Schilddrüse und Psyche

Internistisch-endokrinologische Sicht

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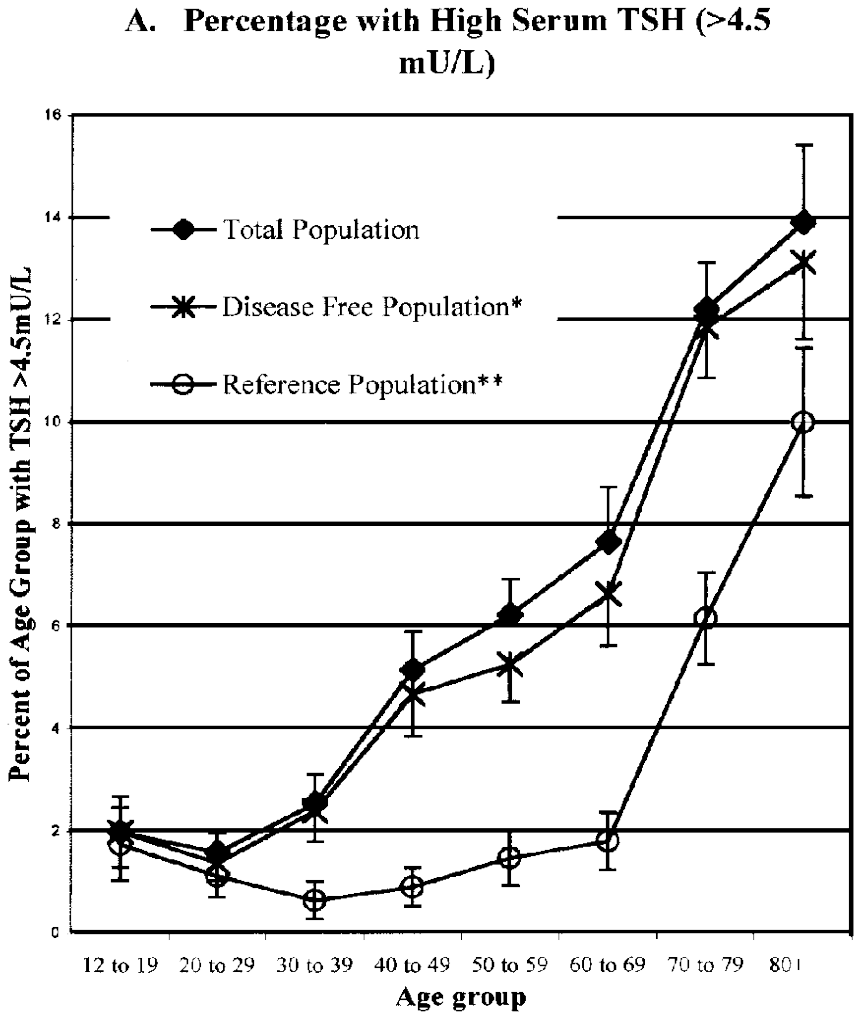
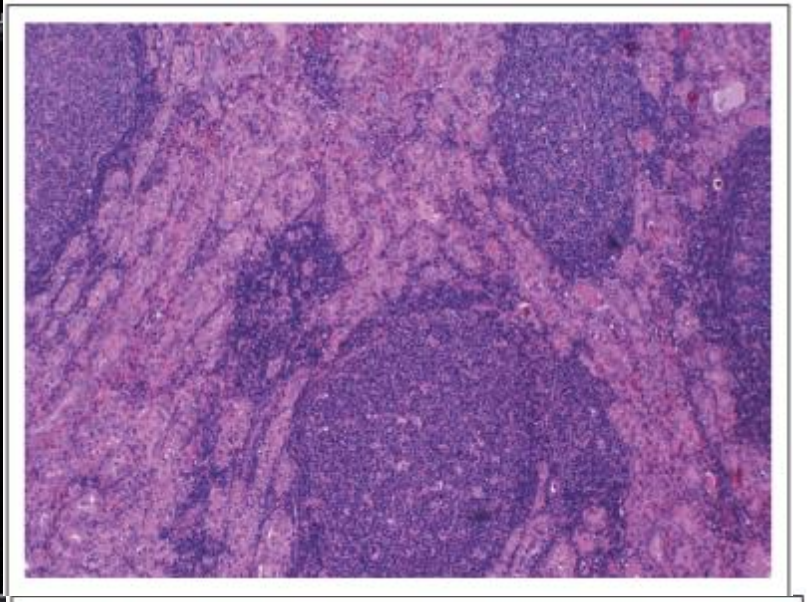
Epidemiologie - Hypothyreose



NHANES III, JCEM 87:489, 2002

Autoimmunthyreoiditis

AIT:



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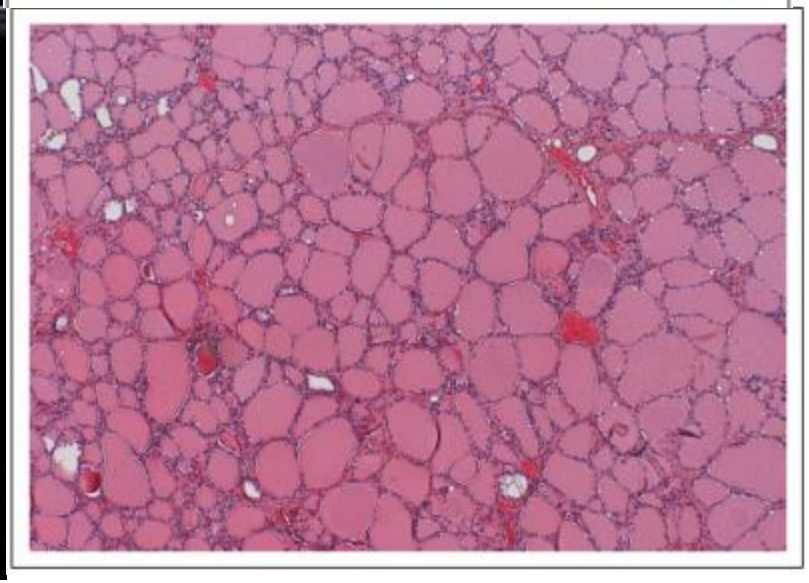
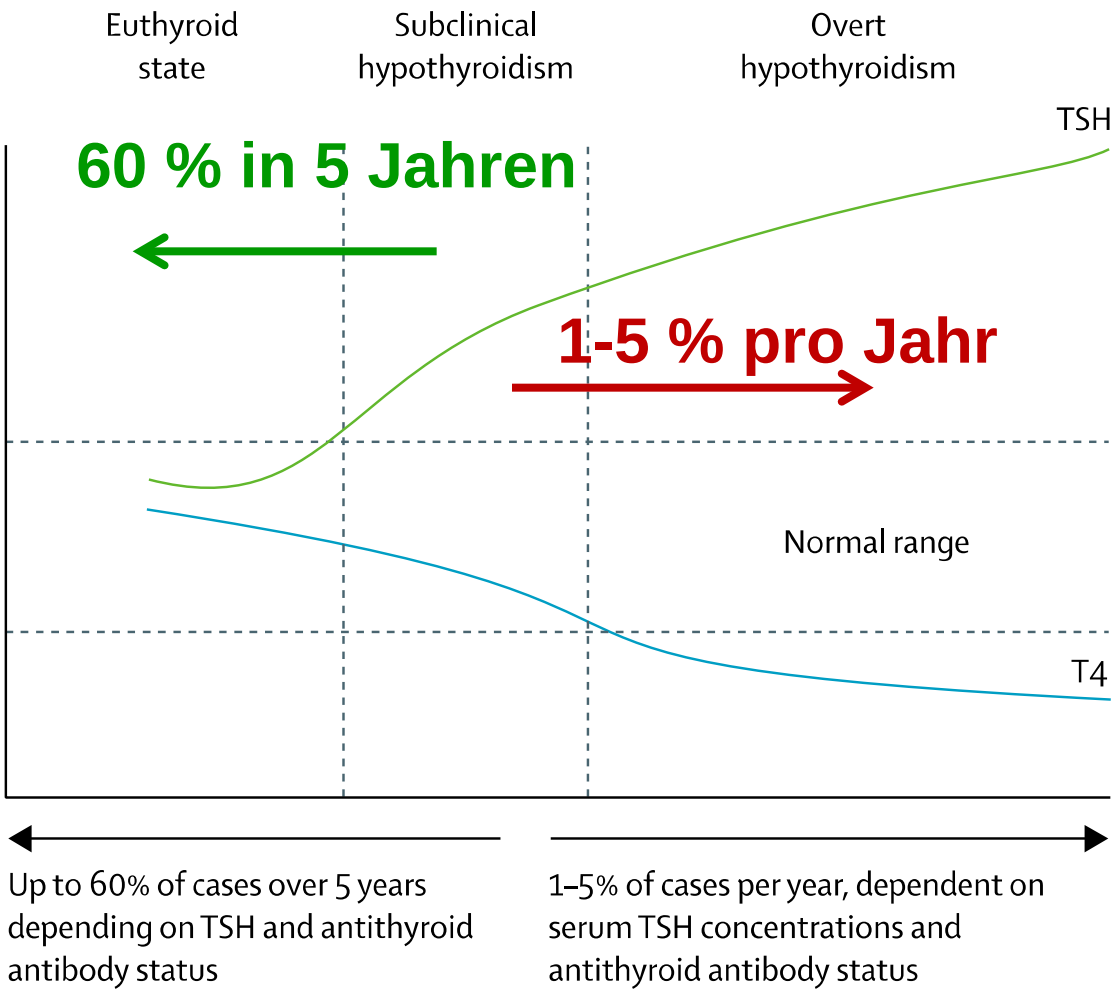


Latente Hypothyreose - Diagnose



RF:
weiblich
hohe AK
hohes TSH

Cooper & Biondi, Lancet 379:1142, 2012

Alter: TSH Normalwerte

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

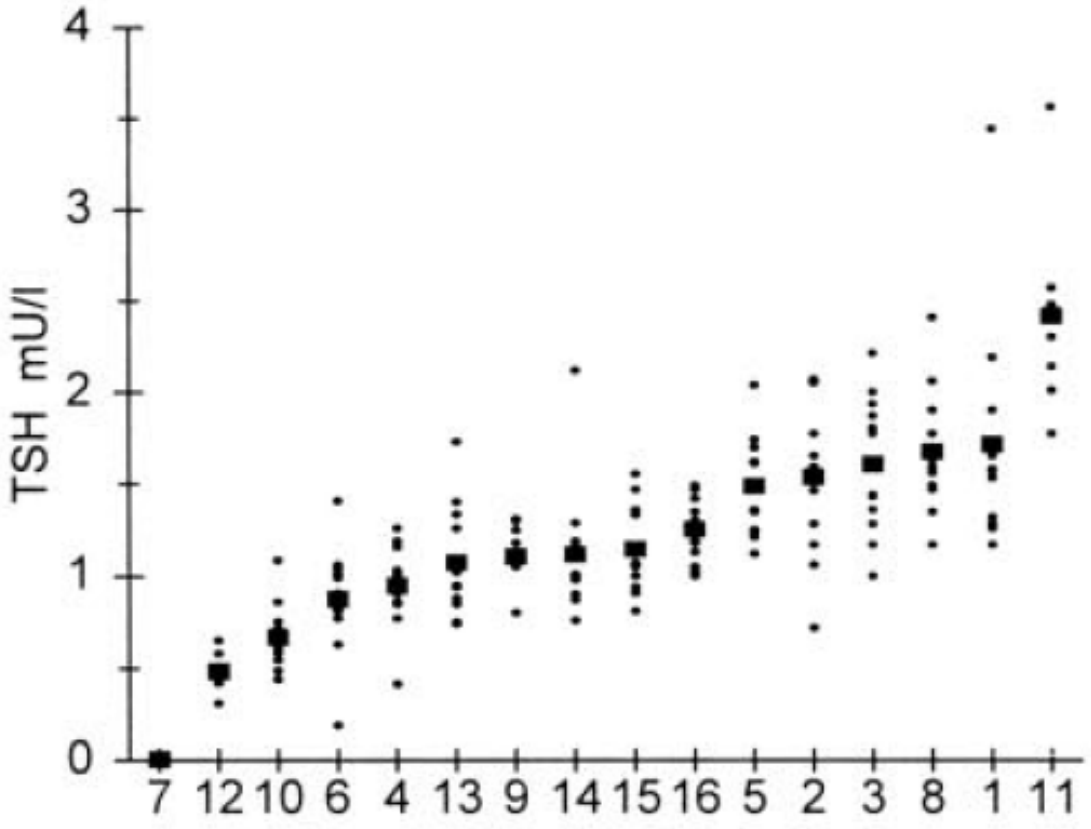
Age (yr)	n	TSH reference range (mU/liter) Lower limit	Mean	Upper limit
<30	304	0.51	1.34	3.54
30–40	299	0.48	1.25	3.21
40–50	269	0.44	1.32	3.92
50–60	321	0.42	1.31	4.09
60–70	334	0.38	1.34	4.70
>70	224	0.52	1.66	5.28
All	1751	0.44	1.35	4.10

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

Bremner et al., JCEM 97:1554, 2012

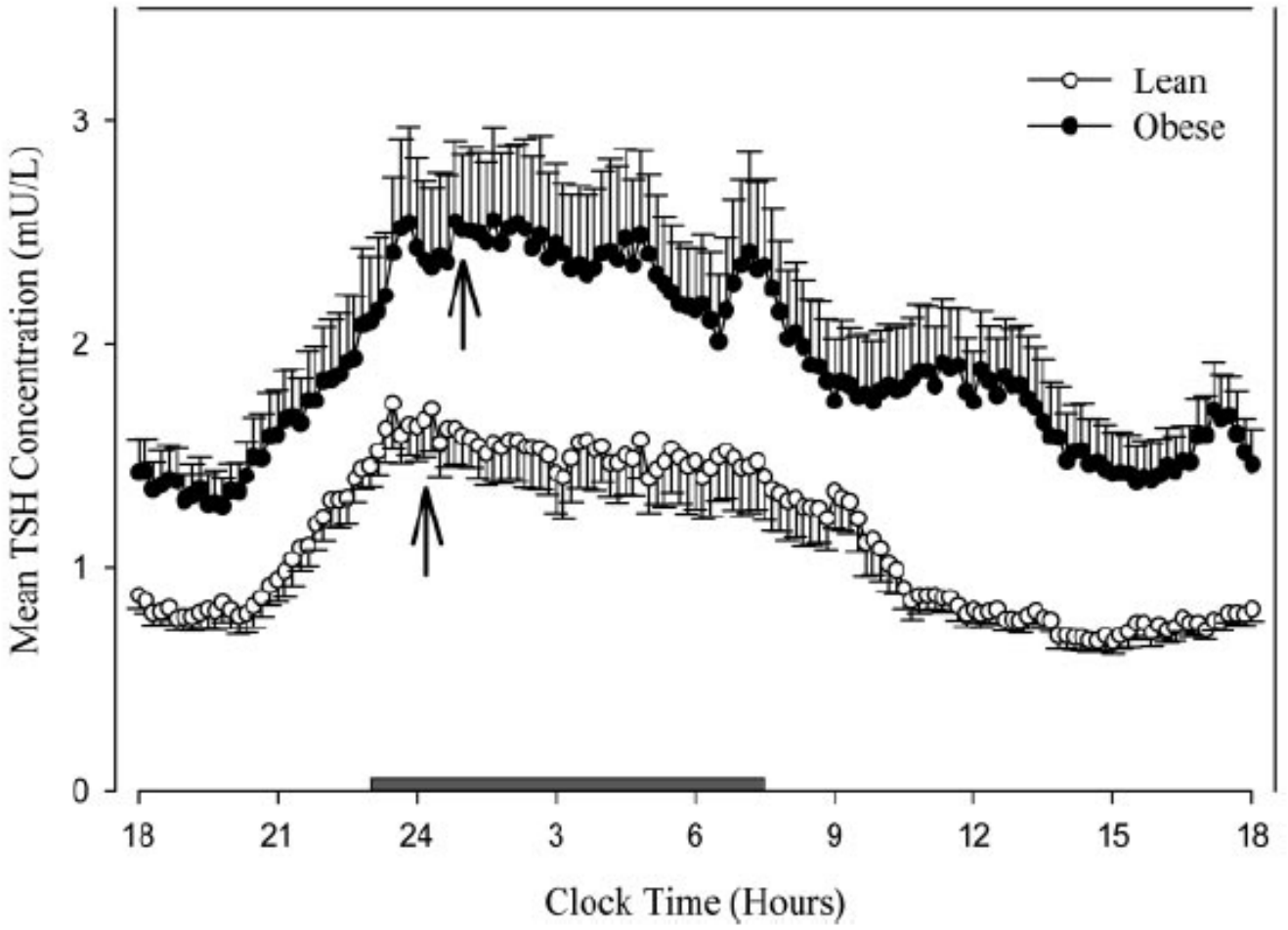
TSH – Individuelle Variation

16 gesunde Männer – monatliche Blutabnahmen



Andersen et al., JCEM 87:1068, 2002

TSH und Adipositas



Kork et al, JCEM, 2005

Symptome sehr oft unspezifisch!

Hypothyreose

Bradykardie
Kälteintoleranz
Gewichtszunahme (leicht)
Verminderte Belastbarkeit

Lethargie, Depression Persönlichkeitsveränderungen
Müdigkeit, Schlafen↑
Abgeschlagenheit, Leistungsfähigkeit ↓
Gedächtnisstörungen

Muskelschwäche
Muskelkrämpfe
Gelenkschmerzen

Obstipation
Infertilität
Libido/Potenzmangel

Oligo-oder Amenorrhoe
Trockene raue, schuppige Haut

Haarausfall, strohiges Haar
Heiserkeit, tiefe, raue Stimme
Übelkeit

Hyperthyreose

Tachykardie, Arrhythmien
Wärmeintoleranz
Gewichtsabnahme
Verminderte Belastbarkeit

Ängstlichkeit, psych. Labilität
Unruhe, Nervosität, Tremor, Einschlafstörungen

Konzentrationsstörungen

Muskelschwäche

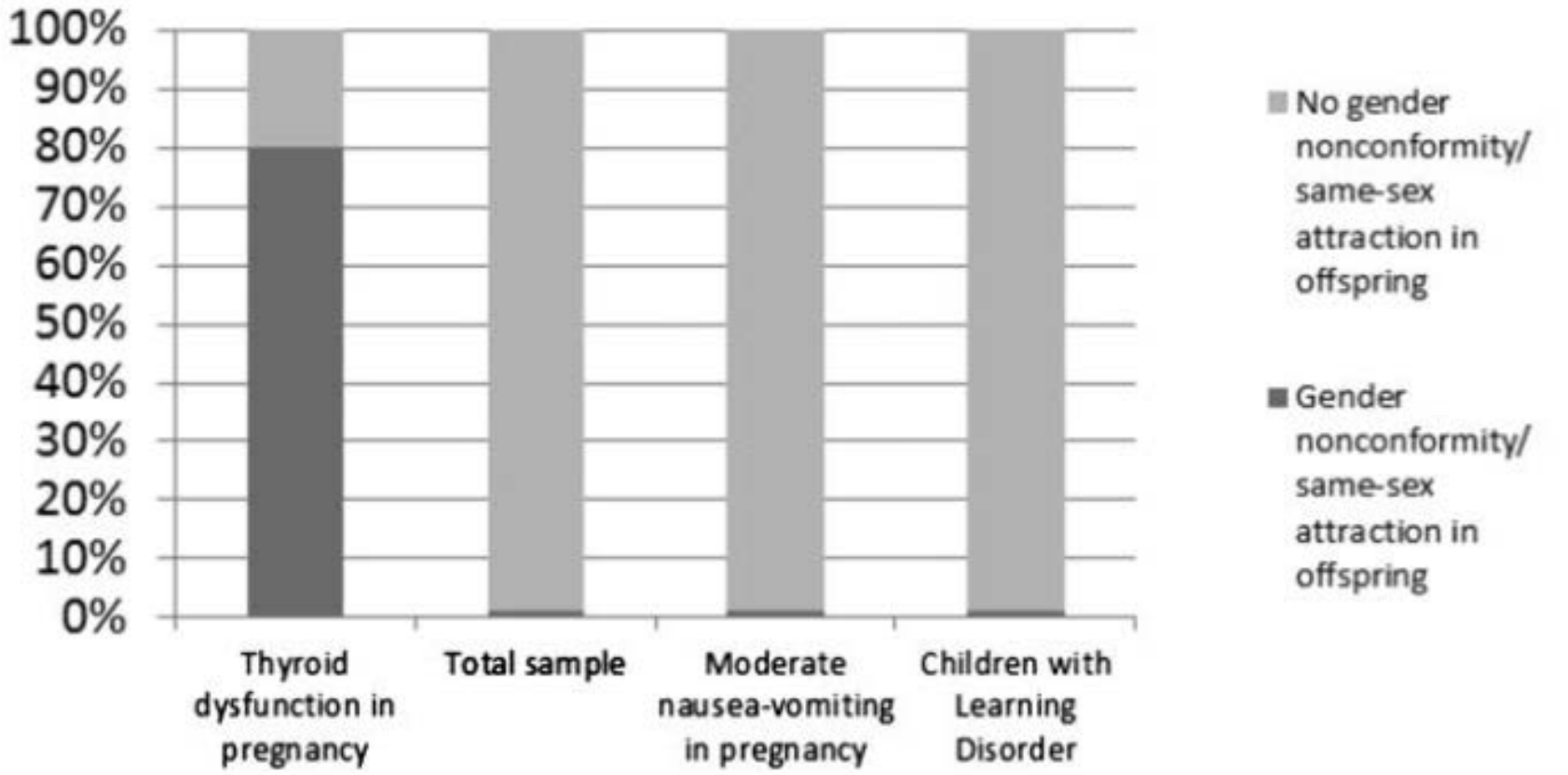
Gelenk- u. Knochenschmerzen

Neigung zu Diarrhoe
Infertilität
Libido/Potenzmangel
Gynäkomastie
Oligomenorrhoe
warme feuchte Haut (Hyperhidrose), Urtikaria
Haarausfall

A.Gessl

Schilddrüse und .....

Schilddrüse und Genderidentität



Sabuncuoglu, Mental Illness 2015

Schilddrüse und Genderidentiät

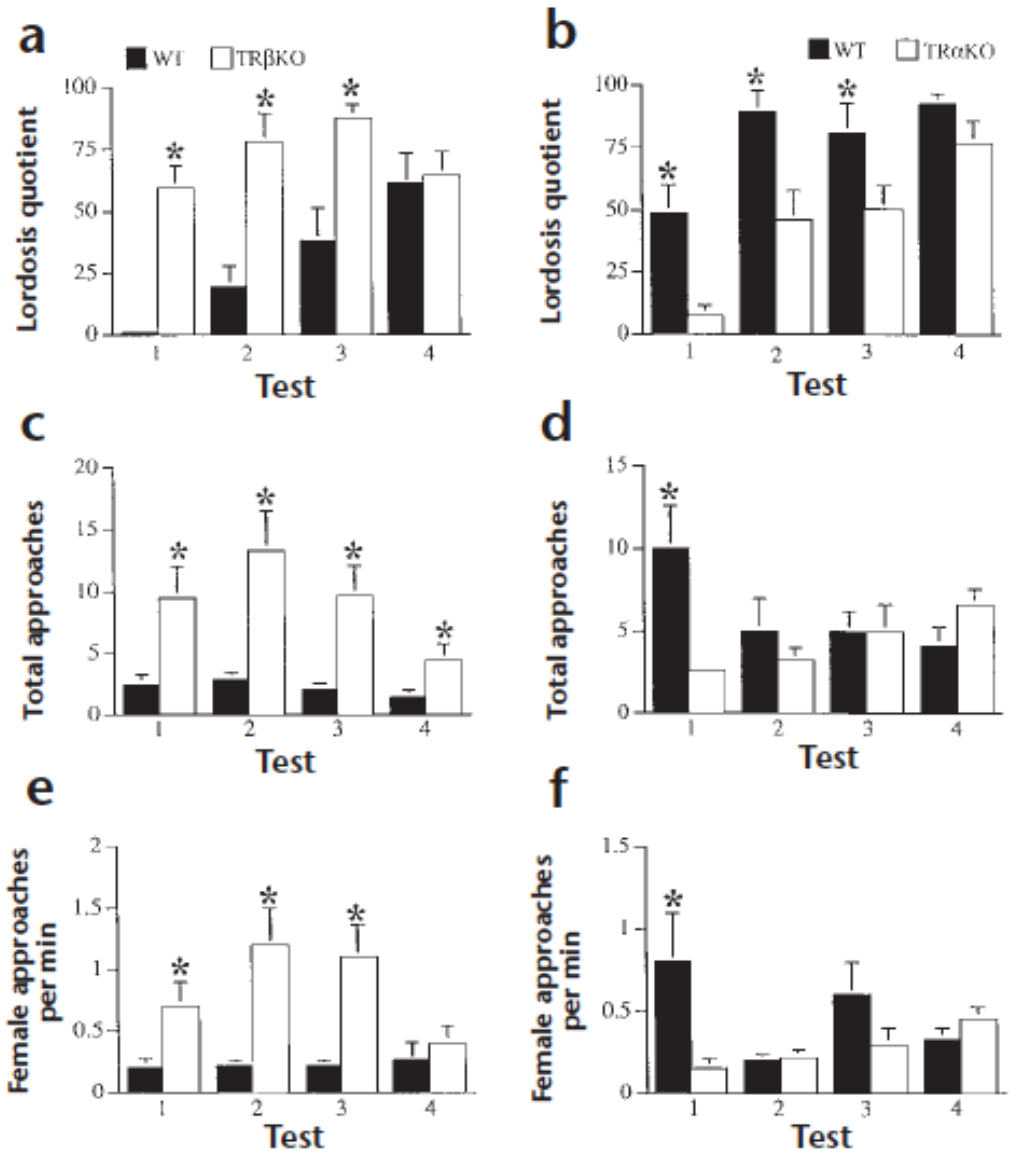
Table 1. Characteristics of the cases presenting with same-sex attraction/gender nonconformity and history of maternal thyroid dysfunction in pregnancy.

Case	Sex	Age	Principal psychiatric diagnosis	Records relating to same-sex attraction/ gender non-conformity	Reported pregnancy thyroid dysfunction in pregnancy	Medication used for thyroid dysfunction	Additional notes
1	M	15	No diagnosis	Effeminate behavior; plucking eyebrows; subject to homophobic bullying at school	Goiter	No -	-
2	M	14	Major depression	Effeminate behavior; in love with a male friend; subject to homophobic bullying at school	Hashimoto thyroiditis	No	-
3	M	10	Anxiety disorder	Shaving body hair; subject to homophobic bullying at school	Hypothyroidism	Yes	-
4	M	11	Learning disorder	Effeminate behavior; subject to homophobic bullying at school	Hashimoto thyroiditis	Yes	-
5	M	11	Asperger disorder	Effeminate behavior; subject to homophobic bullying at school	Hypothyroidism	No	History of postnatal thyroid hormone use for 2 months
6	M	9	ADHD	Parental concerns regarding sexuality; seen peeping other boys' genitals on several occasions	Hashimoto thyroiditis	Yes	-
7	M	17	No diagnosis	Sexual activity with a male friend; admits same-sex orientation	Goiter	No	-
8	M	13	No diagnosis	Sexual play with a male friend; admits same-sex orientation	Hypothyroidism	No	Anti-thyroid medication use before pregnancy
9	M	11	Anxiety disorder	Sexual play with other boys; subject to homophobic bullying at school	Hypothyroidism	No	-
10	M	17	Major depression	Effeminate behavior; in love with a male friend; previously subject to homophobic bullying at school	Hypothyroidism	No	-
11	F	16	Anxiety disorder	An affair with a masculine girl	Hashimoto thyroiditis	No	Also had Hashimoto thyroiditis
12	F	17	ADHD	Sexual activity with a female friend; admits bisexual orientation	Hashimoto thyroiditis	No	Also had Hashimoto thyroiditis

M, Male; F, Female; ADHD, attention deficit/hyperactivity disorder.

Sabuncuoglu, Mental Illness 2015

Schilddrüse und Sexualität

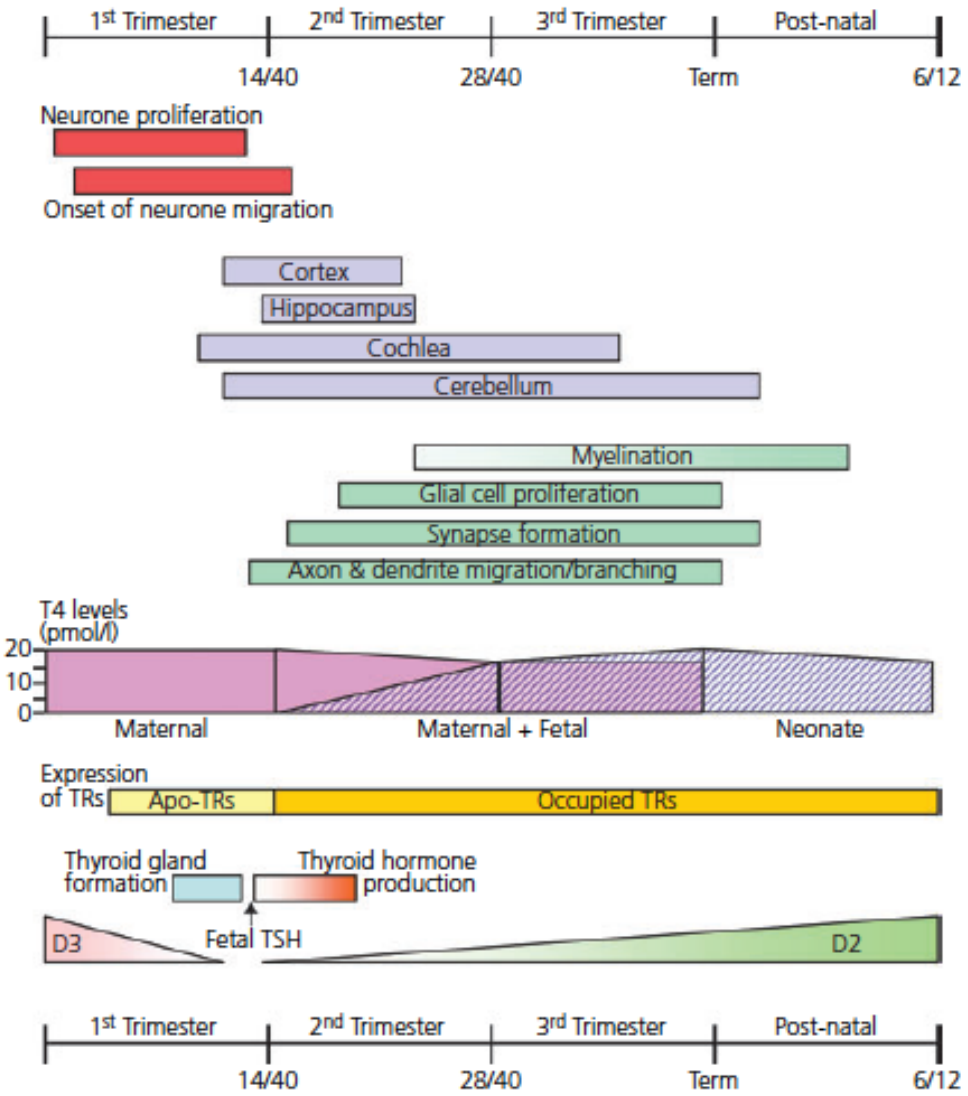


Östogen-stimuliertes Verhalten von weiblichen Mäusen mit
TR-beta KO oder
TR-alpha KO

TR-α1 (cardiac and skeletal muscles)
TR-β1 (brain, liver and kidney)
TR-β2 (limited to the hypothalamus and pituitary)

Dellovade, Nature Neurocience 2000

Schilddrüse und fetale Entwicklung



Williams, J Neuroendocrinology 2008

Leitlinen SD-Schwangerschaft

Europäische SD Gesellschaft 2014

Begriffe:

Latente Hypothyreose: TSH über Trimenon spez. Referenzbereich

Isolierte Hypothyroxinämie: (f)T4 < 2.5 Perzentile (Trimenon spez. Referenzbereiche)

Ursachen: Autoimmun, Jodmangel

Assoziation mit negativen Ergebnissen für Mutter und Kind.
Keine Evidenz für verbesserte Ergebnisse unter T4 Therapie

Lazarus et al., Europ Thyroid Journal 2014

Maternal thyroid function and psychopathology of the child
Maternal Hypothyroidism

Andersen (2014b)	Retrospective; N = 542 100, all live-born singletons born between 1980 and 1990 in Denmark	–	Hospital-diagnosed or treated hypothyroidism before 1996 (N = 3979) (information obtained from DNHR and DNPR)	–	Prescription of anxiolytics, antipsychotics, and antidepressants at least twice (information obtained from DNPR)	15–31 years	Maternal hypothyroidism was associated with an increased risk of prescription of anxiolytics and antipsychotics (adjusted hazard ratio (aHR) 1.23 and 1.22 respectively)
Päkkilä (2014)	Longitudinal; N = 5131 mother–child pairs (Northern Finland Birth Cohort 1986)	TSH, fT4, TPO-Ab	TSH > 3.1 mU/l (first trimester) or TSH > 3.5 mU/l	Mean (SD) = 10.7 (2.8) weeks GA	Rutter B2 scale (teacher-rated); combined ADHD symptoms defined as total Rutter B2 scores of ⩾9 and 3 or more points from ADHD questions	8 years	In general, there were no significant differences in the odds of ADHD symptoms in children born to mothers with high and normal serum TSH, but girls had a 1.4-fold odds of combined ADHD symptoms with every natural log increase in maternal TSH

Moog et al, Neuroscience 2017

Maternal thyroid function and psychopathology of the child

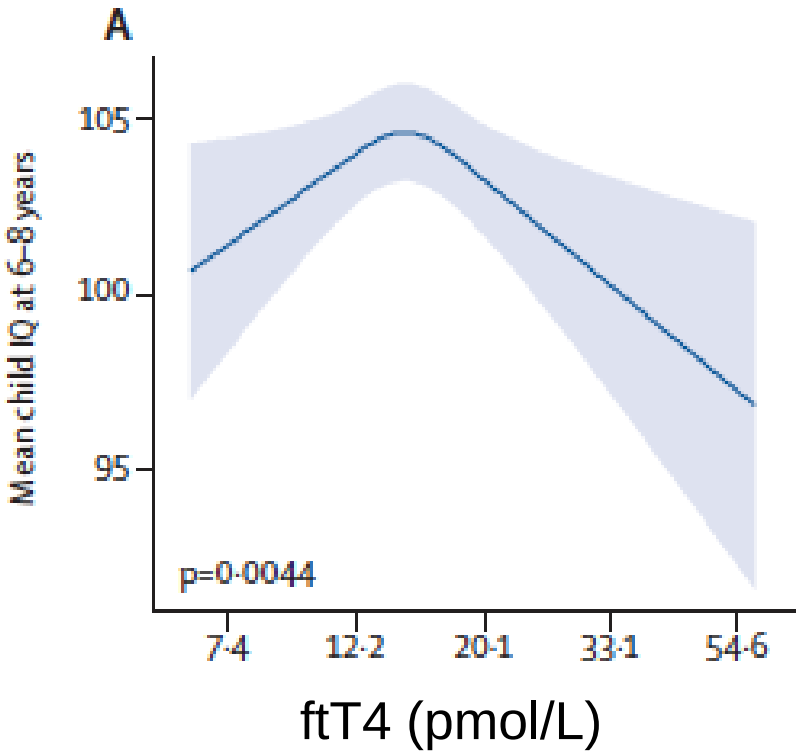
Hypothyoxinemia

Modesto (2015)	Longitudinal; N = 3873 mother–child pairs (Generation R cohort)	TSH, fT4, TPO-Ab	fT4 < 5th percentile and TSH < 2.5 mU/l (n = 127)	Mean (SD) = 13.6 (1.9) weeks GA	CPRS-R:S	Mean (SD) = 8.1 (0.2) years	Children of hypothyroxinemic women had higher scores on the ADHD index (7% increase) but not on the Oppositional scale compared to nonexposed children
Roman (2013)	Longitudinal; N = 4039 mother–child pairs (Generation R cohort)	TSH, fT4, TPO-Ab	fT4 < 10th percentile and TSH < 2.5 mU/l (n = 295)/ fT4 < 5th percentile and TSH < 2.5 mU/l (n = 136)	Mean (SD) = 13. 4 (1.9) weeks GA	PDP subscale of the CBCL 1½ -5, SRS; probable autism defined by a PDP score > 98th per-centile and SRS score in the top 5% of the sample (n = 81)	6 years	Severe maternal hypothyroxinemia (fT4 < 5th percentile) was associated with an increased risk of having a probable autistic child (adjusted Odds Ratio (aOR) = 3.89) and with higher scores on the PDP and SRS

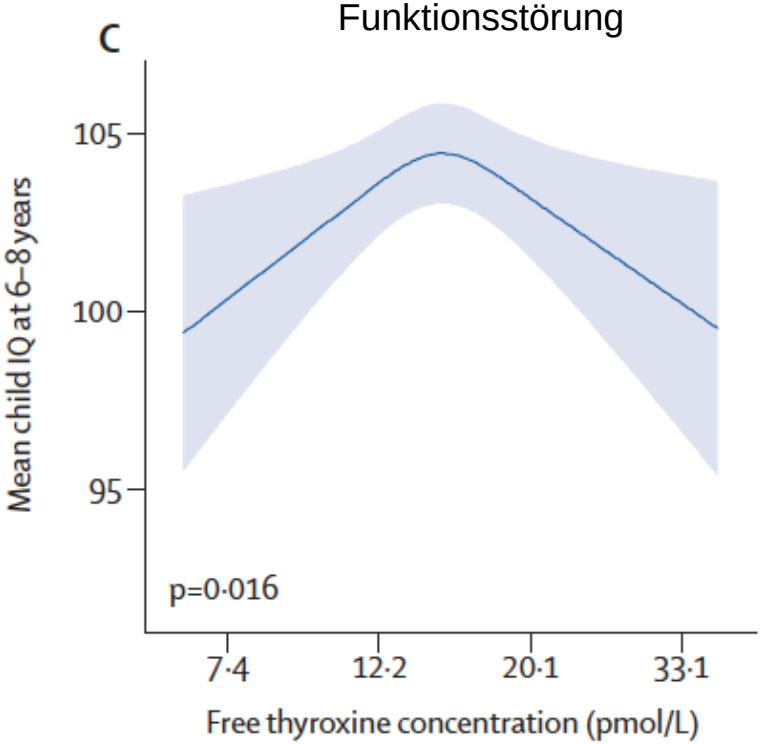
Moog et al, Neuroscience 2017

Zu viel ist auch nicht gut

Generation R Study (Rotterdam)
Blutabnahme in der Schwangerschaft (< 18 SSW)
Nicht verbaler Intelligenztest der Kinder 6 LJ (n = 3839)



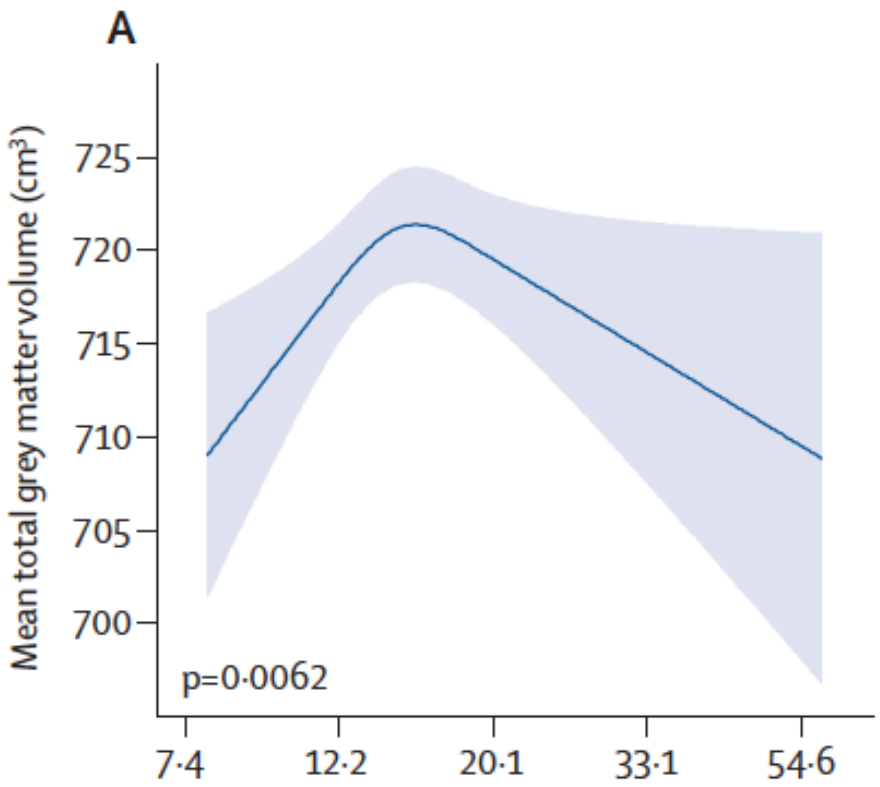
Ohne Mütter mit manifester SD Funktionsstörung



Korevaar et al., Lancet Diabetes Endocrinol 2015

Zu viel ist auch nicht gut !

MRI Scan 8 LJ (n=646)



Korevaar et al., Lancet Diabetes Endocrinol 2015

Therapieziel ?

> 19 Jahre 0.76 - 1.66 ng/dl

Schwangerschaft:

1. Trimenon 0,94 - 1,52 ng/dl

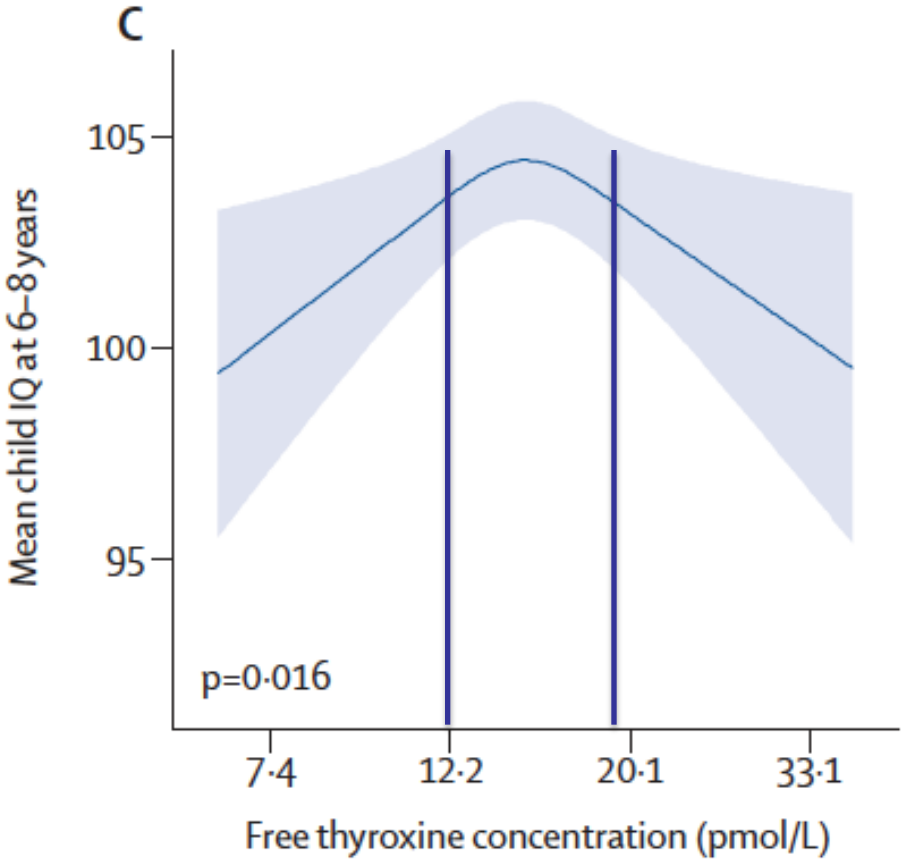
2. Trimenon 0,75 - 1,32 ng/dl

3. Trimenon 0,65 - 1,21 ng/dl

Nur schwache Assoziation TSH mit IQ !

Ohne Mütter mit manifester SD Funktionsstörung

13 SSW



Korevaar et al., Lancet Diabetes Endocrinol 2015

Hyperthyreose – Psyche

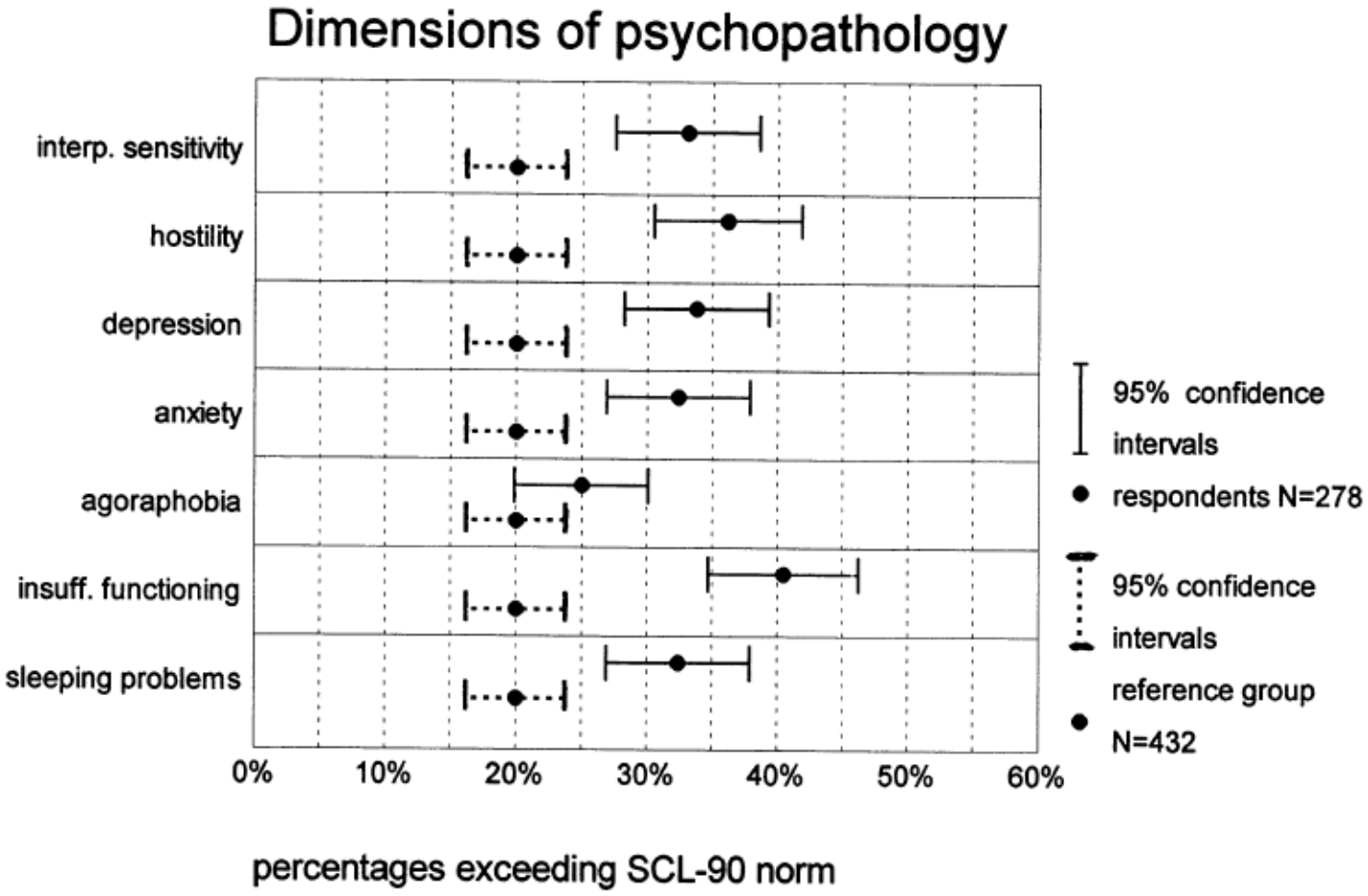
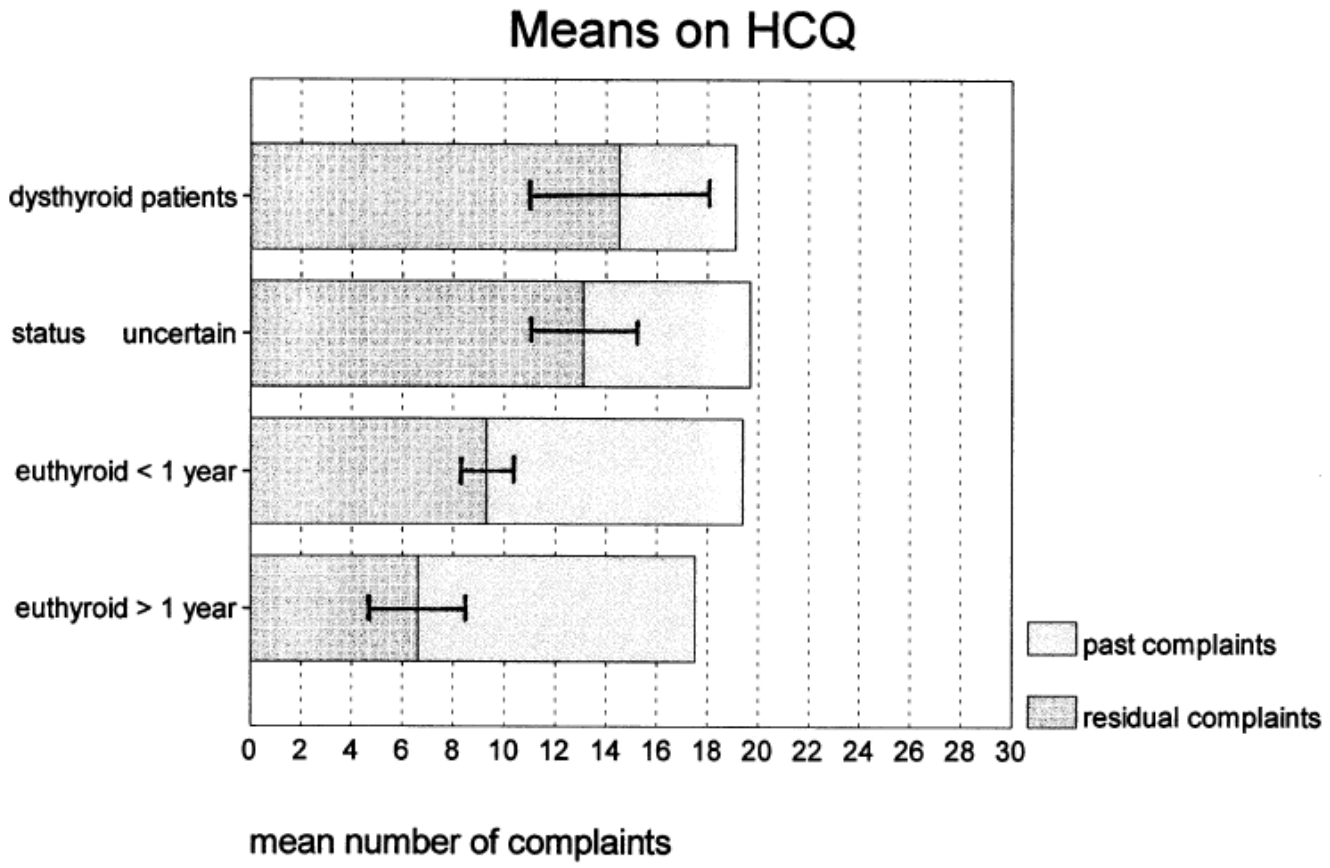


Fig. 2. Dimensions of psychopathology from SCL-90.

Fahrenfort et al., Psychoneuroendocrinology 2000

Hyperthyreose – Psyche



Fahrenfort et al., Psychoneuroendocrinology 2000

Hyperthyreose – fMRI

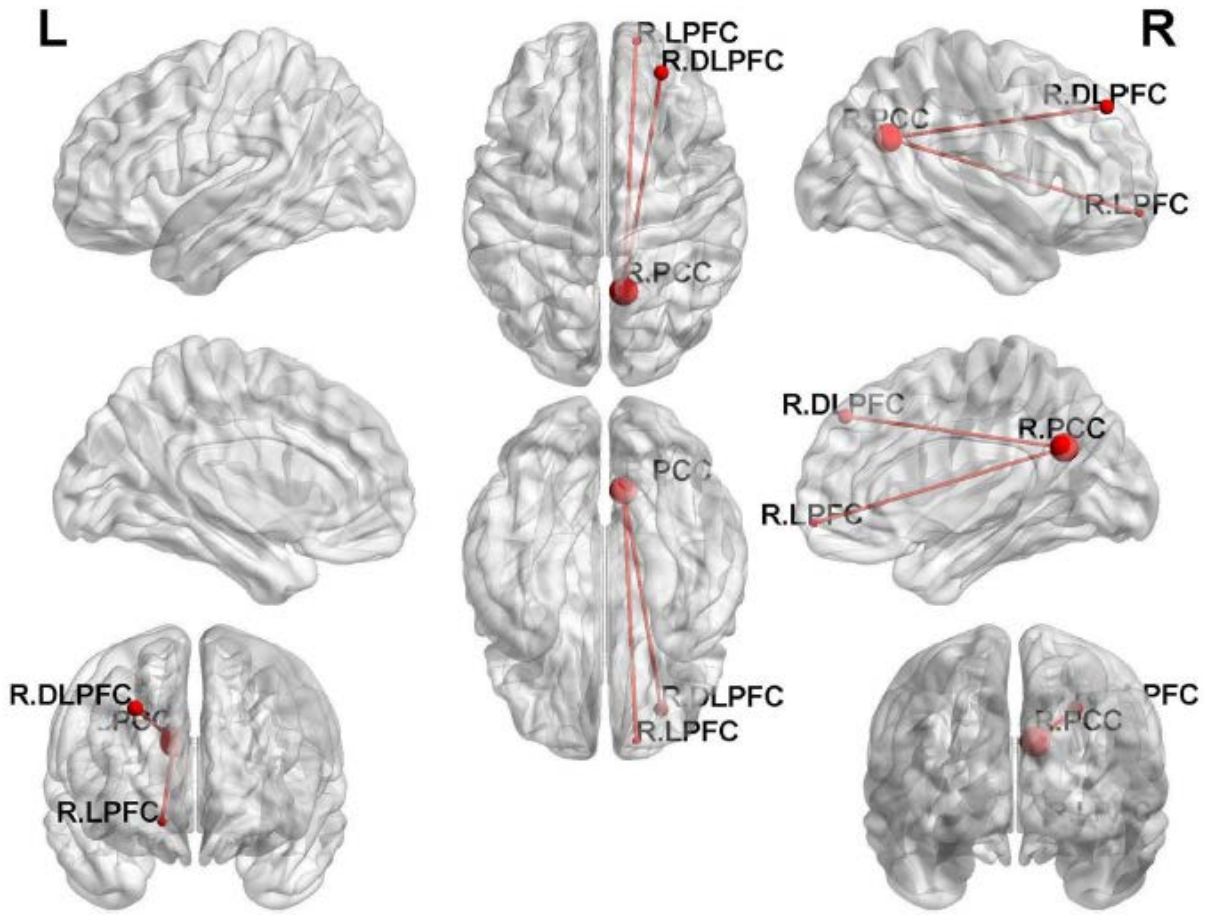
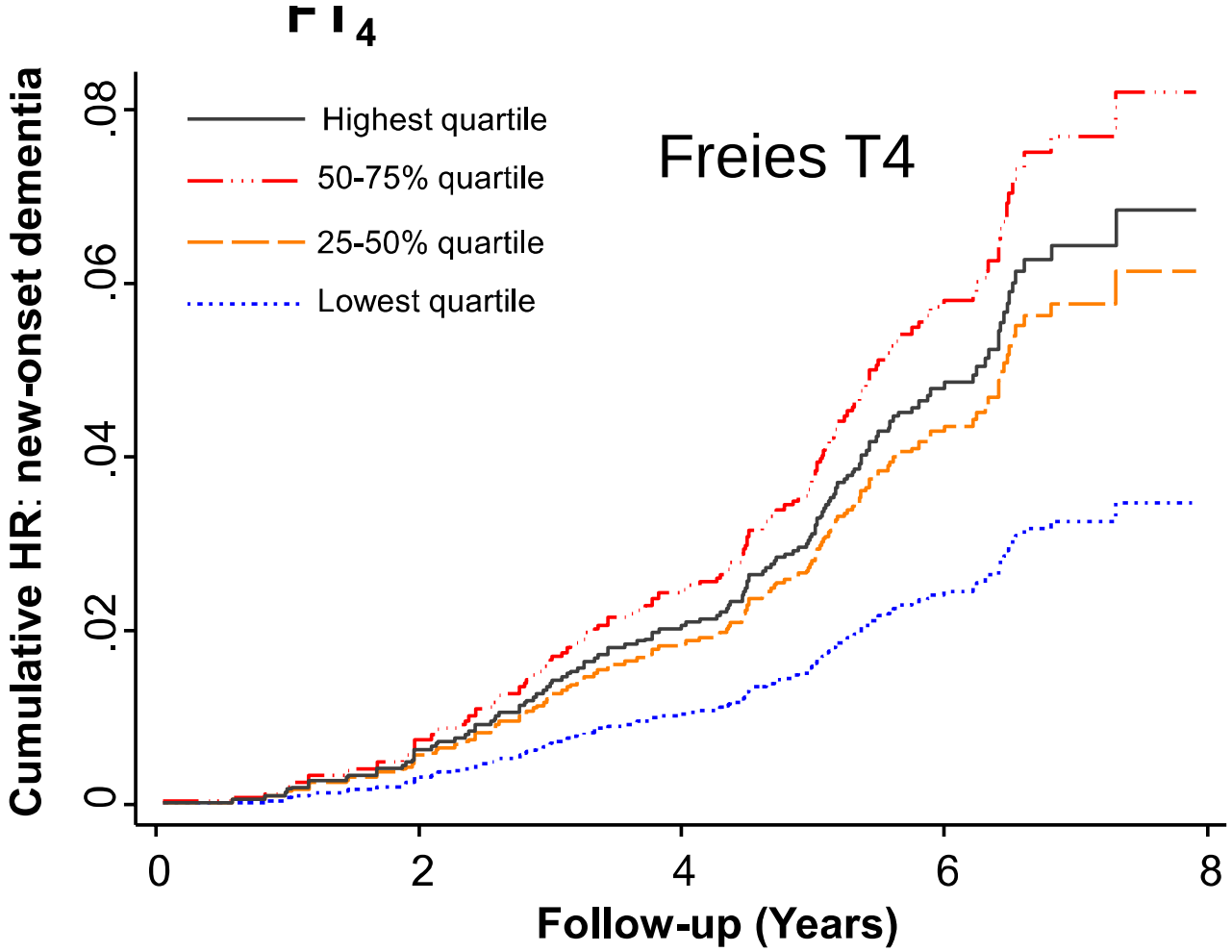


Figure 3. Differences in brain FC in 19 patients before and after one month of anti-thyroid therapy for one month ($p < 0.001$, AlphaSim-corrected or small volume-corrected). The red color indicates increased FC after anti-thyroid therapy compared with hyperthyroidism status.

Liu et al., Scientific Reports 2017

Latente Hyperthyreose – Demenz



Yeap et al., JCEM 2012

Latente Hyperthyreose – Demenz

TABLE 3. Possible mechanism for association of cognitive impairment with SH or low serum TSH

A. Excess circulating thyroid hormone resulting in neuronal loss.
B. Primary neurodegeneration causes reduced central nervous system TRH secretion, hence lower TSH.
C. SH and low TSH are biomarkers for age, and so are associated with other diseases of advanced age including dementias.
D. Subjects with cognitive impairment have a high burden of comorbidity, and association is due to nonthyroidal illness and drug effects on serum TSH.

Gan & Pearce, JCEM 2012

Latente Hyperthyreose – Mortalität

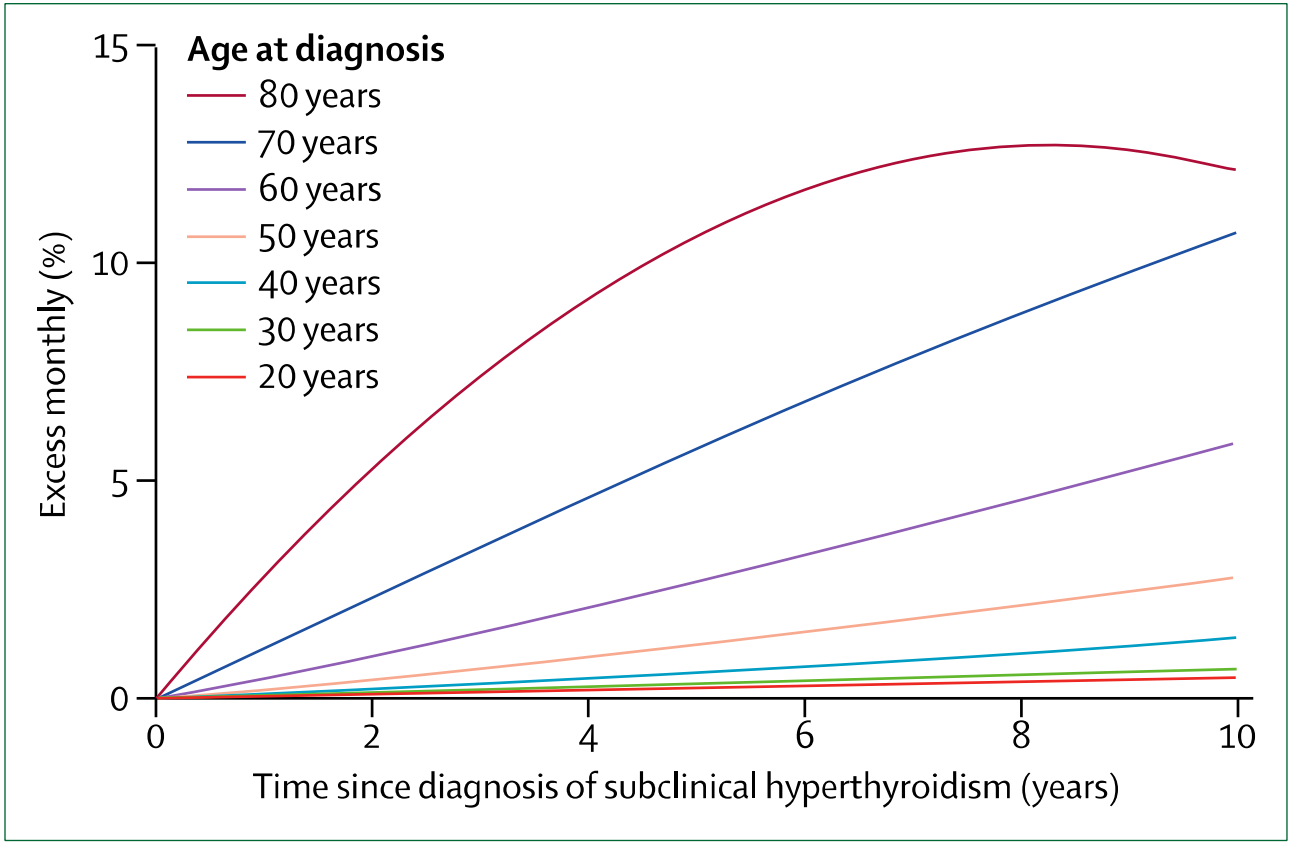
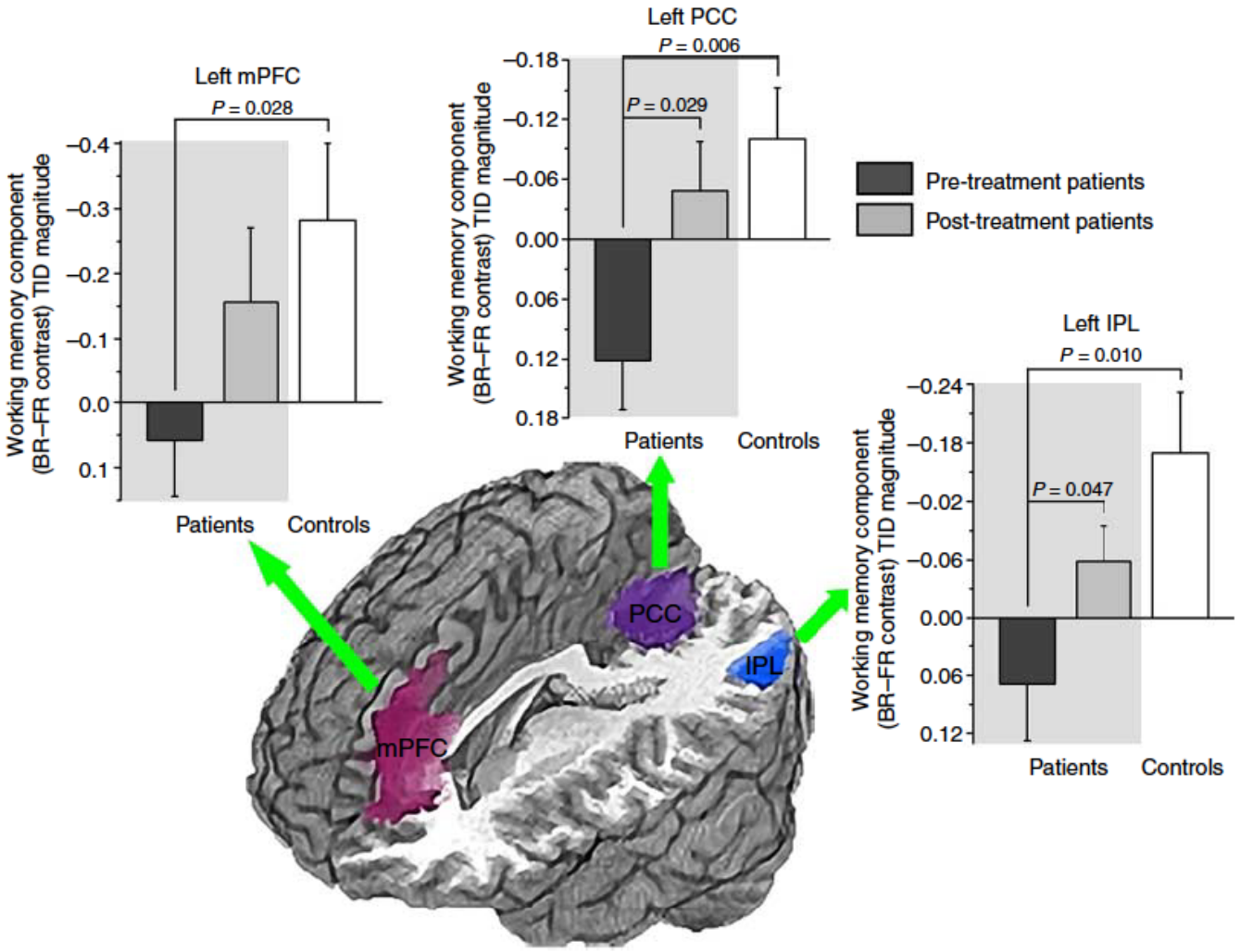


***Figure 3*: Excess all-cause mortality in men with subclinical hyperthyroidism according to a meta-analysis of aggregated data from cohort studies and life-tables**

Cooper & Biondi, Lancet 379:1142, 2012

Manifeste HypOrthyreose:
Gedächtnis



He et al., Eur J Endocrinol 2011

So erschöpft....

Subjects	n	*Self-reported fatigue*	
		%	*RR [CI]*
Euthyroidism	5439	34.0	Reference
Thyroid dysfunction[a]	458	39.6	1.1 [0.9–1.3]
Overt thyrotoxicosis	9	55.6	1.6 [0.7–3.9]
Subclinical thyrotoxicosis	196	37.0	1.0 [0.8–1.3]
Subclinical hypothyroidism	216	42.8	1.1 [0.9–1.4]
Overt hypothyroidism	22	28.6	0.8 [0.4–1.8]

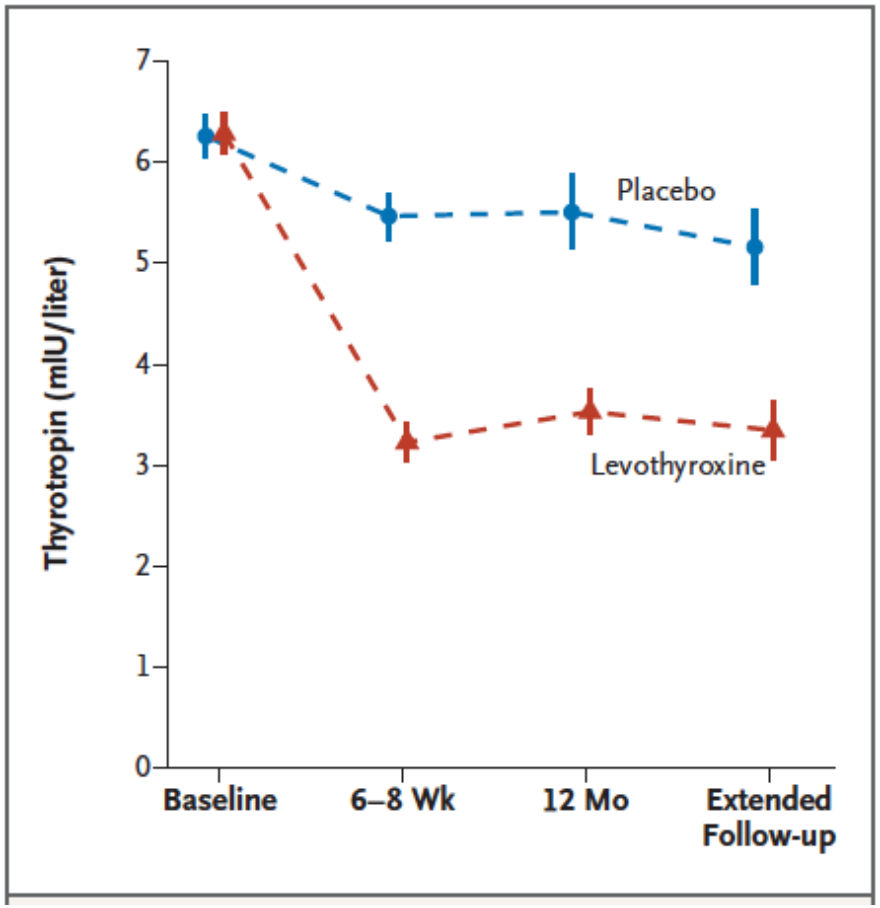
Van de Ven et al., Thyroid 2012

Latente HypOthyreose.....

Subjects	n	*Self-reported fatigue* %	*RR [CI]*
Total population			
Without previously known thyroid disorder	5897	34.4	Reference
With previously known thyroid disorder	328	50.0	1.2 [1.0–1.4][a]
Euthyroid subjects			
Without previously known thyroid disorder	5439	34.0	Reference
With previously known thyroid disorder	221	52.3	1.3 [1.0–1.5][a]
Subjects with thyroid dysfunction			
Without previously known thyroid disorder	458	39.6	reference
With previously known thyroid disorder	107	45.1	1.1 [0.8–1.5]

Van de Ven et al., Thyroid 2012

T4 Therapie bei latenter Hypothyreose



74.4 years, a median dose of 50 µg. We found no differences in the mean change at 1 year in

- Hypothyroid Symptoms
- Tiredness
- Muscle function, cognitive function, blood pressure, BMI,...

Levothyroxine provided no apparent benefits in older persons with subclinical hypothyroidism.

Rodoni et al., NEJM 2017

T4 Therapie macht alles gut ...?

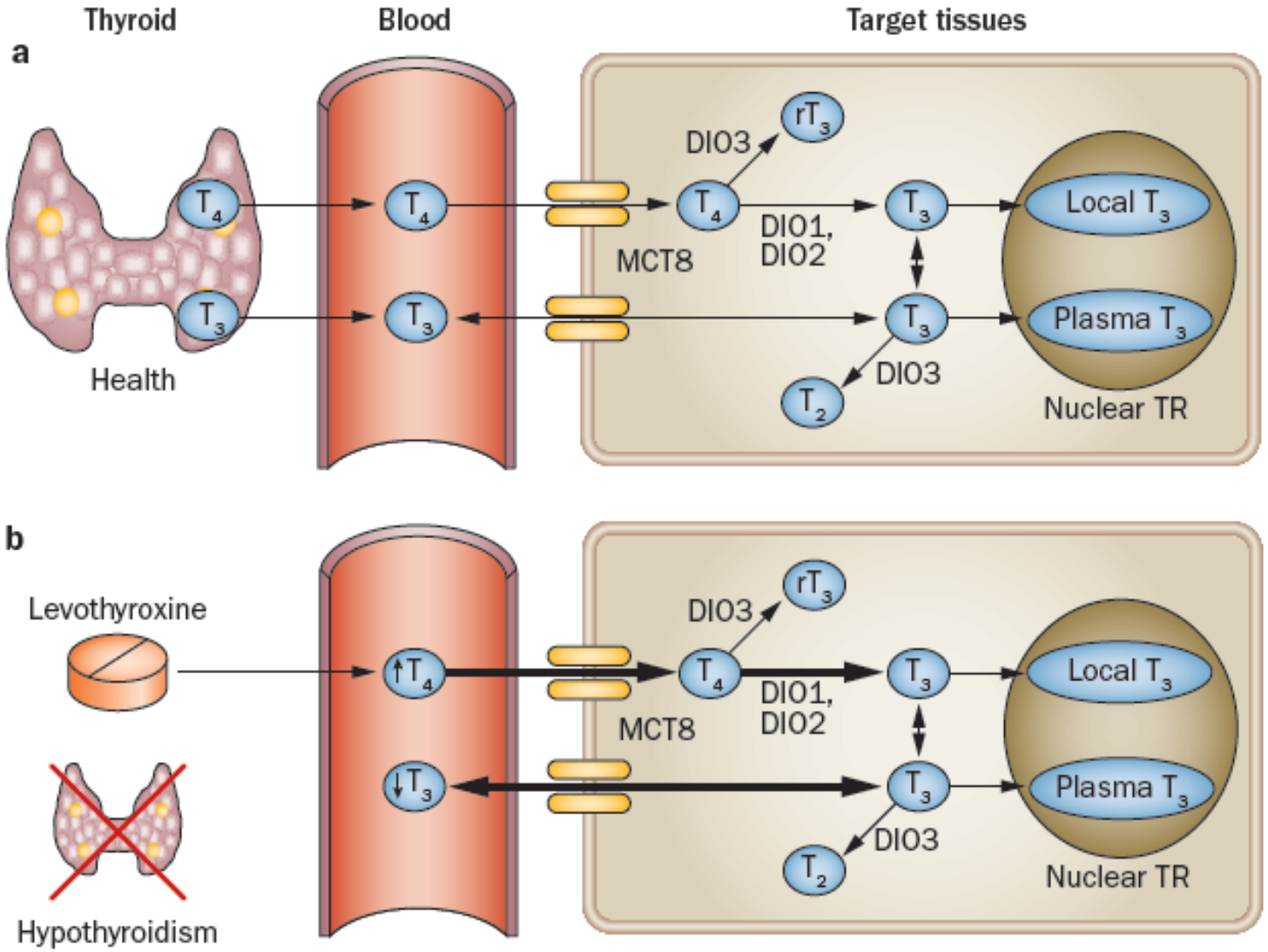
Table 1 | Patient-reported outcomes in hypothyroid patients on levothyroxine

n (Patients/ controls)	Test	Outcome parameter	Results in patients versus controls*	*P* value
UK[32]				
572/535	GHQ-12‡	Score≥3	32.3% versus 25.6%	0.012
583/534	TSQ‡	Score ≥3	46.8% versus 35.0%	<0.001
Netherlands[33]				
140/1,778	MCT‡	Time to complete task	21.6 s versus 17.7 s	0.001
134/124	PASAT§	Total score	146 versus 171	0.001
141/492	CVLT§	Recall score‖	–1.1 versus 0.0	0.001
139/284	RIVER§	Recall score¶	42 versus 50	0.001
140/2,368	SCL-90‡	Total score	156 versus 118	0.001
140/1,068	SF-36§	Mental health score	65 versus 77	0.001
140/1,063	SF-36	Vitality score	43 versus 67	0.001
Norway[34]				
1,546/18,137	HADS‡	Anxiety score ≥8	23.4% versus 18.3%	<0.001
1,546/18,137	HADS	Depression score ≥8	18.4% versus 12.7%	<0.001

*Absolute values, except where units are given. ‡Higher scores indicate worse outcomes. §Higher scores indicate better outcomes. ‖Standardized against a value of 0 in controls. ¶Standardized against a value of 50 in controls. Abbreviations: CVLT, California Verbal Learning Test; GHQ, General Health Questionnaire; HADS, Hamilton Anxiety and Depression Score; MCT, Memory Comparison Task (paper and pencil version); PASAT, Paced Auditory Serial Addition Task; RIVER, Rivermead Behavioural Memory Test Story Recall; SCL-90, Symptom Check List; SF-36, RAND-36 version of the Medical Outcome Study Short Form General Health Survey; TSQ, Thyroid Symptom Questionnaire.

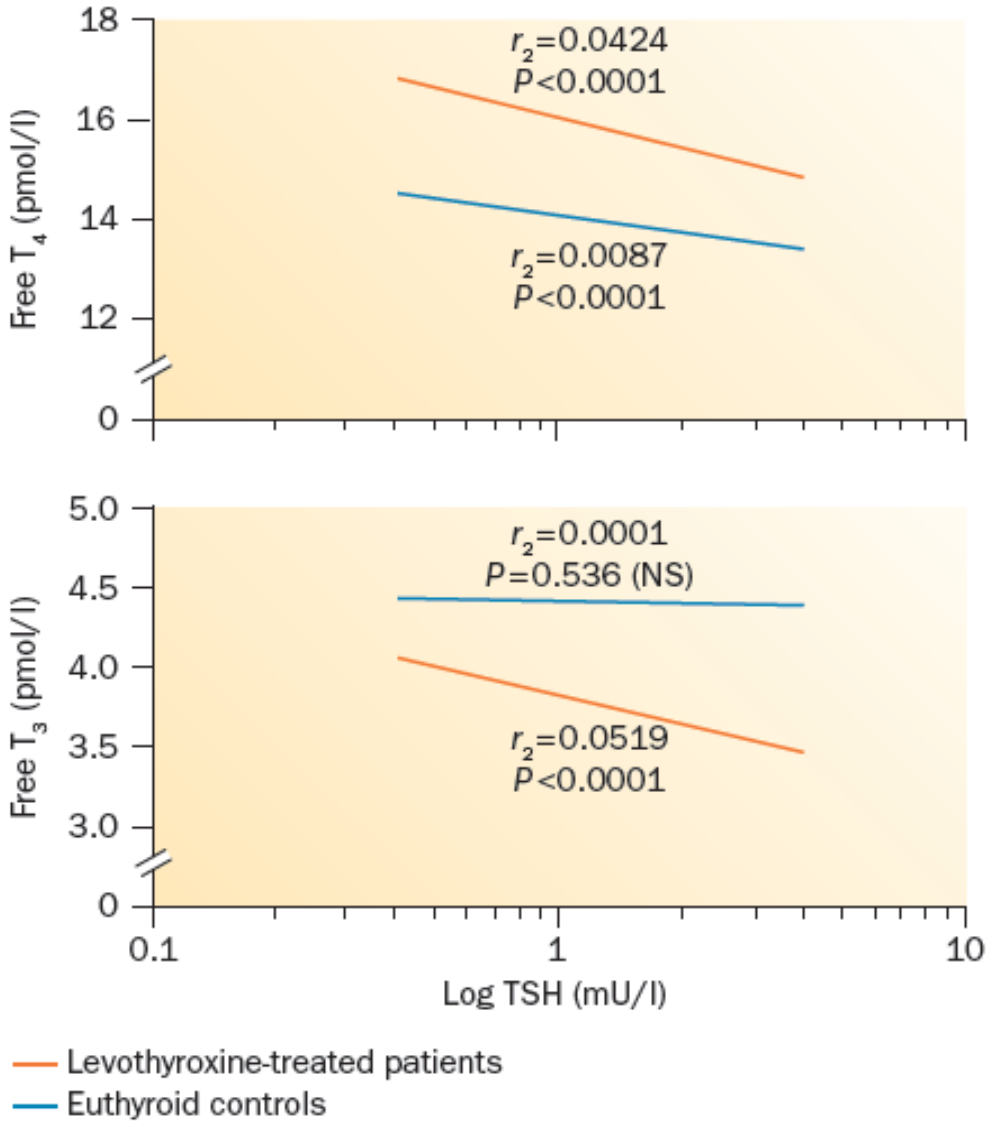
Wiersinga., Nat Rev Endocrinol 2014

T4 Therapie



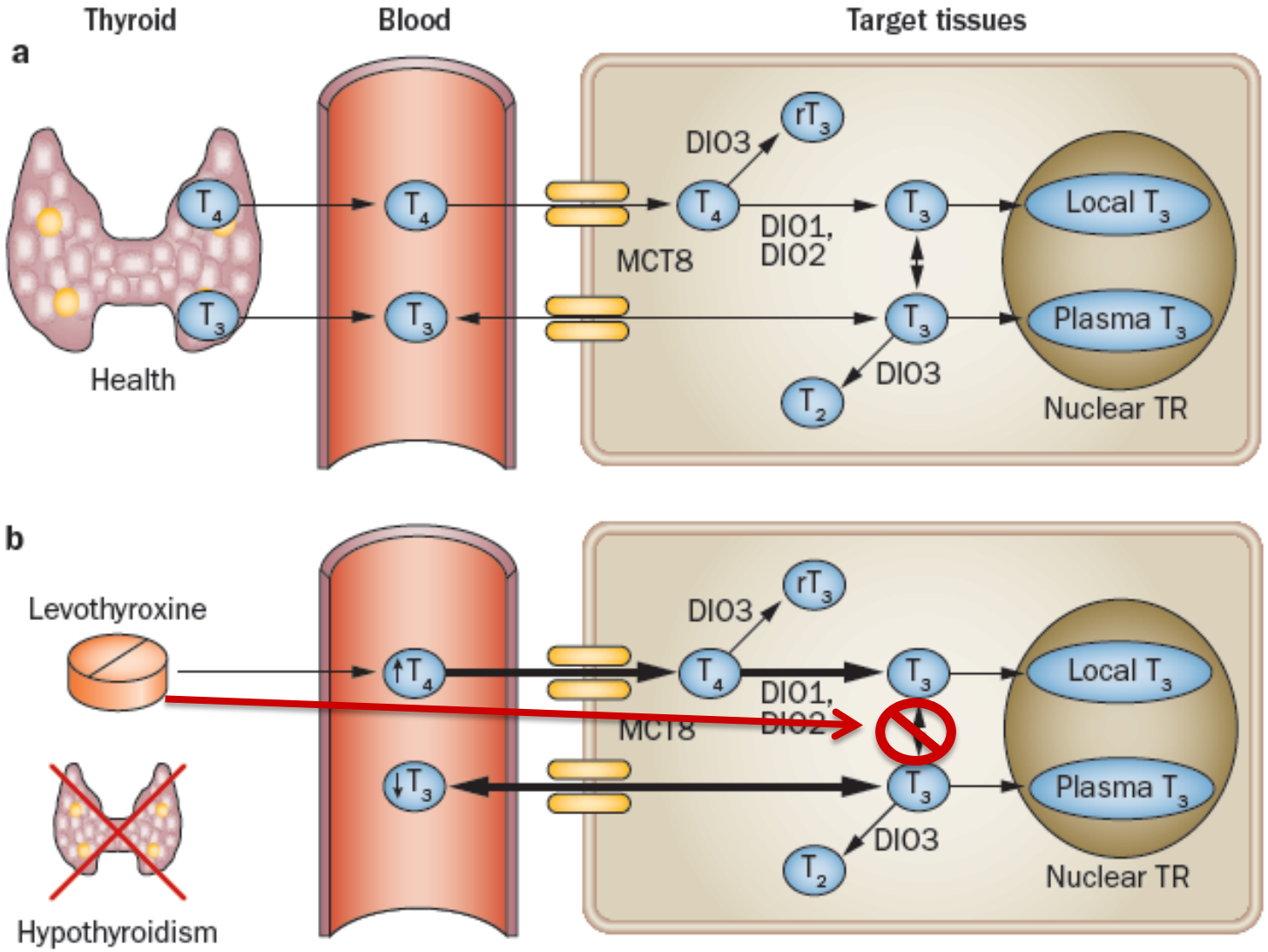
Wiersinga., Nat Rev Endocrinol 2014

T4 Therapie



Wiersinga., Nat Rev Endocrinol 2014

T4 Therapie

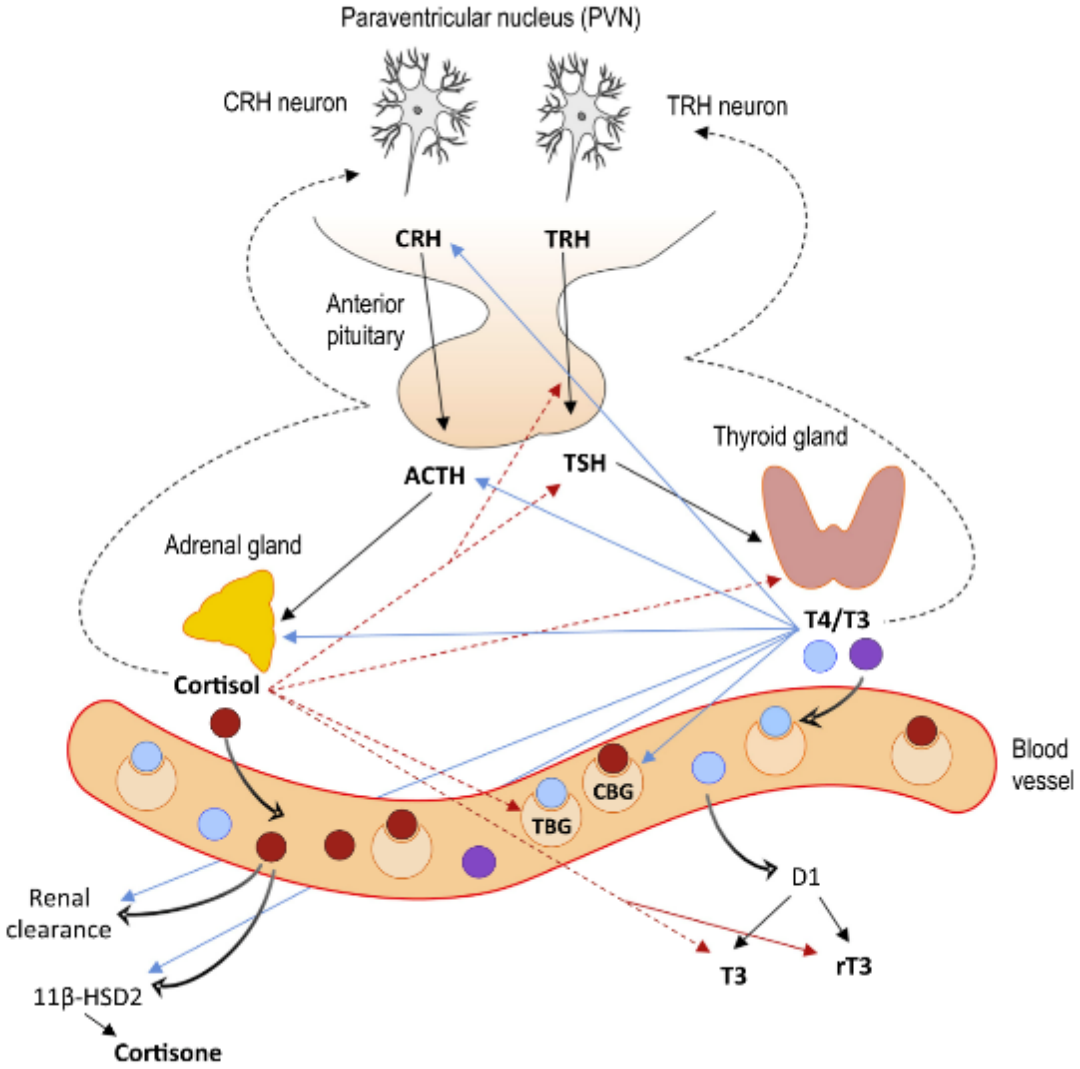


Wiersinga., Nat Rev Endocrinol 2014

Schilddrüse und Affekterkrankungen

Only a fraction of patients with major depression show biomedical signs of thyroid dysfunction (Bauer et al., 2008; Hage and Azar, 2012).

25–30% of depressed patients show a blunted TSH response to TRH (Loosen, 1985). These findings suggest a chronic TRH hypersecretion by the PVN leading to a downregulation of pituitary TRH receptors, which may be mediated by elevated levels of cortisol.

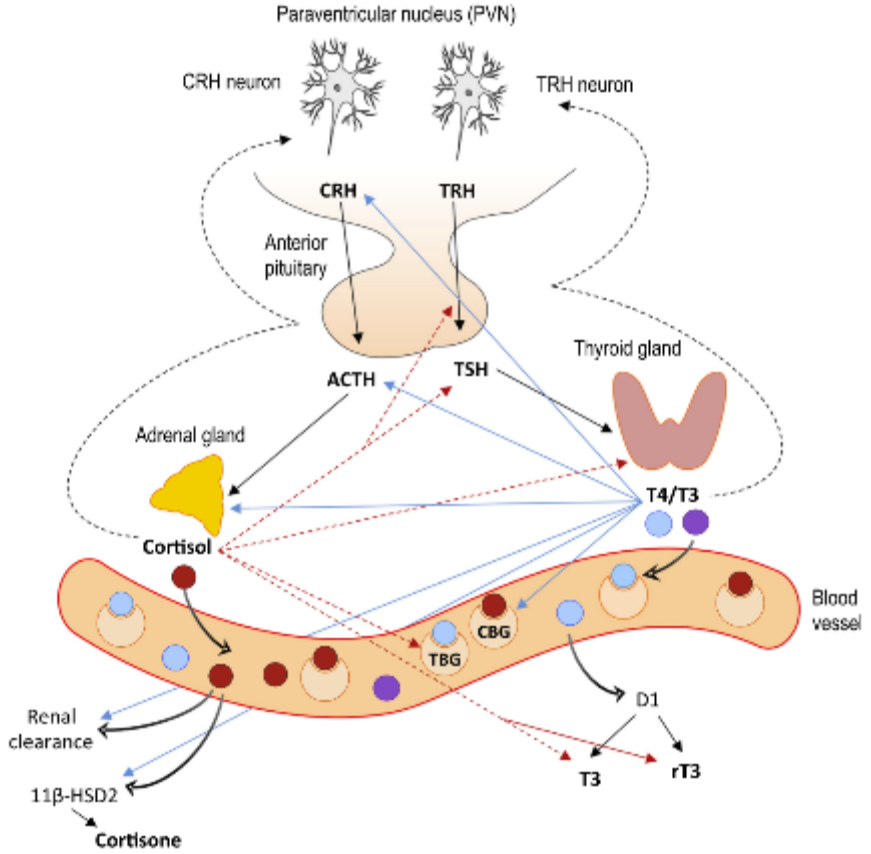


Solid lines represent positive associations, and dashed lines represent negative associations.
Cortisol:

- **inhibitory effect on the release of TSH and THs (T4 and T3)**
- **switch within D1 activity toward a preferential inactivation of T4 into rT3**

THs is associated with a general activation of the HPA axis:

N. K. Moog et al. Neuroscience 342 (2017) 68–100



Hypothesis: Depression is related to brain hypothyroidism together with systemic euthyroidism (Jackson, 1998), perhaps secondary to a cortisol-related decrease in D2 activity (Hidal and Kaplan, 1988).

N. K. Moog et al. Neuroscience 342 (2017) 68–100

Schilddrüse und Affekterkrankungen

Table 1. Treatment of therapy-resistant patients with affective illness with high doses of thyroxine (T_4) (review)

Study	Diagnosis	*n*	T_4 dose (μg/d)	Outcome*	
				Prophylactic	Therapeutic
1. Stancer and Persad (1982)	Rapid-cycling bipolar	10	240–500	8 R, 2 NR	
2. Leibow (1983)	Rapid-cycling bipolar	1	400	1 R	
3. Bauer and Whybrow (1990)	Rapid-cycling bipolar	11	150–400	10 R, 1 NR	
4. Hurowitz and Liebowitz (1993)	Rapid-cycling bipolar	2	200–350	2 R	
5. Baumgartner et al. (1994b)	Bipolar (non-rapid-cycling)	6	250–500	6 R	
6. Bauer et al. (1998)	Unipolar and bipolar	17	300–500	7 R, 1 PR, 2 NR	8 R, 2 PR, 7 NR
7. Rudas et al. (1999)	Chronic depression or dysthymia	9	150–300	4 R	5 R, 1 PR, 3 NR
8. Spoov and Lahdelma (1998)	Major depression	22	200		T_4 augmentation superior to lithium augmentation

* R, responder; PR, partial responder; NR, non-responder.

Baumgartner, Int. J . Neuropsychopharmacology 2000

Schilddrüse und chronischer Stress

Patienten mit „post traumatic stress disorder“

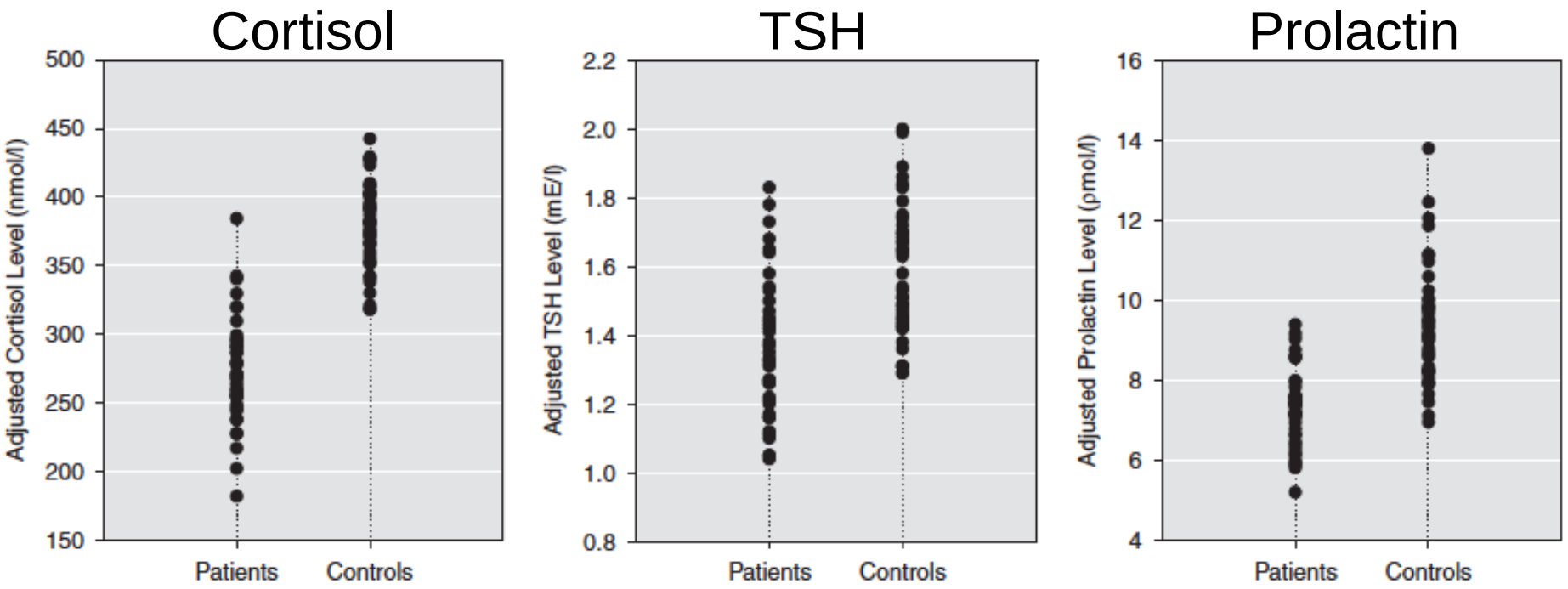
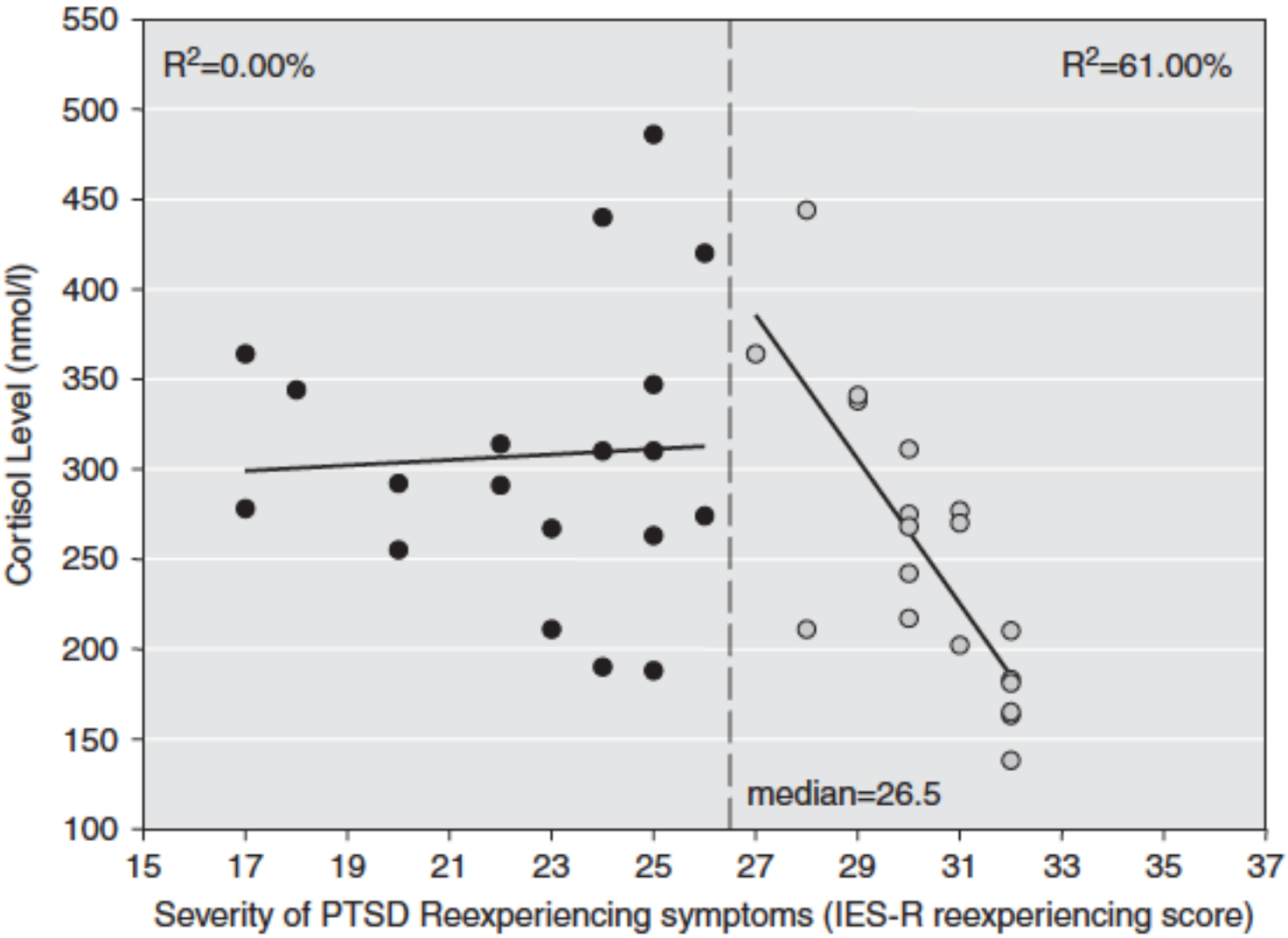


Figure 1 Dot plots for cortisol, TSH and free T4 hormone levels adjusted for sex, sex*group, smoking, smoking*group, age and body mass index (BMI) for PTSD patients and healthy comparisons.

Olff M et al, Psychoneuroendocrinology 2006

Schilddrüse und chronischer Stress



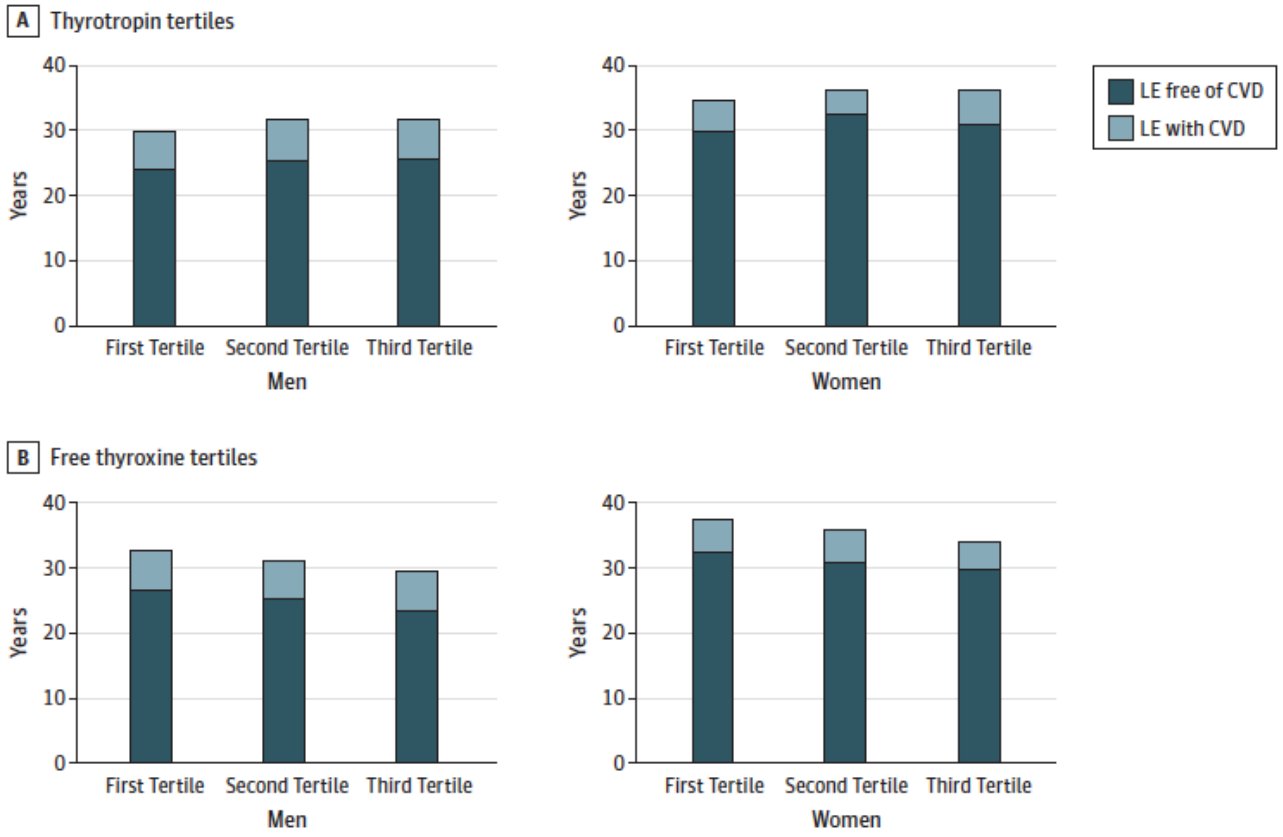
Olff M et al, Psychoneuroendocrinology 2006

Schilddrüse und Lebenserwartung

N=7785, 65 Jahre, 53 % Frauen

Menschen mit niedrig normale Schilddrüsenfunktion leben 3.5 Jahre länger

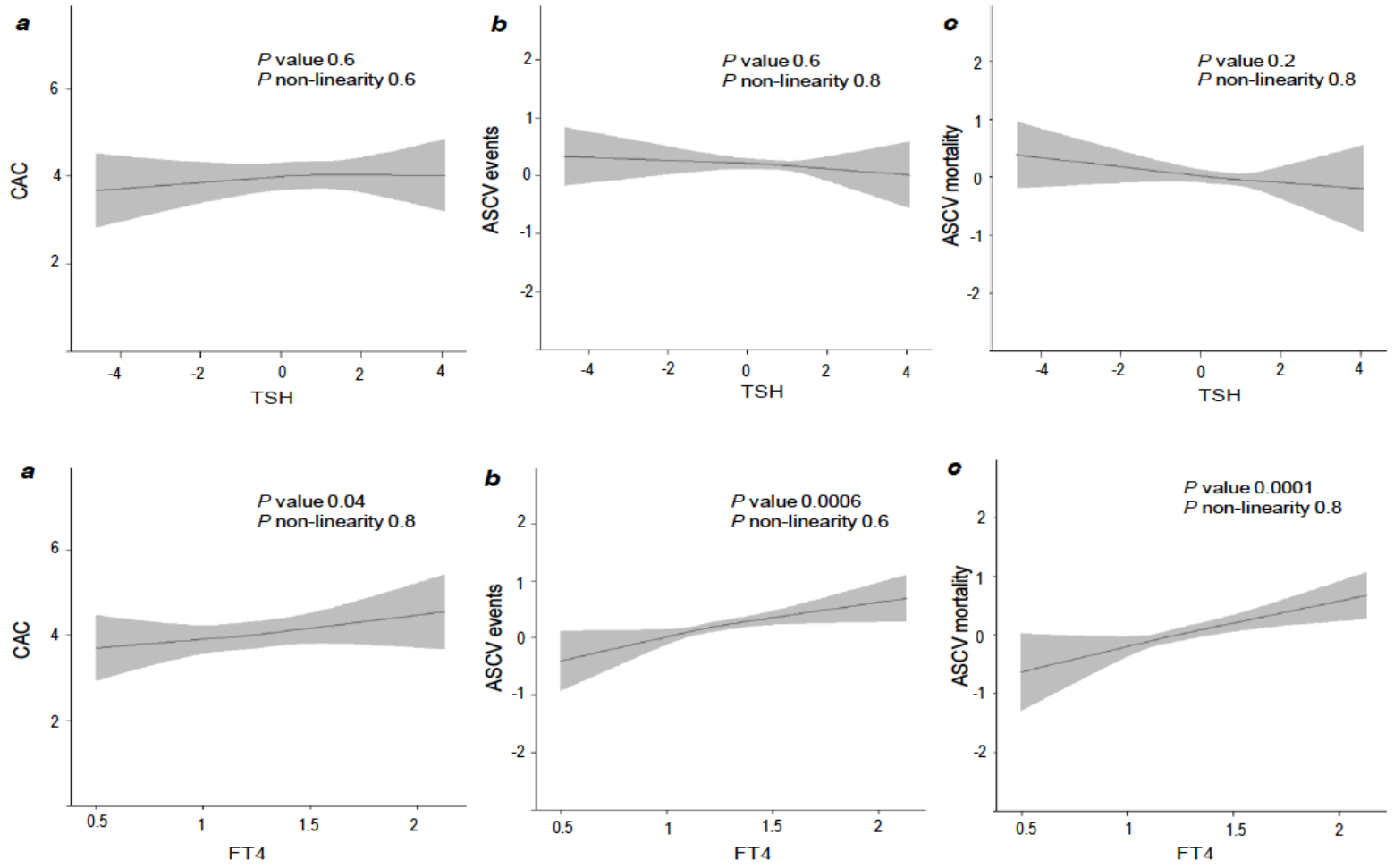
Figure. Life Expectancy (LE) With and Without Cardiovascular Disease (CVD) at Age 50 Years Among Thyrotropin and Free Thyroxine Tertiles, in Men and Women



Rotterdam Study; Bano et al, JAMA 2017

Schilddrüse und Atherosklerose

N=9420, 65 Jahre, 57 % Frauen
fT4 ist mit einem erhöhten Atherosklerose-Rrisiko assoziiert.



Rotterdam Study; Bano et al, Circ Res 2017

Schilddrüse und Psyche

Zusammenfassung:

Manifeste Funktionsstörungen führen zu den bekannten Symptomen, die sich durch Therapie bessern

Einfluss der mütterlichen Schilddrüsenfunktion auf den Feten

Schilddrüse und Psyche

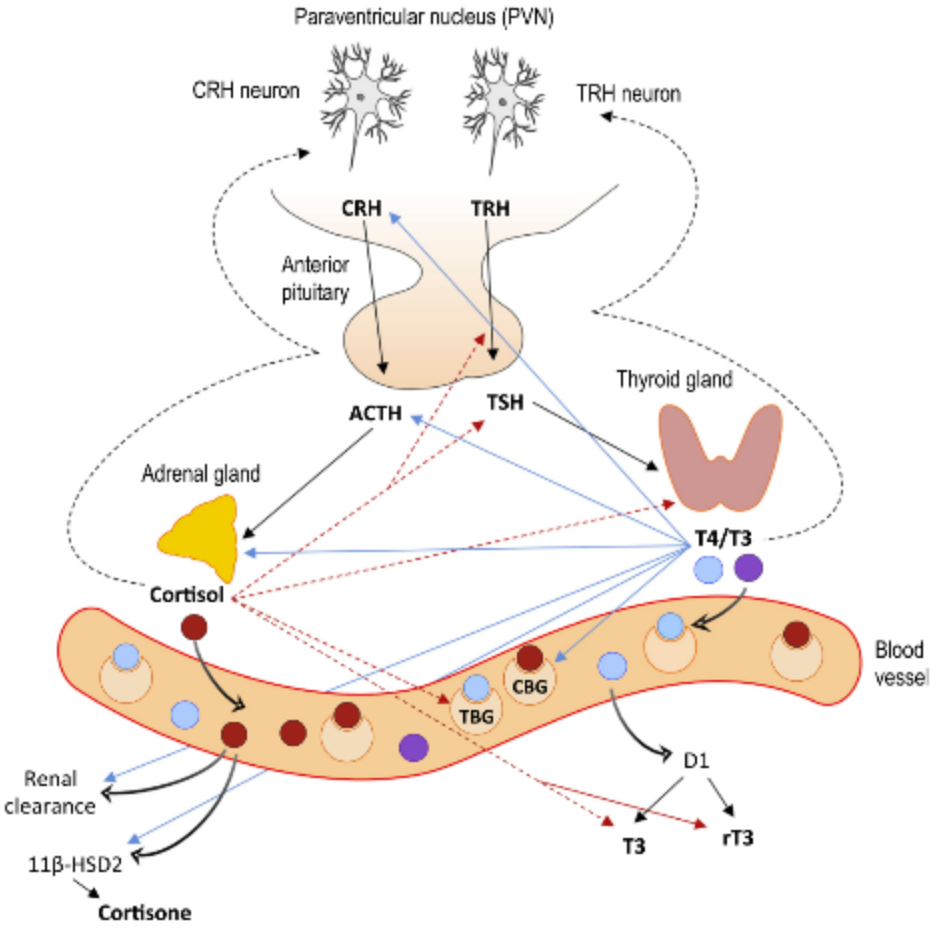
Milde (latente) Funktionsstörungen: unklares Bild

- Schwierigere Labordiagnose

- Patientenselektion („wer sich schlecht fühlt macht SD Test“)
- Wissen um chronische SD Erkrankung macht Symptome ?

- Thyroxintherapie ausreichend um Beschwerden zu bessern ?
- Zentrale Mechanismen unklar

Vielen Dank !



N. K. Moog et al. / Neuroscience 342 (2017) 68–100

Interactive relationship between hormones of the hypothalamic–pituitary–thyroid axis (HPT) and the hypothalamic–pituitary–adrenal (HPA) axis. Depicted are the HPT and HPA axes and the regulatory circuits within the respective systems, as well as the effect of alterations on the level of the adrenal (red arrows) on HPT function and the thyroid (blue arrows) on HPA function. Solid lines represent positive associations, and dashed lines represent negative associations. Increased levels of cortisol have an inhibitory effect on the release of TSH from the pituitary and THs (T4 and T3) from the thyroid, as well as on the synthesis of the carrier protein TBG. Cortisol also promotes a switch within D1 activity toward a preferential inactivation of T4 into rT3, instead of an activation of T4 into T3. Increased availability of THs is associated with a general activation of the HPA axis on all levels and increased levels of the carrier protein CBG. However, THs also promote renal clearance and the metabolism of cortisol into its inactive form cortisone. Abbreviations: 11b-HSD2 = 11b-hydroxysteroid dehydrogenase 2; ACTH = adrenocorticotropic hormone; CBG = cor- tisol-binding globulin; CRH = corticotropin-releasing hormone; D1 = deiodinase 1; rT3 = reverse T3; T3 = triiodothyronine; T4 = thyroxine; TBG = thyroxine-binding globulin; TRH = thyrotropin-releasing

In contrast to other forms of acute and chronic stress, stress associated with traumatic exposures (e.g. post-traumatic stress disorder (PTSD), childhood abuse) has generally been associated with an activation of thyroid function and thyrotoxicosis. As summarized by Wang (2006), elevated T3 concentrations have been reported in several samples of combat veter- ans with PTSD, including World War II, Vietnam, Israeli and Croatian samples. Increased T3 and/or decreased TSH levels were also found in civilian trauma patients (Olff et al., 2006)

GC administration decreases plasma TSH levels and attenuates the pituitary TSH response to TRH stimulation (Faglia et al., 1973; Banos et al., 1979; Ahlquist et al., 1989; Taylor et al., 1995).
A decrease in serum T3 is also observed in athyreotic patients on L-T4 substitution therapy (Duick et al., 1974; Chopra et al., 1975; Degroot and Hoye, 1976), which suggests that these changes are, at least in part, due to a GC-induced shift in the metabolism of T4, whereby

conversion of T4 to T3 is reduced in favor of a conversion of T4 to the inactive metabolite rT3.
Effect of TH administration and thyroid dysfunction on HPA function. Conversely, administration of THs to rats produces hypertrophy of the adrenal gland and increases in corticotrophin-releasing hormone (CRH), ACTH and GC secretion and/or production (Boler and Moore, 1982; Shi et al., 1994; Johnson et al., 2005, 2013). The same phenomenon is seen in hyperthyroid patients (Felber et al., 1959; Hellman et al., 1961; Kenny et al., 1967), although there may be a decreased adreno- cortical reserve in the chronic state, which results in a lower GC response to ACTH stimulation (Tsatsoulis et al., 2000; Johnson et al., 2005). The effect of TH on HPA activity may be partly mediated by an increased metabolic clearance of cortisol from the blood in the hyper- thyroid state (Brown et al., 1958; Kenny et al., 1967), or the preferential metabolism of cortisol into its biologically inac- tive form, cortisone (indicated by increased urinary con- centrations of the cortisone metabolite THE) (Hellman

The opposite phenomenon is seen in thyroidec- tomized or PTU-treated rats as well as in human patients with hypothyroidism. Absence of TH results in decreased adrenal weight (Kamilaris et al., 1991; Tohei, 2004), decreased production of CRH, ACTH and GCs (Hellman et al., 1961; Kenny et al., 1967; Fortier et al., 1970; Shi et al., 1994), a reduced adrenocortical response to ACTH (Kamilaris et al., 1991; Tohei, 2004), and a com- pensatory increase in the ACTH response to CRH (Kamilaris et al., 1991; Tohei, 2004). However, in the hypothyroid state there seems to be also a decreased clearance of cortisol (Br
The opposite phenomenon is seen in thyroidec- tomized or PTU-treated rats as well as in human patients with

Demenz SD Rotterdam study