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Association of Depression and Anxiety Disorders With Autoimmune Thyroiditis
A Systematic Review and Meta-analysis

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IMPORTANCE With a prevalence of 4% to 13% in the United States, autoimmune thyroiditis (AIT) is a major health problem. Besides somatic complications, patients with AIT can also experience psychiatric disorders. The extent of these organic psychiatric diseases in patients with AIT, however, is so far not commonly known.

OBJECTIVE To provide meta-analytic data on the association of depression and anxiety with AIT.

DATA SOURCES Google Scholar, the EBSCO Host databases, the Web of Knowledge, and PubMed were searched from inception through December 5, 2017. Articles identified were reviewed and reference lists were searched manually.

STUDY SELECTION Case-control studies that reported the association between AIT and either depression or anxiety disorders or both were included.

DATA EXTRACTION AND SYNTHESIS Data extraction was performed by multiple observers following the PRISMA guidelines. Two univariate random-effects meta-analyses were performed, and moderators were tested with Bonferroni-corrected meta-regression analysis. Heterogeneity was assessed with the I^2 statistic. Sensitivity analyses tested the robustness of the results. Small study effects were assessed with funnel plots and the Egger test.

MAIN OUTCOMES AND MEASURES The odds ratio of patients with AIT and depression compared with a healthy control group, as well as the odds ratio of patients with AIT and anxiety disorders compared with a healthy control group.

RESULTS Nineteen studies comprising 21 independent samples were included, with a total of 36 174 participants (35 168 for depression and 34 094 for anxiety). Patients with AIT, Hashimoto thyroiditis, or subclinical or overt hypothyroidism had significantly higher scores on standardized depression instruments, with an odds ratio of 3.56 (95% CI, 2.14-5.94; I^2 = 92.1%). For anxiety disorders, patients with AIT, Hashimoto thyroiditis, or subclinical or overt hypothyroidism had an odds ratio of 2.32 (95% CI, 1.40-3.85; I^2 = 89.8%). Funnel plot asymmetry was detected for studies of depression. Study quality assessed with the Newcastle-Ottawa Scale for case-control studies (mean [SD] score: anxiety, 5.77 [1.17]; depression, 5.65 [1.14]; of a possible maximum score of 9) and proportion of females did not modulate the meta-analytic estimate, whereas mean age did.

CONCLUSIONS AND RELEVANCE This meta-analysis establishes the association between AIT and depression and anxiety disorders. Patients with AIT exhibit an increased chance of developing symptoms of depression and anxiety or of receiving a diagnosis of depression and anxiety disorders. This finding has important implications for patients and could lead to the choice of early treatment—and not only psychotherapeutic treatment—of the organic disorder.

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Supplemental content

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Autoimmune thyroiditis (AIT) is a common disease with a prevalence of approximately 4% to 13% in the United States.[1,2] It affects more women than men[1] and its frequency increases with age, up to 20% among elderly females.[3] The prevalence rates differ depending on the diagnostic criteria applied, the decade the study was conducted, and the sample examined. For example, 40% to 45% of women and 20% of men in the United Kingdom and the United States show some degree of focal thyroiditis (1 to 10 foci per cm^2) when examined at autopsy.[4] The terminology concerning hypothyroidism and how it can be traced back to AIT is described in eAppendix 1 and eTable 1 in the Supplement.

In addition, depression and anxiety disorders are pervasive psychiatric diseases with prevalence rates of 6.6% (depression)[5,6] and 18.1% (anxiety disorders)[6] in the United States. These numbers show that examining both AIT and depression or anxiety is of public interest. Conceivable causal associations between the thyroid metabolism and depression or anxiety disorders are described in eAppendix 1 in the Supplement.

Recently, the connection between autoimmunity and psychiatric disorders has been discovered for various autoimmune diseases. *N*-methyl-D-aspartate receptor hypofunction caused by immunoglobulin antibodies, for instance, has been found to be associated with the development of schizophrenia and psychoses.[7,8] Moreover, meta-analytic information suggests that tic disorders are associated with a significant increase in antistreptolysin O titers.[9] Further results indicate that autoimmune explanatory approaches are possible for bipolar disorders[10] or Alzheimer disease.[11] With the introduction of new immunologic techniques and the expansion of immunoneuropsychiatric research, evidence is accumulating that at least a subset of psychiatric disorders has an autoimmune basis.[12] Considering these insights, our analysis will contribute to a further clarification of the psychiatric associations with autoimmune thyroid disease.

There are a variety of consequences for patients with AIT. On the somatic side, hypothyroidism leads to alterations in cardiovascular function such as higher blood pressure due to increased systemic vascular resistance[13] and advanced atherosclerosis.[14] Furthermore, AIT contributes to a higher risk of infertility and early miscarriage,[15] as well as to weight gain even after treatment with thyroxine.[16]

Less is known about specific psychiatric burden of symptoms in patients with AIT. Studies describe a cumulative occurrence of mood disorders and symptoms of depression among patients in a hypothyroid state, as well as frequent thyroid diseases among patients with depression.[17-21] Moreover, fewer studies describe symptoms of anxiety in patients with AIT.[17,21-24] Occasional investigations study other (neuro) psychological symptoms associated with AIT, such as attentional and executive disturbances,[25] fatigue,[16] or reduction in quality of life.[26,27]

Despite growing interest in the psychiatric implications of AIT, most published studies still focus on its somatic effects. A further investigation of this association has importance for public health, physicians, and patients. Societal and economic costs caused by depression and anxiety disorders are high[28,29] and can be lowered by appropriate and early treatment. By quantitatively summarizing the results concerning AIT as a possible root of some mood disorders, the awareness for this association increases and a proper thyroid and antidepressant treatment can be implemented beyond psychotherapy. Furthermore, screening tests for symptoms of depression and anxiety in patients with AIT and for AIT in patients with depression and anxiety could be established.

To our knowledge, there are only a few qualitative reviews describing an association between AIT and the development of depression and anxiety disorders,[22,30-32] whereas no quantitative analysis concerning this topic exists. Consequently, there are no numbers of an overall association of AIT with depression and anxiety. We overcome this existing limited evidence by conducting what is, to our knowledge, the first meta-analysis testing the association of depression or anxious symptoms among individuals with AIT or any other form of hypothyroidism compared with healthy controls. We hypothesize that patients with hypothyroidism have a substantially higher risk of developing these psychiatric diseases irrespective of sex and age.

Key Points

Question To what extent are depression and anxiety associated with autoimmune thyroiditis when estimated meta-analytically?

Findings In this systematic review and meta-analysis of 19 studies comprising 36 174 participants, patients with autoimmune thyroiditis showed significantly higher depression and anxiety disorder scores compared with healthy controls.

Meaning The evident association between autoimmune thyroiditis and depression and anxiety has important implications for the information of patients and could lead to the choice of early treatment—and not only psychotherapeutic treatment—of the organic disorder.

Methods

Search Strategy

The 2-step literature search comprised Google Scholar, the EBSCO Host databases (including PsycINFO, PsycArticles, PSYNDEX, ERIC, Medline), the Web of Knowledge, and PubMed. The search was conducted from inception until December 5, 2017, and included abstracts in English and German. The following search terms were combined in several ways: *Hashimoto's thyroiditis*, *hypothyroidism*, *autoimmune thyroiditis*, *Hashimotothyreoiditis*, *autoimmunthyreoiditis*, *depression*, *depressive*, *mood*, *mental*, *anxiety*, *depression*, and *angst*. In a second step, the reference lists of articles retrieved were searched manually. The abstracts of all these articles were screened using our selection criteria. On the basis of a full-text review the remaining articles were checked for eligibility following the PRISMA statement[33] (eTable 2 in the Supplement).

Selection Criteria

If the following criteria were met, studies were included: publication from 1992 to 2017, studies were published in English or German, and participants in the experimental group received a diagnosis of Hashimoto thyroiditis, AIT, or subclinical, latent, or overt hypothyroidism. The use of diverse terminology concerning AIT required a clear distinction regarding which terms to include in this meta-analysis. Hashimoto thyroiditis and autoimmune thyroiditis are used as synonyms in most of the studies even though there is a slight difference[4] between the 2 conditions (eTable 1 in the Supplement). Subclinical or latent hypothyroidism is a form of hypothyroidism in which patients have a serum thyrotropin concentration above the statistically defined upper limit of the reference range when the serum free thyroxine concentration is within its reference range.[3] Studies show that at least 50% of the individuals with serum thyrotropin levels higher than 5 mIU/L and 80% of the individuals with levels higher than 10 mIU/L have thyroid antibodies.[4] Because of these high percentages, we included subclinical or latent hypothyroidism beyond Hashimoto thyroiditis and AIT for our analysis. The American Thyroid Association additionally states that "the overwhelming majority of cases [of hypothyroidism] are due to primary thyroid gland failure because of chronic autoimmune (Hashimoto's) thyroiditis..."[34(p811)] Therefore, we included samples of patients with overt hypothyroidism, as well. Additional selection criteria included a control group free from any thyroid disease and depression and anxiety disorders that were assessed via standardized instruments. Standardized instruments were defined as those with consistent questions, conditions for administering, scoring procedures, and interpretations. We included both categorical and dimensional measures; for inclusion, a study must report enough data to compute effect sizes. Data not directly reported were extracted indirectly from associated values.

Exclusion criteria comprised the following: abstracts or pilot data, articles published in languages other than English or German, no quantitative assessment of depression and anxiety disorders, and articles in which the values for depression and anxiety in the experimental group were presented without a comparison with a healthy control group. It was furthermore not possible to retrieve scores from a representative norm sample to use as control group. An additional exclusion criterion was study participants comprising pregnant women. Pregnancy affects the thyroid system, leading to alterations in free triiodothyronine, free thyroxine, and thyrotropin levels[35] and could thus bias the results of our analysis. The literature search was summarized according to the PRISMA guidelines[36] (eTable 2 in the Supplement).

Recorded Variables

Data extraction was performed by 2 investigators (E.-M.S. and T.W.G.) according to the previously defined coding protocol (eTable 3 in the Supplement). Disagreement was resolved by discussion and compromise on the extracted values.

For the outcome variable, on the one hand we extracted the baseline sample size and the number of patients with clinically relevant scores on the depression or anxiety assessment instrument. On the other hand, we extracted the mean and SD scores on the depression or anxiety test for both groups to circumvent missing values. In the case of 2 studies,[37,38] we used values of the representative norming sample found in the instruments' manuals[39,40] as scores for the control group, since the original control group comprised patients with goiter. All recorded variables can be found in the coding protocol (eTable 3 in the Supplement).

We collected additional moderators as stated in the Statistical Analysis section. Quality was assessed via the Newcastle-Ottawa Scale for case-control studies.[41] This tool consists of 3 categories (selection, comparability, and exposure) with a total of 8 items (eTable 4 in the Supplement). A study can be awarded a maximum of 1 star for each item within the selection and exposure category and a maximum of 2 stars can be given for comparability. A higher overall quality sum score reflects superior study quality.

Statistical Analysis

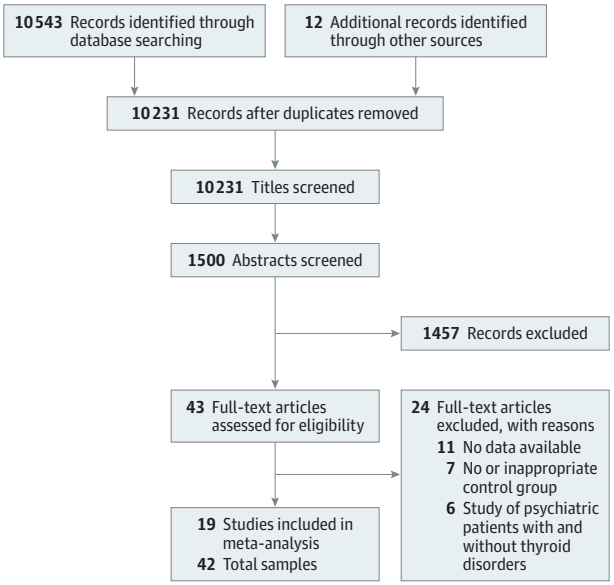
The outcome measure was the odds ratio (OR) of patients with AIT and depression compared with a healthy control group, as well as the OR of patients with AIT and anxiety disorders compared with a healthy control group. The OR was calculated as the proportion of the probability to have psychiatric symptoms while being in the experimental group and the probability to have psychiatric symptoms while being in the control group.

A meta-analysis was conducted using the metafor package[42] within the R open-source software environment, version 3.3.2.[43] The R code and output used in this meta-analysis are available in eAppendix 2 in the Supplement. We performed 2 univariate meta-analyses using restricted maximum likelihood estimation in the function rma.uni(). Nonindependence among effect sizes was accounted for by aggregating. Heterogeneity among effect sizes within data sets was assessed via the I^2 statistic. This statistic can be interpreted as the percentage of the total variability in a set of effect sizes owing to between-studies variability.[44] The Cochrane handbook[44] proposes a tentative classification where I^2 of 30% to 60% indicates moderate heterogeneity, I^2 of 50% to 90% indicates substantial heterogeneity, and I^2 greater than 75% indicates considerable heterogeneity.

To explain residual heterogeneity and to understand the potential effect of contextual factors on the outcome, we ran prespecified meta-regression analyses for the moderators study quality, proportion of females, and mean age. Thereby the slope of the meta-regression line (β coefficient) indicates the strength of the association between moderator and outcome. The meta-regressions were Bonferroni corrected for multiple testing. We used Akaike information criteria for small sample size to indicate whether meta-regression models were more or less parsimonious than the intercept-only model.

We performed 1 prespecified subgroup analysis investigating the difference in the outcome measure between studies assessing the level of thyroid peroxidase antibodies (and

Figure 1. PRISMA Flow Diagram



thus verifying the diagnosis of AIT) and studies that did not assess the antibodies. A second post hoc subgroup analysis was conducted to examine whether dimensional measures led to different results than categorical measures.

Publication bias and small study effects were assessed with the funnel function of R, which produced contour-enhanced funnel plots for the visual detection of asymmetries. In addition, the Egger regression test for the detection of asymmetry in the funnel plot[45] was conducted. We considered analyses to be biased if the intercept differed from zero at $P = .10$ as the authors originally proposed.[45]

We evaluated the sensitivity of our analyses by comparing fitted models with and without effect sizes that we assume to be influential outliers. Influential outliers were defined as standardized residual values exceeding 3.0 and hat values (ie, diagonal elements of the hat matrix) greater than 2 times the average hat value.[46] $P < .05$ (1-sided) was considered statistically significant, except for the regression test for small study effects as stated above.

Results

Database

The literature search (**Figure 1**) identified 19 independent articles and 42 partly dependent samples since some articles contributed more than 1 sample. We identified 26 samples dealing with depression and 16 with anxiety (**Table**).

A total of 11 samples comprised patients with Hashimoto thyroiditis, 11 samples comprised patients with AIT, 8 samples comprised patients with subclinical hypothyroidism, and 12 samples comprised patients with overt hypothyroidism. The distinction between these 3 subtypes of hypothyroidism refers mostly to terminological differences (eAppendix 1 in the Supplement). Age, sex, instruments used to assess the psychiatric diagnosis, the country of the study population, and prevalence rates for depression and anxiety are detailed in eTable 5 in the Supplement.

Table. Meta-analytic Association Between Autoimmune Thyroiditis and Depression and Anxiety Disorders

Characteristic	Psychiatric Diagnosis	
	Depression	Anxiety Disorders
Samples, No.	26	16
Patients analyzed, No.	35 168	34 094
Autoimmune thyroiditis compared with healthy controls, odds ratio (95% CI)	3.56 (2.14-5.94)	2.32 (1.40-3.85)
Between-group heterogeneity, *Q*	205.8	104.4
P value	<.001	<.001
I^2 statistic, %	92.1	89.8

Meta-analytic Association Between AIT and Depression

A total of 26 samples reported outcome data for the different forms of hypothyroidism and depression (Table). In most of the cases, depression was assessed by self-descriptive questionnaires (eg, 10 of the samples [38.5%] used versions of the Beck Depression Inventory[39,47] and 2 of the samples [7.7%] used the Hospital Anxiety and Depression Scale[48]), whereas only few studies used questionnaires or interviews filled in by diagnosticians (eg, 5 of the samples [19.2%] used the Hamilton Depression Scale[49] and 4 of the samples [15.4%] used variations of the Composite International Diagnostic Interview[50,51]). Studies that defined psychiatric disorders via cutoff values of dimensional measures were concordant in their definitions.

We found that the chance of developing symptoms of depression that were of clinical relevance is 3.5 times higher among patients with hypothyroidism compared with healthy controls (OR, 3.56; 95% CI, 2.14-5.94) (Table). **Figure 2** shows the overall association of AIT with symptoms of depression.[17,19,21,23,25,27,37,38,52-61]

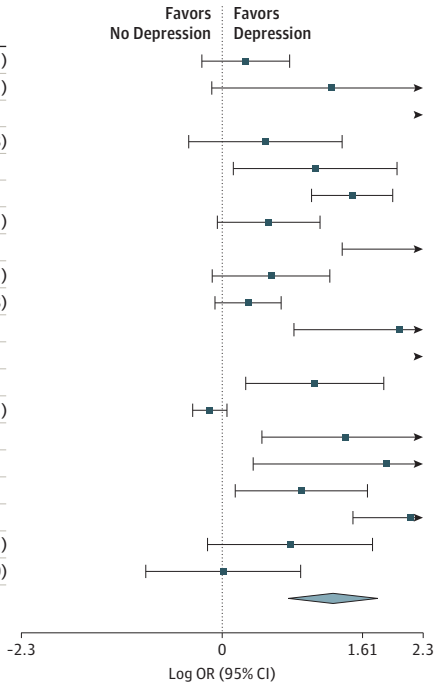
Meta-analytic Association Between AIT and Anxiety Disorders

A total of 16 samples reported outcome data for the different forms of hypothyroidism and anxiety disorders (Table). Owing to a lack of data, it was not possible to detect differences among the diverse forms of anxiety disorders. Anxiety was mostly assessed via self-descriptive questionnaires (eg, 2 of the samples [12.5%] used the Beck Anxiety Inventory,[62] 2 of the samples [12.5%] used the Hospital Anxiety and Depression Scale,[48] and 3 of the samples [18.8%] used the State-Trait Anxiety Inventory[40]) and was sometimes assessed using questionnaires or interviews filled in by diagnosticians (eg, 5 of the samples [31.3%] used variations of the Composite International Diagnostic Interview[50,51]). Studies that defined psychiatric disorders via cutoff values of dimensional measures were concordant in their definitions.

We found that the chance of developing anxiety disorders is more than 2 times higher among patients with hypothyroidism compared with healthy controls (OR, 2.32; 95% CI,

Figure 2. Forest Plot Showing the Meta-analytic Estimate for Depression and Autoimmune Thyroiditis

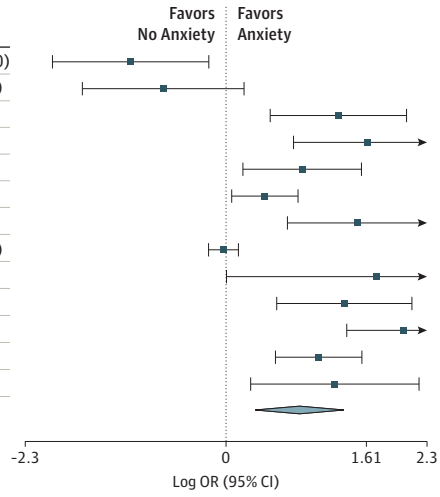
Source	No. of Patients	OR (95% CI)
Van de Ven,[52] 2016	906	0.27 (-0.23 to 0.77)
Quinque,[53] 2015	18	1.25 (-0.12 to 2.61)
Kirim et al,[19] 2012	201	4.35 (3.43 to 5.28)
Gulseren et al,[27] 2006	116	0.50 (-0.38 to 1.38)
Gulseren et al,[27] 2006	116	1.07 (0.13 to 2.00)
Demartini et al,[54] 2014	246	1.49 (1.02 to 1.96)
Ittermann et al,[17] 2015	1714	0.53 (-0.06 to 1.12)
Constant et al,[25] 2006	49	2.42 (1.38 to 3.46)
Yalcin et al,[21] 2017	124	0.56 (-0.11 to 1.23)
Bunevicius et al,[55] 2007	348	0.30 (-0.08 to 0.68)
Krysiak et al,[56] 2016	69	2.03 (0.82 to 3.25)
Krysiak et al,[56] 2016	69	3.97 (2.53 to 5.41)
Carta et al,[57] 2004	222	1.06 (0.27 to 1.85)
Engum et al,[23] 2005	30175	-0.14 (-0.34 to 0.05)
Pop et al,[58] 1998	583	1.41 (0.46 to 2.36)
Carta et al,[59] 2005	95	1.89 (0.36 to 3.42)
Zettinig et al,[60] 2003	76	0.91 (0.15 to 1.67)
Giynas Ayhan et al,[61] 2014	119	2.16 (1.50 to 2.82)
Schinhammer,[37] 2010	50	0.78 (-0.17 to 1.72)
Franke,[38] 2013	57	0.01 (-0.88 to 0.90)
Heterogeneity: $Q = 205.78$; $df = 19$; ($P = .00$); $I^2 = 92.1\%$		1.27 (0.76 to 1.78)



Forest plot of log odds ratios (ORs) in studies investigating symptoms of depression in patients with autoimmune thyroiditis. The overall odds ratio was 3.56 (95% CI, 2.14-5.94). Studies cited twice contributed more than 1 independent sample to the analysis.

Figure 3. Forest Plot Showing the Meta-analytic Estimate for Anxiety and Autoimmune Thyroiditis

Source	No. of Patients	OR (95% CI)
Gulseren et al,[27] 2006	116	-1.09 (-1.99 to -0.20)
Gulseren et al,[27] 2006	116	-0.72 (-1.65 to 0.21)
Ittermann et al,[17] 2015	1714	1.29 (0.51 to 2.07)
Constant et al,[25] 2006	49	1.62 (0.77 to 2.47)
Yalcin et al,[21] 2017	124	0.87 (0.19 to 1.55)
Bunevicius et al,[55] 2007	348	0.44 (0.06 to 0.82)
Carta et al,[57] 2004	222	1.50 (0.70 to 2.31)
Engum et al,[23] 2005	30175	-0.03 (-0.20 to 0.14)
Carta et al,[59] 2005	95	1.72 (0.00 to 3.44)
Zettinig et al,[60] 2003	76	1.35 (0.58 to 2.13)
Giynas Ayhan et al,[61] 2014	119	2.03 (1.38 to 2.69)
Grabe et al,[63] 2005	1006	1.06 (0.57 to 1.56)
Schinhammer,[37] 2010	50	1.25 (0.28 to 2.21)
Heterogeneity: $Q = 104.41$; $df = 12$; ($P = .00$); $I^2 = 89.8\%$		0.84 (0.33 to 1.35)



Forest plot of log odds ratios (ORs) in studies investigating symptoms of anxiety in patients with autoimmune thyroiditis. The overall odds ratio was 2.32 (95% CI, 1.40-3.85). Studies cited twice contributed more than 1 independent sample to the analysis.

1.40-3.85) (Table). **Figure 3** shows the overall effect of AIT on anxiety disorders.[17,21,23,25,27,37,55,57,59-61,63]

Sensitivity Analysis, Publication Bias, and Meta-regression

There were significant amounts of heterogeneity, both for the depression model ($Q = 205.8$; $P < .001$; $I^2 = 92.1\%$) and the anxiety model ($Q = 104.4$; $P < .001$; $I^2 = 89.8\%$) (Table). Sensitivity analyses revealed no statistical outliers except for 1 study[19] touching the upper limit of the acceptable residual range (−3 to 3). Thus, the robustness of our results was confirmed.

Concerning anxiety, there was no evidence of small study effects indicated by Egger regression tests. The Egger test for depression, however, revealed significant asymmetries in the distribution of published studies and thus suggests publication bias.

Slope (β), 95% CIs, and P values for meta-regression models investigating study quality, proportion of females, and mean age are detailed in eTable 6 in the Supplement. We found only 1 significant effect at a Bonferroni-corrected threshold of $P = .008$, indicating that the extent of symptoms of depression is moderated by the participants' mean age (β = -0.0971; $P = .004$). The 2 subgroup analyses revealed no significant effect on the association of AIT and depression or anxiety.

Discussion

Although underexplored, the association between AIT and depression and anxiety is an important topic with implications for both patients and physicians. Autoimmune thyroiditis is a common disease with high prevalence rates (4%-13% in the United States[1,2]) that increase with advancing age.[3] To address this importance, we report what is, to our knowledge, the first meta-analytic review of psychiatric issues among patients with hypothyroidism that examines a large data set of 19 studies with a total of 36 174 participants. Our robust results are in accordance with the hypothesis that patients with AIT have a higher chance to show symptoms of depression and anxiety compared with healthy controls.

Taking as a basis a general 12-month prevalence for depression of 6.6%[5,6] and a general 12-month prevalence for anxiety disorders of 18.1%[6] in the United States, we conclude with ORs of 3.56 (depression) and 2.32 (anxiety) that approximately 23.8% of patients with AIT experience depression and approximately 41.6% of patients with AIT experience anxiety disorders. That implies that 3% of the US population (approximately 9.7 million people) has depression and 5.4% of the US population (approximately 17.5 million people) has anxiety disorders concomitantly with AIT. Thus, 45.5% of depressive disorders and 29.8% of anxiety disorders are associated with this endocrine disease. The instruments used in the studies of this analysis do not always reflect symptoms within the 12 months before study participation (as a 12-month prevalence implies). Nevertheless, none of the instruments assess symptoms or diagnoses dating back more than 12 months but, instead, assess shorter periods (eg, 2 weeks with the Beck Depression Inventory[39,47] or 1 week with the Hamilton Depression Scale.[49] Hence, percentages in this paragraph are very likely underestimated. Prevalence rates for AIT in European countries are comparable with those in this study, varying between 5% and 14%,[64,65] emphasizing the global relevance of these findings. Assuming that depression and anxiety disorders are illnesses that often appear together[66] with a comorbidity of up to 57.5%,[5,67] patients with AIT have a high risk of experiencing combined depression and anxiety disorder (eg, depression and panic disorder[68]). These circumstances further amplify the relevance of our meta-analytic review.

Out of 3 moderators (study quality, proportion of females, and mean age) only mean age altered the association between AIT and depression (eTable 6 in the Supplement). Results and interpretation of the moderator analyses are discussed in eAppendix 3 of the Supplement.

Based on qualitative reviews there were strong indications of a higher prevalence of depression and anxiety among patients with hypothyroidism. Marangell and Callahan[30] describe first studies investigating a link between the thyroid gland and the brain using positron emission tomography paradigms and Hendrick and colleagues[32] point to a high occurrence of hypothyroidism among patients with therapy-resistant depression. Despite these indications, no direct association between particular alterations in brain regions because of AIT and the development of a depressive disorder was found.[18,69] Regarding anxiety, first symptoms among patients with hypothyroidism are often generalized agitation or extreme restlessness.[22] As some of the symptoms of hypothyroidism comprise higher blood pressure[13] and sensations of nightly tachycardia,[70,71] it is presumable that this condition leads to a facilitated development of generalized anxiety disorder. Owing to a lack of data, it was not possible to test for this hypothesis in our meta-analytic review.

Our results entail various implications for physicians in practice. Clinical experience shows that patients often seek medical attention owing to psychiatric symptoms but are unaware of AIT. As AIT is a chronic disease,[34] so are symptoms of depression and anxiety associated with it. Both anxiety and depression have persistent courses owing to, among other factors, learning mechanisms accompanying the diseases: learned helplessness in the case of depression[72] and classical fear conditioning[73] contribute to a long-term maintenance of psychiatric symptoms. Autoimmune thyroiditis, however, can appear in phases (euthyroid vs hypothyroid)[74] and is thus not always traceable as the root cause of these symptoms, impeding correct diagnoses and further appropriate therapy. Depression and anxiety disorders associated with a thyroid disease require different treatment than usual. Occasionally, there are conditions when a thyroidectomy is indicated.[75] Regarding pharmacotherapy, an extension of possible medication must be taken into consideration. Besides typical levothyroxine treatment, selenium supplementation can help to reduce the amount of thyroid antibodies and improve mood or well-being.[76] Furthermore, an early administration of antidepressants could be indicated to attenuate the chronic course of AIT. Thyroid metabolism is associated with the brain serotonin system[77]; thus, selective serotonin reuptake inhibitors are appropriate medications to treat depression in patients with AIT.[78] Classical, tricyclic antidepressants, however, are not suited for patients with hypothyroidism. On the one hand, patients with hypothyroidism do not respond as well to tricyclic antidepressants as patients with depression who are euthyroid[32,68] and, on the other hand, typical adverse effects of tricyclic antidepressants such as weight gain already occur in patients with hypothyroidism[16] and can be further enhanced. It is consequently important to administer modern antidepressants with a neutral effect on weight. Moreover, patients with AIT and no symptoms of depression or anxiety must be aware of the vulnerability to develop psychiatric issues. As a consequence, both a screening for psychiatric symptoms is advisable in patients with AIT and a test for AIT is recommended in patients with depression and anxiety disorders. This test must not be narrowed down to thyrotropin levels and free triiodothyronine and free thyroxine but should comprise thyroid peroxidase antibodies as well. In population-based studies, only 4% to 5% of patients show elevated thyrotropin levels, whereas 13% to 23% are positive for thyroid peroxidase

antibodies.[1,2,64,65,79] If only the thyrotropin level is measured, a diagnostician will miss many patients with AIT detectable by assessment of thyroid peroxidase antibodies and ultrasonography.[79] As this meta-analysis clearly shows the higher prevalence of depression and anxiety in patients with hypothyroidism, it contributes to enhanced awareness and thus to faster diagnoses and appropriate treatment of patients.

Strengths and Limitations

Our analysis comprises a profound and extensive literature search, presents data of sufficient quality, and computes outcome measures independent of the studies' risk of bias. Nevertheless, there are some limitations of this study. The high levels of heterogeneity and funnel plot asymmetry for depression could result in slightly overestimated effect sizes. Furthermore, case-control studies bear the methodical risk of "superhealthy" controls and reduced generalizability owing to selection and information bias. A detailed description of strengths and limitations of our analysis can be found in eAppendix 3 in the Supplement.

Future research should focus on more specific analyses, such as differentiating the various forms of hypothyroidism (eTable 1 in the Supplement) or investigating its association with subforms of anxiety. Moreover, it is important to examine the influence of AIT on concrete symptoms of depression and thus clarify the causal relationship behind this association. In a next step, the interaction of thyroid hormones and brain regions responsible for depression or anxiety should be further researched. Overall, it is necessary to develop a biopsychosocial model about the origin of depression and anxiety that also comprises AIT.

Conclusions

Autoimmune thyroiditis is associated with depression and anxiety disorders. It is thus important to enhance awareness among physicians about this connection to accelerate the diagnostic process. In patients with depression and anxiety disorders, a test for AIT should be performed and in patients with AIT, a screening for psychiatric symptoms is necessary. Advantages for patients are appropriate treatment taking into consideration early administration of antidepressants and facilitated coping owing to a better (biopsychosocial) understanding of their disease.

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Study concept and design: Grömer.
Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: Siegmann, Grömer.
Critical revision of the manuscript for important intellectual content: All authors.
Statistical analysis: Siegmann.
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