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No association between anti-thyroidperoxidase antibodies and bipolar disorder: a study in the Dutch Bipolar Cohort and a meta-analysis

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ABSTRACT

Background: Thyroid autoimmunity has been associated with bipolar disorder (BD). However, results from previous studies on the seroprevalence of anti-thyroid peroxidase antibodies (TPO-abs) in BD are inconsistent.
Objectives: The aim of the present study is to investigate whether the seroprevalence and titer levels of TPO-abs are related to BD.
Method: TPO-abs were measured in plasma samples of 760 patients with bipolar disorder, 261 first-degree relatives and 363 controls by enzyme-linked immunosorbent assay (ELISA). To address methodological limitations of previous studies, we assessed clinical characteristics with several (self-reported) questionnaires to investigate whether TPO-abs positivity is related to particular clinical subgroups of BD patients. We performed an additional meta-analysis of seroprevalences of TPO-abs in BD patients including data from present and previous studies.
Results: Seroprevalence or titer levels of TPO-abs did not significantly differ between patients with BD, their first-degree relatives, and controls. In BD patients, the prevalence of TPO-abs was unrelated to specific clinical factors, including lithium use. Our meta-analysis of twelve studies showed an overall odds ratio of 1.3 (CI 95 %: 0.7–2.3; p = 0.30), reaffirming the absence of an association of BD with TPO-abs.
Conclusions: In the largest study of TPO-abs in BD to date, our findings indicate that TPO-abs are not associated with (the risk for) bipolar disorder.

1. Introduction

Several lines of evidence suggest that the immune system is involved in the pathophysiology of bipolar disorder (BD). However, how the immune system contributes to BD is yet unclear. Epidemiological studies in large population cohorts have shown that a diagnosis of an autoimmune disease is a risk factor for BD (Benros et al., 2013), (Eaton et al., 2010), (Wang et al., 2017), (Cremaschi et al., 2017). Since it is well-known that autoimmune diseases co-segregate in families, it is hypothesized that autoimmunity may play a role in the pathogenesis of BD.

Autoimmunity is defined as an immune response against the body caused by autoreactive T-lymphocytes and antibodies that recognize self-antigens, the so-called auto-antibodies. To further evaluate whether autoimmune processes play a role in BD, the seroprevalence and titer levels of a range of auto-antibodies has been investigated (Padmos et al., 2004), (Spivak et al., 1996). Most studies have focused on thyroid peroxidase antibodies (TPO-abs) since mood disorders and circulating thyroid antibodies are very prevalent in the general population. Thyroid peroxidase antibodies can cause autoimmune thyroid disease, like Hashimoto thyroiditis. However, the presence of TPO-abs is not specific to thyroid autoimmune disorder, because the antibodies are also present in the general population (especially in women and the elderly) (Vanderpump, 2011), (Laurberg et al., 1998). Several theories have been proposed to define the presence of TPO-Abs to BD pathogenesis: 1) TPO-abs themselves induce an autoimmune reaction in the

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brain resembling a bipolar-like manic psychotic episode (Müssig et al., 2005), (Bocchetta et al., 2016), 2) TPO-abs precede the clinical thyroid failure phase (ie. raised TSH, reduced fT4) for many years, and thyroid dysfunction is associated with symptoms such as depression and mood lability (Chakrabarti and Subho, 2011), 3) Use of lithium may influence auto-immune processes in the thyroid gland (Smigan et al., 1984), (Wilson et al., 1991), or 4) A common intrinsic defect can lead to activation of the immune system and/or BD (O'Dushlaine et al., 2015).

Several case-control studies investigated the seroprevalence or titer of TPO-abs in relation to BD (Barbuti et al., 2017). The first studies revealed an increased seroprevalence of anti-TPO in BD compared to controls (Kupka et al., 2002), (Lazarus et al., 1986). However, more recent data did not confirm this finding (Cobo et al., 2015), (Kuman Tunçel et al., 2017). A systematic review by Barbuti et al. indicated that the prevalence of TPO-abs may be increased in BD patients, but only during a depressive or mixed-mood episode (Barbuti et al., 2017). These researchers also investigated the association between thyroid autoimmunity and lithium use, but could not confirm it (Barbuti et al., 2017). In addition, previous studies have shown increased seroprevalence rates of TPO-abs in first-degree family members of BD patients, suggesting that autoimmune thyroiditis and BD share an increased inherited risk (Vonk et al., 2007), (Wals et al., 2001). However, two recently published studies could not replicate these findings (Snijders et al., 2017), (Cobo et al., 2015).

In summary, results regarding the seroprevalence of anti-thyroid peroxidase antibodies (TPO-abs) in BD patients are inconsistent. Several methodological issues hampered studies so far; discrepancies between studies may be a result of small sample sizes and/or heterogeneity in regards to variables like age, gender, study setting, and methodological differences. Therefore, our aim was to investigate in the Dutch Bipolar Cohort (DBC) whether the seroprevalence and titer levels of TPO-abs in plasma of BD patients are increased compared to their first-degree relatives and controls. This comprehensively phenotyped cohort of Dutch ancestry is the largest study to date (n = 1394) to investigate the association between TPO-abs and BD. Clinical variables were also assessed to evaluate whether the presence of TPO-abs is associated with specific subgroups within the BD cohort. To understand the results of our study in the context of previous research, we performed a meta-analysis on seroprevalences of TPO-abs in BD. To create an interpretative and evaluative framework, we reviewed the literature is both qualitatively and quantitatively. By addressing the methodological limitations of previous studies, this study aims to clarify the relation between seroprevalence of TPO-abs and BD.

2. Methods and materials

2.1. Medical ethics

The Medical Ethical Review Board of the UMC Utrecht approved both studies and all participants gave written informed consent. The demographics of the participants are summarized in Table 1.

2.2. Study population

2.2.1. Patients with bipolar disorder and first-degree relatives

This study is comprised of BD patients and first-degree relatives (parents, children, and siblings) from the Dutch bipolar cohort (DBC) (Vreeker et al., 2016). In total, the study included 760 subjects affected with bipolar I or bipolar II disorder according to DSM-IV criteria and 261 first-degree relatives; for all participants frozen plasma was available. BD diagnosis was confirmed via the Structured Clinical Interview for DSM-IV (SCID-I) (First et al., 1997). The Mini-international Neuropsychiatric Interview (Sheehan et al., 1998) was used to confirm/establish psychopathology in first-degree relatives. The study design and recruitment procedure for study subjects have previously been described in detail (Vreeker et al., 2016).

In short, participants were recruited via clinicians, the Dutch patients' association, pharmacies, advertisements, and individuals who previously participated in scientific studies. Inclusion criteria were: age ≥ 18 years, at least three Dutch-born grandparents, a decent understanding of the Dutch language, and no medical illness that could affect BD, verified with a medical history inventory. First-degree relatives included parents, children, and siblings were invited through the patients who participated in the study. First-degree relatives diagnosed with BD were excluded from further analysis. To investigate whether TPO-abs positivity is related to particular clinical subgroups of BD patients, clinical characteristics such as severity, medication use and the age of illness onset of BD patients were assessed with several (self-reported) questionnaires.

2.2.2. Controls

Controls originate from the DBC (n = 132) as well as the Dutch Genetic Risk and Outcome in Psychosis cohort (GROUP) (n = 241). Both studies originate from the same geographical region. Study design, recruitment procedure, and inclusion criteria of both control populations were previously described in detail (Vreeker et al., 2016), (Korver et al., 2012). We included all available plasma samples from controls of both studies (DBC and GROUP) that meet inclusion criteria. Inclusion criteria for study subjects were: age ≥ 18 years, a decent command of the Dutch language, no history of a major axis I psychiatric disorder (psychotic disorders and major mood disorders according to DSM-IV criteria) and no lithium use.

2.3. Laboratory testing

Plasma samples of participants were collected between 2009 and 2011 and stored at −80 °C. The method Immulite was used to assess TPO-abs in our previous studies (Hillegers et al., 2007), (Vonk et al., 2007). Since this method is not available anymore, we measured IgG class antibodies against TPO with an enzyme-linked immunosorbent assay (ELISA; IBL Laboratories, Hamburg, Germany). The performance of this ELISA was compared with Immulite (Milenia assay, DPC, Breda, The Netherlands) for 60 samples and showed a correlation coefficient of 0.87 for seroprevalence and 0.81 for titer levels. The ELISA's were performed according to the manufacturer's protocol. In short, plasma samples were pre-diluted (1:101) and tested on a 96-well pre-coated microplate. Plasma samples of patients, first-degree relatives, and controls were equally distributed on the plates. After incubation for 30 min at room temperature and extensive washing, horseradish peroxidase-labeled anti-human IgG antibodies were added. After incubation for another 30 min and extensive washing, tetramethylbenzidine was added to each well and the reaction was stopped with H_2SO_4 after 30 min. The results were recorded as optical density (OD) at 450 nm. Each plate contained a cut-off control provided with the assay. Samples with an OD above the cut-off control scored positive, and below, negative. Positive samples were further analyzed using the calibration curve provided with the test to determine the titer levels (expressed inunits/mL).

2.4. Statistical analysis

A priori, we performed a power analysis based on findings of earlier research that assumed an odds ratio of 2.2 (Kupka et al., 2002). We aimed to reach sufficient power to assess differences between BD and HC. We estimated that 225 subjects would be sufficient to obtain 80 % power at an α-level of 0.05. Statistical analysis was performed using SPSS. We used pearson's chi-square tests, student t-tests, and ANOVA to compare categorical and continuous variables between various groups. In the case of non-normally distributed data, we used a Mann Whitney U test Additionally, we performed a logistic regression analysis to estimate the odds ratio for bipolar disorder in TPO-abs positive subjects as compared to TPO-abs negative subjects with adjustment for age and gender.

Table 1
Demographic characteristics.

	Bipolar Patients (n = 760)	Family-members (n = 261)	Controls DBC (n = 122)	Controls GROUP (n = 241)	Controls total (n = 363)	P-value
Gender	335 (44.1)	87 (33.3)	70 (57.4)	112 (46.5)	182 (50.1)	[a]: 0.057
Male, n (%)	425 (55.9)	174 (66.7)	52 (42.6)	129 (53.5)	181 (49.9)	[b]: **0.002***
Female, n (%)						[c]: **< 0.001***
Age in years, mean (SD)	49.4 (12.4)	55.4 (15.6)	49.0 (12.9)	34.1 (10.5)	39.1 (13.4)	[a]: **< 0.001***
						[b]: **< 0.001***
						[c]: **< 0.001***
Psychiatric Diagnosis	747 (98.3)	–	–	–	–	
Bipolar disorder type I, n (%)	13 (1.7)	–	–	–	–	
Bipolar disorder type II, n (%)	–	166 (58.0)	100 (82.0)	241 (100.0)	341 (93.9)	
No psychiatric diagnosis, n (%)	–	95[#] (33.2)	22[##] (18.0)	–	22[##] (6.1)	
Other, n (%)						
Family-member	–	45 (17.2)	–	–	–	
Father, n (%)	–	63 (24.1)	–	–	–	
Mother, n (%)	–	33 (12.6)	–	–	–	
Brother, n (%)	–	78 (29.9)	–	–	–	
Sister, n (%)	–	42 (16.1)	–	–	–	
Child, n (%)						
Age of onset in years, median (IQR)	29.0 (16.0)	–	–	–	–	
Current mood episode	62 (8.2)	–	–	–	–	
Depressed, n (%)	47 (6.2)	–	–	–	–	
Hypomanic, n (%)	23 (3.0)	–	–	–	–	
Manic, n (%)	4 (0.5)	–	–	–	–	
Mixed, n (%)	624 (82.1)	–	–	–	–	
Unknown, n (%)						
Last mood episode	360 (47.4)	–	–	–	–	
Depressed, n (%)	81 (10.7)	–	–	–	–	
Hypomanic, n (%)	226 (29.7)	–	–	–	–	
Manic, n (%)	19 (2.5)	–	–	–	–	
Mixed, n (%)	74 (9.7) 97 (12.8)	–	–	–	–	
Unknown, n (%)						
Rapid cycling, n (%)						
Inventory of Depressive Symptomatology (IDS)	367 (48.3)	–	–	–	–	
No depressive symptoms, n (%)	225 (29.6)	–	–	–	–	
Mild depression, n (%)	111 (14.6)	–	–	–	–	
Moderate depression, n (%)	29 (3.8)	–	–	–	–	
Severe depression, n (%)	11 (1.4)	–	–	–	–	
Very severe depression, n (%)	17 (2.2)	–	–	–	–	
Unknown, n (%)						
Altman Self Rating Mania scale (ASRM)	632 (83.1)	–	–	–	–	
No manic symptoms, n (%)	113 (14.9)	–	–	–	–	
Manic symptoms, n (%)	15 (2.0)	–	–	–	–	
Unknown, n (%)						
Medication use	493 (64.9)	–	–	–	–	
Lithium at the moment, n(%) *Dosage in mg, median (IQR)*	800.0 (400.0)	–	–	–	–	
	9.0 (15.0)	–	–	–	–	
Duration in years, median (IQR)	0.7 (0.2)	–	–	–	–	
Blood level in mg/L, median (IQR)	681 (89.6)	–	–	–	–	
Lithium ever used, n (%)	364 (53.5)	–	–	–	–	
Responder, n (%)	185 (27.1)	–	–	–	–	
Non-Responder, n (%)	132 (19.4)	–	–	–	–	
Unknown, n (%)	77 (10.1)	–	–	–	–	
Carbamazepine, n (%)	500.0 (500.0)	–	–	–	–	
Dosage in mg, median (IQR)	11.5 (15.5)	–	–	–	–	
Duration in years, median (IQR)	179.0 (22.8)	–	–	–	–	
Valproate, n (%)	1200.0(600.0)	–	–	–	–	
Dosage in mg, median (IQR) Duration in years, median (IQR)	5.0 (8.0)					
Global Assessment of Functioning (GAF), median (IQR)	65.0 (20.0)	–	–	–	–	

DBC = Dutch bipolar cohort. GROUP = Genetic Risk and Outcome of Psychosis. N = Number. SD = standard deviation. [a] Bipolar patients versus controls total. [b] Bipolar patients versus family members. [c] Family members versus controls total. *Significant difference ($p < 0.05$).

[#] = Depression ($n = 51$), anxiety disorder ($n = 17$), substance abuse ($n = 10$), adjustment disorder ($n = 4$), attention deficit hyperactive disorder ($n = 3$), eating disorder ($n = 3$), somatization disorder ($n = 2$), post-traumatic stress disorder ($n = 1$), schizoaffective disorder ($n = 1$), unknown ($n = 3$).

[##] = Substance abuse ($n = 8$), anxiety disorder ($n = 7$), adjustment disorder ($n = 3$), eating disorder ($n = 1$), attention deficit hyperactive disorder ($n = 1$), unknown ($n = 2$).

2.5. Meta-analysis

See Supplementary Methods for details on the literature search, quality check assessment, and statistics.

3. Results

3.1. Demographics

The demographic characteristics of the study participants are shown in Table 1. The mean age significantly differs between BD patients (mean age 49 years, SD 12.4), first-degree relatives (mean age 55 years, SD 15.6), and controls (mean age 39 years, SD 13.4) ($p < 0.001$). Significantly more women were present in the relatives group (66.7 %) compared to the patient (55.9 %) and control groups (49.9 %) ($p < .001$ resp. $p < 0.001$).

3.1.1. TPO-abs in bipolar patients and controls

A significantly increased seroprevalence of TPO-abs was found in women compared to men (11.0 % resp. 5.3 %, p < 0.001). The seroprevalence was higher in study subjects with an age above 45 years compared to subjects below 45 years (9.7 % resp. 6.8 %), but did not reach significance (p = 0.07) (see Table S1). TPO-abs seroprevalence did not differ between bipolar patients (8.4 %), and controls (9.1 %) ($\eta^2 = 0.011$, $p = 0.964$). Also, median titer levels for seropositive TPO-abs cases did not differ significantly between patients and controls total. (see Table 2). TPO-abs positivity or titer levels did not show an association with medication use either, including the use of lithium and blood levels of lithium. Other clinical variables, such as the age of BD onset and severity, were also not related to TPO-abs seroprevalence (see supplemental Table S1).

3.1.2. Adjustment for age and gender

No significant differences were found between bipolar patients and controls after adjustment for age and gender (p = 0.123).

3.1.3. TPO-abs in first-degree relatives

TPO-abs seroprevalence did not differ between first-degree relatives (8.0 %), BD patients (8.4 %), and controls (9.1 %) ($\eta^2 = -0.006$, $p = 0.538$ resp. $\eta^2 = 0.018$, $p = 0.402$). Titer levels of seropositive cases were not statistically significant between first-degree relatives, patients, and controls (see Table 2).

3.1.4. Adjustment for age and gender

After adjustment for age and gender, we found that the seroprevalence of TPO-abs was lower in first-degree relatives compared to controls at a trend level (p = 0.067), but no differences were found between BD patients and first-degree relatives (p = 0.369).

3.2. Meta-analysis

Twelve studies were identified including a total of 1609 BD participants and 1046 HC participants (including the DBC). Information on the number of study participants, methodological design, and outcome measurement for the individual studies are provided in Table 3. The mean age of the participants was 44.3 years (SD 3.2) and 58.9 % the sample were female (as reported by 9 of the 12 studies). When all twelve studies were combined, we obtained an overall OR of 1.3 (CI 95 %: 0.7–2.3; p = 0.30) for the association between TPO-abs and BD (see Fig. 1). Exclusion of the DBC did not show a significant effect on the OR (overall OR 1.5 CI 95 %: 0.8–2.8, p = 0.25).

The effect of potential moderators (age, gender, year of publication (YOP)) on OR was studied by a meta-regression analysis. A meta-regression with the prevalence of the female gender did not show a significant effect on the OR. As shown before, a significant increase of the OR was observed with increasing age (intercept =-5.91, slope = 0.14, p = 0.03). To evaluate whether OR's differed between different age groups, the study samples were divided into two categories (> 45 yrs and < 45 yrs). However, the difference in OR was not significant between the two age groups (z = 0.3, p = 0.14) and there was still evidence of dispersion within different age subgroup (data not shown). Meta-regression with YOP was analyzed with a significant decline of the OR (intercept = 145.8, slope = -0.07, p < 0.001) over subsequent years. Post-hoc subanalysis showed a significant difference in OR in publications before the year 2003 (overall OR: 2.3 95 % CI 1.1–6.4) compared to studies published after the year 2003 (overall OR: 0.88 95 % CI 0.6–1.4) (see supplemental Figure S2).

4. Discussion

Epidemiological and genetic studies, as well as case-control studies assessing peripheral immune markers, suggest that the immune system is implicated in the pathogenesis of BD (Benros et al., 2013), (Barbosa et al., 2014), (O'Dushlaine et al., 2015). Since a high comorbidity of autoimmune diseases and BD has been reported and both diseases co-segregate in families, autoimmunity is proposed as one of the mechanisms that may play a role in the pathogenesis of BD (Wang et al., 2017), (Cremaschi et al., 2017), (Eaton et al., 2010). In the largest BD study to date, including a reference group of relatives of these BD patients, we investigated whether autoimmunity against the thyroid gland is related to BD. Our study confirms previous studies (Laurberg et al., 1998),(Vanderpump, 2011) reporting that age and female gender are associated with higher seroprevalences. However, we did not find evidence for an increased prevalence or titer level of thyroid auto-antibodies in the plasma of patients with BD compared to controls, nor did we find such evidence after adjustment for gender and age. The TPO-abs level was also not elevated in first-degree relatives of BD patients compared to controls. TPO-abs positivity was not related to specific clinical factors within subgroups of BD patients. A systematic review

Table 2
Seroprevalence of TPO-Abs in bipolar patients, family members and controls.

	Bipolar Patients (n = 760)	Family-members (n = 261)	Controls DBC (n = 122)	Controls GROUP (n = 241)	Controls Total (n = 363)	P-value	P-value adjustment age/gender
TPO	64 (8.4)	21# (8.0)	12 (9.8)	21 (8.7)	33 (9.1)	[a]: 0.709	[a]: 0.123
Positive, n (%)	696 (91.6)	240 (92.0)	110 (90.2)	220 (91.3)	330 (90.9)	[b]: 0.850	[b]: 0.369
Negative, n (%)						[c]: 0.647	[c]: 0.067
TPO-level	235.8	153.9	136.6	551.9 (658.9)	274.9	[a]: 0.648	[a]: 0.520
Median (IQR)	(441.5)	(266.3)	(681.7)		(660.1)	[b]: 0.237	[b]: 0.146
						[c]: 0.231	[c] **0.037***

DBC = Dutch bipolar cohort. GROUP = Genetic Risk and Outcome of Psychosis. N = Number.SD = standard deviation. [a] Bipolar patients versus controls total. [b] Bipolar patients versus family members. [c] Family members versus controls total.*Significant difference ($p < 0.05$).
# = $n = 6$ Diagnosed with a depressive disorder and $n = 1$ with an anxiety disorder.

Table 3
Summary of included studies.

Article	Technique	Treshhold	Groups	Mean age (SD#)	Gender female (%)	*N*	% Ab +
Bartalena et al., 1990	ELISA	NA	Rapid cycling bipolar women	43 (22–78)	11 (100.0)	11	9.1
			Non rapid cycling bipolar women	46 (21–75)	11 (100.0)	11	9.1
			Healthy females	NA	11 (100.0)	11	9.1
Cobo et al., 2015	ECLIA	15 u.arb/ml	Bipolar I patients	45.1 (15.0)	129 (54.0)	239	15.6
			Healthy controls	42.1 (16.4)[a]	71 (65.7)[a]	108	18.8
Hornig et al., 1999	H	1 : 100	Bipolar I and II patients	49.3 (14.5)	61 (59.2)	103	12.6
			Control	41.1 (11.5)	8 (36.4)	22	13.6
Kuman et al. 2017	CLIA	36*	Patients on lithium diagnosed with bipolar disorder	43.1 (11.4)	45 (53.6)	84	10.7
			Control subjects	39.7 (10.4)	39 (60.0)	65	23.1
Kupka et al., 2002	ELISA	10 U/ml	Bipolar outpatients	45 (23–83)	114 (50.4)	226	28.3
			General population	57.5 (55-60)	152 (60.3)	252	13.4
Lazarus et al., 1986a	ELISA	25 U/ml	Bipolar manic depressive outpations before treatment with lithium	49.3 (28–71)	20 (54.0)	37	43.2
			Normal controls with family history without thyroid disease	NA	NA	27	0.0
Margari et al., 2015	CLIA	60 U/ml	Bipolar disorder patients	NA	NA	11	9.1
			Healthy, normal volunteers	42.08 (8.0)	15 (38.5)	39	5.4
Schiemann and Hengst, 2002	NA	100 U/ml	Manic-depressive patients receiving lithium for > 6 months	44.5 (14.2)	12 (60.0)	20	5.0
			Age- and gender-matched euthyroid volunteers	44.1 (13.8)	12 (60.0)	20	0.0
Sidhom et al., 2012	ELISA	Threshold manufacturer	Bipolar patients	38.9 (10.2)	6 (37.5)	16	0.0
			Healthy, age and sex matched blood donors	41.2 (7.6)	9 (22.0)	41	7.3
Snijders et al. (Present study)	ELISA	Threshold manufacturer	Bipolar patients	49.4 (12.4)	425 (55.9)	760	8.4
			Healthy controls	39.1 (13.4)	181 (49.9)	363	9.1
Vonk et al., 2007	ELISA	25 U/ml	Bipolar index twins	41.3 (10.1)	35 (69.0)	51[b]	27.0
			Control twins	41.2 (9.3)	55 (79.0)	70	16.0
Wilson et al., 1991	H	1 : 100	Patients treated with lithium for manic depression without pre-existing thyroid disease	47 (15.2)	27 (67.5)	40	15.0
			Healthy volunteers with no history of thyroid disease	41 (10.3)	24 (60.0)	40	0.0

Abbreviations: ELISA: enzyme-linked immunosorbent assay ECLIA: Electrochemicolumi-nescence. CLIA: Chemiluminescent sequential immunometric assay. H: Haemagglutinatio. NA: not applicable. #If SD is not given in article, age range is reported. [a]Thyroid autoantibodies measured in n = 96, mean age and gender only given in total healthy control sample.[b]Bipolar Index Twin is included in final analysis (*n* = 51). *Units per volume were not given.

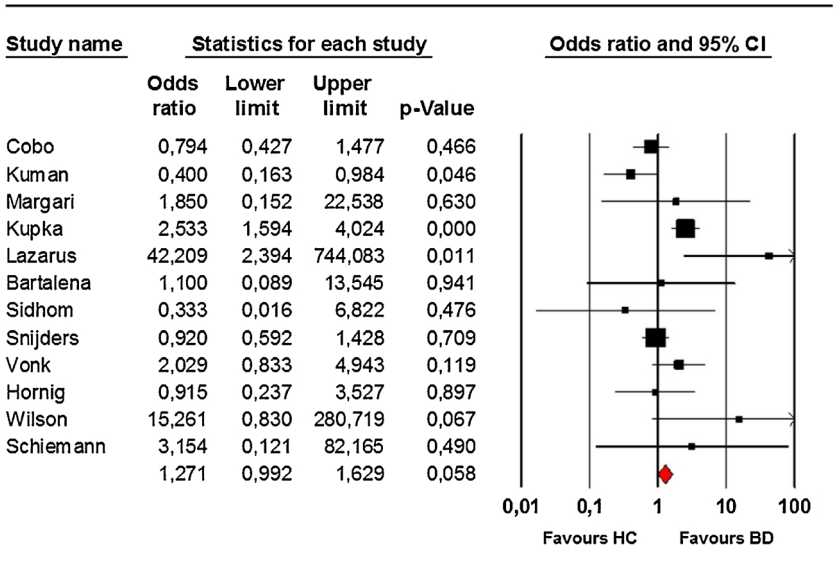

Fig. 1. Meta-analysis of thyroid autoantibodies in bipolar disorder. Evidence for publication bias was not found by visual examination by Funnel Plot or an Egger's test (p = 0.59). The heterogeneity of the results was moderate-high (coefficient I2 = 63 %; Q (11) = 30.1, p = 0.002). The studies with the highest weight were those by Kupka et al., 2002, Cobo et al. 2016 and the present study (15 % resp. 17 % resp 17 %). The exceptionally large effect OR of Lazarus et al., 1986a,b was identified as outlier (z = 2.20, p = 0.011). Without this study, the overall OR reduced to 1.2 (95 % CI 0.72–1.96), but heterogeneity remained high (58 %) and Q-value was significant (p = 0.007).

and meta-analysis of the seroprevalence of TPO-abs in BD confirmed the absence of such a relation in the broader literature.

4.1. TPO-abs in bipolar patients and controls

Our results on the seroprevalence of TPO-abs in the DBC are also in line with recent findings of several other studies, showing no association between BD and TPO-abs (Cobo et al., 2015), (Kuman Tunçel et al., 2017). However, our results are in contrast with three older studies that reported significant or borderline significant OR between 2.5 and 4.2 (John H. Lazarus et al., 1986), (Kupka et al., 2002), (Wilson et al., 1991). The quality assessment of the studies provides possible explanations for their observed higher seroprevalence of TPO-abs (see supplemental Table S2). The participants in these studies varied considerably in age and gender between patients and controls. From these studies, it is not clear whether the researchers adjusted for age and gender. In addition, the studies of Wilson et al. selected patients with "manic depression", but this was not confirmed by a structured

interview; similarly, Lazarus et al. selected controls with no family history of thyroid disease (Wilson et al., 1991), (Lazarus et al., 1986). Kupka et al. selected patients and controls from different countries (patients from the United States versus controls from the Netherlands (Kupka et al., 2002)), which could interfere with outcomes considering that there exist geographic variations in the frequency of TPO-Abs (Meisinger et al., 2012). The large majority of included studies did not control for confounding factors such as age, gender, and/or use of medication, as shown in our quality assessment, since careful evaluation of possible confounding factors is essential when trying to relate TPO-abs to BD. In the DBC, detailed phenotypic information of included study participants was available and adjustment for age and gender were accounted for, and other possible clinical confounding factors such as medication use, stage, course, and duration of disease were not associated with the presence of BD (see Supplemental Table S1). Another possible explanation for discrepancies among studies is lack of power. Sample sizes that achieved sufficient power ($n = 225$, based on a prior power analysis) were not met by the majority of the studies. Only the DBC and study by Kupka et al. exceeded the number of necessary subjects ($n \geq 225$) to obtain 80 % power at an α-level of 0.05 (Kupka et al., 2002). Overall, underpowered studies are more likely to be affected by publication bias (Button et al., 2013). Furthermore, studies with low statistical power carry the risk of both false positive and negative findings and are more likely to report and analyze data selectively (Button et al., 2013). These shortcomings pose an important limitation to the outcomes of previously published studies in this field. To reduce the risk of misinterpretation of data due to the chance of false positive or negative findings, we analyzed TPO-abs as continuous measurement (average titer levels). However, no significant differences were found between BD and HC in the DBC and other studies (Cobo et al., 2015), (Hornig et al., 1999).

Differences in methodological quality may also explain these contradicting results, reflected in the negative association between the OR and year of publication (displayed in supplemental Figure S2 of the meta-analysis). Large variability in the methodology to measure TPO-abs may have contributed to differences in results. The seroprevalence rates reported in our study are similar to seroprevalence rates of 5–17 % reported in the general population (Vanderpump, 2011), (Knudsen et al., 1999), (Laurberg et al., 1998), but considerably lower compared to rates of 15–28 % reported in other BD studies (Kupka et al., 2002), (Cobo et al., 2015), (Kuman Tunçel et al., 2017). An explanation could be differences in the sensitivities and the specificities of used assays. To maximize the comparability of our data, we intended to use the same antibody measurement test (Immulite) that was previously used in two large studies of our group (Hillegers et al., 2007), (Vonk et al., 2007); however, this method was no longer applicable. Therefore, we randomly selected 60 subjects of these two large studies to test three different assays a priori. Outcomes of the three assays were compared with the Immulite method and the assay with the highest correlation coefficient for both seroprevalence and titer levels was used upon further testing.

4.2. TPO-Abs and clinical factors in BD

A recent systematic review summarized several studies, showing that there is evidence of increased prevalence of circulating thyroid autoantibodies in depressed and mixed BD patients (Barbuti et al., 2017). In the DBC, we conducted additional analyses including several clinical variables such as mood state, and severity, but could not confirm this association (see supplemental Table S1). In line with this systematic review, our study also did not confirm an association between lithium and BD. Altogether, these findings indicate that screening for TPO-abs is not indicated in BD or specific clinical subgroups.

4.3. TPO-Abs in first-degree relatives

Previous studies suggest a possible genetic relationship between autoimmune thyroiditis and BD (Wilson et al., 1991), (Kupka et al., 2002), (Snijders et al., 2016); however, we could not confirm that TPO-abs are more common in family members of patients diagnosed with BD. Epidemiological studies on this topic showed that autoimmune thyroiditis in families was not significantly associated with an increased risk for BD (Eaton et al., 2010).

4.4. Limitations cohort

Limitations of our study include the cross-sectional design and measuring of TPO-abs years after disease onset, and the inclusion of controls from two different studies. Although the TPO-abs tests were performed at the same time, the sampling of the controls of the GROUP study was performed between 2008–2010 and sampling of the DBC controls between 2011–2015, indicating that GROUP plasma samples were stored for 1–7 years longer. However, long-term storage appears to have a minimal effect on protein in plasma (Mitchell et al., 2007). Younger age in the control group is mainly a result of the inclusion of controls from the GROUP cohort (mean age of 34.1 years, SD 10.5), but the exclusion of GROUP controls did not alter the outcomes (see Table 1). The DBC did not exclude controls with psychiatric diagnosis other than mood or psychotic disorders. Previous studies showed that anxiety disorder is related to TPO-abs positivity (Carta et al., 2004), so we excluded in our data subjecs with an anxiety disorders, which did not affect the outcomes (data not shown).

This is not a population based cohort, but a selected subgroup of BD patients, their first-degree relatives and controls in the Netherlands, which could interfere with the results. Previous literature suggests that increased prevalence rates of TPO-abs are only present in specific subgroups of BD patients, during depressed or mixed mood episodes or at early-onset of the disease (Barbuti et al., 2017), (Hillegers et al., 2007). However, most patients in the DBC are euthymic (approximately 10 % was in an established depressed or mixed mood episode) and the onset of the disease is for most patients years ago. Future studies should analyze the presence of TPO-abs in these specific subgroups.

4.5. Meta-analysis TPO-Abs in BD

Additionally, a meta-analysis on seroprevalences of TPO-Abs in BD was performed to understand the outcomes of our study in the context of the existing literature. The quality of the studies examined was medium-high, and it was higher in the more recent studies due to the introduction of more sensitive methods to test for antibodies and increased comparability of cases and controls due to matching and/or adjustment for confounders (see supplemental Table S2). Barbuti et al., 2017 stated that due to the high heterogeneity of studies, pooling of studies was not possible (Barbuti et al., 2017). In order to reduce heterogeneity among studies, we defined the inclusion criteria of meta-analysis closely and included only a limited number of studies ($n = 12$) (Barbuti et al., 2017). Despite this careful analysis, heterogeneity remained high, probably because of the inclusion of one heterogeneous outlier study (Lazarus et al., 1986), the differences in study populations, and the sensitivity of TPO-Abs tests used. A negative association between the OR and year of publication has been found. Subanalysis showed that studies with statistically significant results were more often published before the year 2003 and that differences in TPO-abs seroprevalence in BD compared to HC diminished over time (see supplemental Figure S2). An explanation could be the use of more sensitive recent methods. However, when performing additional post-hoc subanalyses for several different tests (ELISA, Haemagglutination or (E) CLIA), the results were not significant (data not shown). Overall, no significant association was found between TPO-abs and BD, also with the exclusion of the DBC. This is in line with epidemiological studies

that show a relative risk of around 1.05 for autoimmune thyroid disease (95 % CI 0.72–1.52, $p > 0.05$) in mood disorder patients. This evidence is not quite as strong as that for thyroid disease in general where a range of relative risk between 1.28 and 6.26 (95 % CI 3.77–10.40, $p < 0.001$) has been reported (Benros et al., 2013), (Cremaschi et al., 2017), (Forty et al., 2014). However, we were unable to evaluate the effect of BD, and in particular lithium, on thyroid function due to the lack of determination of TSH, T3, T4, and dietary iodine deficiencies. Future studies should address these questions.

5. Conclusion

To conclude, in this largest and most-comprehensive study in BD patients worldwide, there is no evidence for increased TPO-abs seroprevalences or titer levels. No differences in seroprevalence or titer levels of TPO-abs were found between patients with BD, their first-degree relatives, and controls. The prevalence of TPO-abs was unrelated to clinical factors, including lithium use. Results are supported by our meta-analysis including twelve studies and taking into account important confounders.

Author statement

M.P Boks, R.A. Ophoff, E. Regeer and M.H.J. Hillegers designed the study. M.P. Boks, L. de Witte, G.J.L.J. Snijders and M.H.J. Hillegers wrote the protocol. M.P. Boks, R.A. Ophoff, included all participants and provided the data necessary for our analysis. C. van der Laan, G.J.L.J. Snijders and M. Litjens assessed thyroid function. G.J.L.J. Snijders, C. van der Laan and D. van den Berk undertook the statistical analyses and managed the literature searches and analyses. G.J.L.J. Snijders wrote the draft of the manuscript. M.J.H. Begemann supervised the statistical analysis. A. Berdenis van Berlekom supervised the meta-analysis. L. de Witte, M.H.J. Hillegers and R. Kahn assisted the preparation and proofreading of the manuscript. All authors contributed to and have approved the final manuscript.

Declaration of Competing Interest

All authors declare that they have no conflict of interest.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.psyneuen.2019.104518.

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