Latente Hypothreose im Alter

NICHT behandeln!

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Med. Univ. Wien

SD-Funktionsstörung Prävalenz

N = 75 076 Frauen, Follow up 28 Jahre

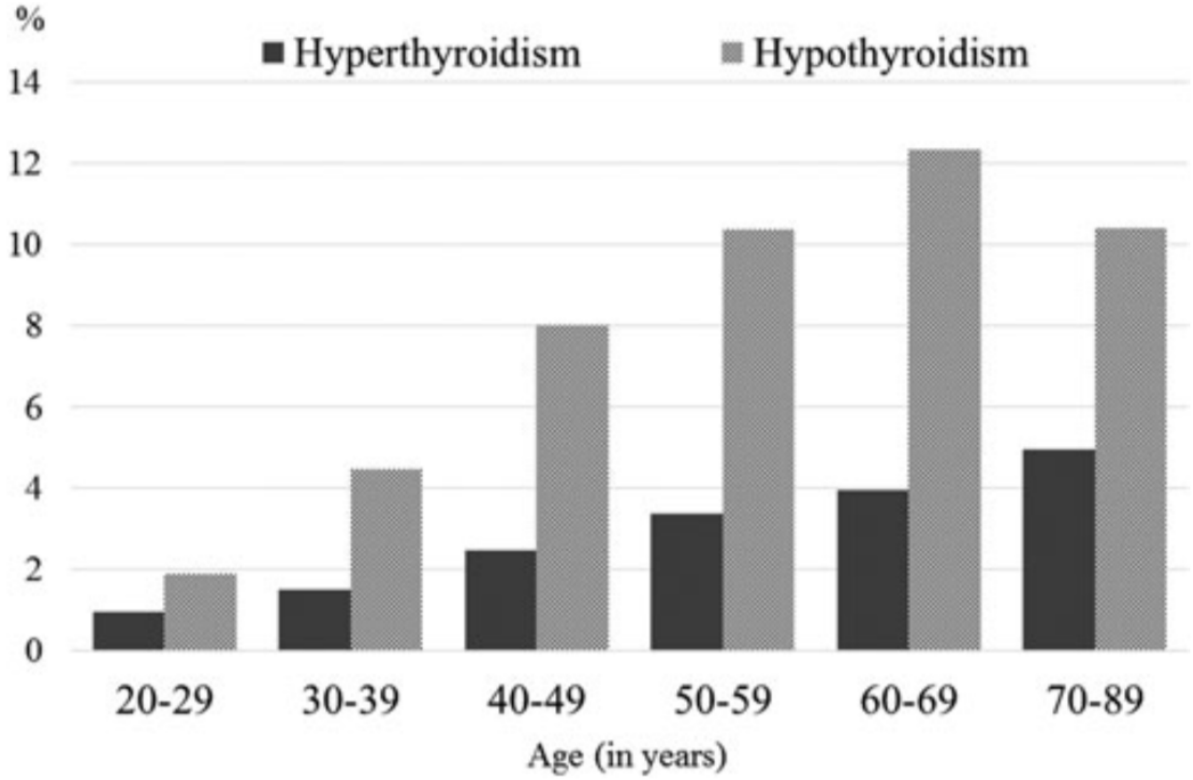


FIG. 1. Baseline prevalence of self-reported thyroid dysfunction by age group.

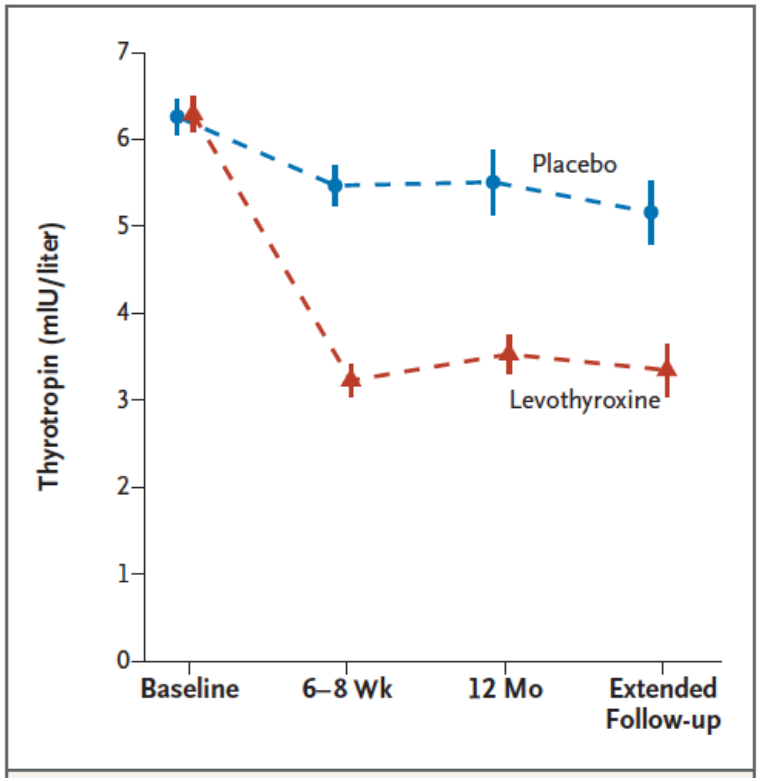
Journy et al., Thyroid 2017

Latente Hypothyreose:

Relevanz für den Patienten ?

T4 bei latenter Hypothyreose

N=737, >65 years, latente Hypothreose
(TSH 4.60 - 19.99 mIU per liter; fT4 normal).

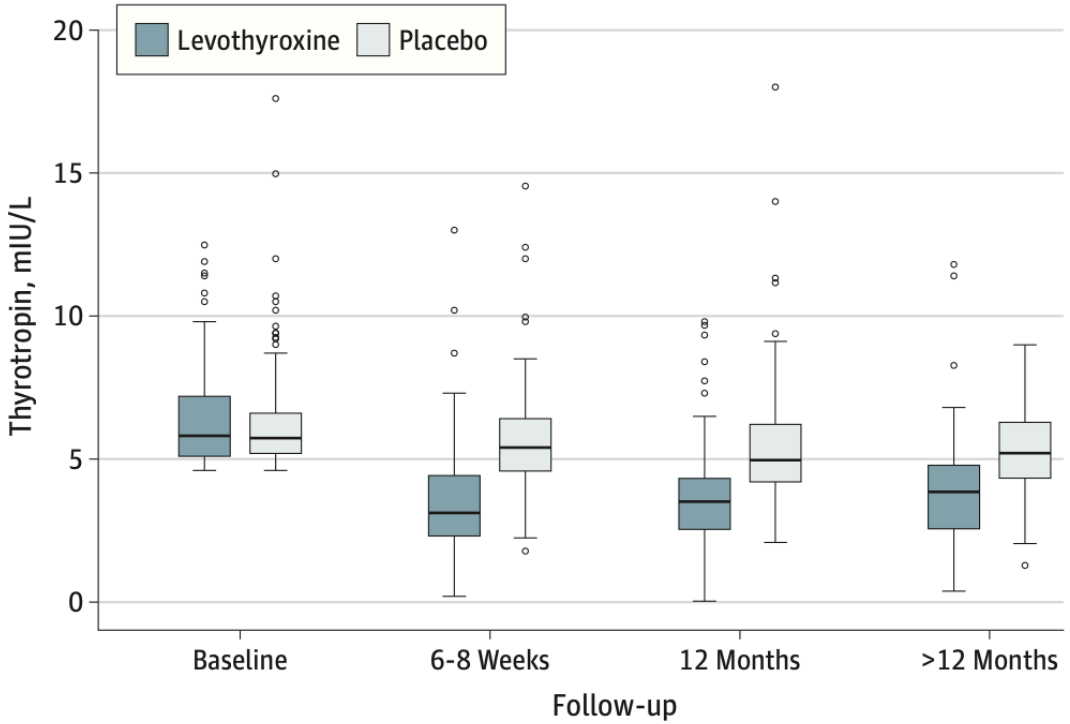


„We found no differences in the mean change at 1 year in the Hypothyroid Symptoms Score or the Tiredness score. No beneficial effects of levothyroxine were seen on secondary-outcome measures.“

Stott et al, NEJM, 2017

T4 bei latenter Hypothyreose

N = 112 T4; 139 Placebo, > 80 Jahre



No. of participants				
Levothyroxine	112	104	93	50
Placebo	139	129	117	58

Mooijaart et al, JAMA, 2019

T4 bei latenter Hypothyreose

Table 3. End-of-Study Outcomes 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		End of Study			
Prespecified Secondary Outcome	Levothyroxine	Placebo	Levothyroxine	Placebo	Adjusted Difference (95% CI)[a]	*P* Value
ThyPRO hypothyroid symptoms score[b]	22.2 (19.4) (n = 93)	19.9 (19.5) (n = 124)	19.9 (19.6) (n = 93)	18.2 (19.9) (n = 124)	−0.48 (−6.88 to 5.91)	.88
ThyPRO Tiredness score[b]	24.9 (21.4) (n = 93)	25.1 (19.4) (n = 124)	29.5 (18.2) (n = 93)	30.2 (23.3) (n = 124)	−0.77 (−7.07 to 5.54)	.81
EuroQol-5D[b]	0.777 (0.212) (n = 93)	0.812 (0.209) (n = 124)	0.763 (0.228) (n = 93)	0.806 (0.213) (n = 124)	−0.024 (−0.097 to 0.049)	.52
EuroQol VAS[b]	74.88 (14.68) (n = 93)	73.94 (14.20) (n = 123)	74.10 (11.97) (n = 93)	74.28 (14.32) (n = 123)	−1.60 (−6.16 to 2.96)	.49
Handgrip strength, kg[b]	24.9 (9.3) (n = 89)	24.1 (10.4) (n = 109)	19.4 (8.0) (n = 89)	21.8 (10.6) (n = 109)	−1.43 (−4.17 to 1.31)	.31
Letter-digit coding test[b]	22.0 (7.1) (n = 85)	21.9 (7.7) (n = 109)	21.6 (9.2) (n = 85)	20.5 (7.1) (n = 109)	1.24 (−0.30 to 2.78)	.11
Barthel index[b]	19.3 (1.5) (n = 91)	19.4 (1.2) (n = 117)	19.0 (1.9) (n = 91)	19.1 (2.1) (n = 117)	0.09 (−0.33 to 0.52)	.66
Instrumental activities of daily living[b]	13.3 (1.3) (n = 91)	13.2 (1.5) (n = 117)	12.4 (2.4) (n = 91)	12.7 (2.3) (n = 117)	−0.40 (−0.92 to 0.13)	.14

Abbreviation: ThyPRO, Thyroid-Related Quality of Life Patient-Reported Outcome; VAS, visual analog scale.

[a] Adjusted difference was estimated in linear mixed-effects regression models predicting change from baseline to end of the study with study site, sex, and intervention as stratification variables and study as random effect.

[b] For scale definitions see Table 1 footnotes.

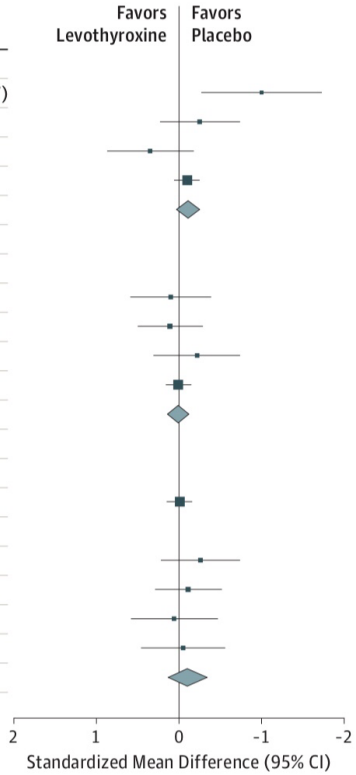
Mooijaart et al, JAMA, 2019

T4 Therapie Metaanalyse

Lebensqualität

Figure 1. Randomized Clinical Trials of Levothyroxine Therapy in Subclinical Hypothyroidism Quality-of-Life and Mood-Related Outcomes

Source	Quality of Life/Mood Scale	No. of Participants: Levothyroxine	No. of Participants: Placebo	Standardized Mean Difference (95% CI)	Weight, %
General quality of life					
Kong et al,[27] 2002	General Health Questionnaire at 6 mo	20	14	-1.00 (-1.73 to -0.27)	3.70
Jorde et al,[26] 2006	General Health Questionnaire at 12 mo	35	32	-0.25 (-0.74 to 0.23)	8.42
Reuters et al,[31] 2012	Short Form 36 at 6 mo	32	25	0.35 (-0.18 to 0.87)	7.02
Stott et al,[12] 2017	EQ-5D at 12 mo	318	320	-0.10 (-0.25 to 0.06)	80.86
Subtotal				-0.11 (-0.25 to 0.03)	100.00
Overall effect: $I^2 = 66.7\%$; $P = .03$					
Thyroid-related symptoms					
Meier et al,[22] 2001	Billewicz score at 12 mo	31	32	0.10 (-0.39 to 0.59)	7.34
Razvi et al,[32] 2007	ThyD QoL at 3 mo	100	100	0.11 (-0.29 to 0.50)	11.66
Reuters et al,[31] 2012	Zulewski score at 6 mo	32	25	-0.22 (-0.74 to 0.31)	6.52
Stott et al,[12] 2017	ThyPRO hyperthyroid score at 12 mo	318	320	0.01 (-0.15 to 0.16)	74.48
Subtotal				0.01 (-0.12 to 0.14)	100.00
Overall effect: $I^2 = 0.0\%$; $P = .79$					
Fatigue and tiredness					
Stott et al,[12] 2017	ThyPRO tiredness score at 12 mo	318	320	-0.01 (-0.16 to 0.15)	100.00
Depressive symptoms					
Jorde et al,[26] 2006	Beck Depression Inventory at 12 mo	35	32	-0.26 (-0.74 to 0.22)	24.09
Parle et al,[16] 2010	HADS at 12 mo	52	42	-0.11 (-0.52 to 0.29)	33.72
Reuters et al,[31] 2012	Beck Depression Inventory at 6 mo	32	25	0.06 (-0.47 to 0.58)	20.39
Najafi et al,[24] 2015	Beck Depression Inventory at 3 mo	30	30	-0.05 (-0.56 to 0.46)	21.80
Subtotal				-0.10 (-0.34 to 0.13)	100.00
Overall effect: $I^2 = 0.0\%$; $P = .84$					



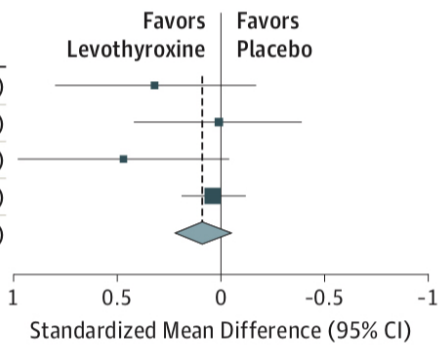
Feller et al, JAMA, 2018

T4 Therapie Metaanalyse

Kognitive Funktion

Figure 2. Randomized Clinical Trials of Levothyroxine Therapy in Subclinical Hypothyroidism Outcomes on Cognitive Function

Source	Cognition Function Scale	No. of Participants		Standardized Mean Difference (95% CI)	Weight, %
		Levothyroxine	Placebo		
Jorde et al,[26] 2006	Composite cognitive score at 12 mo	35	32	0.32 (-0.17 to 0.80)	7.72
Parle et al,[16] 2010	MMSE score at 12 mo	52	42	0.01 (-0.39 to 0.42)	10.87
Aghili et al,[25] 2012	Wechsler memory score at 3 mo	30	30	0.47 (-0.04 to 0.98)	6.82
Stott et al,[12] 2017	Letter-Digit Coding Test score at 18 mo	318	320	0.04 (-0.12 to 0.19)	74.59
Overall effect: $I^2 = 14.7\%$; $P = .32$				0.09 (-0.05 to 0.22)	100.00



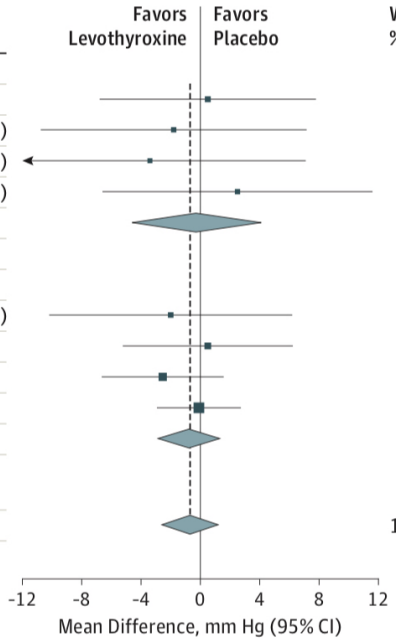
Feller et al, JAMA, 2018

T4 Therapie Metaanalyse

Blutdruck

Figure 3. Randomized Clinical Trials of Levothyroxine Therapy in Subclinical Hypothyroidism Outcomes on Systolic Blood Pressure

Source	No. of Participants		Systolic Blood Pressure, mm Hg (95% CI)		Mean Difference, mm Hg (95% CI)	Weight, %
	Levothyroxine	Placebo	Levothyroxine	Placebo		
After 3-6 mo of treatment						
Monzani et al,[33] 2001	10	10	117.3 (104.0-130.6)	116.8 (98.0-135.6)	0.5 (-6.8 to 7.8)	6.68
Razvi et al,[32] 2007	100	100	132.8 (88.1-177.5)	134.6 (89.7-179.5)	-1.8 (-10.8 to 7.2)	4.42
Nagasaki et al,[36] 2009	48	47	128.8 (77.6-180.0)	132.2 (81.0-183.4)	-3.4 (-13.9 to 7.1)	3.22
Ersoy et al,[29] 2012	30	30	131.7 (96.6-166.8)	129.2 (94.1-164.3)	2.5 (-6.6 to 11.6)	4.33
Subtotal					-0.3 (-4.6 to 4.1)	18.65
Overall effect: $I^2 = 0.0\%$; $P = .84$						
After 12 mo of treatment						
Monzani et al,[34] 2004	23	22	112.0 (82.6-141.4)	114.0 (88.5-139.5)	-2.0 (-10.2 to 6.2)	5.29
Yazici et al,[35] 2004	23	22	123.6 (104.4-142.8)	123.1 (103.9-142.3)	0.5 (-5.2 to 6.2)	10.82
Zhao et al,[11] 2016	210	159	136.0 (96.6-175.5)	138.6 (99.7-177.4)	-2.5 (-6.6 to 1.6)	21.02
Stott et al,[12] 2017	318	320	138.3 (101.6-175.0)	138.4 (103.5-173.3)	-0.1 (-2.9 to 2.7)	44.22
Subtotal					-0.8 (-2.9 to 1.3)	81.35
Overall effect: $I^2 = 0.0\%$; $P = .75$ Heterogeneity between groups: $P = .83$						
Overall					-0.7 (-2.6 to 1.2)	100.00
Overall effect: $I^2 = 0.0\%$; $P = .95$						



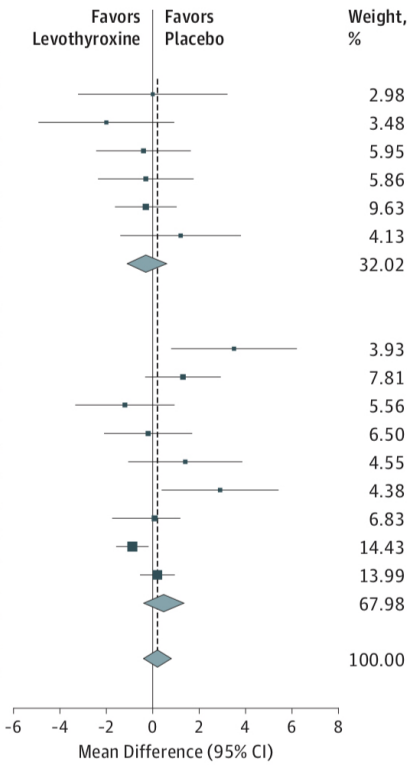
Feller et al, JAMA, 2018

T4 Therapie Metaanalyse

BMI

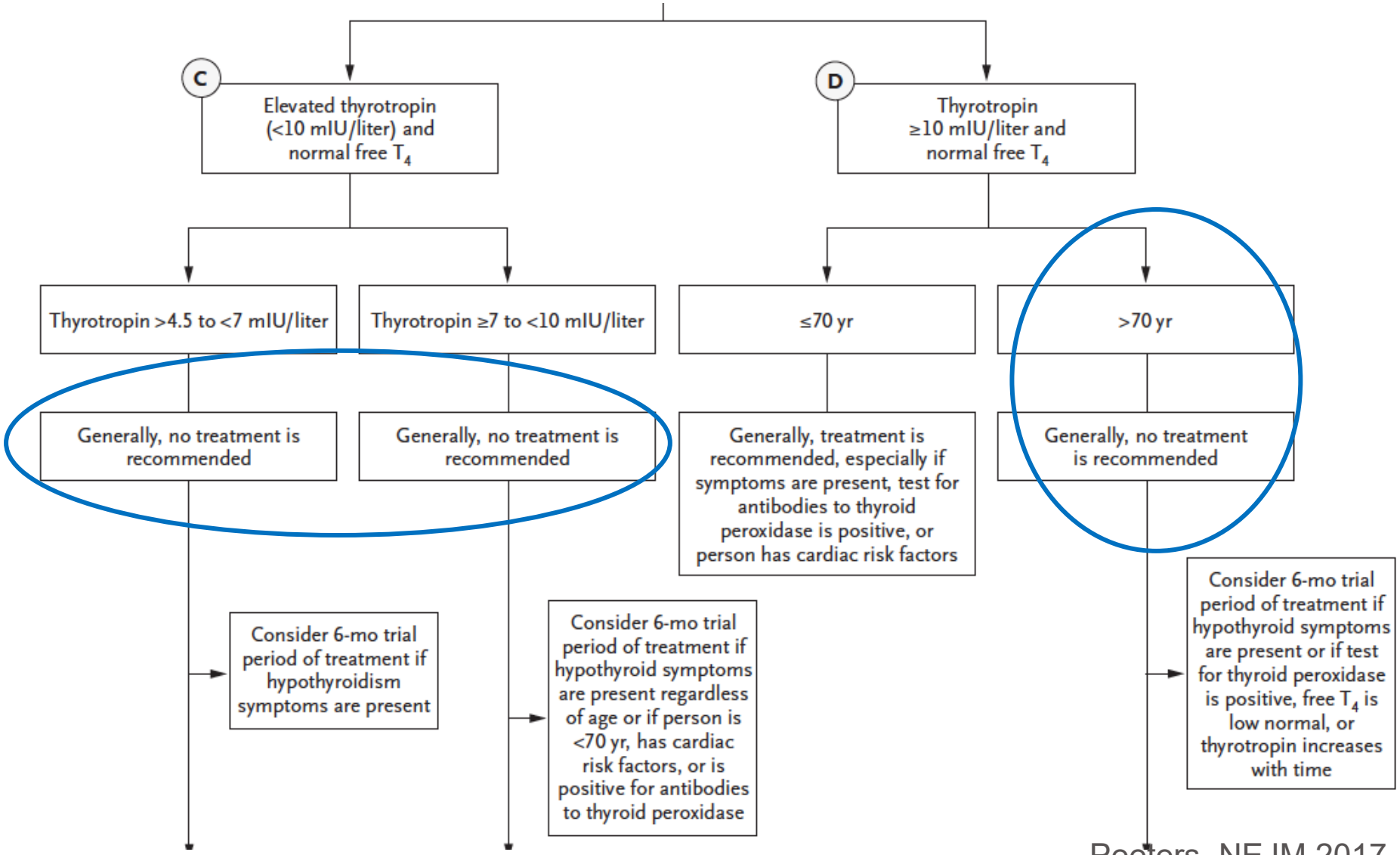
Figure 4. Randomized Clinical Trials of Levothyroxine Therapy in Subclinical Hypothyroidism Outcomes on Body Mass Index

Source	No. of Participants		Body Mass Index (95% CI)		Mean Difference (95% CI)	Weight, %
	Levothyroxine	Placebo	Levothyroxine	Placebo		
After 3-6 mo of treatment						
Monzani et al,[33] 2001	10	10	23.1 (13.9-32.3)	23.1 (18.8-27.4)	0.0 (-3.2 to 3.2)	2.98
Kong et al,[27] 2002	20	14	25.4 (19.1-31.7)	27.4 (17.8-37.0)	-2.0 (-4.9 to 0.9)	3.48
Caraccio et al,[38] 2005	12	11	22.3 (16.4-28.2)	22.7 (19.0-26.4)	-0.4 (-2.4 to 1.6)	5.95
Razvi et al,[32] 2007	100	100	28.1 (17.9-38.3)	28.4 (18.0-38.8)	-0.3 (-2.4 to 1.8)	5.86
Nagasaki et al,[36] 2009	48	47	21.8 (15.5-28.1)	22.1 (15.4-28.8)	-0.3 (-1.6 to 1.0)	9.63
Ersoy et al,[29] 2012	30	30	30.1 (18.3-41.9)	28.9 (20.7-37.1)	1.2 (-1.4 to 3.8)	4.13
Subtotal					-0.3 (-1.1 to 0.6)	32.02
Overall effect: $I^2 = 0.0\%$; $P = .76$						
After 12 mo of treatment						
Cooper et al,[23] 1984	17	16	28.1 (22.9-33.3)	24.6 (15.0 -34.2)	3.5 (0.8 to 6.2)	3.93
Caraccio et al,[39] 2002	24	25	24.1 (18.0-30.2)	22.8 (17.5-28.1)	1.3 (−0.3 to 2.9)	7.81
Monzani et al,[34] 2004	23	22	23.7 (16.8-30.6)	24.9 (17.5-32.3)	-1.2 (-3.3 to 0.9)	5.56
Yazici et al,[35] 2004	23	22	22.8 (16.1-29.5)	23.0 (16.9-29.1)	-0.2 (-2.1 to 1.7)	6.50
Iqbal et al,[37] 2006	32	32	28.4 (17.0-39.8)	27.0 (19.0-35.0)	1.4 (-1.1 to 3.9)	4.55
Teixeira et al,[30] 2008	11	15	27.4 (21.1-33.7)	24.5 (18.0-31.0)	2.9 (0.4 to 5.4)	4.38
Cabral et al,[28] 2011	14	18	25.8 (21.3-30.2)	25.7 (19.8-31.6)	0.1 (-1.7 to 1.9)	6.83
Zhao et al,[11] 2016	210	159	25.8 (19.6-32.0)	26.7 (19.7-33.6)	-0.9 (-1.6 to -0.2)	14.43
Stott et al,[12] 2017	318	320	27.9 (17.9-37.9)	27.7 (18.7-36.7)	0.2 (-0.6 to 1.0)	13.99
Subtotal					0.5 (-0.4 to 1.3)	67.98
Overall effect: $I^2 = 64.9\%$; $P = .004$						
Overall					0.2 (-0.4 to 0.8)	100.00
Overall effect: $I^2 = 45.5\%$; $P = .03$						



Feller et al, JAMA, 2018

Latente Hypothyreose – wann behandeln ?



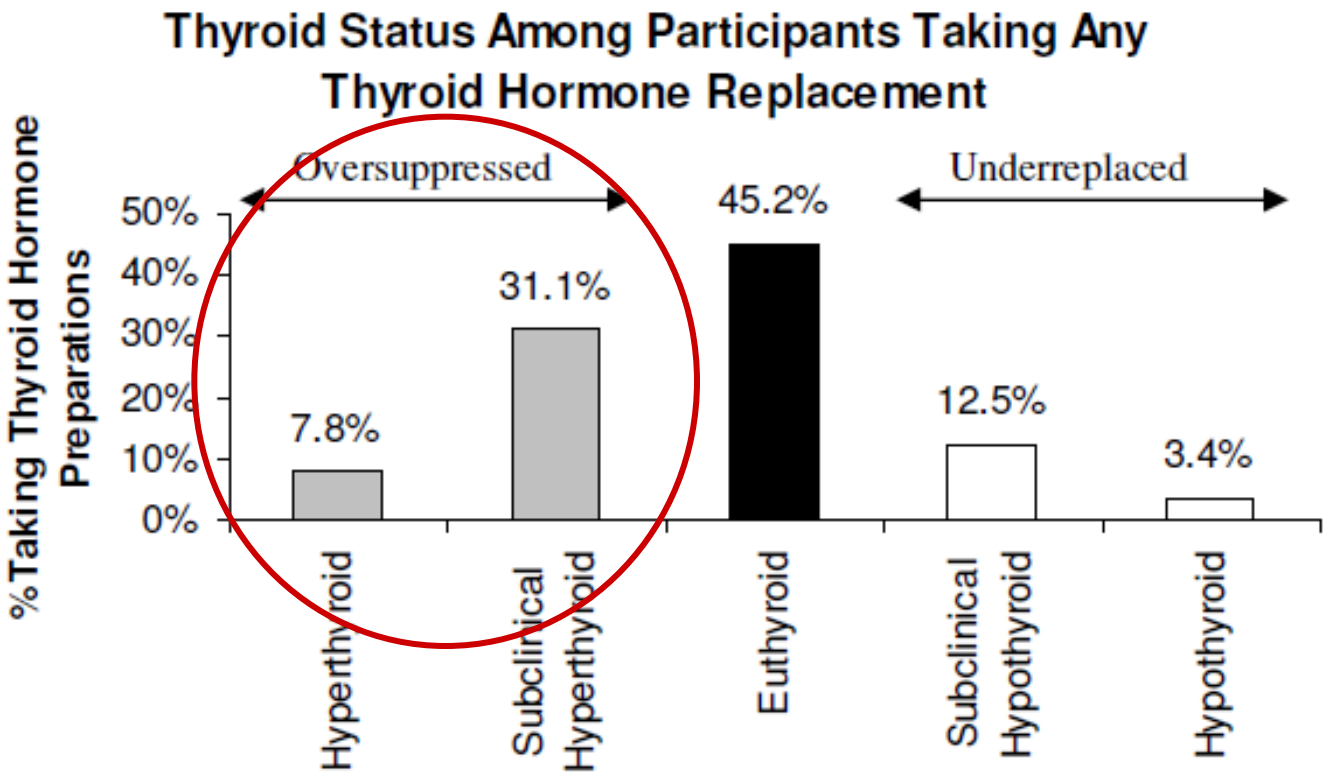
Peeters, NEJM 2017

Leichte latente Hypothyreose:

T4 hilft nix – schad nix ?

Gefahr der Übertherapie !

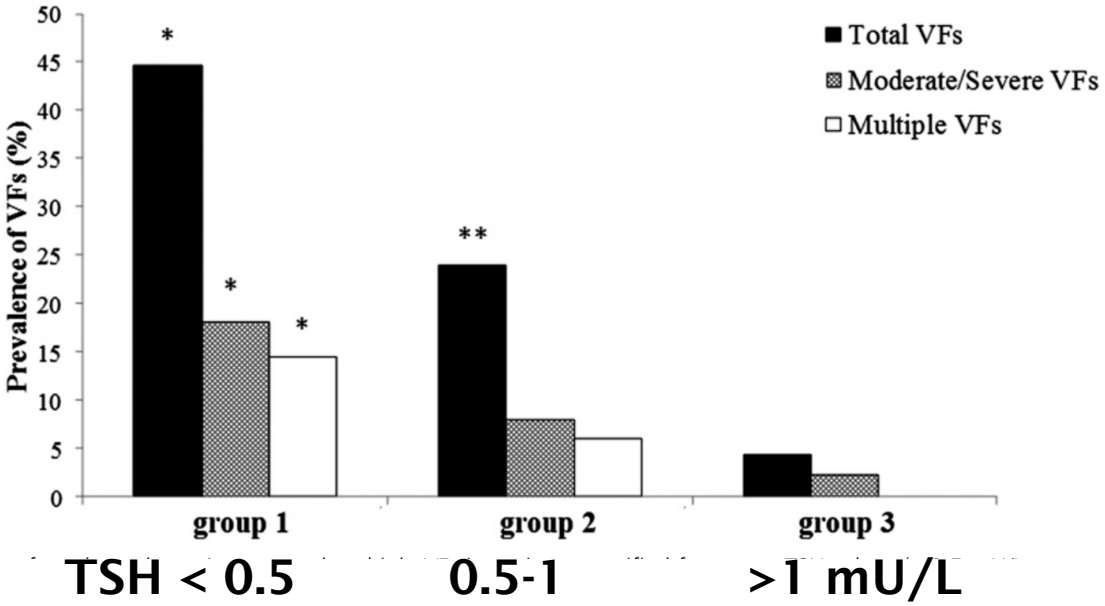
ältere (> 65 a) Patienten in Pennsylvania:

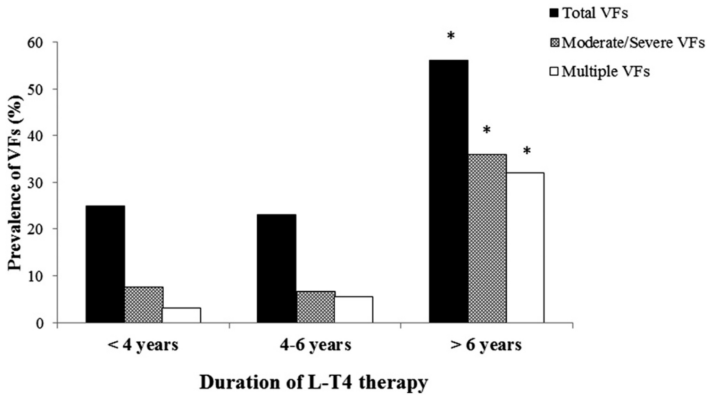


~ 40 % Übersubstitution !

JCEM doi:10.1210/jc.2008-1696, 2009

T4 Therapie nach SD Ca – WK Frakturen





Mazziotti et al., JCEM 2018

Latente Hyperthyreose – Mortalität

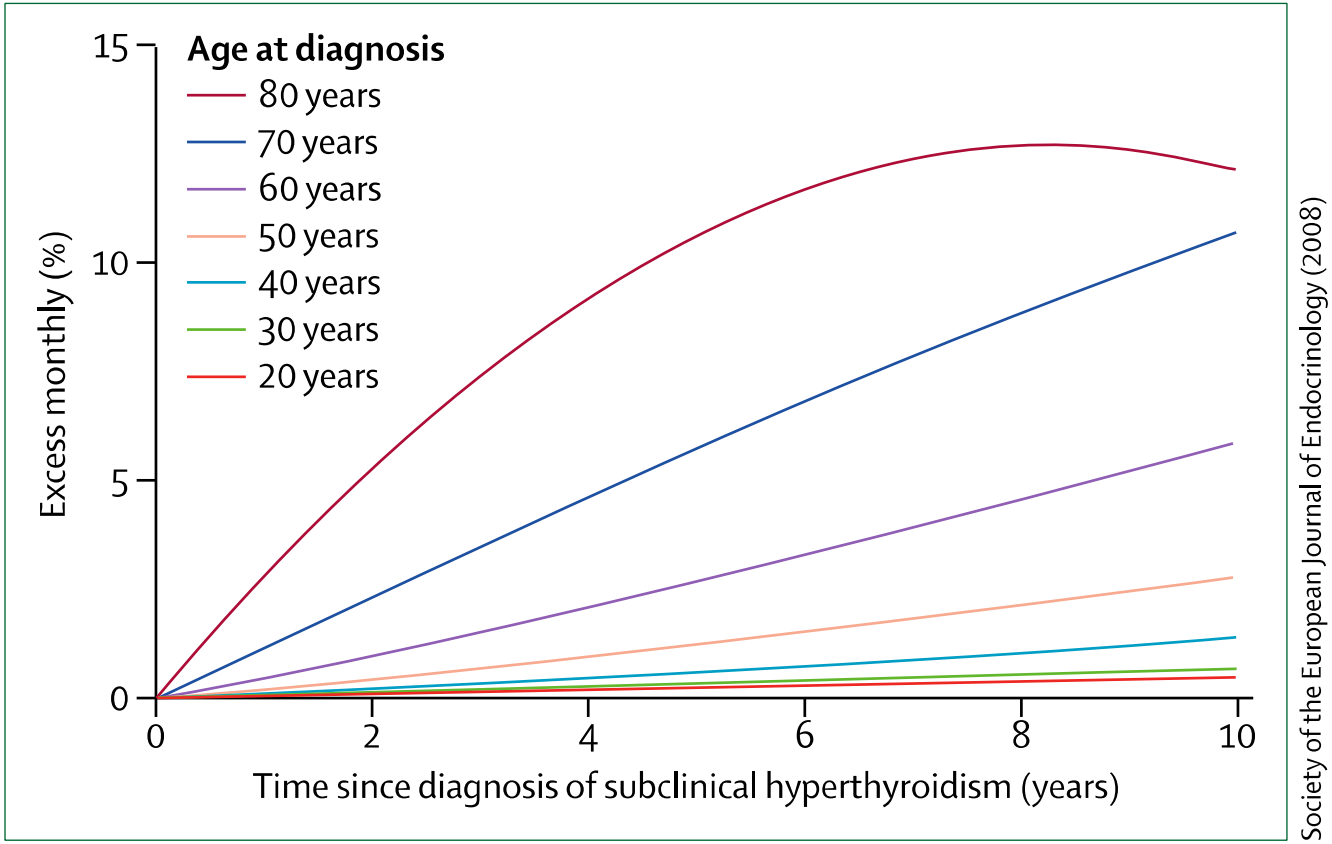
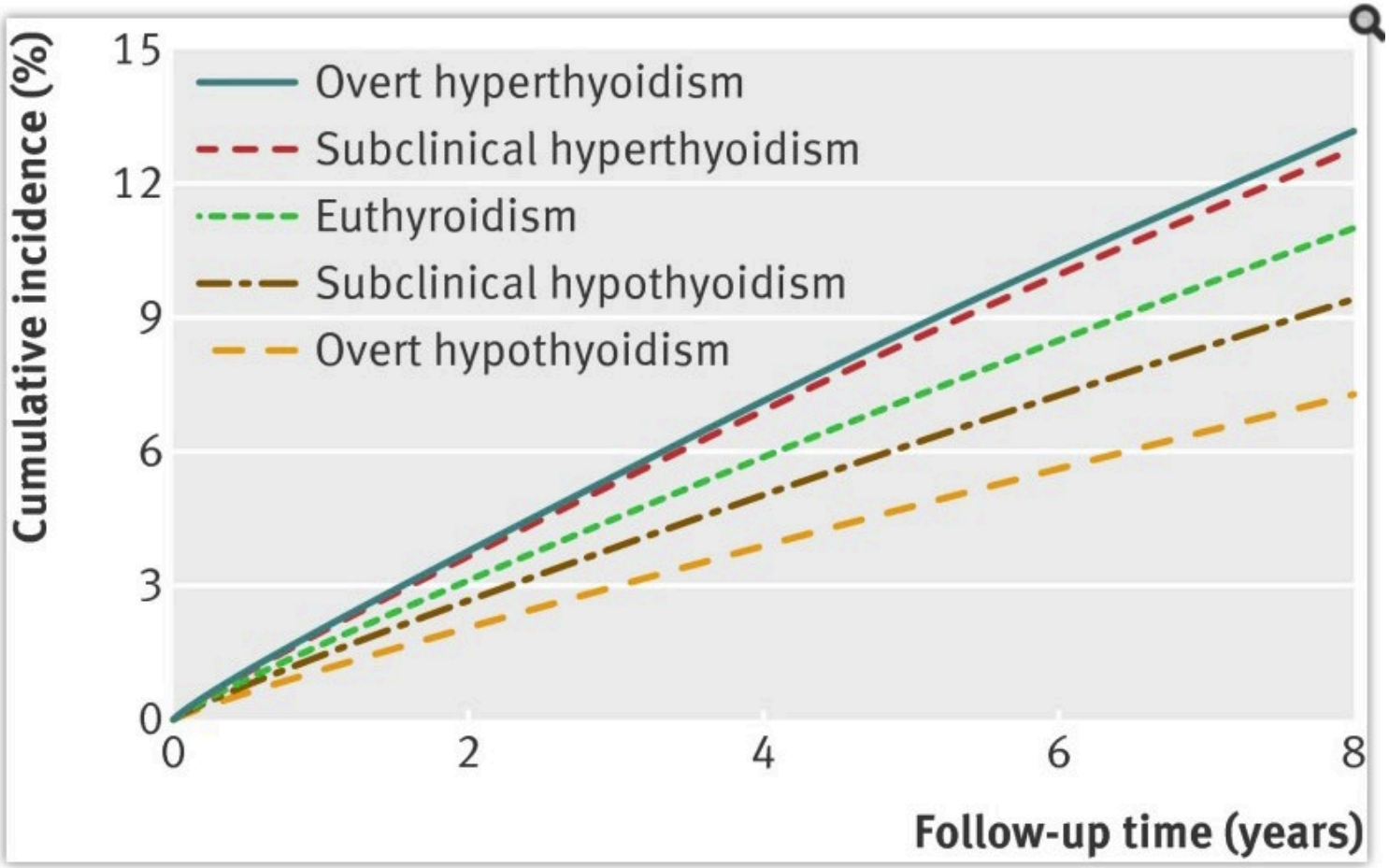


Figure 3: **Excess all-cause mortality in men with subclinical hyperthyroidism according to a meta-analysis of aggregated data from cohort studies and life-tables**

Cooper & Biondi, Lancet 379:1142, 2012

Schilddrüse und Vorhofflimmern

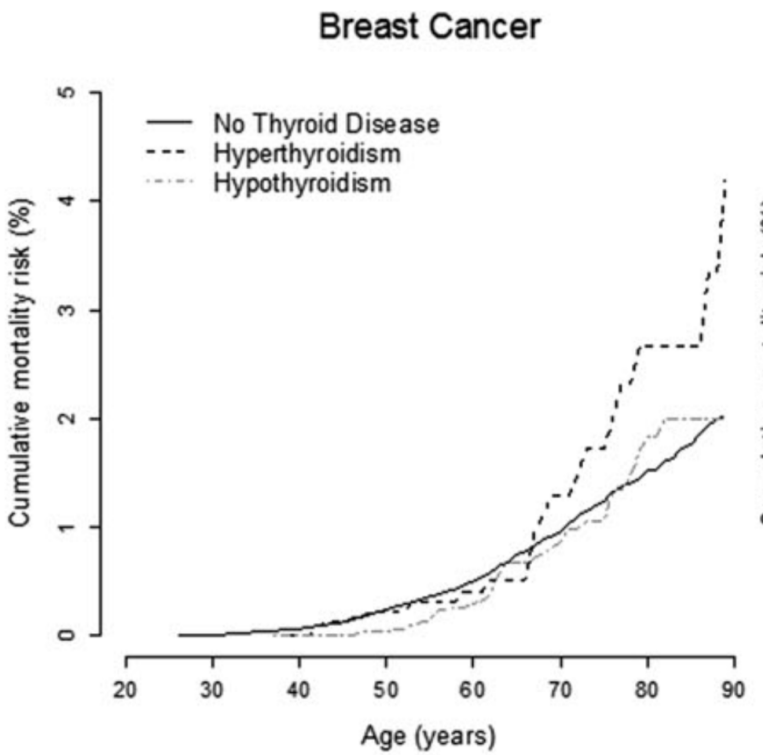
Register N=586 460, 65 Jahre, 57 % Frauen



Selmer et al, BMJ 2017

SD: unbekannte Komorbititäten ?

N = 75 076 Frauen, Follow up 28 Jahre

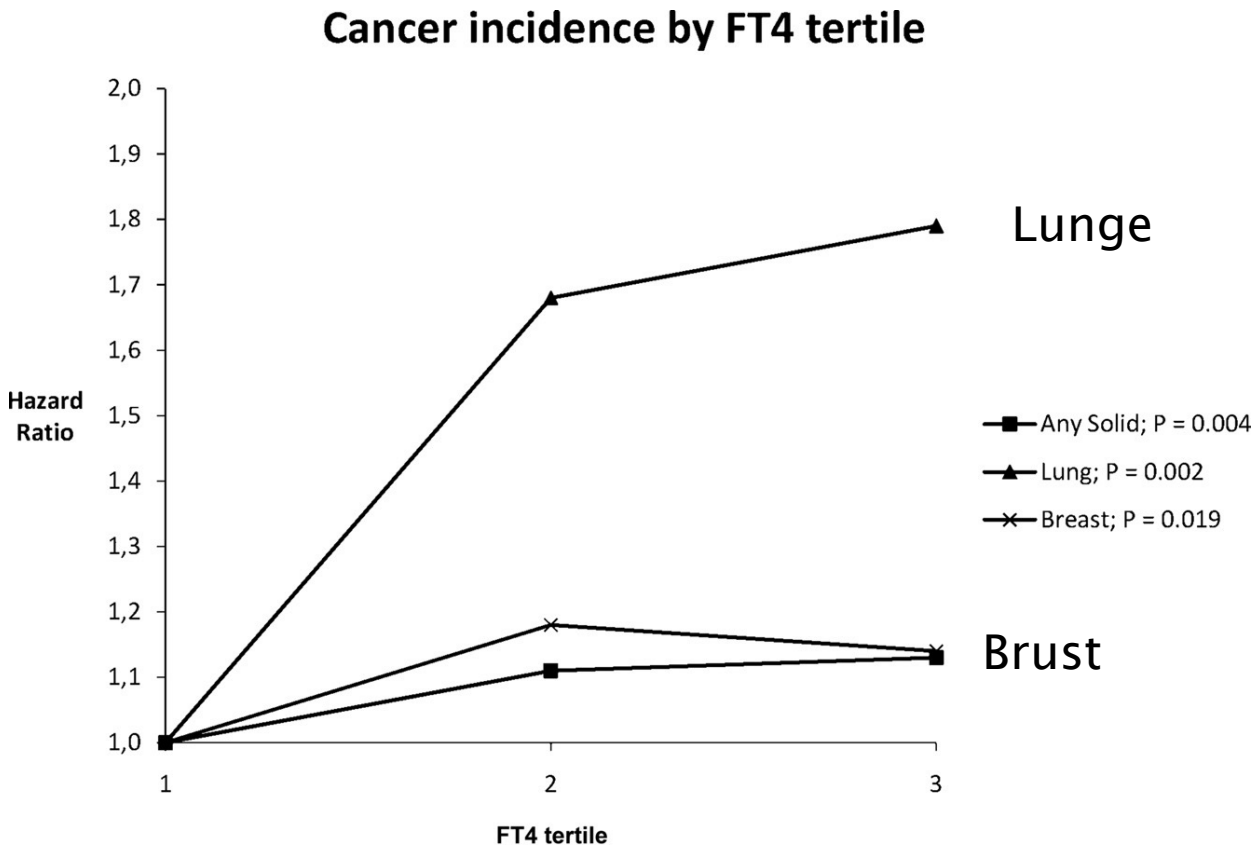


Hyperthyreose

Journy et al., Thyroid 2017

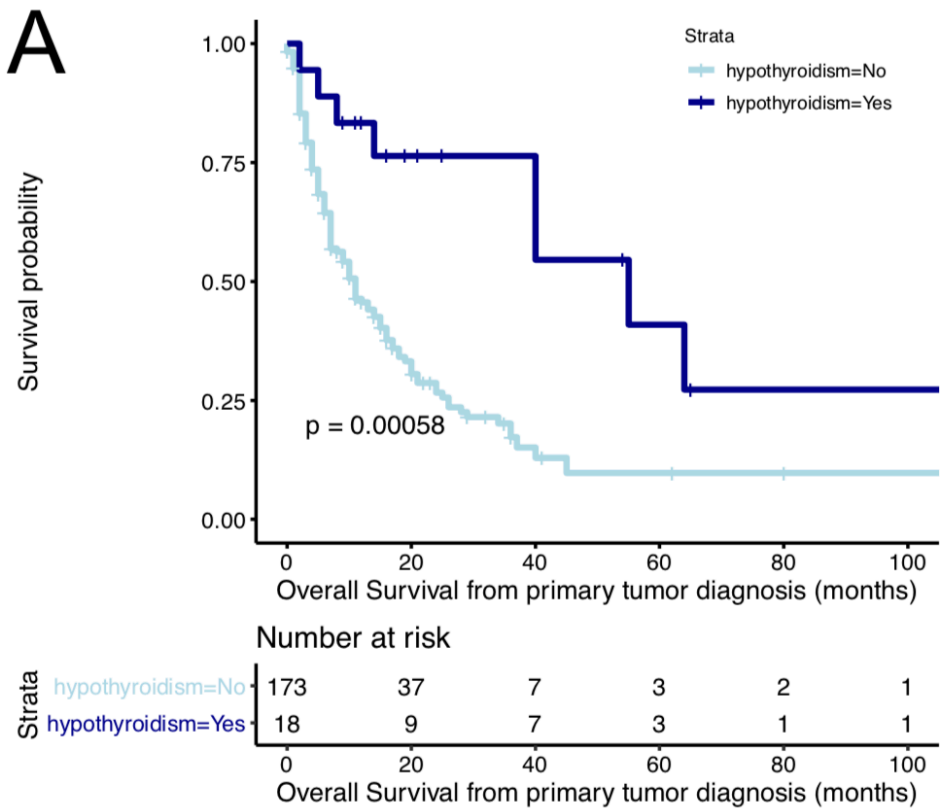
SD und Krebs

Prospective population-based cohort study including 10 318 participants for whom baseline measurements of FT4 and/or TSH were available



Rotterdam Study; Kahn et al., JCEM 2016

SD und Überleben bei Tumorpatienten



Patienten mit Hirnmetastasen ab Diagnose des Tumors

Onkologie
Med. Univ. Wien

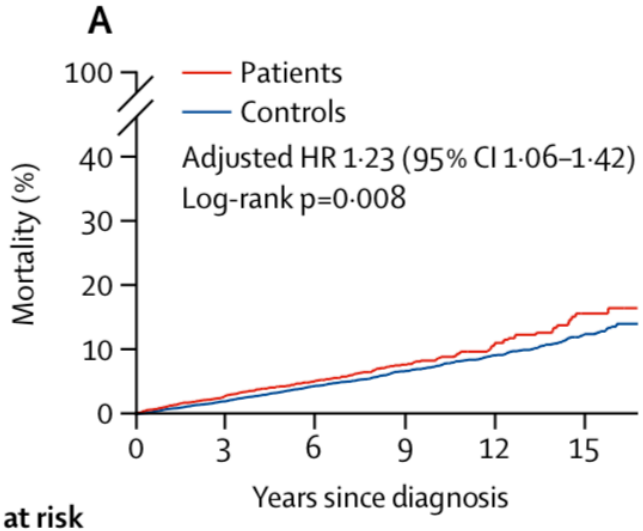
Berghoff et al., submitted

KEINE Behandlung einer latenten Hypothyreose im Alter !

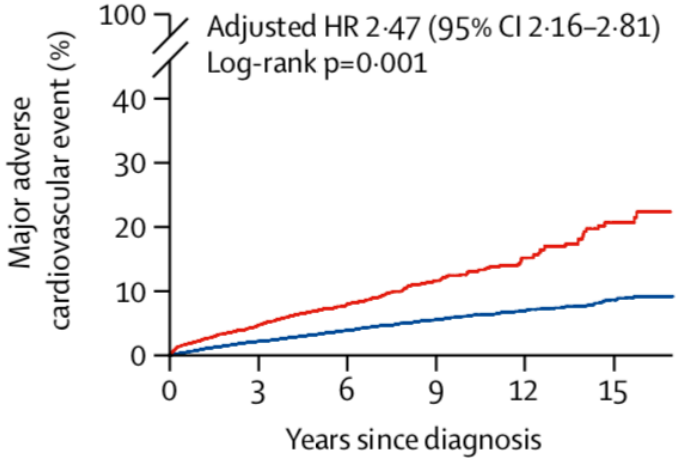
Vielen Dank !

M. Basedow und Mortalität

Mortalität



Major CV event



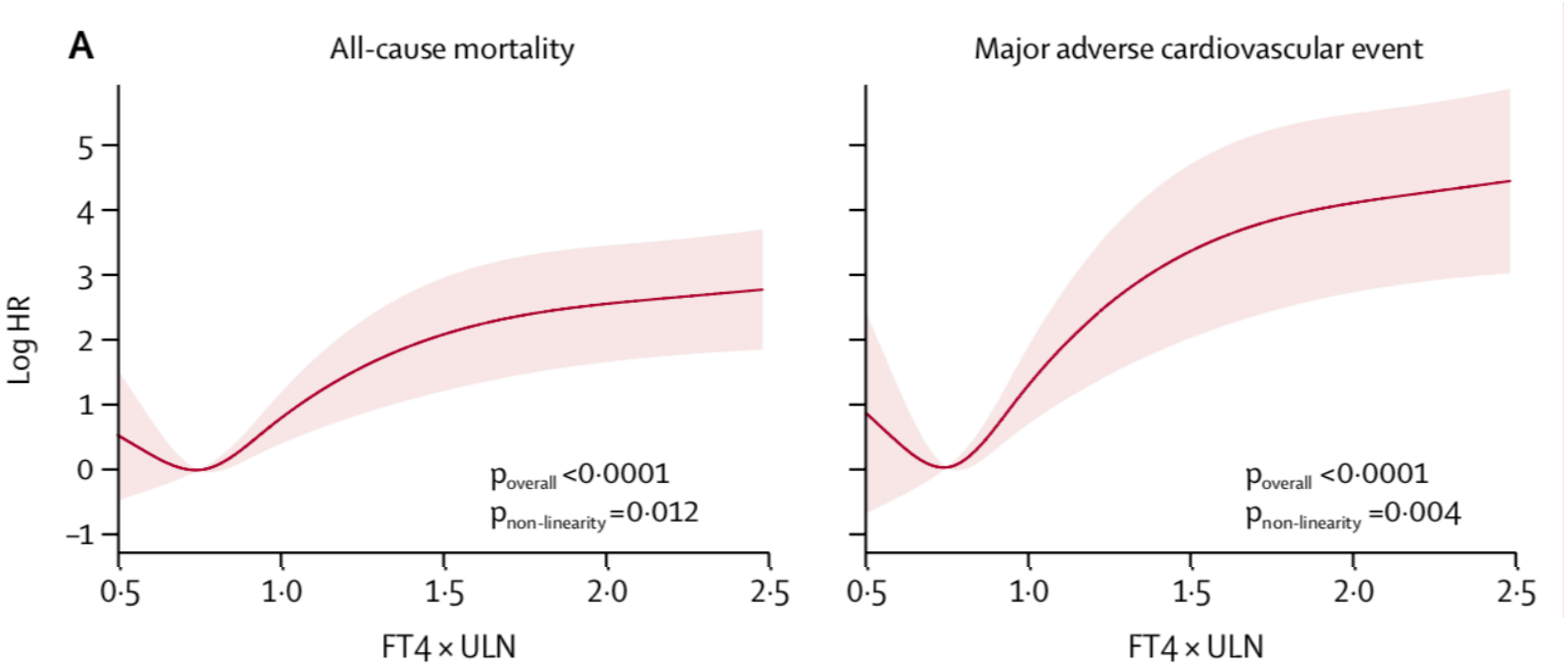
Number at risk

Patients	4189	3041	1771	847	427	181
Controls	16756	12381	7234	3538	1782	828

	4189	2982	1721	821	410	173
	16756	12353	7279	3602	1843	874

Onyebuchi et al., Lancet Diabetes&Endocrinology 2019

M. Basedow und Mortalität



fT4 nach einem Jahr

Onyebuchi et al., Lancet Diabetes&Endocrinology 2019

M. Basedow und Mortalität

4981 patients with Graves Disease

- Increased all-cause mortality compared with controls (HR 1·22)
- Compared with the antithyroid drug group, mortality was lower in radioiodine group with resolved hyperthyroidism (HR 0.5) but not with unresolved hyperthyroidism group (HR 1,51)
- Persistently low TSH concentrations at 1 year after diagnosis were associated with increased mortality independent of treatment method (HR 1·55)

Early and complete resolution of hyperthyroidism in patients with Graves' disease is associated with improved survival compared with less effective control.

Onyebuchi et al., Lancet Diabetes&Endocrinology 2019