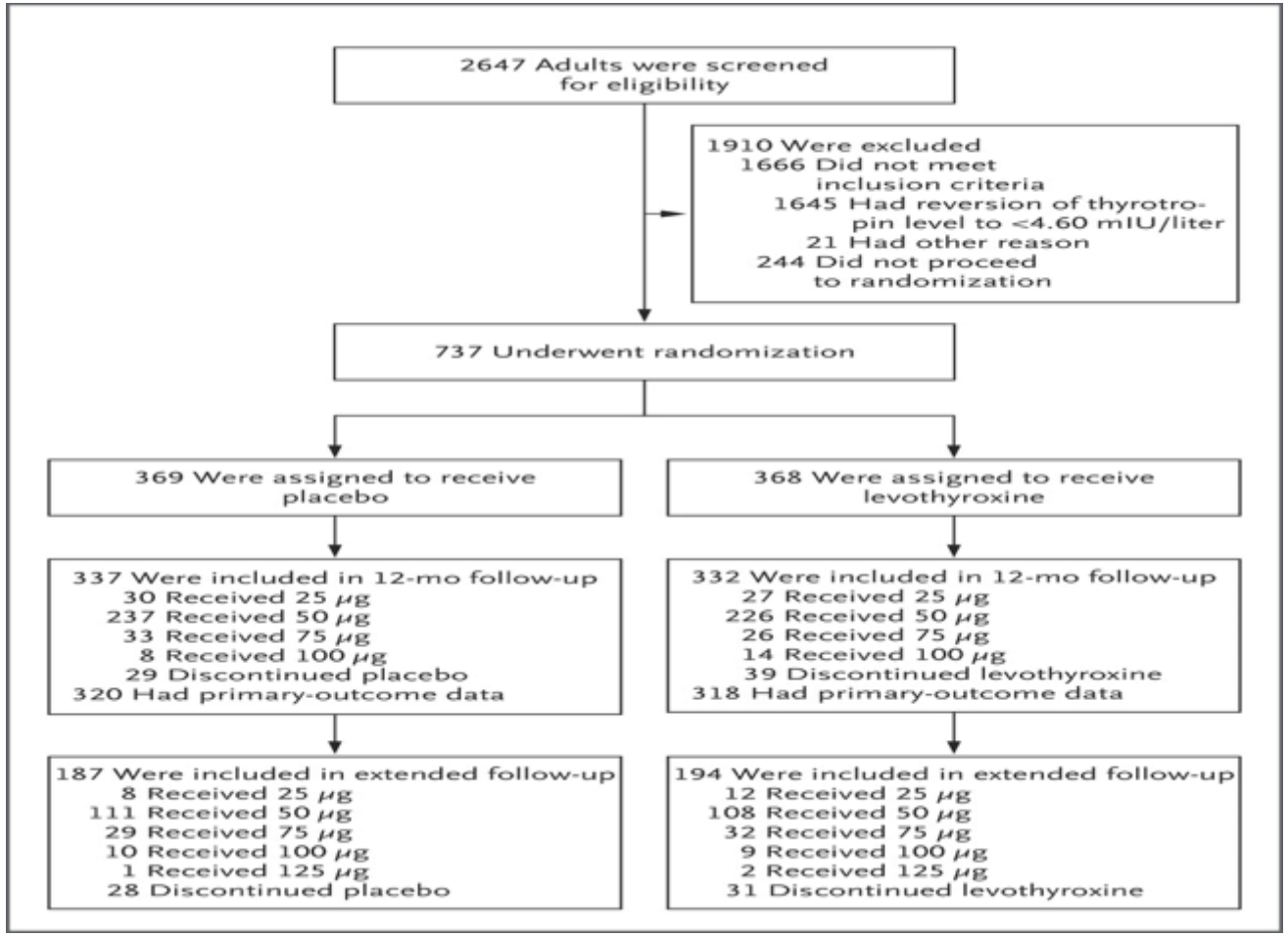
# Symptoms of subclinical hypothyroidism

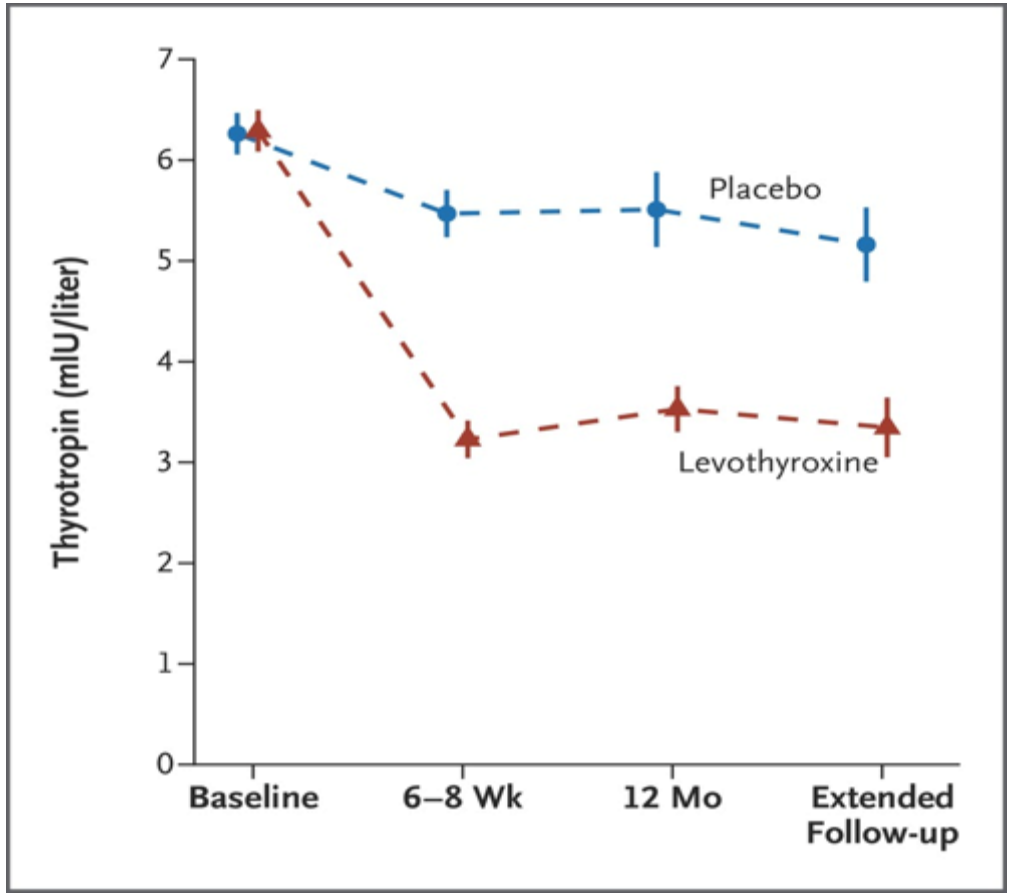
The percentage of euthyroid subjects compared with those with an elevated thyrotropin (TSH) level who reported each symptom




Canaris GJ, et al. Arch Intern Med 2000;160(4):526–34.

# Does treatment with levothyroxine improve symptoms in older people (65+) with subclinical hypothyroidism (TRUST trial)?




Stott DJ, et al. N Engl J Med 2017;376:2534–44.

# TRUST trial results

**Table 2. Outcomes at 12 Months and Extended Follow-up.***

| Variable | Baseline | | At 12 Mo | | | | At Extended Follow-up Visit† | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Placebo (N=369) | Levothyroxine (N=368) | Placebo (N=320) | Levothyroxine (N=318) | Difference (95% CI) | P Value | Placebo (N=187) | Levothyroxine (N=194) | Difference (95% CI) | P Value |
| Thyrotropin — mIU/liter | 6.38±2.01 | 6.41±2.01 | 5.48±2.48 | 3.63±2.11 | −1.92 (−2.24 to −1.59) | <0.001 | 5.28±2.50 | 3.47±2.08 | −1.88 (−2.32 to −1.45) | <0.001 |
| Median (IQR) | 5.76 (5.10 to 6.94) | 5.70 (5.12 to 6.83) | 4.90 (3.91 to 6.46) | 3.16 (2.45 to 4.22) | — | — | 4.94 (3.78 to 6.26) | 3.00 (2.26 to 4.16) | — | — |
| **Primary outcomes‡** | | | | | | | | | | |
| Hypothyroid Symptoms score | 16.9±17.9 | 17.5±18.8 | 16.7±17.5 | 16.6±16.9 | 0.0 (−2.0 to 2.1) | 0.99 | 15.2±15.9 | 17.9±9.1 | 1.0 (−1.9 to 3.9) | 0.50 |
| Tiredness score | 25.5±20.3 | 25.9±20.6 | 28.6±19.5 | 28.7±20.2 | 0.4 (−2.1 to 2.9) | 0.77 | 31.9±22.1 | 30.2±20.5 | −3.5 (−7.0 to 0.0) | 0.05 |
| **Secondary outcomes** | | | | | | | | | | |
| EQ-5D descriptive score | 0.847±0.171 | 0.846±0.187 | 0.853±0.191 | 0.833±0.212 | −0.025 (−0.050 to 0.000) | 0.05 | 0.829±0.209 | 0.864±0.188 | 0.040 (0.005 to 0.075) | 0.03 |
| EQ VAS score | 76.5±16.3 | 78.4±15.3 | 77.4±13.7 | 77.3±15.6 | −1.3 (−3.2 to 0.6) | 0.18 | 77.2±13.5 | 76.8±14.2 | −0.8 (−3.2 to 1.7) | 0.56 |
| Hand-grip strength — kg | 27.5±11.3 | 28.0±10.2 | 27.1±11.2 | 27.5±10.5 | −0.1 (−0.9 to 0.7) | 0.84 | 24.9±10.6 | 24.4±10.1 | −0.6 (−1.7 to 0.6) | 0.34 |
| Blood pressure — mm Hg | | | | | | | | | | |
| Systolic | 140.4±18.9 | 141.2±18.7 | 138.4±17.8 | 138.3±18.7 | 0.1 (−2.1 to 2.4) | 0.90 | 137.5±19.2 | 136.8±17.6 | 1.1 (−4.1 to 2.1) | 0.51 |
| Diastolic | 74.8±11.7 | 74.1±11.6 | 73.5±11.1 | 72.8±11.4 | −0.1 (−1.5 to 1.3) | 0.93 | 72.3±11.4 | 72.0±11.5 | 0.5 (−1.4 to 2.4) | 0.59 |
| Body-mass index | 27.7±4.6 | 28.1±5.3 | 27.7±4.6 | 27.9±5.1 | 0.0 (−0.2 to 0.2) | 0.89 | 27.2±4.5 | 27.9±4.9 | 0.2 (−0.1 to 0.5) | 0.30 |
| Waist circumference — cm | 97.5±12.8 | 98.5±13.6 | 96.8±13.1 | 98.0±13.2 | 0.4 (−0.4 to 1.3) | 0.34 | 96.0±13.8 | 97.6±13.4 | 0.3 (−0.9 to 1.5) | 0.66 |
| **Adverse symptom assessment** | | | | | | | | | | |
| Hyperthyroid Symptoms score§ | 10.5±11.2 | 10.5±11.2 | 10.3±11.3 | 10.5±10.8 | 0.6 (−0.7 to 1.9) | 0.35 | 9.8±11.0 | 11.1±11.7 | 0.7 (−1.2 to 2.5) | 0.46 |

Stott DJ, et al. N Engl J Med 2017;376:2534–44.

# Does treatment with levothyroxine improve hypothyroid symptoms in 80+ individuals?

**Table 2. Outcomes at 12 Months for Participants in a Study of the Association Between Levothyroxine Treatment and Thyroid-Related Symptoms Among Adults Aged 80 Years and Older With Subclinical Hypothyroidism**

| | Mean (SD) | | | | | |
|---|---|---|---|---|---|---|
| | Baseline | | 12 Months | | | |
| Outcomes | Levothyroxine | Placebo | Levothyroxine | Placebo | Adjusted Difference (95% CI)[a] | *P* Value |
| **Co-primary outcomes** | (n = 90) | (n = 122) | (n = 90) | (n = 122) | | |
| ThyPRO hypothyroid symptoms score[b] | 21.7 (19.5) | 19.8 (19.6) | 19.3 (18.2) | 17.4 (18.1) | 1.27 (−2.69 to 5.23) | .53 |
| ThyPRO tiredness score[b] | 25.2 (21.5) | 25.1 (19.5) | 28.2 (20.0) | 28.7 (19.9) | −0.10 (−4.51 to 4.31) | .96 |
| **Prespecified secondary outcomes** | | | | | | |
| Thyrotropin, mIU/L | 6.50 (1.80) (n = 90) | 6.20 (1.48) (n = 116) | 3.69 (1.81) (n = 90) | 5.49 (2.21) (n = 116) | −1.97 (−2.49 to −1.45) | <.001 |
| EuroQol-5D[c] | 0.785 (0.199) (n = 90) | 0.811 (0.210) (n = 122) | 0.754 (0.268) (n = 90) | 0.785 (0.244) (n = 122) | −0.012 (−0.063 to 0.039) | .64 |
| EuroQol VAS[d] | 75.27 (14.59) (n = 90) | 73.98 (14.26) (n = 122) | 74.16 (13.67) (n = 90) | 73.67 (13.58) (n = 122) | −0.42 (−3.57 to 2.72) | .79 |
| Handgrip strength, kg | 25.4 (9.4) (n = 81) | 24.7 (10.2) (n = 114) | 23.4 (9.7) (n = 81) | 23.0 (9.2) (n = 114) | −0.27 (−1.79 to 1.25) | .73 |
| Blood pressure, mm Hg | (n = 90) | (n = 122) | (n = 90) | (n = 122) | | |
| Systolic | 144.4 (19.4) | 146.2 (20.7) | 141.3 (19.0) | 142.6 (20.7) | −0.42 (−5.23 to 4.39) | .86 |
| Diastolic | 71.3 (11.8) | 72.3 (12.3) | 68.7 (11.9) | 69.6 (12.5) | −0.31 (−3.06 to 2.44) | .83 |
| Weight | 76.5 (13.1) (n = 90) | 75.1 (12.3) (n = 121) | 76.2 (12.7) (n = 90) | 73.9 (12.3) (n = 121) | 0.97 (0.11 to 1.82) | .03 |
| Body mass index | 27.7 (4.4) (n = 90) | 27.5 (3.9) (n = 121) | 27.6 (4.4) (n = 90) | 27.1 (3.9) (n = 121) | 0.38 (0.08 to 0.68) | .01 |
| Waist circumference, cm | 99.0 (11.6) (n = 90) | 98.0 (10.9) (n = 121) | 99.0 (11.4) (n = 90) | 96.5 (11.7) (n = 121) | 1.52 (0.09 to 2.95) | .04 |

Mooijaart SP, et al. JAMA 2019;322(20):1–11.

# Does treatment with levothyroxine improve symptoms and quality of life in younger people with subclinical hypothyroidism?

TABLE 4. The effect of treatment with L-thyroxine *vs.* placebo on QoL[a]

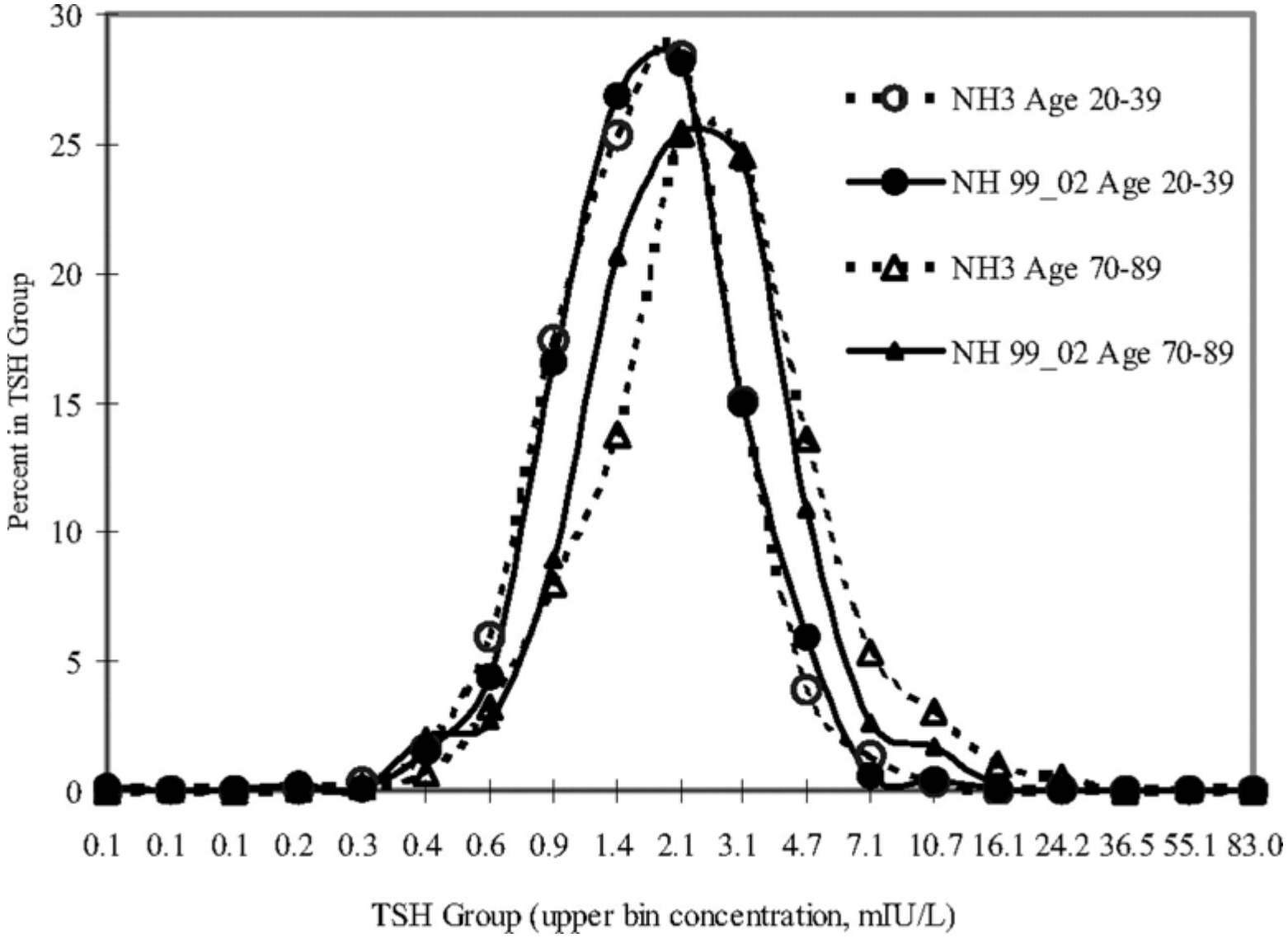
| Questionnaire (ThyDQoL) | All patients (n = 100) | | | | | Discordant TFTs excluded (n = 71) | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | L-thyroxine (SD) | Placebo (SD) | Adjusted difference (95% CI)[b] | *P* value | Corrected *P* value[c] | L-thyroxine (SD) | Placebo (SD) | Adjusted difference (95% CI)[b] | *P* value | Corrected *P* value[c] |
| T-QoL | −1.1 (1) | −1.2 (0.9) | 0.2 (0.02 to 0.36) | 0.04 | 0.24 | −1 (0.9) | −1.2 (1) | 0.3 (0.08 to 0.52) | 0.01 | 0.06 |
| Sex life | −2.3 (2.7) | −2.7 (2.8) | 0.3 (0.02 to 0.7) | 0.03 | 0.18 | −1.9 (2.6) | −2.4 (2.9) | 0.3 (0.05 to 0.7) | 0.01 | 0.06 |
| Motivation | −3.6 (2.7) | −3.7 (2.7) | 0.4 (−0.4 to 0.9) | 0.16 | | −3.1 (2.8) | −3.8 (2.8) | 0.9 (0.1 to 1.7) | 0.009 | 0.05 |
| Worries about future | −2.5 (3) | −2.8 (2.9) | 0.2 (−0.2 to 0.7) | 0.23 | | −2 (2.9) | −2.6 (3) | 0.4 (−0.2 to 1.1) | 0.07 | |
| AWI-18 | −2.7 (2.4) | −2.8 (2.3) | 0.1 (−0.3 to 0.5) | 0.45 | | −2.3 (2.3) | −2.7 (2.3) | 0.3 (0.01 to 0.6) | 0.01 | 0.06 |

Razvi S, et al. J Clin Endocrinol Metab 2007;92(5):1715–23.

# Why don’t symptoms of hypothyroidism improve in older people with levothyroxine, but may improve in younger ones?

- Symptoms are non-specific and may be unrelated
- Higher TSH level in older people is physiological
- The TSH may have been transiently elevated
- The majority of trials did not specifically recruit patients with grade II subclinical hypothyroidism

# Aging and TSH




Surks MI and Hollowell JG. J Clin Endocrinol Metab 2007;92(12):4575–82.

# Does treatment with levothyroxine improve cognitive function in older people (65+) with subclinical hypothyroidism?

**TABLE 4.** Depression and cognitive function scores over time

| | | | 6 months | | | | 12 months | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Score | Group | Baseline, mean (SE) | n | Mean (SE) | Adjusted[a] mean (SE) | Group difference between adjusted means (95% CI) | n | Mean (SE) | Adjusted[a] mean (SE) | Group difference between adjusted means (95% CI) | *P* value[b] |
| HADS | $T_4$ | 3.38 (0.37) | 49 | 3.92 (0.40) | 3.78 (0.27) | 0.28 (−0.56–1.11) | 49 | 3.61 (0.36) | 3.55 (0.27) | 0.18 (−0.64–1.00) | 0.82 |
| | Placebo | 2.88 (0.45) | 33 | 3.18 (0.43) | 3.50 (0.32) | | 36 | 3.31 (0.47) | 3.37 (0.31) | | |
| MEAMS | $T_4$ | 11.72 (0.13) | 46 | 11.67 (0.07) | 11.56 (0.09) | −0.02 (−0.32–0.27) | 46 | 11.78 (0.07) | 11.67 (0.09) | 0.07 (−0.21–0.36) | 0.57 |
| | Placebo | 11.21 (0.16) | 32 | 11.47 (0.16) | 11.58 (0.11) | | 36 | 11.44 (0.20) | 11.60 (0.11) | | |
| MMSE | $T_4$ | 28.26 (0.30) | 48 | 28.90 (0.19) | 29.00 (0.38) | 1.19 (0.01–2.36) | 46 | 28.28 (0.29) | 28.24 (0.38) | 0.03 (−1.12–1.17) | 0.18 |
| | Placebo | 28.17 (0.36) | 33 | 27.82 (0.91) | 27.82 (0.45) | | 36 | 28.25 (0.37) | 28.22 (0.43) | | |
| SCOLP | $T_4$ | 1.91 (0.46) | 49 | 1.43 (0.38) | 1.04 (0.30) | 0.21 (−0.71–1.14) | 49 | 1.69 (0.43) | 1.29 (0.30) | −0.44 (0.46–1.36) | 0.59 |
| | Placebo | 0.71 (0.57) | 33 | 0.39 (0.54) | 0.82 (0.36) | | 36 | 0.22 (0.58) | 0.84 (0.35) | | |
| Trail Making A | $T_4$ | 45.72 (2.32) | 49 | 47.65 (3.28) | 46.54 (2.62) | −3.33 (−11.39–4.73) | 48 | 44.52 (2.62) | 45.33 (2.63) | −1.44 (−9.42–6.53) | 0.52 |
| | Placebo | 50.29 (2.81) | 33 | 49.00 (4.82) | 49.87 (3.11) | | 36 | 46.97 (3.55) | 46.78 (3.05) | | |
| Trail Making B | $T_4$ | 110.57 (15.89) | 49 | 106.61 (8.73) | 104.24 (7.71) | −14.00 (−37.83–9.82) | 48 | 96.67 (9.62) | 100.65 (7.75) | −13.46 (−37.15–10.22) | 0.95 |
| | Placebo | 131.46 (19.72) | 32 | 119.13 (18.56) | 118.24 (9.21) | | 34 | 108.38 (14.12) | 114.11 (9.07) | | |
| Trail Making B−A | $T_4$ | 65.76 (14.81) | 49 | 58.96 (6.42) | 57.97 (6.75) | −11.01 (−31.98–9.96) | 48 | 52.15 (6.53) | 54.55 (6.80) | −12.72 (−33.50–8.06) | 0.86 |
| | Placebo | 82.63 (18.38) | 32 | 70.31 (14.21) | 68.97 (8.14) | | 34 | 63.76 (11.72) | 67.27 (7.97) | | |

[a] Adjusted by baseline score.

[b] Group by time interaction.

Parle J, et al. J Clin Endocrinol Metab 2010;95(8):3623–32.

# Cardiovascular association

Increased incidence of myocardial infarction in some population-based studies

## Rotterdam (women >55 years)

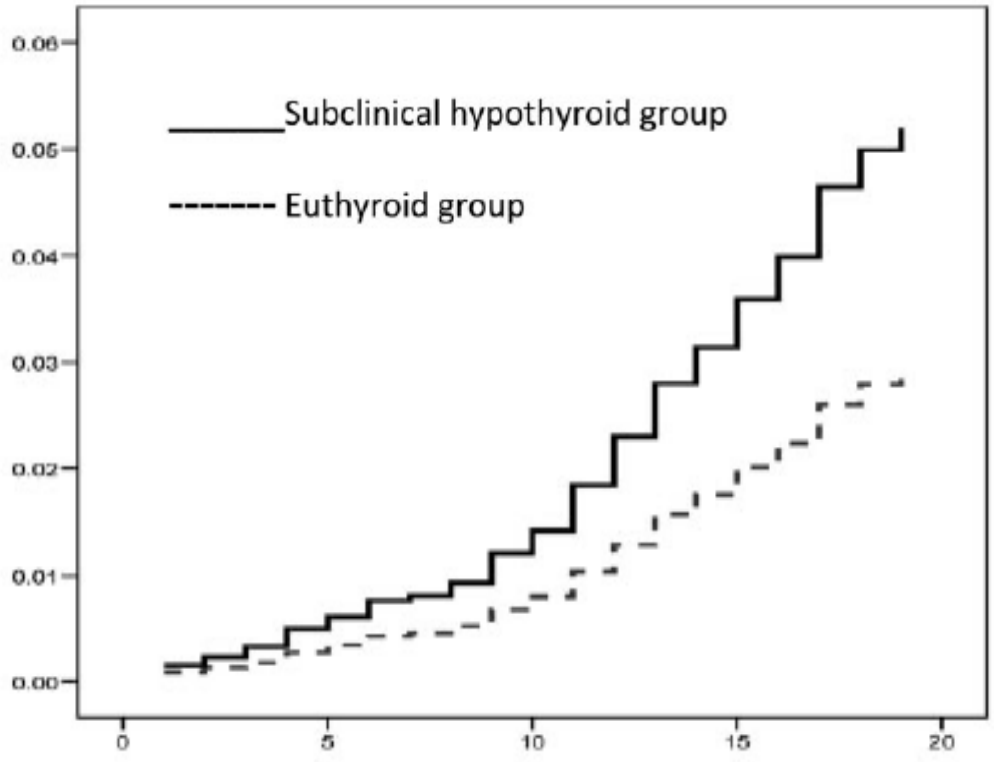
**Table 4. Attributable Risk Percentages and Population Attributable Risk Percentages for Subclinical Hypothyroidism and Classic Risk Factors for Cardiovascular Disease Associated with Incident Myocardial Infarction in Women in the Rotterdam Study**

| Risk Factor | Age-Adjusted Relative Risk* | Attributable Risk | Population Attributable Risk |
|---|---|---|---|
| | | % | |
| Subclinical hypothyroidism | 2.5 | 60 | 14 |
| Hypercholesterolemia | 2.4 | 58 | 18 |
| Hypertension | 1.6 | 38 | 14 |
| Smoking | 2.0/1.2† | 50/17‡ | 15 |
| Diabetes mellitus | 2.4 | 58 | 14 |

* Determined by using Cox proportional hazards regression analysis.
† Age-adjusted relative risk and attributable risk percentage for current compared with never smokers.
‡ Age-adjusted relative risk and attributable risk percentage for past compared with never smokers.

Hak AE, et al, Ann Intern Med 2000;132(4):270–8.

## Whickham (men and women followed-up for 20 years)




Razvi S, et al. J Clin Endocrinol Metab 2010;95(4):1734–40.

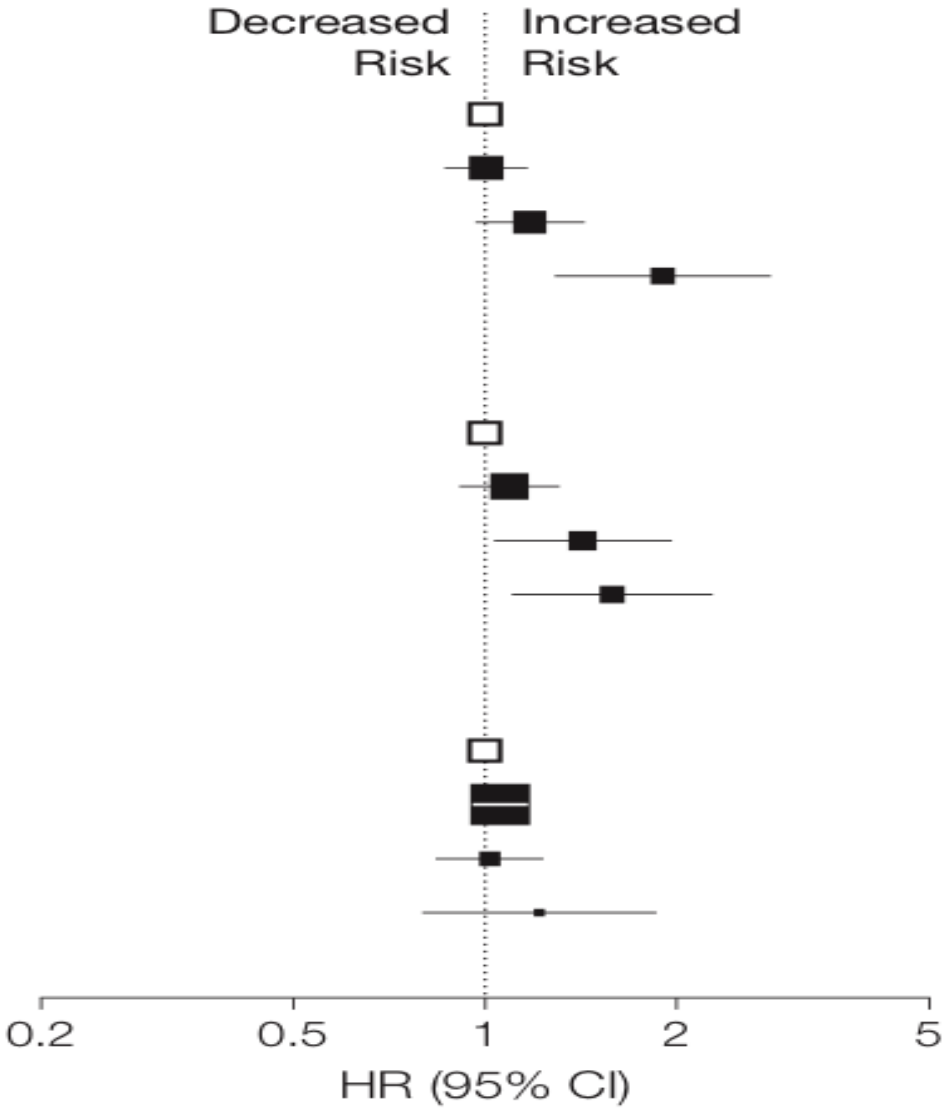
# Patient level meta-analysis looking at the association between subclinical hypothyroidism and cardiovascular disease

- 55,287 Participants
- 11 Studies
- 9664 Deaths; 2168 from coronary heart disease
- Subclinical hypothyroidism defined as TSH 4.5–19.99 mU/L with normal FT4 levels

Rodondi N, et al. JAMA 2010;304(12):1365–74.

# Patient level meta-analysis

| | HR Ratio (95% CI) |
|---|---|
| **CHD Events by TSH Level, mIU/L[b]** | |
| 0.5-4.49 | 1 [Reference] |
| 4.5-6.9 | 1.00 (0.86-1.18) |
| 7.0-9.9 | 1.17 (0.96-1.43) |
| 10-19.9 | 1.89 (1.28-2.80) |
| | *P*<.001 for trend |
| **CHD Mortality by TSH Level, mIU/L[c]** | |
| 0.5-4.49 | 1 [Reference] |
| 4.5-6.9 | 1.09 (0.91-1.30) |
| 7.0-9.9 | 1.42 (1.03-1.95) |
| 10-19.9 | 1.58 (1.10-2.27) |
| | *P* =.005 for trend |
| **Total Mortality by TSH Level, mIU/L[d]** | |
| 0.5-4.49 | 1 [Reference] |
| 4.5-6.9 | 1.06 (0.96-1.17) |
| 7.0-9.9 | 1.02 (0.84-1.24) |
| 10-19.9 | 1.22 (0.80-1.87) |
| | *P* =.39 for trend |

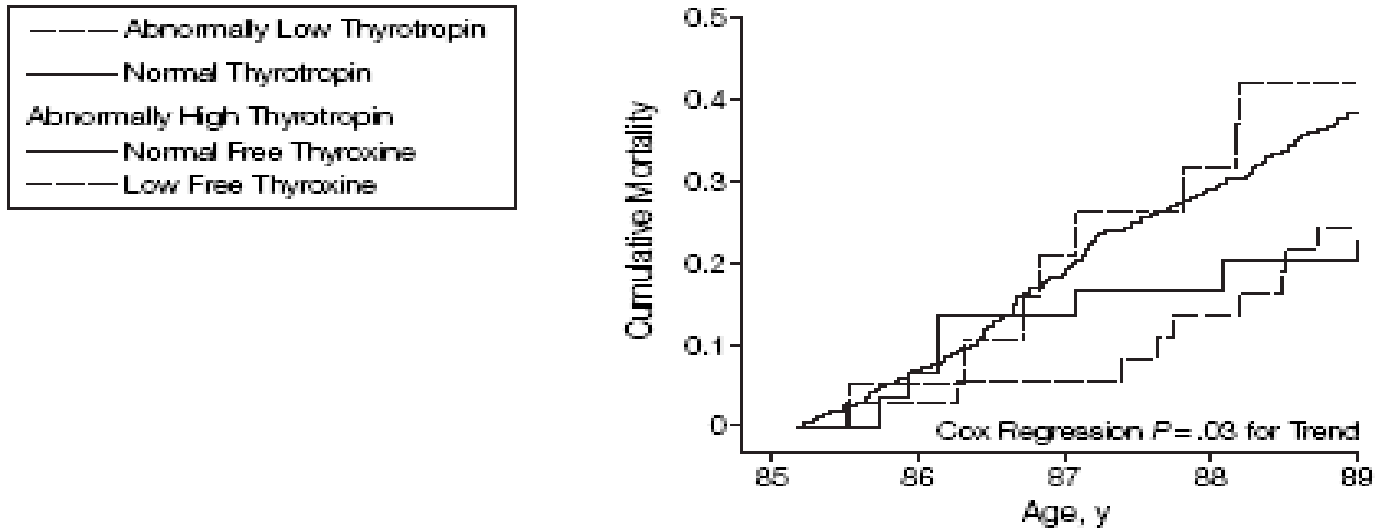



Rodondi N, et al. JAMA 2010;304(12):1365–74.

# Does treatment improve CV risk factors?

- Modest reduction in LDL cholesterol
- Improvement in endothelial function
- Reduction in carotid intima media thickness in younger but not older patients
- No effect on blood pressure
- No significant effect on weight

# Mortality in 85 year-old adults based on TSH at baseline

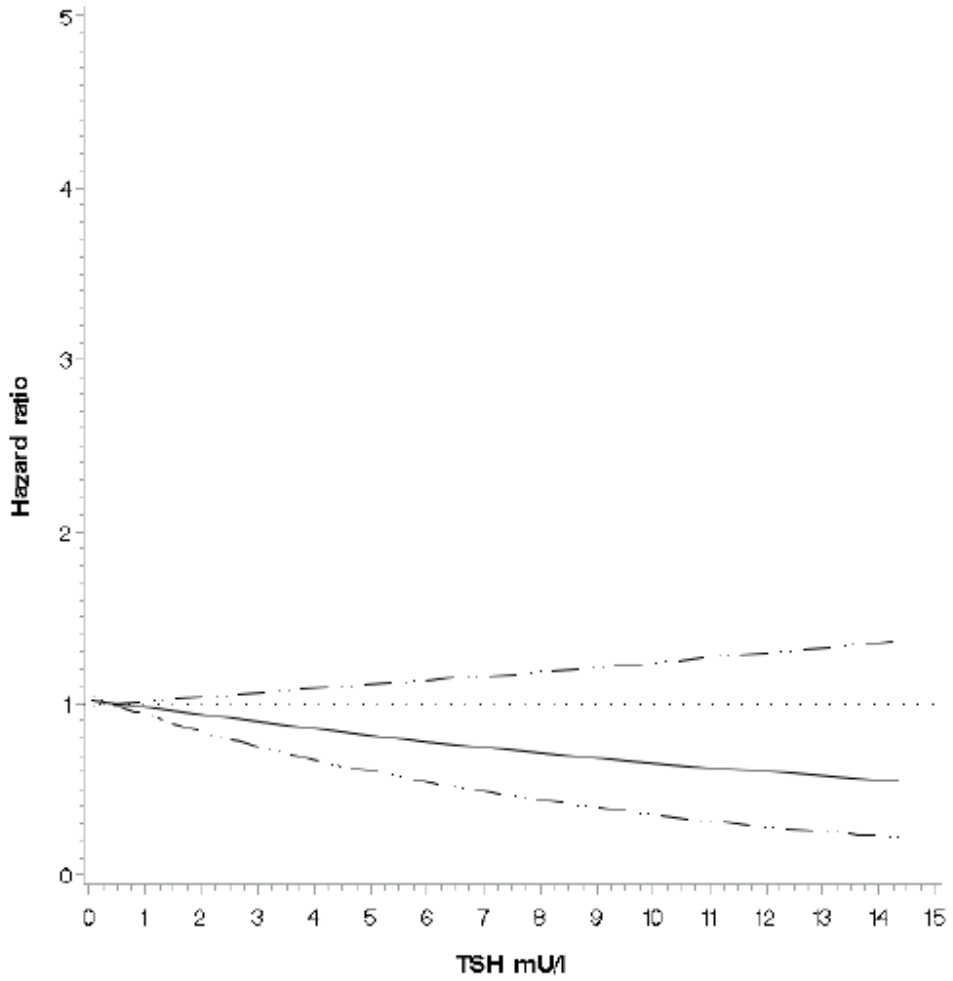


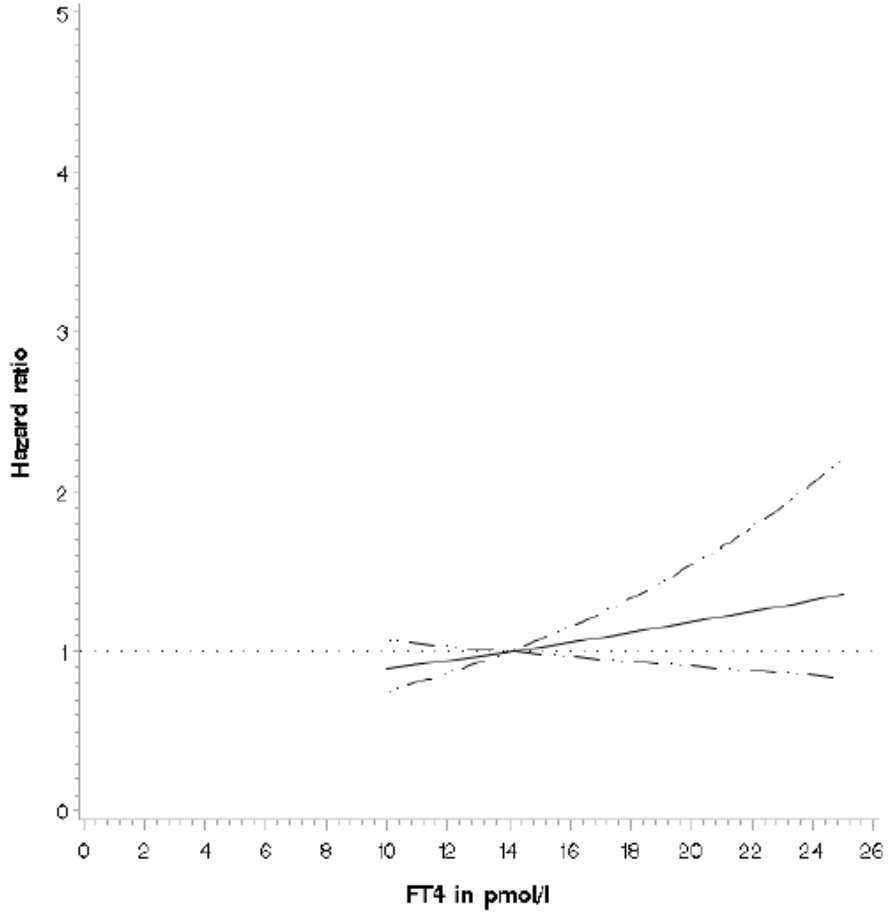

| | | | | | |
|---|---|---|---|---|---|
| Abnormally Low Thyrotropin | 19 | 18 | 15 | 13 | 11 |
| Normal Thyrotropin | 472 | 441 | 385 | 335 | 287 |
| Abnormally High Thyrotropin | | | | | |
| Normal Free Thyroxine | 30 | 28 | 26 | 25 | 23 |
| Low Free Thyroxine | 37 | 36 | 35 | 32 | 28 |

Plasma thyrotropin levels below 0.3 mIU/L were considered to be abnormally low; levels above 4.8 mIU/L were considered to be abnormally high. Plasma free thyroxine levels below 1.01 ng/dL (13 pmol/L) were considered to be abnormally low; levels between 1.01 and 1.79 ng/dL (13 and 23 pmol/L) were considered to be normal.

Gussekloo J, et al, JAMA 2004;292(21):2591–9.

# Newcastle 85+ study – all cause mortality




Pearce SH, et al. J Clin Endocrinol Metab 2016;101(11):4385–94.

# Summary for cardiovascular disease

- Associated with higher CV risk when TSH >10 mU/L
- May be associated with higher CV risk in younger (<65 years) people
- Very modest improvements in CV risk factors or surrogate markers with treatment
- Higher TSH in older people may not be detrimental and may even be beneficial

# Progression to overt hypothyroidism

- Risk is dependent on level of TSH increase (highest when TSH >10 mU/L)
- Risk is also higher in TPOAb positive individuals
- Rate of progression is variable and could take many years in some people
- Has to be balanced with the risk of spontaneous normalisation of TSH in a significant proportion of individuals

# Spontaneous normalisation of TSH over 12 months

**TABLE 3.** Thyroid function over time

| Group | Baseline | | 6 months | | | 12 months | | |
|---|---|---|---|---|---|---|---|---|
| | TSH [median, (IQR), range] | Free $T_4$ [median, (IQR), range] | TSH [median, (IQR), range] | Free $T_4$ [median, (IQR), range] | Proportion in euthyroid range | TSH [median, (IQR), range] | Free $T_4$ [median, (IQR), range] | Proportion in euthyroid range |
| $T_4$ | 6.6 (6–8.5), 5.6–28.9 | 12.9 (11.7–13.7), 9.4–16.8 | 4.0 (2.7–4.6), 0.8–20.6 | 15.4 (14.9–17.4), 9.5–19.4 | 82.2% | 3.7 (2.8–4.9), 0.2–6.9 | 16.2 (14.2–17.3), 12.8–24.8 | 84.4% |
| Placebo | 6.65 (5.9–8.3), 5.6–20.5 | 12.45 (11.4–13.2), 9.6–16.7 | 6.4 (5.0–8.5), 1.2–19.0 | 12.5 (11.2–14.2), 9.6–21.1 | 34.5% | 5.45 (3.9–9.2), 0.9–17.3 | 12.85 (11.4–14.4), 9.7–22.2 | 50.0% |

Significant difference in TSH level between the placebo and $T_4$ groups at both 6 and 12 months (Mann-Whitney *U* test $z = 5.1$, $P < 0.0001$; $z = 3.8$, $P = 0.0002$).

Parle J, et al. J Clin Endocrinol Metab 2010;95(8):3623–32.

# Miscarriage association

**Table 1.** Odds of Miscarriage by First-Trimester Serum TSH Level

| TSH, mU/L | Total, n | Miscarriages, n | Percentage Miscarried | Unadjusted Odds of Miscarriage | 95% CI | *P* Value[a] | Adjusted Odds of Miscarriage[b] | 95% CI[b] | *P* Value[a,b] |
|---|---|---|---|---|---|---|---|---|---|
| <0.2 | 36 | 6 | 16.7 | 0.97 | 0.37, 2.51 | | 1.14 | 0.62, 1.93 | |
| 0.2–2.5 | 199 | 34 | 17.1 | 1.00 | | .02# | 1.00 | | .008# |
| 2.51–4.5 | 151 | 29 | 19.2 | 1.15 | 0.66, 2.00 | | 1.09 | 0.61, 1.93 | |
| 4.51–10 | 122 | 32 | 26.2 | 1.73 | 1.00, 2.98 | | 1.80 | 1.03, 3.14 | |
| >10 | 41 | 17 | 41.5 | 3.44 | 1.66, 7.08 | | 3.95 | 1.87. 8.37 | |

There were 549 individuals in the model: 431 deliveries and 118 miscarriages. The reference category is the recommended first-trimester TSH: 0.2–2.5 mU/L.

[a] Test for trend comparing the odds of miscarriage by TSH levels above 2.5 mU/L to the reference category of 0.2–2.5 mU/L.

[b] Adjusted for age, calendar year of pregnancy, diabetes during or before pregnancy, and social class.

Taylor PN, et al. J Clin Endocrinol Metab 2014;99(10):3895–902.

# CAT trial

**Table 2. Standardized Full-Scale Child IQ and Scores on the Child Behavior Checklist (CBCL) and the Behavior Rating Inventory of Executive Function, Preschool Version (Brief-P), According to Study Group.***

| Test | Screening Group (N=390) | Control Group (N=404) | Difference (95% CI) (Control Group – Screening Group)† | P Value |
|---|---|---|---|---|
| IQ | | | | |
| Mean | 99.2±13.3 | 100.0±13.3 | 0.8 (–1.1 to 2.6) | 0.40 |
| <85 (% of children) | 12.1 | 14.1 | 2.1 (–2.6 to 6.7) | 0.39 |
| CBCL T score‡ | | | | |
| Mean | 44.4±12.4 | 45.1±13.6 | 0.7 (–1.2 to 2.5) | 0.49 |
| Brief-P T score§ | | | | |
| Median | 40 | 40 | 0 | 0.59 |
| Interquartile range | 47–55 | 47–55 | | |

Lazarus JH, et al. N Engl J Med 2012;366(6):493–501.

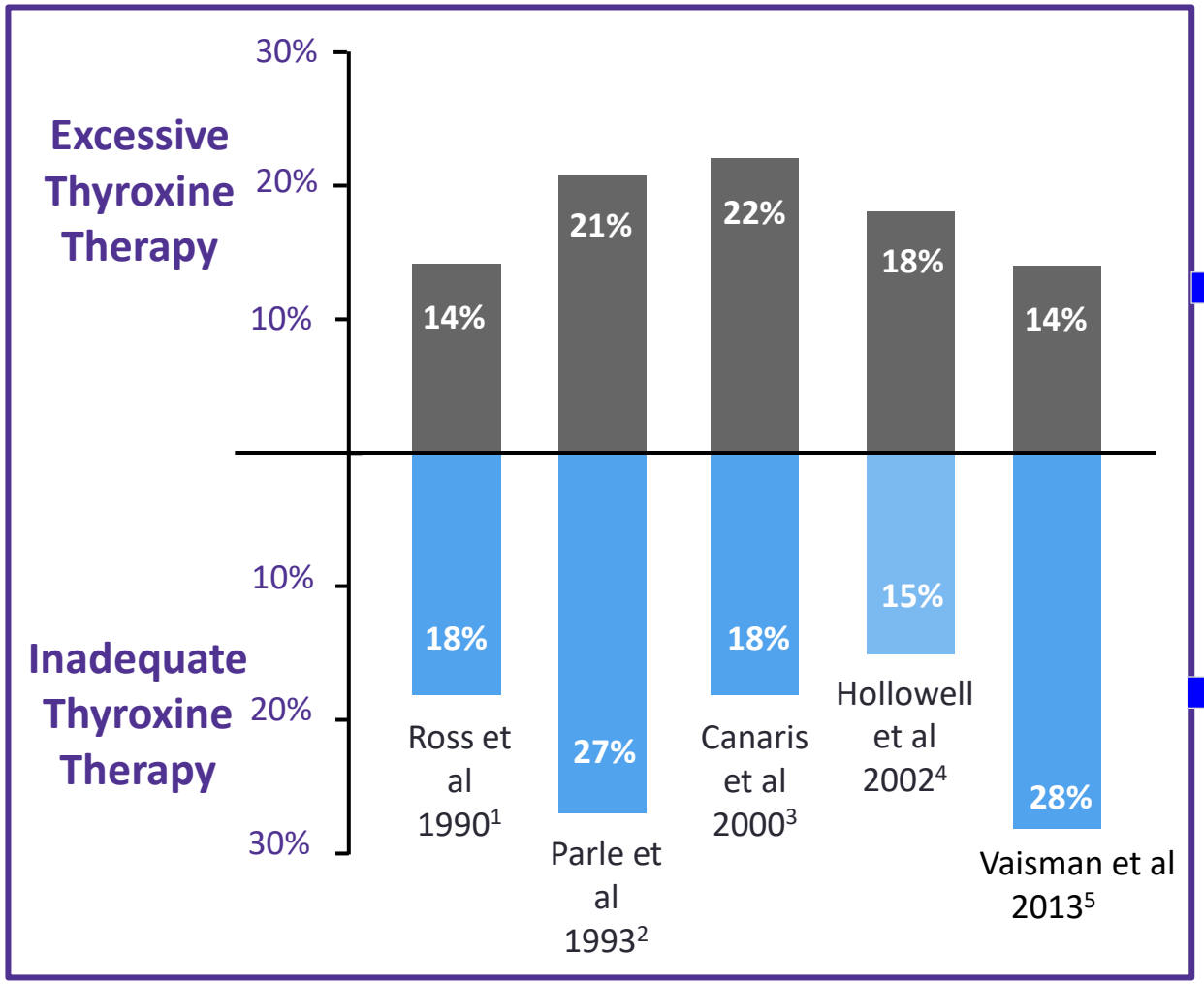
# Casey trial

**Table 2. Pregnancy and Neonatal Outcomes.***

| Outcome | Subclinical Hypothyroidism | | | Hypothyroxinemia | | |
|---|---|---|---|---|---|---|
| | Levothyroxine (N=339) | Placebo (N=338) | P Value | Levothyroxine (N=263) | Placebo (N=261) | P Value |
| **Maternal** | | | | | | |
| Week of gestation at delivery | 39.1±2.5 | 38.9±3.1 | 0.57 | 39.0±2.4 | 38.8±3.1 | 0.46 |
| Preterm birth — no. (%) | | | | | | |
| At <34 wk | 9 (3) | 10 (3) | 0.81 | 10 (4) | 7 (3) | 0.47 |
| At <37 wk | 31 (9) | 37 (11) | 0.44 | 31 (12) | 20 (8) | 0.11 |
| Placental abruption — no. (%) | 1 (<1) | 5 (1) | 0.12 | 3 (1) | 2 (1) | 1.00 |
| Gestational hypertension — no. (%) | 33 (10) | 36 (11) | 0.69 | 20 (8) | 24 (9) | 0.51 |
| Preeclampsia — no. (%) | 22 (6) | 20 (6) | 0.76 | 9 (3) | 11 (4) | 0.64 |
| Gestational diabetes — no. (%) | 25 (7) | 22 (7) | 0.66 | 21 (8) | 24 (9) | 0.62 |
| **Fetal or neonatal†** | | | | | | |
| Stillbirth or miscarriage — no. (%) | 4 (1) | 7 (2) | 0.36 | 2 (1) | 5 (2) | 0.28 |
| Neonatal death — no. (%) | 0 | 1 (<1) | 0.50 | 1 (<1) | 1 (<1) | 1.00 |

Casey BM, et al. N Engl J Med 2017;376(9):815–825.

# Risks of under- and over-treatment




- AF
- Osteoporosis

- Dyslipidemia (LDLc )
- Risk of atherosclerotic CVD
- Risk of congestive heart failure
- Risk of reversible cardiomyopathy

1. Ross DS, et al. J Clin Endocrinol Metab 1990;71(3):764-9. 2. Parle JV, et al. Br J Gen Pract 1993;43(368):107-9. 3. Canaris GJ, et al. Arch Intern Med 2000;160(4):526-34. 4. Hollowell JG, et al. J Clin Endocrinol Metab 2002;87(2):489-99. 5. Vaisman F, et al. J Endocrinol Invest 2013;36(7):485-8.

# ETA guidelines

European Thyroid Journal

Guidelines

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## 2013 ETA Guideline: Management of Subclinical Hypothyroidism

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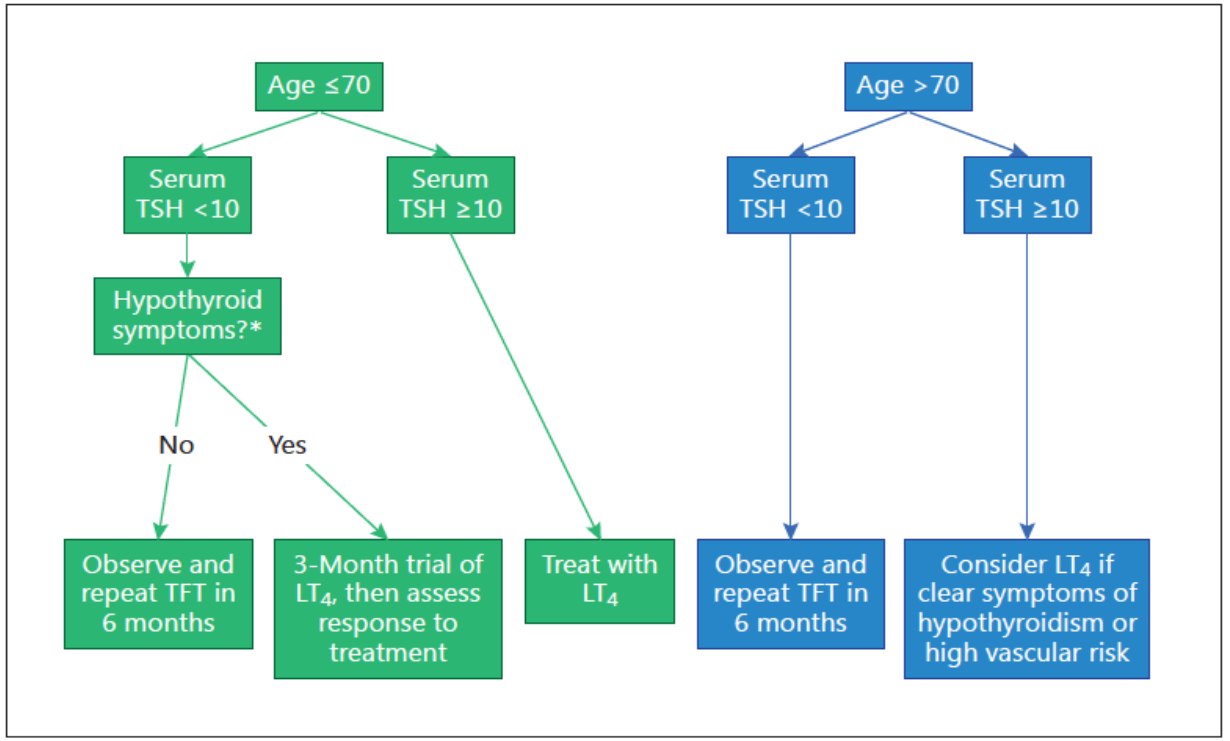


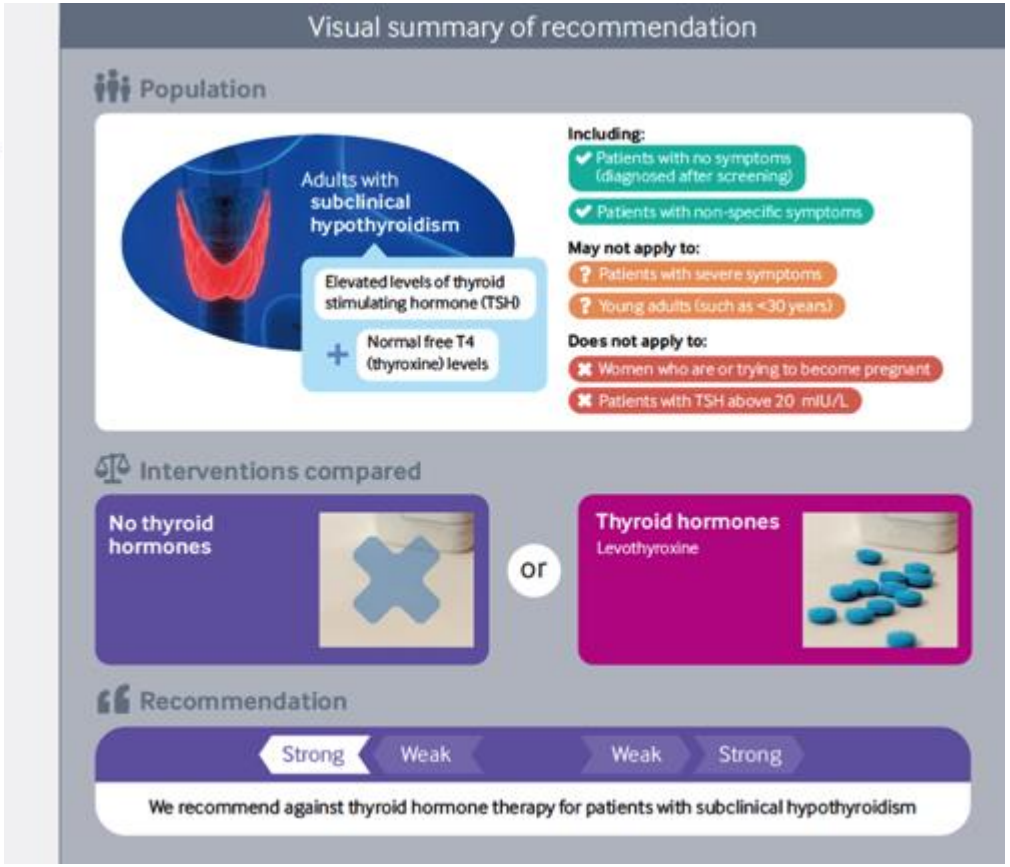
# Recent recommendations ……

thebmj

RAPID RECOMMENDATIONS

## Thyroid hormones treatment for subclinical hypothyroidism: a clinical practice guideline

G E Bekkering,[1 2] T Agoritsas,[3 4] L Lytvyn,[4] A F Heen,[5] M Feller,[6 7] E Moutzouri,[6 7] H Abdulazeem,[8] B Aertgeerts,[1 2] D Beecher,[9] JP Brito,[10] P D Farhoumand,[11] N Singh Ospina,[12] N Rodondi,[6 7] M van Driel,[13] E Wallace,[14] M Snel,[15] P M Okwen,[16] R Siemieniuk,[17] P O Vandvik,[18 19 20] T Kuijpers,[21] M Vermandere[1]




Bekkering GE et al, BMJ 2019;365:2006

# American Thyroid Association Pregnancy Guidelines

■ **RECOMMENDATION 29**

Subclinical hypothyroidism in pregnancy should be approached as follows:

(a) LT4 therapy is recommended for
- TPOAb-positive women with a TSH greater than the pregnancy-specific reference range (see Recommendation 1).

**Strong recommendation, moderate-quality evidence.**
- TPOAb-negative women with a TSH greater than 10.0 mU/L.

**Strong recommendation, low-quality evidence.**

(b) LT4 therapy may be considered for
- TPOAb-positive women with TSH concentrations >2.5 mU/L and below the upper limit of the pregnancy-specific reference range.

**Weak recommendation, moderate-quality evidence.**
- TPOAb-negative women and TPOAb-negative women with TSH concentrations greater than the pregnancy-specific reference range and below 10.0 mU/L.

**Weak recommendation, low-quality evidence.**

(c) LT4 therapy is not recommended for
- TPOAb-negative women with a normal TSH (TSH within the pregnancy-specific reference range or <4.0 mU/L if unavailable).

**Strong recommendation, high-quality evidence.**

Alexander EK, et al. Thyroid 2017;27(3):315–89.

# Starting therapy and monitoring treatment in elderly hypothyroid patients

- Most older (>65 years) patients with mildly raised serum TSH levels do not require treatment with LT4
- The initial starting dose should be between 50–75 mcg/day (and even lower in patients with existing ischemic heart disease)
- Serum TSH should be measured 6–8 weeks after starting therapy
- Aim should be to keep serum TSH within the reference range …maybe even towards the upper limit
- Once treatment is established, annual TSH checks are sufficient
- Avoid low or suppressed serum TSH levels

# Summary

- Subclinical hypothyroidism is common particularly in women and older people
- Most older people with mild subclinical hypothyroidism (TSH <10 mU/L) do not require treatment
- Subclinical hypothyroidism in pregnancy should be treated if TPOAb is positive or if TSH levels are >10 mU/L
- A personalised approach is required in managing individuals with subclinical hypothyroidism and several factors have to be considered, including age, level of TSH, and comorbidities
- When treatment is initiated, the aim should be to keep serum TSH levels within the reference range.


Newcastle University
Thank you for your attention