Increased Prevalence of Subclinical Hypothyroidism and Thyroid Autoimmunity in Depressed Adolescents:

Results From a Clinical Cross-Sectional Study in Comparison to the General Pediatric Population

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ABSTRACT

Objective: The study was undertaken to determine the prevalence of subclinical and overt thyroid dysfunction as well as thyroid autoimmunity in depressed adolescents in comparison to the general pediatric population. Additionally, the relationship between parameters of thyroid function and Beck Depression Inventory-II (BDI-II) scores was examined.

Methods: Parameters of thyroid function (thyrotropin, free thyroxine, thyroid peroxidase antibodies) and prevalence of thyroid dysfunction and autoimmunity were determined in 360 adolescents (11–19 years) with at least mild depression (BDI-II score > 13) between June 2016 and December 2019 and in a representative reference cohort without evidence of impaired mental health from a nationwide survey (German Health Interview and Examination Survey for Children and Adolescents [KiGGS], 2003–2006).

Results: There was a higher prevalence of thyroid peroxidase antibody positivity in depressed adolescents (mean ± SD BDI-II, 30.0 ± 10.4) compared to KiGGS participants (depressed adolescents: 5.8%, 95% CI [3.7–8.6]; odds ratio [OR] 1.9, $P = .009$, $d = 0.36$; KiGGS participants: 3.1%, 95% CI [2.5–3.9]). The prevalence of subclinical hypothyroidism was likewise higher in depressed adolescents (9.1%, 95% CI [6.3–12.4] vs KiGGS participants: 2.1%, 95% CI [1.6–2.7]; OR 4.7, $P < .001$, $d = 0.85$), but no other types of thyroid dysfunction had a higher prevalence. There was no significant relationship between parameters of thyroid function and BDI-II scores, as examined by multiple regression considering relevant covariates. The positive results were verified in a subsample of patients with a confirmed diagnosis of depression (N = 284).

Conclusions: The prevalence of subclinical hypothyroidism and of thyroid autoimmunity in depressed adolescents is increased. The etiology of these observations is not well understood, and further studies to examine the underlying relationship are required. Moreover, thyroid autoimmunity may constitute an additional risk factor for depression on its own.

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Thyroid dysfunction and thyroid autoimmunity are known to affect mental health in adults. A recent large-scale meta-analysis confirmed a 3.3-fold increased risk for depression in hypothyroidism and autoimmune thyroiditis.[1,2] In contrast, information on thyroid dysfunction in children and adolescents with depression is scarce, and studies are difficult to interpret due to conflicting findings, small sample size, and sample heterogeneity.[3] However, recently, Luft et al[4] published results on thyroid function in about 1,000 children and adolescents diagnosed with depression. In this cohort, 6% were affected by subclinical hypothyroidism (SCHYPO), defined by thyrotropin (TSH) levels above the age-specific reference range in lieu of normal free thyroxine (fT_4) values. Less than 1% displayed a biochemical constellation of overt hypothyroidism with significantly elevated TSH and reduced fT_4 levels, which led the authors to conclude that screening for thyroid dysfunction is indicated only in patients who display typical signs of overt hypothyroidism.[4]

Hashimoto thyroiditis, an autoimmune disorder of the thyroid gland, is the most common cause of thyroid dysfunction in children and adolescents. In adults, there is increasing evidence that thyroid autoimmunity itself may pose a risk factor for impaired mental health.[1,5–7] Several mechanisms have been proposed to provide a theoretical framework for the relationship between thyroid autoimmunity and mental health. For example, Hashimoto thyroiditis is supposed to affect cerebral inflammation and myelinization[5,6,8] as well as the release of neurotransmitters,[9] thereby influencing neurocognition independent of thyroid functioning.[1,5,6,10,11]

Clinical Points

- Preliminary evidence suggests an increased prevalence of thyroid dysfunction in adolescent depression, but its relation to thyroid autoimmunity remains to be determined.
- An increased risk of subclinical hypothyroidism but also autoimmunity in adolescent depression was found.
- Based on the risk of progression to overt hypothyroidism if thyroid autoimmunity is present, assessment of thyroid function is suggested in depressed adolescent patients.

The present study was intended to examine the prevalence of thyroid autoimmunity and to replicate findings by Luft et al[4] in depressed adolescents. Additionally, the prevalence of thyroid dysfunction and autoimmunity was assessed in a representative reference cohort of German adolescents without impaired mental health from a nationwide survey (German Health Interview and Examination Survey for Children and Adolescents [KiGGS]), allowing our study to provide risk estimates.

Based on recent findings of Luft et al[4] and Siegmann et al,[1] an increased prevalence of SCHYPO (H_1), as well as thyroid autoimmunity (H_2), but not overt hypothyroidism (H_3), was hypothesized in depressed adolescents. No hypotheses were derived regarding the prevalence of subclinical and overt hyperthyroidism in depressed adolescents due to conflicting previous results.[4,12,13]

METHODS

Study Design and Participants—Clinical Sample

Data for the depressed adolescents were derived from the baseline assessments of a 2-arm parallel-group, double-blind randomized controlled trial that investigated the effect of 25-hydroxyvitamin D deficiency (≤ 12 ng/mL [equivalent to ≤ 30 nmol/L]; German Clinical Trials Register identifier: DRKS00009758; N = 217) on depressive symptoms in psychiatric inpatients or day patients treated at the Department of Child and Adolescent Psychiatry, Psychosomatics and Psychotherapy (LVR-Klinikum Essen), Essen, Germany.[14,15] Additionally, data from the follow-up study Nutrition and Mental Health, an ongoing cross-sectional study focusing on the relationship between nutrition and psychiatric disorders, were utilized. Until the end of 2019, data from 143 subjects were available. Both studies were conducted in accordance with the Declaration of Helsinki and approved by the local Ethics Committee (No. 15–6363-BO).

Patients were eligible for inclusion if they were (1) aged 11 to 18.9 years and (2) at least mildly depressed with a Beck Depression Inventory-II (BDI-II) sum score > 13. Exclusion criteria were a concurrent diagnosis of severe somatic disease and/or intellectual disability (IQ < 70).

Diagnostic Instruments

Patients with a total BDI-II score > 13 were classified as depressed.[16] The BDI-II is a self-reported questionnaire, including 21 items covering *DSM-IV* diagnostic criteria for major depressive disorder (MDD).[17,18]

As the BDI-II is designed as a screening tool for depression, the diagnosis of MDD was confirmed either by the semistructured interview Schedule for Affective Disorders and Schizophrenia for School-Aged Children—Present and Lifetime Version (K-SADS-PL) according to *DSM-IV*[19] (91.4% of patients) or by a clinical assessment according to *ICD-10* (8.6%) if no K-SADS-PL was performed.

Study Design and Participants—KiGGS Study

The prevalence of thyroid dysfunction and of autoimmunity in the German general adolescent population were determined based on primary data of the first wave of the KiGGS survey. Details on the study design have been described elsewhere.[20] Briefly, a representative cohort of 17,641 children and adolescents aged 0 and 18 years was studied between 2003 and 2006 by the Robert Koch Institute to determine the health status of German children and adolescents.[20]

KiGGS participants with available information on parameters of thyroid function (TSH, fT_4, and thyroid peroxidase antibody [TPO-Ab] titers) and without evidence of a psychiatric disorder were included (N = 6,479; 3,127 girls; see Supplementary Methods for details).

TPO-Ab titers in children and adolescents are age- and sex-specific,[21–23] a phenomenon that is not yet considered by reference ranges for TPO-Ab assays. To allow for a meaningful comparison of prevalence figures, the largest possible random subsample of eligible KiGGS participants was selected according to the distribution of age and sex in the depressed patients by employing the complex samples procedure implemented in SPSS 25.0 (IBM; Armonk, New York) and used for all subsequent analyses (N = 2,329). In all subsequent analyses, data from depressed adolescents were pooled and handled irrespective of vitamin D status, as vitamin D sufficient (≥ 12 ng/dL) and deficient patients (< 12 ng/dL) did not differ regarding thyroid functioning and autoimmunity (for details, see Supplementary Methods, Supplementary Results, and Table 1).

Laboratory Studies

As the parameters of thyroid function were assessed using different laboratory analysis systems and assays for the 2 study groups (Table 2) and to correct for effects of age and sex, TSH and fT_4 concentrations were z-transformed (see Supplementary Methods). The blood sampling procedure in depressed adolescents is described in the Supplementary Methods and elsewhere[24] for the KiGGS participants.

Statistical Analysis

Overview. Data handling and statistical analyses were performed with SPSS. Results were considered significant at $P < .05$ when specific hypotheses were tested (H_{1-3}). Analyses without hypotheses were tested 2-tailed and corrected for multiple comparisons controlling the false discovery rate at $q < 0.05$.[25]

Table 1. Characteristics of Depressed Adolescents and Participants in the KiGGS Survey[a]

	Clinical Sample						
	All Patients (N = 360)	Vitamin D Sufficient > 12 ng/dL (n = 203)	Vitamin D Deficient < 12 ng/dL (n = 157)	TPO-Ab Positive (n = 21)	Subclinical Hypothyroidism (n = 31)	No Thyroid Dysfunction (n = 289)	KiGGS Subsample (N = 2,329)
Age, mean (SD)	15.85 (1.55)	15.80 (1.61)	15.87 (1.57)	16.14 (0.35)	15.57 (1.68)	15.84 (1.17)	14.88 (1.75)
z-BMI, mean (SD)	0.07 (1.45)	−0.05 (1.46)	0.24 (1.45)	0.29 (1.67)	0.39 (1.73)	0.01 (1.45)	−0.07 (0.98)
Sex, female, %	73.6	75.4	71.3	90.5	67.7	73.4	73.6
BDI-II score, mean (SD)	30.00 (10.36)	30.33 (10.54)	29.58 (10.14)	32.19 (9.68)	28.03 (9.89)	30.11 (10.30)	Not assessed
BDI-II severity category, %							
Mild	15.8	14.8	17.2	19.0	22.6	14.2	
Moderate	36.1	35.5	36.9	14.3	38.7	37.7	
Severe	48.1	49.8	45.9	66.7	38.7	48.1	
MDD diagnosis, %[b]	78.9	72.9	86.6	85.7	71.0	79.2	Not assessed
Vitamin D, mean (SD), ng/mL	14.87 (7.08)	19.56 (5.93)	8.81 (2.00)	14.11 (6.77)	14.56 (6.98)	14.83 (7.10)	18.57 (10.30)
z-TSH, mean (SD)[c]	0.66 (1.07)	0.69 (0.91)	0.61 (1.24)	0.46 (2.45)	2.36 (0.43)	0.57 (0.78)	0.03 (1.02)
z-fT_4, mean (SD)[c]	−0.04 (1.03)	−0.02 (1.04)	−0.06 (1.01)	−0.12 (0.96)	0.04 (0.76)	−0.06 (1.05)	0.03 (1.02)
TPO-Ab positivity, %	5.8	4.9	7.0	100	19.4*	…[d]	3.1
TPO-Ab, mean (SD), IU/mL	32.49 (131.14)	23.45 (77.43)	44.18 (160.50)	360.78 (378.01)	114.90 (295.71)	12.19 (4.59)	13.58 (84.76)
L-thyroxine, %	2.2	2.0	1.9	19*	3.2	…[d]	1.0
Thyroid disease, %	2.5	2.5	2.5	19*	3.2	…[d]	3.8
Psychotropic medication, %	22.5	21.7	23.6	23.8	19.4	20.8	…[d]
Oral contraceptive use, %	8.6	8.4	8.9	14.3	12.9	8.0	10.7
Smoking, %	20.3	21.7	18.5	4.8	16.1	21.8	19.8

[a]Depressed adolescents with thyroid dysfunction other than subclinical hypothyroidism or thyroid peroxidase antibody positivity are not considered in the table. *Z*-standardized variables are labeled with the prefix "z" (eg, *z*-TSH).
[b]MDD according to *DSM-IV* based on the Schedule for Affective Disorders and Schizophrenia for School-Aged Children—Present and Lifetime Version (91.4% of patients) or according to *ICD-10* based on clinical assessment (8.6% of patients).
[c]A total of 19 patients had missing information on TSH, fT_4, or both.
[d]0 by definition.
*Significant difference in comparison to depressed adolescents with no thyroid dysfunction.
Abbreviations: BDI-II = Beck Depression Inventory-II, BMI = body mass index, fT_4 = free thyroxine, KiGGS = German Health Interview and Examination Survey for Children and Adolescents, MDD = major depressive disorder, TPO-Ab = thyroid peroxidase antibody, TSH = thyrotropin.

Table 2. Assays Employed in the Clinical Sample and KiGGS Study and Their Characteristics

Parameter	Assay	Assay Type	Interassay Variation	Detection Range	Cutoff Level
Clinical sample					
TSH	Siemens ADVIA Centaur	CLIA	< 4.3%	0.008–150 mIU/L	
fT_4	Siemens ADVIA Centaur	CLIA	< 4.6%	0.1–12 ng/dL	
TPO-Ab	Siemens IMMULITE 2000	ECLIA	< 6.5%	5–1,000 IU/mL	> 35 IU/mL
25(OH)D	Siemens ADVIA Centaur	CLIA	< 5.2%	4.2–150 ng/mL	
KiGGS					
TSH	Roche Elecsys 2010	ECLIA	< 3.9%	0.005–100 mIU/L	
fT_4	Roche Elecsys 2010	ECLIA	< 5.3%	0.023–7.77 ng/dL	
TPO-Ab	Thermo Fisher ImmunoCAP	FEIA	< 7.2%	33.4–3,600 IU/mL	> 100 IU/mL

Abbreviations: 25-hydroxyvitamin D = 25(OH)D, CLIA = chemiluminescent immunoassay, ECLIA = electrochemiluminescent immunoassay, FEIA = fluorescent enzyme immunoassay, fT_4 = free thyroxine, KiGGS = German Health Interview and Examination Survey for Children and Adolescents, TPO-Ab = thyroid peroxidase antibody, TSH = thyrotropin.

Prevalence figures. The prevalence of TPO-Ab positivity (TPO+), its prevalence in SCHYPO as well as the prevalence of SCHYPO in TPO+ were estimated in a random subsample of the KiGGS participants as outlined above and compared to depressed patients by χ^2 tests of independence and Fisher's exact test in case of cell counts < 5. Effect size was determined by the odds ratio (OR) and converted to Cohen *d* according to Borenstein et al.[26] The same procedure of analysis was also applied to compare the prevalence of all types of thyroid dysfunction (see Table 3 for definitions) between depressed patients and KiGGS participants.

A sensitivity analysis regarding the prevalence of TPO+ was conducted applying a cutoff level twice the recommended threshold specified by the manufacturer to avoid conclusions based on spurious thyroid autoimmunity (for details, see Supplementary Methods). Results regarding the prevalence of thyroid dysfunction and autoimmunity were verified in a subsample of patients with a BDI-II score above 13 and a confirmed diagnosis of depression. Sensitivity analyses were considered exploratory and, therefore, not corrected for multiple comparisons.

In depressed adolescents, the frequency of TPO+ and presence of SCHYPO was compared between adolescents with mild (BDI-II score 14–19), moderate (20–28), and severe (29–63) depression.[18] Considering the observation of an increased prevalence of SCHYPO in obesity,[27] we also examined the relationship between categorical body mass index (BMI) (underweight: < 10th percentile, normal: 10th–90th percentile, overweight: 90th–97th percentile, obese: > 97th percentile) and the frequency of SCHYPO in depressed adolescents. All analyses relied on χ^2 tests of independence.

Multiple regression. In depressed adolescents and in the subsample of patients with SCHYPO and with TPO+, the relationship between BDI-II scores and *z*-standardized hormone levels (TSH and ft_4) and TPO-Ab levels was assessed by multiple regression combining a standard hierarchical approach with a stepwise regression. Covariates with

Table 3. Definitions of Thyroid Disorders[a]

Thyroid Category	*z*-TSH SD	*z*-fT_4 SD	Additional Criteria
Subclinical hypothyroidism	> 1.96	−1.96 < *z*-fT_4 < 1.96	
Severe subclinical hypothyroidism	> 10[b]	−1.96 < *z*-fT_4 < 1.96	
Overt hypothyroidism	> 1.96	*z*-fT_4 < −1.96	
Subclinical hyperthyroidism	< −1.96	−1.96 < *z*-fT_4 < 1.96	
Overt hyperthyroidism	< −1.96	*z*-fT4 > 1.96	
No thyroid dysfunction	−1.96 < *z*-TSH < 1.96	−1.96 < *z*-fT_4 < 1.96	No thyroid autoimmunity No preexisting thyroid disease No levothyroxine

[a]Euthyroid patients with a preexisting thyroid disease other than Hashimoto disease were excluded from the analyses (N = 4). *Z*-standardized variables are labeled with the prefix "*z*" (eg, *z*-TSH).
[b]mIU/L.
Abbreviations: fT_4 = free thyroxine, SD = standard deviation, TSH = thyrotropin.

Table 4. Detailed Statistical Results Comparing Depressed Adolescents With KiGGS Survey Participants[a]

Thyroid Disorder	Prevalence in Clinical Cohort	Prevalence in KiGGS	Test Statistic	*P*	OR	Effect Size	FDR-Corrected
Thyroid autoimmunity (TPO-Ab > 35 IU/mL)	5.8% [3.7–8.6]	3.1% [2.5–3.9]	$\chi^2_{1, N=2,670} = 6.73$	.009	1.91 [1.16–3.15]	0.36	no
Thyroid autoimmunity (TPO-Ab > 70 IU/mL)	3.9% [2.2–6.2]	2.1% [1.6–2.7]	$\chi^2_{1, N=2,670} = 4.38$	.037	1.88 [1.03–3.45]	0.35	no
Subclinical hypothyroidism	9.1% [6.3–12.4]	2.1% [1.6–2.7]	$\chi^2_{1, N=2,670} = 49.96$	1.6×10^{-12}	4.65 [2.92–7.41]	0.85	no
Severe subclinical hypothyroidism	0.3% [0.0–1.2]	0.1% [0.0–0.3]	FET	.336	3.42 [0.31–37.84]	…[b]	yes
Overt hypothyroidism	0%	0.1% [0.0–0.3]	FET	.999	…[c]	…	yes
Subclinical hyperthyroidism	0.6% [0.1–1.8]	1.9% [1.4–2.5]	FET	.080	0.30 [0.07–1.24]	…	yes
Overt hyperthyroidism	0.3% [0.0–1.3]	0.3% [0.2–0.6]	FET	1.000	0.85 [0.11–6.84]	…	yes

[a]95% confidence intervals shown in brackets.
[b]Effect sizes are reported only for significant findings.
[c]0% prevalence in depressed adolescents, therefore no OR.
Abbreviations: FDR = false discovery rate, FET = Fisher exact test, KiGGS = German Health Interview and Examination Survey for Children and Adolescents, OR = odds ratio, TPO-Ab = thyroid peroxidase antibody.

potential influence on thyroid function (vitamin D, intake of antidepressant[28–30] and psychotropic drugs,[31] thyroid hormone medication, use of oral contraceptives,[32,33] smoking,[34,35] and *z*-standardized BMI[36]) were entered as first block of regressors and assessed via stepwise regression. Then, *z*-standardized TSH and fT_4 as well as TPO-Ab titers were entered as second block of regressors. The combined variance, which was accounted for in BDI-II scores by the independent variables (thyroid parameters), was assessed by testing the change in R^2 against zero.

RESULTS

Prevalence of TPO-Ab Positivity

There was a significantly higher prevalence of TPO+ in depressed patients (5.8%) than in KiGGS participants (3.1%) considering the age and sex distribution of the clinical sample ($P = .009$, Table 4).

Despite a statistical trend, there was no difference regarding the prevalence of SCHYPO between depressed patients (28.6%, 95% CI [12.5–49.6]) and KiGGS participants (8.2%, 95% CI [3.4–16.0]) affected by TPO+ ($\chi^2_{1, N=94} = 6.07$, $P = .024$; OR = 4.47, 95% CI [1.26–15.79]) when correcting for multiple comparisons. However, a significantly higher percentage of depressed adolescents than KiGGS participants was affected by TPO+ as well as SCHYPO (depressed: 1.7%, 95% CI [0.7–3.3]; KiGGS: 0.3%, 95% CI [0.1–0.5]; $\chi^2_{1, N=2,689} = 13.93$, $P = .003$; OR = 6.56, 95% CI [2.11–20.52]).

The severity of depression was not associated with TPO+, as an equal fraction of patients with TPO+ was observed in the groups with mild (7.0%), moderate (2.3%), and severe (8.1%) depressive symptoms ($\chi^2_{2, N=360} = 4.70$, $P = .096$).

Prevalence of Thyroid Dysfunction

Data from 23 patients were not considered for analysis: in 19 patients, TSH, fT_4, or both were not assessed, and 4 patients with a preexisting thyroid disease other than Hashimoto disease were excluded.

There was a significantly increased prevalence of SCHYPO (9.1%) in depressed patients in comparison to KiGGS participants (2.1%, $P = 1.6 \times 10^{-12}$). However, neither the risks for severe subclinical (depressed: 0.3%, KiGGS: 0.1%; $P_{\text{Fisher's exact test (FET)}} = .336$) and overt hypothyroidism (depressed: 0.0%, KiGGS: 0.1%; $P_{FET} = .999$) nor subclinical (depressed: 0.6%; KiGGS: 1.9%; $P_{FET} = .080$) and overt hyperthyroidism (depressed: 0.3%; KiGGS: 0.3%; $P_{FET} = 1.000$) were increased in depressed adolescents compared to KiGGS participants.

In depressed adolescents (19.4%, 95% CI [8.2–35.4]) and KiGGS participants (12.2%, 95% CI [5.1–23.3]) affected by SCHYPO, there was no significant difference in the prevalence of TPO+ ($\chi^2_{1, N=80} = 0.75$, $P = .386$).

Likewise, in thyroid autoimmunity, the severity of depression was not associated with SCHYPO, as an equal fraction of patients with SCHYPO was observed in patients with mild (13.5%), moderate (9.7%), and severe (7.3%) depression ($\chi^2_{2, N=341} = 1.91$, $P = .384$). Despite a descriptive

Table 5. Results of the Multiple Regression Analysis in Depressed Adolescents (N = 341)[a]

Variables	β	*t* Value	*P*	R^2 Model
Model 1				
Smoking	0.11	2.16	.031	.065
z-BMI	0.12	2.23	.027	
Oral contraceptives	0.12	2.34	.020	
Psychotropic drugs	0.15	2.89	.004	
Model 2				
Smoking	0.11	1.97	.049	.072
z-BMI	0.13	2.47	.014	
Oral contraceptives	0.13	2.37	.018	
Psychotropic drugs	0.15	2.69	.007	
z-TSH	−0.08	−1.46	.146	
z-fT_4	−0.03	−0.55	.582	
TPO-Ab	−0.02	−0.28	.777	

[a]Model 1 includes covariates entered as a first block of regressors and chosen by stepwise regression. Model 2 includes the covariates identified by the previous step of analysis as well as thyroid parameters. *Z*-standardized variables are labeled with the prefix "*z*" (eg, *z*-TSH). β = standardized regression coefficient.
Abbreviations: BMI = body mass index, fT_4 = free thyroxine, TPO-Ab = thyroid peroxidase antibody, TSH = thyrotropin.

tendency, the prevalence of SCHYPO was independent of categorical *z*-standardized BMI of depressed patients (underweight: 5.6%, normal weight: 8.4%, overweight: 9.8%, obese: 19.4%; $\chi^2_{1,\,N=341} = 4.93$, $P = .177$).

Sensitivity Analyses

Except for a slightly lower prevalence of SCHYPO (8.2%) in patients with a confirmed diagnosis of depression, all of the above-reported prevalence figures regarding thyroid dysfunction and autoimmunity were confirmed by sensitivity analyses (for details, see Supplementary Results and Supplementary Table 2).

Regression Analysis

In depressed adolescents, BDI-II scores were associated with thyroid hormone levels neither by bivariate correlation analysis (*z*-TSH: $r_{353} = -0.08$, $P = .126$; *z*-fT_4: $r_{339} = -0.04$, $P = .482$) nor by multiple regression considering the covariates smoking, psychotropic drugs, oral contraceptives, and BMI (see Table 5). This also applied to TPO-Ab titers (TPO-Ab: $r_{358} = -0.00$, $P = .974$). Moreover, the combined parameters (*z*-TSH, *z*-fT_4, TPO-Ab titers) did not account for a significant proportion of variance in BDI-II scores ($R^2_{\text{change|thyroid}}\ F_{3,333} = 0.81$, $P = .488$), which also applied to the subsample of depressed adolescents affected by SCHYPO and TPO+ (for details, see Supplementary Results and Supplementary Table 3).

DISCUSSION

In the present study of 360 depressed adolescents, an increased prevalence of thyroid autoimmunity and SCHYPO in comparison to the general pediatric population was found and confirmed by sensitivity analyses. Subsequently, these prevalence figures will be discussed in greater detail with a focus on the pathophysiology of thyroid autoimmunity in depression and their clinical implications, especially regarding the utility of screening for thyroid dysfunction in depressed adolescents.

Prevalence of TPO-Ab Positivity

The finding of an increased prevalence of TPO+ is well in line with hypothesis H_2 based on results from a recent large-scale meta-analysis in adults in whom a 3.3-fold increased risk of depression in thyroid dysfunction and autoimmunity[1,2] was found. Importantly, 71.4% of depressed adolescents with TPO+ of the present study were biochemically euthyroid, which may indicate that TPO+ constitutes a risk for depression, independent of thyroid functioning. Moreover, the increased prevalence of TPO+ in adolescents as well as in adults argues for a pathophysiologic relevance of thyroid autoimmunity in the etiology of depression in at least a subsample of patients regardless of age.

In addition to this epidemiologic evidence, there is accumulating evidence for a pathophysiologic framework indicating how thyroid and systemic autoimmunity may affect mental health in a significant manner.[5,7,8,37] It has been shown that TPO-Abs bind to cerebellar astrocytes,[8] potentially mediating a direct effect on the brain. Moreover, the presence of TPO-Abs may indicate an autoimmune involvement of the central nervous system (CNS), as CNS-Abs were detected in a significant proportion of adult patients with Hashimoto thyroiditis.[6,10,38] These CNS-Abs disturb myelogenesis, induce inflammation, and potentially impair neurotransmission,[5,38] which may causally contribute to the clinical phenotype of Hashimoto thyroiditis, including an increased risk of depression,[1,39] suicidal tendencies,[40] and reports of encephalopathy.[38,41]

Considering these findings in adults, further studies are needed to determine the prevalence of CNS-Abs in (depressed) children and adolescents affected by Hashimoto thyroiditis and to explore the relationship between the presence of CNS-Abs and the mental health phenotype in thyroid autoimmunity.

Thyroid Dysfunction

While neither the prevalence of overt hypothyroidism nor the prevalence of subclinical and overt hyperthyroidism was increased in comparison to the general pediatric population (for details, see Supplementary Discussion), SCHYPO was observed in 9.1% of at least mildly depressed adolescents, which is in line with hypothesis H_1. These numbers are slightly higher than in the study by Luft et al,[4] possibly due to differences in the study designs regarding the time of day when blood was sampled and different criteria for the diagnosis of depression (for details, see Supplementary Discussion). Thus, further studies are needed to provide a reliable estimate of the prevalence of SCHYPO in adolescent depression considering established confounders of thyroid functioning and a diagnosis of SCHYPO based on 2 independent TSH measurements. However, despite a short half-life of TSH of about 30 to 60 minutes, variations in serum TSH levels are intraindividually small[42] and even smaller in

SCHYPO than in euthyroidism.[43] Thus, the diagnosis of SCHYPO has quite likely been assigned correctly in the present study.[44]

Despite slightly diverging estimates of the prevalence of SCHYPO in depressed adolescents, its prevalence is significantly increased compared to the general pediatric population. However, whether SCHYPO is causally related to depression remains unclear. A recent meta-analysis of epidemiologic studies found a significant relationship between SCHYPO and depression only in elderly adults,[45] and in a meta-analysis of intervention studies comprising 2,192 adults of the general population with SCHYPO, no beneficial effects of levothyroxine treatment on health-related quality of life, including depressive symptoms, were described.[46] In addition to these findings, so far, no plausible pathophysiologic mechanism by which SCHYPO would affect mental health in biochemically euthyroid individuals has been presented. In accordance with the meta-analyses, no relationship between thyroid parameters and depression in the depressed adolescents was detected in the present study, not even in those patients affected by SCHYPO. Thus, SCHYPO may be the consequence rather than the cause of an unknown mechanism either favoring depression or resulting from depression. However, the mechanisms discussed to explain the etiology of SCHYPO in depression, including increased cortisol levels[47,48] as well as altered serotonin[49,50] and catecholamine signaling,[49,50] have not conclusively been confirmed.[49–51] To summarize, the exact nature of the relationship between SCHYPO and depression remains to be determined by future studies, as discussed below.

Implications, Limitations, and Future Directions

Neither the European nor the American Thyroid Association[44,52] recommends treatment for subclinical hypothyroidism in children and adolescents with a TSH < 10 mIU/L. Despite a prevalence of SCHYPO of 9.1%, a TSH level > 10 mIU/L was found in only a single patient in the present study, which corresponds to a prevalence of 0.3% of subclinical hypothyroidism in depressed adolescents in need of treatment. In other studies, in at least 70% of patients with a TSH between 5.5 and 10, subclinical hypothyroidism rarely progresses to overt hypothyroidism but resolves spontaneously within 5 years.[44] However, whether this observation also applies to depressed adolescents is unknown. The risk for thyroid autoimmunity in depressed adolescents is increased almost 2-fold, and the risk for SCHYPO in TPO+ is increased more than 4-fold. This results in a significant, 6.6-fold increased risk of thyroid dysfunction in depressed adolescents with thyroid autoimmunity. These patients are at least in need of follow-up, since children and adolescents with Hashimoto thyroiditis *and* SCHYPO are prone to experience deterioration of thyroid functioning in comparison to children and adolescents with SCHYPO but *without* Hashimoto thyroiditis.[44]

Based on these results, clinicians should biochemically assess thyroid function in depressed adolescents and test for thyroid autoimmunity in patients with SCHYPO to identify those who are at risk for progression to overt hypothyroidism. These suggestions apply irrespective of the severity of depression at the time of diagnosis.

However, the present study does not allow causal implication of thyroid dysfunction or autoimmunity in the etiology of adolescent depression due to its cross-sectional design. Thus, caution is warranted to avoid reverse causation, especially when considering the inconclusive and partially contradictory findings in adults regarding the relationship between (subclinical) thyroid dysfunction and mental health[45,46] and its hypothesized underlying mechanisms.[49–51] Moreover, the results of the present study should independently be confirmed, and the diagnosis of autoimmune thyroiditis should be verified by ultrasonography of the thyroid gland even though it is likely that patients of the present study who evidenced TPO+ and SCHYPO were affected by Hashimoto thyroiditis.

Considering these limitations as well as the limitations from previous studies, longitudinal studies are needed to understand the role and natural history of thyroid dysfunction and autoimmunity in adolescent depression.[50] To further explore the meaning of systemic autoimmunity in depressed adolescents with thyroid autoimmunity, future research should also address the prevalence of antibodies targeting the CNS as well as the effect of immunosuppressive therapy on (treatment-resistant) depression in depressed adolescents with CNS autoimmunity, as this approach has proven successful in patients affected by Hashimoto encephalopathy[53] and may provide causal evidence of the meaning of CNS-Abs in depression.

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Supplementary Material

Article Title: Increased Prevalence of Subclinical Hypothyroidism and Thyroid Autoimmunity in Depressed Adolescents: Results From a Clinical Cross-Sectional Study in Comparison to the General Pediatric Population

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List of Supplementary Material for the article

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Supplementary Material

Increased Prevalence of Subclinical Hypothyroidism and Thyroid Autoimmunity in Depressed Adolescents: Results from a Clinical Cross-Sectional Study in Comparison to the General Pediatric Population

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Overview

Methods

Questionnaires - KiGGS

The Strength and Difficulties Questionnaire (SDQ) screens for mental health symptoms as well as positive attitudes in children and adolescents assessing 5 dimensions (emotional symptoms, conduct problems, hyperactivity/inattention, peer relationship problems, and prosocial behavior) by 25 items. Each item is scored on a 3-point Likert scale (0-2) with higher scores indicating more problems. By summing the subscores from each dimension, a total score can be calculated and used to classify results as normal, borderline, or abnormal [1].

Health-related quality of life (HRQoL) was measured by the KINDL-R, which consists of 24 items assessing 6 dimensions of HRQoL (physical well-being, emotional well-being, self-esteem, family, friends, everyday functioning) scored on a five-point Likert scale (1-5). A total score can be calculated and transformed to values between 0 to 100. Higher scores indicate a better quality of life [2]. While in children younger than 11 years we used the scores on the parent-proxy form of self-administered questionnaires, in children older than 11 years we referred to the scores of the self-report form of the questionnaires [3].

Criteria for Reference Sample – KiGGS

Unimpaired mental health was defined by a score on the KINDL-R above the 10. percentile, a score on the SDQ indicating no significant mental health problem (i.e., no classification of the SDQ total score as 'abnormal'), no attendance of a psychiatrist or psychologist within the last 12 months, and no intake of psychotropic drugs

Anthropometric Measures

A physical examination was performed upon admission, including assessment of body length and body weight.

Height was determined in upright posture using a wall-mounted stadiometer. Height was recorded with a precision of 0.1 cm. Bodyweight was measured wearing underwear by an electronic scale displaying weight with a precision of 0.1 kg. BMI was determined by the ratio of weight in kg and the height in meters squared (kg/m^2) [4].

Laboratory Studies – Blood sampling

Blood samples from depressed patients were obtained from an antecubital vein in monovettes® (Sarstedt, Germany) in the early morning after an overnight fast. Aliquots were transferred at 4° C within an hour after blood sampling to the laboratory of the University Hospital Essen for analyses.

Blood samples from participants of the KiGGS survey were collected after a median fasting period of 2 hours using a vacutainer system. Whole blood was stored at 4°C and serum at -40°C before the transfer of samples to the central laboratory of the RKI within 3 days after sample collection [5].

Laboratory Studies – z-Transformation

The z-transformation of laboratory parameters was performed employing RefCurv (Version 0.4.4, https://refcurv.com [6]) relying on the information of the distribution of TSH and fT4 concentrations from age- and sex-specific percentile charts, which have been published for participants of the KiGGS survey [5] or were provided by Siemens based on an individual data usage agreement in addition to information from the package insert.

The same procedure was applied to z-transform BMI data from participants of the present study as well as the KiGGS survey according to reference data for German children and adolescents [4].

Statistical Analysis – Confounder: Vitamin D Level

TPO+ has been related to vitamin D levels, even though the evidence is limited [7,8]. To investigate a significant effect of vitamin D deficiency on thyroid autoimmunity, we compared TPO-Ab titer, TSH, and fT4 concentrations between depressed patients with (< 12 ng/dl) and without vitamin D deficiency (> 12 ng/dl) by two-sample t-tests. Also, we tested for bivariate correlations between vitamin D status and thyroid functioning and thyroid

autoimmunity. As the H_0 (*no* difference) was the favored outcome, no correction for multiple comparisons was applied.

Statistical Analysis – Miscellaneous

Likelihood ratio confidence intervals (CI, 95%), that have been shown to provide superior results in low prevalence conditions [9], were estimates for the prevalence of TPO+ as well as subclinical and overt thyroid dysfunction in both samples.

The Kolmogorov-Smirnov test assessed the normality of the dependent variable (BDI-II scores) and residuals in multiple regression. The non-normally distributed BDI-II score was rank-transformed according to Templeton [10], preserving its mean and standard deviation. The (modified) Breusch-Pagan test evaluated homoscedasticity, and the Durbin-Watson test excluded the autocorrelation of residuals. Outlier detection relied on Cook's distance.

Statistical Analysis - Demographics

Depressed patients with TPO+ or thyroid dysfunction were compared to depressed patients without thyroid dysfunction (no subclinical or overt thyroid dysfunction, no thyroid autoimmunity, no pre-existing, physician-diagnosed thyroid disease, no levothyroxine prescription) concerning age and BMI by two-sample t-tests. χ2-tests of independence and Fisher's exact test in case of cell counts < 5 were employed for comparisons with regard to the variables outlined in Supplementary Table 1. All analyses were corrected for multiple comparisons, as outlined above.

Results

Vitamin D Status

There was no significant difference in z-standardized TSH ($t(353) = 0.72$, $p = .472$; s. Table 3) or fT4 levels ($t(339) = 0.36$, $p = .717$) as well as TPO-Ab titers ($t(358) = -1.61$, $p = .108$) between vitamin D deficient and sufficient depressed adolescents in the present study. Moreover, vitamin D status did neither correlate with z-standardized TSH ($r(353 = .01$, $p = .847$) and fT4 levels ($r(339) = .04$, $p = .435$) nor TPO-Ab titers ($r(358) = -.09$, $p = .079$).

Demographics

Depressed adolescents affected by TPO+ significantly differed from depressed adolescents without thyroid dysfunction regarding the frequency of pre-existing, physician-diagnosed thyroid disease ($p_{Fisher's\ exact\ test\ (FET)} = 1.6 \times 10^{-5}$; see Table 3 for summary statistics and Supplementary Table 1 for detailed statistical results) as well as the frequency of levothyroxine prescription ($p_{FET} = 1.6 \times 10^{-5}$). In depressed adolescents with SCHYPO, only the frequency of thyroid autoimmunity ($p_{FET} = 5 \times 10^{-6}$) was significantly higher than in depressed adolescents with unremarkable thyroid function.

Sensitivity Analyses

When only subjects with TPO-Ab levels two-fold above the cut-off were considered, the prevalence of TPO+ in adolescent depression remained increased in comparison to the general adolescent population without evidence of impaired mental health (clinical sample: 3.9%, 95%-CI [2.2–6.2]; KiGGS survey: 2.1%, 95%-CI [1.6–2.7]; OR 1.88, 95%-CI [1.03-3.45], p=.037, Table 4).

Comparing the prevalence of thyroid dysfunction and autoimmunity between participants of the KiGGS survey and the subsample of patients with a BDI-II diagnosed depression ascertained by either the K-SADS-PL or clinical assessment, we found the same pattern of

findings with very similar prevalence figures as in patients with a diagnosis of a MDD solely based on the BDI-II (s. Supplementary Table 2).

Multiple Regression – SCHYPO and TPO+

In SCHYPO, BDI-II scores were neither associated with thyroid hormone levels considering bivariate correlations (z-TSH: $r(29) = -.21$, $p = .257$; z-fT4: $r(29) = .25$, $p = .184$, TPO-Ab: $r(29) = -.04$, $p = .818$) nor multiple regression (s. Table 3) or the variance in BDI scores accounted for by thyroid parameters ($R^2_{thyroid}$ $F(3, 27) = 1.01$, $p = .405$). This also applied to depressed adolescents with TPO+ (z-TSH: $r(19) = -.10$, $p = .657$; z-fT4: $r(19) = .08$, $p = .718$, TPO-Ab: $r(19) = -.16$, $p = .503$, $R^2_{thyroid}$ $F(3, 17) = 0.26$, $p = .851$; Supplementary Table 3).

Discussion

Prevalence of Thyroid Dysfunction and Autoimmunity in the General Pediatric Population

The prevalence of TPO+ in children and adolescents of the KiGGS survey without evidence of impaired mental health was determined at 3.1%, which is well in line with results from 2 previous studies (2.9% - 3.4%[11,12]) but below estimates from another 3 studies (4.6 – 8.2%; [13,14,15]), even when considering the upper limit of the confidence interval for TPO+. Without comparing each previous study with the present study in detail, comparability between studies is limited. The studies conducted by Taubner et al. [13] (~4.6%, age range 12-20 years), Kaloumenou et al. [14] (8.2%, Tanner stage ≥ II) and Zois et al. [15] (8.2%, 12-18 years) but also the study conducted by Kabelitz et al. [12] were sampled from single cities in either Germany (Leipzig, Berlin) or Greece (Athens, Konitsa). As shown by Loviselli et al. [11], there is considerable heterogeneity in the prevalence of TPO+ even between communities from the same region with comparable iodine supply (0% - 7.3%, on average 2.9%). Thus, results from these studies might have been regionally confounded in contrast to the present and representative sample of German children and adolescents from the KiGGS survey.

The prevalence of SCHYPO of 2.1% in the general pediatric population of the KiGGS study agrees with 2 previous studies and an estimated prevalence of SCHYPO of 1.7% to 2.9% [16,17]. Both these estimates originate from representative studies highlighting the need to exclude regional confounding as likely present in studies investigating the prevalence of TPO+ and discussed above.

Prevalence in SCHYPO

Recently, Luft et al. [18] reported a prevalence of SCHYPO of 6.1%. Unfortunately, the time of day when blood was sampled is not mentioned. In the present study, blood was drawn in the early morning when TSH levels peak[19], which may explain a higher prevalence of SCHYPO in comparison to the study by Luft et al. [18]. Moreover, in the present study, the evaluation of thyroid functioning relied on age- and sex-specific reference ranges but not a fixed cut-off, which may also explain different prevalence figures between studies.

Despite these considerations regarding methodological aspects of the evaluation of thyroid functioning, the diagnosis of depression in the present study and study by Luft et al. [18] relied on different criteria. Luft et al. [18] report that diagnoses were established according to DSM-IV and DSM-5 criteria, but this information is not detailed. In the present study, we found a prevalence of SCHYPO of 9.1% when depression was diagnosed according to the BDI-II and 8.2% when diagnosed according to the K-SADS-PL or clinical assessment. Despite only a small difference in these figures and widely overlapping confidence intervals, the lower bound of the confidence interval for SCHYPO in adolescent depression according to the K-SADS-PL or clinical assessment (5.7%) includes the prevalence of SCHYPO reported by Luft et al. [18]. Thus,

when depression is diagnosed according to the DSM-IV criteria as operationalized by BDI-II, the number of depressed adolescents with SCHYPO may slightly be overestimated when considering the sample by Luft et al. [18] as reference.

Thyroid Dysfunction other than SCHYPO

In contrast to SCHYPO, there was no evidence of an increased risk of either overt hypothyroidism or subclinical and overt hyperthyroidism. In contrast, Leo et al. [20] reported a prevalence of subclinical hyperthyroidism of 6.7% in 134 psychiatric adolescents inpatients, which is well above the finding of the present study and a recent study by Luft et al. [18]. The sample size of the present study as well as the study by Luft et al. [18], however, were (much) larger. Moreover, recent findings relied on latter generations of TSH assays with higher precision in the lower measurement range and on more reliable pediatric reference ranges for TSH [21] than in the study by Leo et al. [20]. Also, the study by Leo et al. [20] was not confined to patients with depression but included patients with diverse psychiatric diagnoses. Thus, we conclude that there is likely no increased prevalence of subclinical hyperthyroidism in adolescent depression.

Zader et al. [22] recently reported a 3.4-fold increased risk of depression in children and adolescents (primarily) affected by overt autoimmune hyperthyroidism, also referred to as Grave's disease, with a crude incidence of 1:3.000 to 1:10.000 [23,24]. Considering these prevalence figures, a patient with overt hyperthyroidism due to Grave's disease in a sample of depressed adolescents is unlikely. Indeed, the only patient to evidence a laboratory pattern of overt hyperthyroidism in the present study was a patient on inadequate levothyroxine replacement therapy. Summarizing, considering the prevalence of Grave's disease in children and adolescents, the finding by Zader et al. [22] is well in line with results from the present as well as previous studies regarding the prevalence of overt hyperthyroidism in adolescent depression.

subgroup 1	subgroup 2	test	variable	p-value	test statistics	df
no thyroid affection	TPO-Ab positive	t-test	age	.361	-0.92	308
		t-test	z-BMI	.419	-0.81	308
		FET	sex	.117		
		t-test	BDI-II	.367	-0.90	308
		$\chi 2$	BDI-II severity	.095	4.67	2
		FET	L-Thyroxin	**.00002**		
		FET	thyroid disease	**.00002**		
		$\chi 2$	psychotropic medication	.782	0.11	1
		FET	oral contraceptive	.402		
		FET	smoking	.090		
no thyroid affection	subclinical hypothyroidism	t-test	age	.420	0.81	318
		t-test	z-BMI	.190	-1.31	318
		$\chi 2$	sex	.504	0.45	1
		t-test	BDI-II	.287	1.07	318
		FET	L-Thyroxin	.097		
		$\chi 2$	BDI-II severity	.397	1.85	2
		FET	thyroid disease	.097		
		$\chi 2$	psychotropic medication	.854	0.03	1
		FET	oral contraceptive	.728		
		$\chi 2$	smoking	.463	0.54	1
		FET	TPO positive	**.0000005**		

Supplementary Table 1. Statistical results of the comparison of anthropometric and demographic variables as well as covariates among depressed adolescents. FET = Fisher's exact test. SPSS does not provide a test statistic. $\chi 2$ = $\chi 2$ test of independence. t-test = two-sample t-test. Bold typed p-values indicate significant differences between the indicated groups.

thyroid disorder	prevalence (%)	test statistic	p-value	OR
thyroid autoimmunity (TPO > 35 IU/ml)	6.3 [3.9 - 9.6]	$\chi^2(1, N = 2{,}613) = 7.73$	.005	2.09 [1.23 - 3.56]
thyroid autoimmunity (TPO > 70 IU/ml)	4.2 [2.3 - 7.0]	$\chi^2(1, N = 2{,}613) = 5.00$	.025	2.05 [1.08 - 3.91]
subclinical hypothyroidism	8.2 [5.3 - 11.9]	$\chi^2(1, N = 2{,}597) = 33.69$	6.4×10^{-9}	4.16 [2.47-7.00]
severe subclinical hypothyroidism	0.4 [0.0 - 1.6]	FET	.290	4.16 [0.38 - 45.97]
overt hypothyroidism	0.0	FET	1.000	*
subclinical hyperthyroidism	0.4 [0.0 - 1.6]	FET	.067	0.19 [0.03 - 1.39]
overt hyperthyroidism	0.4 [0.0 - 1.6]	FET	1.000	1.09 [0.14 - 8.72]

Supplementary Table 2. Comparison of depressed adolescents with a BDI-II score above 13 and a confirmed diagnosis according to the K-SADS-PL or clinical assessment with the KiGGS survey participants. Prevalence in percent, in brackets 95% confidence interval. FET = Fisher`s exact test, SPSS does not provide a test statistic. OR = odds ratio, FDR = false discovery rate. * 0% prevalence in depressed adolescents, therefore no OR. Note: Altogether 16 patients had missing information on TSH, fT4 or both.

Depressed adolescents with subclinical hypothyroidism (N=31)

Model	variables	β	t-value	p	R^2 model
1	#			n.s.	
	#			n.s.	
	#			n.s.	
	#			n.s.	
2	z-TSH	-0.19	-0.95	.349	.101
	z-fT4	0.31	1.53	.138	
	TPO-Ab	0.14	0.64	.526	

Depressed adolescents with TPO-Ab positivity (N=21)

Model	variables	β	t-value	p	R^2 model
1	#			n.s.	
	#			n.s.	
	#			n.s.	
	#			n.s.	
2	z-TSH	-0.12	-0.35	.731	.044
	z-fT4	-0.09	-2.60	.798	
	TPO-Ab	-0.20	0.77	.454	

Supplementary Table 3. Results of the multiple regression analysis from depressed adolescents with subclinical hypothyroidism and TPO-Ab positivity. Model 1 includes covariates entered as a first block of regressors and chosen by stepwise regression. Model 2 includes the covariates identified by the previous step of analysis as well as the thyroid parameters. β = standardized regression coefficient, z-standardized variables are labeled with the prefix 'z' (e.g., z-TSH). n.s. = not significant.

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