Journal of Endocrinological Investigation
https://doi.org/10.1007/s40618-022-01761-2

ORIGINAL ARTICLE

Chronic urticaria and thyroid autoimmunity: a meta-analysis of case–control studies

D. Tienforti[1] · F. Di Giulio[1] · L. Spagnolo[1] · C. Castellini[1] · M. Totaro[1] · M. Muselli[2] · S. Francavilla[1] · M. G. Baroni[1,3] · A. Barbonetti[1]

Received: 3 January 2022 / Accepted: 7 February 2022
© The Author(s) 2022

Abstract

Purpose Autoimmunity has been implicated in some patients with idiopathic chronic urticaria (CU). Because of the frequency of autoimmune thyroid diseases, their association with CU deserves special attention. We tested both the existence and the extent of an association between thyroid autoimmunity and CU.

Methods A thorough search of PubMed, Scopus, Web of Science, and Cochrane databases was performed. Studies reporting the positivity rate for anti-thyroperoxidase antibodies (TPOAbs) in people with (cases) and without CU (controls) were included. Quality of the studies was assessed by the Newcastle–Ottawa Scale. Between-study heterogeneity was assessed by Cochrane Q and I^2 tests, and the odds ratio (OR) for TPOAbs positivity was combined using random-effects models.

Results Nineteen studies provided information about TPOAbs positivity on 14,351 patients with CU and 12,404 controls. The pooled estimate indicated a more than fivefold increased risk of exhibiting TPOAbs positivity in the group with CU (pooled OR 5.18, 95% CI 3.27, 8.22; $P<0.00001$). Correction for publication bias had a negligible effect on the overall estimate (pooled adjusted OR: 4.42, 95% CI 2.84, 6.87, $P<0.0001$). Between-study heterogeneity was established ($I^2=62\%$, $P_{\text{for heterogeneity}}=0.0002$) and when, according to meta-regression models, a sensitivity analysis was restricted to the 16 studies with the highest quality scores, the OR for TPOAbs positivity rose to 6.72 (95% CI 4.56, 9.89; $P<0.00001$) with no significant heterogeneity ($I^2=31\%$, $P_{\text{for heterogeneity}}=0.11$).

Conclusions Patients with CU have a five-to-nearly sevenfold higher risk of displaying TPOAbs positivity. All patients with CU may well be offered a screening for thyroid autoimmunity.

Keywords Systematic review · Autoimmune thyroiditis · Anti-thyroperoxidase antibodies · Urticaria

Introduction

The term "urticaria" is widely used to define a skin manifestation characterized by the onset of itchy, fleeting wheals of variable size, shape, and distribution. These features arise from a series of pathophysiological events, including vasodilation, increased blood flow, and vascular permeability related to the activation and degranulation of mast cells, a process that can reflect both immunological and non-immunological mechanisms. Using a temporal criterion, urticaria can be classified into acute and chronic: in chronic urticaria (CU), manifestations occur daily or nearly daily and last for more than 6 weeks [1, 2]. In about 75% of patients, causes remain undefined, configuring the idiopathic CU [3]; however, many different pathogenic mechanisms have been proposed, including the occurrence of autoimmunity. Indeed, in some patients, CU may be associated with autoimmune diseases (AID) or, more generally, with positivity for autoantibodies [4, 5]. Among the possible associations, that between CU and thyroid autoimmunity has attracted interest, especially because of the epidemiological dimension of the autoimmune thyroid diseases.

✉ A. Barbonetti
arcangelo.barbonetti@univaq.it

1 Andrology Unit, Department of Life, Health and Environmental Sciences, University of L'Aquila, L'Aquila, Italy

2 Epidemiology Division, Department of Life, Health and Environmental Sciences, University of L'Aquila, L'Aquila, Italy

3 Neuroendocrinology and Metabolic Diseases, IRCCS Neuromed, Pozzilli, Isernia, Italy

Published online: 18 February 2022

The association between CU and Hashimoto's thyroiditis was first described in 1983 by Leznoff and colleagues [6], who demonstrated the presence of anti-microsomal antibodies in 12% of patients suffering from idiopathic CU (i.e., twice the frequency of controls). Since then, many case–control studies have investigated such an association [6–11]; nevertheless, with very few exceptions [6, 12, 13], these reports have the major limitation of a low sample size and produced inconclusive results. While most studies found a significantly higher risk of thyroid autoimmunity in CU [6, 8, 12–19], some authors have found no association [20–27], while others have even documented a negative association between the two conditions [28]. Intriguingly, autoimmune thyroid diseases can also be associated with other skin disorders with autoimmune pathogenesis, namely non segmental vitiligo, where anti-thyroperoxidase antibodies (TPOAbs) can be detected [29].

On this basis, we carried out a systematic review and meta-analysis of the available case–control studies to comprehensively assess the overall risk of thyroid autoimmunity in people with diagnosis of CU.

Methods

The meta-analysis was conducted according to the Cochrane Collaboration and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [30]; it also complies with the guidelines for Meta-Analyses and Systematic Reviews of Observational Studies (MOOSE) [31]. PRISMA and MOOSE Checklists have been presented as Supplementary Table 1 and Supplementary Table 2, respectively.

The study protocol was registered in the international prospective registry for systematic reviews (PROSPERO) with registration number: CRD42021274422.

Systematic search strategy

A systematic search was performed in PubMed, SCOPUS, Web of Science, and Cochrane Library, including the following free and vocabulary terms: "thyroid autoimmunit*", "autoimmune thyroid disease*", "TPOAb*", "anti-thyroperoxidase antibod*", "urticaria", using the Boolean functions AND/OR. The search was restricted to English language, published up to December 2021. If it was not clear from the abstract whether the study contained relevant data, the full text was retrieved. The reference lists of the identified papers were also scrutinized to find possible additional pertinent studies.

Inclusion/exclusion criteria

The outcome of interest was the relationship between CU and positivity for TPOAbs. The eligibility criteria were the following: (1) observational case–control studies, enrolling patients with (cases) and without CU (controls); (2) availability of odds ratio (OR) for having TPOAbs positivity or data for its calculation in both groups. Duplicates were rigorously checked and removed. Studies with missing/incomplete or unsuitable data or lacking to assess the outcome of interest were excluded. Three independent reviewers (D.T., F.D.G., and L.S.) assessed the eligibility of each selected paper; any disagreement was resolved via discussion involving a fourth reviewer (A.B.).

Data extraction

Data were extracted from the selected articles by including the first author, publication year, geographic region, mean age of participants, the number of events (TPOAbs positivity), and the total number of participants in cases and controls. Additional information, such as TPOAbs assay methods and positivity cut-offs, male-to-female ratio, levels of thyroid stimulating hormone (TSH), percentages of patients with thyroid dysfunction (hypo- and hyperthyroidism), and/or severe urticaria (angioedema), was also extracted when available. Where data were missing or inconsistent, the authors were contacted to obtain the necessary information.

Assessment of study reporting quality

The quality of the studies was assessed using the Newcastle–Ottawa Scale (NOS) [32]. The score was calculated from 0 to 9, and studies with a score of at least 7 were considered to be of good quality. The evaluation was performed independently by three reviewers (D.T., C.C., and M.T.), involving a fourth reviewer (A.B.) to solve any discrepancies in judgment.

Statistical analysis

The relationship between thyroid autoimmunity and CU was assessed by calculating the aggregate OR (95% CI) for TPOAbs positivity comparing cases and controls. Mantel–Haenszel estimates were combined in a random-effects model [33], which is more conservative than the fixed-effects model [34], because it accounts for heterogeneity in the calculation of the overall estimate. Study-specific estimates, their precision, and the presence of heterogeneity among them were visualized using forest plots. The Cochran's χ^2 (Cochran's Q) and I^2 tests were carried out to analyze statistical heterogeneity between

the results of different studies. $I^2 > 50\%$ and/or $P < 0.05$ indicated substantial heterogeneity.

Publication bias was explored through the funnel plot [35] and the Egger's test [36]. To correct for publication bias, the Duval and Tweedie's 'trim-and-fill' analysis was carried out [37], as previously reported [38]. Briefly, in the presence of asymmetric funnel shape, this test detects putative missing studies to rebalance the distribution and provides an adjusted pooled estimate taking the additional studies into account, thus correcting the analysis for publication bias.

To detect possible sources of the between-study heterogeneity, available covariates that could affect the estimates were included in linear meta-regression models.

Data were analyzed using the R statistical software (version 3.6.3; R Foundation for Statistical Computing, Vienna, Austria), using the "metafor" package, and the Review Manager (RevMan) of the Cochrane Library (version 5.3; The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark).

Results

Selection of studies

The electronic search yielded a total of 684 articles. After removal of duplicates, 389 articles were obtained, of which 361 were excluded, because they were deemed irrelevant based on title and/or abstract reading. Thus, as shown in Fig. 1, a total of 28 articles were identified, of which 19 met the inclusion criteria [6, 8, 12–28].

Details of the main characteristics of the papers included in the quantitative analysis are shown in Table 1.

Quality of included studies

The quality rating of the studies, based on the NOS, is presented in Table 2. The score ranged from 5 to 9. Sixteen studies were judged to be of good quality, having been assigned a score of ≥ 7, whereas 3 articles were of moderate quality. In particular, in the studies by Leznoff and colleagues [6] and Cho et al. [28], a possible bias arose from the definition of controls, as their clinical characteristics were not clearly defined.

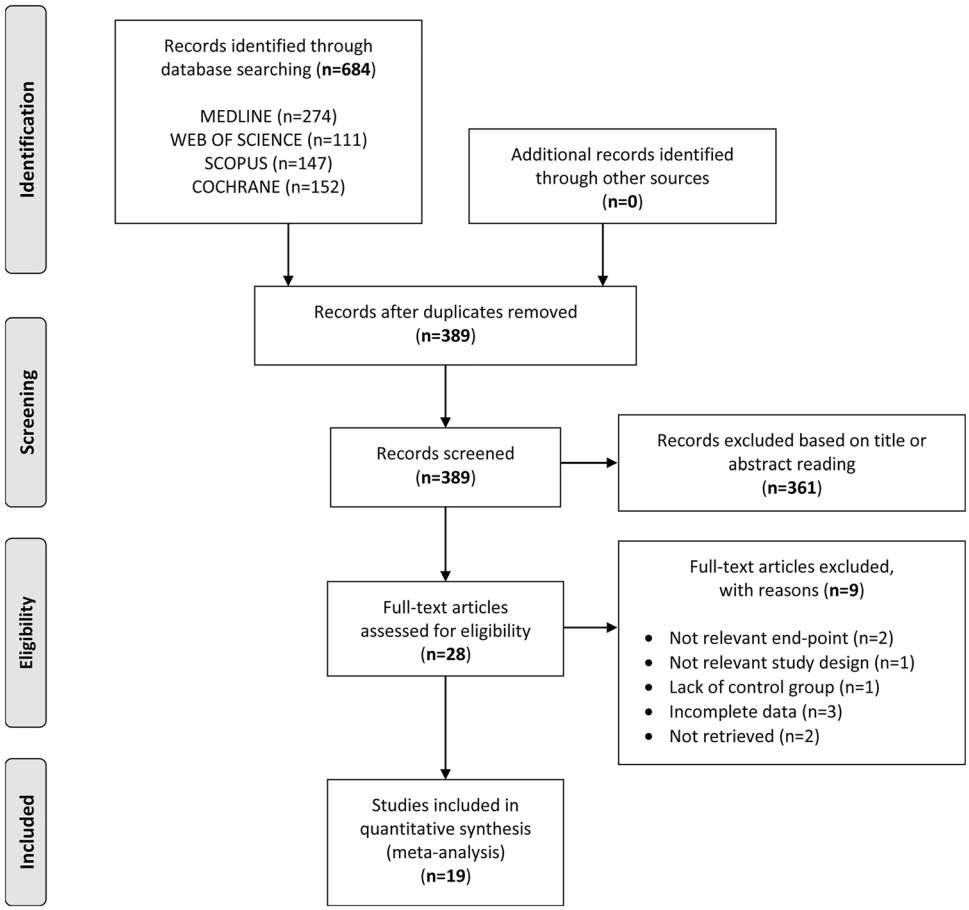


Fig. 1 Flow diagram showing an overview of the study selection process

Table 1 Details of the main characteristics of the 19 articles included in the quantitative analysis

Study	Region	Mean age (years)	CU group: TPOAbs + /total	Control group: TPOAbs + /total	TPOAbs assay methods	TPOAbs positivity cut-off	Females (%)	Mean TSH levels (mU/L)	HypoT (%)	HyperT (%)	AE (%)
Leznoff, 1983 [6]	Canada	NR	17/140	27/477	HA	≥ 1:100	70.0	NR	2.1	2.1	NR
Turktas, 1997 [24]	Turkey	37.0	9/94	4/80	IRMA	≥ 100 IU/ml	72.0	NR	3.2	1	70.2
Ryhal, 2001 [8]	USA	48.0	5/25	0/75	NR	NR	NR	NR	NR	NR	NR
Verneuil, 2004 [25]	France	43.0	8/45	1/30	ELISA	> 25 IU/ml	78.0	NR	0	0	33.3
Cebeci, 2006 [15]	Turkey	40.0	23/140	8/181	NR	NR	73.0	1.9	0.7	1.4	42.9
Aamir, 2008 [14]	Pakistan	37.0	13/30	0/30	HA	≥ 1:100	100.0	1.8	10	NR	NR
Nuzzo, 2011 [19]	Italy	31.5	12/54	5/108	NR	> 110 IU/ml	NR	NR	18.5	NR	18.5
Al-Balbeesi, 2011 [20]	Saudi Arabia	41.0	18/68	1/22	HA	≥ 1:100	90.0	NR	NR	NR	NR
Confino-Cohen, 2012 [12]	Israel	45.0	598/12778	54/10714	NR	NR	66.0	NR	10	2.6	NR
Wan, 2013 [26]	Taiwan	NR	5/60	0/40	NR	NR	NR	0.6	0	0	NR
Yadav, 2013 [27]	India	33.0	14/80	2/40	ELISA	NR	56.0	NR	NR	NR	NR
Alpay, 2013 [21]	Turkey	46.0	6/50	2/50	NR	NR	78.0	NR	6	NR	NR
Ghaffari, 2013 [22]	Iran	29.0	5/78	2/67	NR	NR	70.5	NR	1.3	NR	30.8
Cho, 2013 [28]	USA	39.0	3/27	4/19	ECLIA	≥ 35 IU/ml	85.0	1.1	NR	NR	NR
Okba, 2015 [23]	Egypt	36.0	20/80	4/40	IFAT	NR	77.5	4.6	18.8	13.7	NR
Diaz Angulo, 2015 [13]	Spain	44.0	70/343	5/282	EIA	> 90 IU/ml	70.5	NR	3.8	1.2	NR
Magen, 2016 [18]	Israel	34.0	13/41	3/44	NR	> 75 IU/ml	68.0	2.3	NR	NR	NR
Kasumagic-Halilovic, 2017 [17]	Bosnia	40.0	12/70	1/70	ECLIA	> 34 IU/ml	57.0	NR	NR	NR	NR
Czarnecka-Operacz, 2017 [16]	Poland	42.0	32/148	0/35	RIA	> 34 IU/ml	98.0	1.7	2.7	NR	54

TPOAbs anti-thyroid peroxidase antibodies, *AE* angioedema, *CU* chronic urticaria *ECLIA* electrochemiluminescence immunoassay, *EIA* enzyme immunoassay, *ELISA* enzyme linked immunosorbent assay, *HA* hemoagglutination, *HyperT* Hyperthyroidism, *HypoT* Hypothyroidism, *IFAT* indirect immunofluorescence antibody test, *IRMA* Immunoradiometric assay, *IU* international units, *NR* not reported, *RIA* radioimmunoassay, *TSH* thyroid stimulating hormone

Table 2 Newcastle–Ottawa Scale for the quality assessment of case–control studies

Study	Selection				Comparability		Exposure			Total
	Definition of exposure	Representa-tiveness	Selection of controls	Definition of controls	On age	On other risk factors	Assessment of exposure	Same methods of ascertainment for cases and controls	Nonre-sponse rate	
Aamir, 2008 [14]	1	1	1	1	1	0	1	1	1	8
Al-Balbeesi, 2011 [20]	1	1	1	1	1	0	1	1	1	8
Alpay, 2013 [21]	1	1	0	0	1	0	1	1	1	6
Cebeci, 2006 [15]	1	1	1	1	1	1	1	1	1	9
Cho, 2013 [28]	1	1	0	0	0	0	1	1	1	5
Confino-Cohen, 2012 [12]	1	1	1	1	1	1	1	1	1	9
Czarnecka-Operacz, 2017 [16]	1	1	1	1	1	1	1	1	1	9
Diaz Angulo, 2015 [13]	1	1	1	1	1	1	1	1	1	9
Ghaffari, 2013 [22]	1	1	1	1	1	1	1	1	1	9
Kasumagic-Halilovic, 2017 [17]	1	1	1	1	1	1	1	1	1	9
Leznoff, 1983 [6]	1	1	1	0	0	0	1	1	0	5
Magen, 2016 [18]	1	1	0	1	1	1	1	1	1	8
Nuzzo, 2011 [19]	1	1	1	1	1	1	1	1	1	9
Okba, 2015 [23]	1	1	0	1	1	1	1	1	1	8
Ryhal, 2001 [8]	1	1	1	1	0	0	1	1	1	7
Turktas, 1997 [24]	1	1	0	1	1	1	1	1	1	8
Verneuil, 2004 [25]	1	1	1	1	1	1	1	1	1	9
Wan, 2013 [26]	1	1	0	1	1	1	1	1	1	8
Yadav, 2013 [27]	1	1	1	1	1	1	1	1	1	9

Summary of results

Overall, the 19 studies included in the meta-analysis provided information on 14,351 patients with CU (cases) and 12,404 subjects without CU (controls), resulting in an overall crude rate of TPOAbs positivity of 3.8%. The pooled OR indicated a more than fivefold increased risk of exhibiting TPOAbs positivity in the group with CU (pooled OR 5.18, 95% CI 3.27, 8.22; $P<0.00001$; Fig. 2). The analysis revealed a significant between-study heterogeneity ($I^2=62\%$, $P_{\text{for heterogeneity}}=0.0002$).

Publication bias

The asymmetrical shape of the funnel plot (Fig. 3) suggested the presence of a publication bias. Although the Egger's test revealed a not significant degree of asymmetry ($t=-1.05$, $P=0.31$), the trim-and-fill test identified three putative missing studies on the left side of the distribution (Fig. 3). However, the inclusion of these additional studies resulted in a negligible effect on the overall estimate (pooled adjusted OR: 4.42, 95% CI 2.84, 6.87, $P<0.0001$; $I^2=58.7\%$, $P_{\text{for heterogeneity}}<0.0001$).

Heterogeneity analysis

As between-study heterogeneity in the pooled analysis was found (Fig. 2), linear meta-regression analyses were carried out to detect possible sources of the variability. Among available covariates that could affect the estimates, including publication year, overall prevalence of thyroid autoimmunity, male-to-female ratio, TSH levels, rate of thyroid dysfunction (hypo- and hyperthyroidism), rate of severe urticaria (angioedema), and NOS quality score, only this

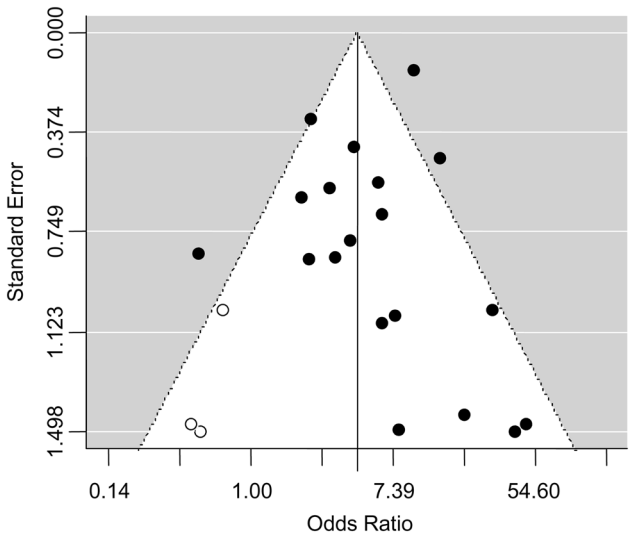


Fig. 3 Funnel plot of case–control studies of the association between chronic urticaria and thyroid autoimmunity. Trim-and-fill test identified three putative missing studies (white circles) on the left side of the distribution

Study or Subgroup	CU Events	CU Total	Controls Events	Controls Total	Weight	Odds Ratio M-H, Random, 95% CI
Aamir et al. [14]	13	30	0	30	2.1%	47.06 [2.63, 840.99]
Al- Balbeesi et al. [20]	18	68	1	22	3.4%	7.56 [0.95, 60.34]
Alpay et al. [21]	6	50	2	50	4.6%	3.27 [0.63, 17.07]
Cebeci et al. [15]	23	140	8	181	8.3%	4.25 [1.84, 9.83]
Cho et al. [28]	3	27	4	19	4.7%	0.47 [0.09, 2.39]
Confino-Cohen et al. [12]	598	12778	54	10714	11.0%	9.69 [7.33, 12.82]
Czarnecka-Operacz et al. [16]	32	148	0	35	2.2%	19.81 [1.18, 331.70]
Díaz-Angulo et al. [13]	70	343	5	282	7.9%	14.21 [5.65, 35.74]
Ghaffari et al. [22]	5	78	2	67	4.6%	2.23 [0.42, 11.87]
Kasumagic-Halilovic et al. [17]	21	70	1	70	3.5%	29.57 [3.85, 227.25]
Leznoff et al. [6]	17	140	27	477	9.4%	2.30 [1.22, 4.36]
Magen et al [18]	13	41	3	44	5.8%	6.35 [1.65, 24.33]
Nuzzo et al. [19]	12	54	5	108	6.9%	5.89 [1.95, 17.74]
Okba et al. [23]	20	80	4	40	6.7%	3.00 [0.95, 9.48]
Ryhal et al. [8]	5	25	0	75	2.0%	40.51 [2.15, 763.20]
Turktas et al. [24]	9	94	4	80	6.4%	2.01 [0.60, 6.80]
Verneuil et al. [25]	8	45	1	30	3.3%	6.27 [0.74, 53.02]
Wan et al. [26]	5	60	0	40	2.0%	8.03 [0.43, 149.32]
Yadav et al. [27]	14	80	2	40	5.1%	4.03 [0.87, 18.69]
Total (95% CI)		**14351**		**12404**	**100.0%**	**5.18 [3.27, 8.22]**
Total events	892		123			

Heterogeneity: Tau² = 0.48; Chi² = 47.38, df = 18 (P = 0.0002); I² = 62%
Test for overall effect: Z = 6.99 (P < 0.00001)

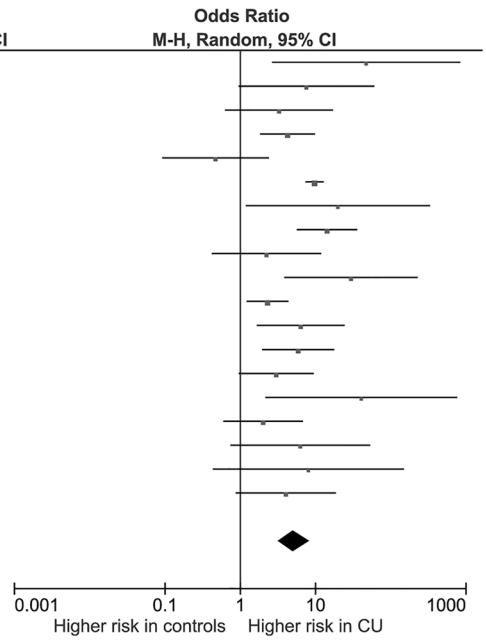


Fig. 2 Forest plot of odds ratios for thyroid autoimmunity in subjects with and without chronic urticaria. Diamond indicates the overall estimate (width of the diamond represents 95% CI). Boxes indicate the weight of individual studies in the pooled result. *CI* confidence interval, *CU* chronic urticaria, *df* degrees of freedom, *M–H* Mantel–Haenszel

latter contributed significantly to the heterogeneity (Supplementary Fig. 1): a higher study NOS score was significantly associated with the report of a higher risk for thyroid autoimmunity in patients with CU compared to controls (β-coefficient = 0.36, 95% CI 0.15, 0.58; $P = 0.001$).

As shown in Fig. 4, when, according to the meta-regression results, a sensitivity analysis was restricted to studies with an NOS score ≥ 7, the OR for TPOAbs positivity rose to 6.72 (95% CI 4.56, 9.89; $P < 0.00001$) with decrease of heterogeneity to a no longer significant degree ($I^2 = 31\%$, $P_{\text{for heterogeneity}} = 0.11$).

Discussion

The genesis of spontaneous CU has been considered idiopathic for many years, but the identification of autoantibodies in some patients has given rise to the new concept of "autoimmune urticaria" [39]. In this view, as immune dysregulation factors are shared by both urticaria and autoimmune thyroiditis [40, 41], it might be expected that the two entities may often coexist in the same patient. This association, albeit widely investigated, still remains somehow uncertain due to a number of limitations of the studies, including the small sample sizes, heterogeneity among the results, and the different diagnostic criteria used to define thyroid autoimmunity.

In the present meta-analysis of 19 rigorously selected case–control studies, the diagnosis of CU was associated with an approximately fivefold higher risk of exhibiting positivity for TPOAbs, a marker of chronic autoimmune thyroiditis. In the analysis restricted to studies with higher quality scores, the OR of the association increased to 6.72 (95% CI 4.56, 9.89) with a not significant heterogeneity.

The mechanisms underlying the association between CU and thyroid autoimmunity are not fully elucidated. An immune-regulatory role of TSH would be supported by some evidence on the effect of levothyroxine treatment that, in some studies, led to improvements of urticaria clinical features [7, 42, 43], an effect believed to be mediated by the decrease in TSH levels [42]. However, other studies failed to demonstrate the efficacy of levothyroxine [44, 45], and even when an effect has been found, it was challenged by the limited sample size of the study populations together with the lack of a control group. Although the studies included in this meta-analysis largely lacked information about levothyroxine treatment, the role of TSH seems to be unlikely as meta-regression analyses showed no significant influence of either TSH levels or the rate of thyroid dysfunction (hypo- or hyperthyroidism) on the association under investigation.

One of the pieces of evidence that mostly supports the autoimmune genesis of CU is based on the observation that 45% and 55% of patients with CU display anti-IgE and anti-FcεRI antibodies, respectively, whose titre exhibits a well-documented correlation with the positivity of the autologous serum skin test [46]. The evidence of an autoimmune pathogenesis of CU creates the basis for theorizing the existence of common immunopathologic mechanisms shared by CU and autoimmune thyroiditis [40, 41]. One mediator called into play is the interleukin 6 (IL6). In vitro experiments

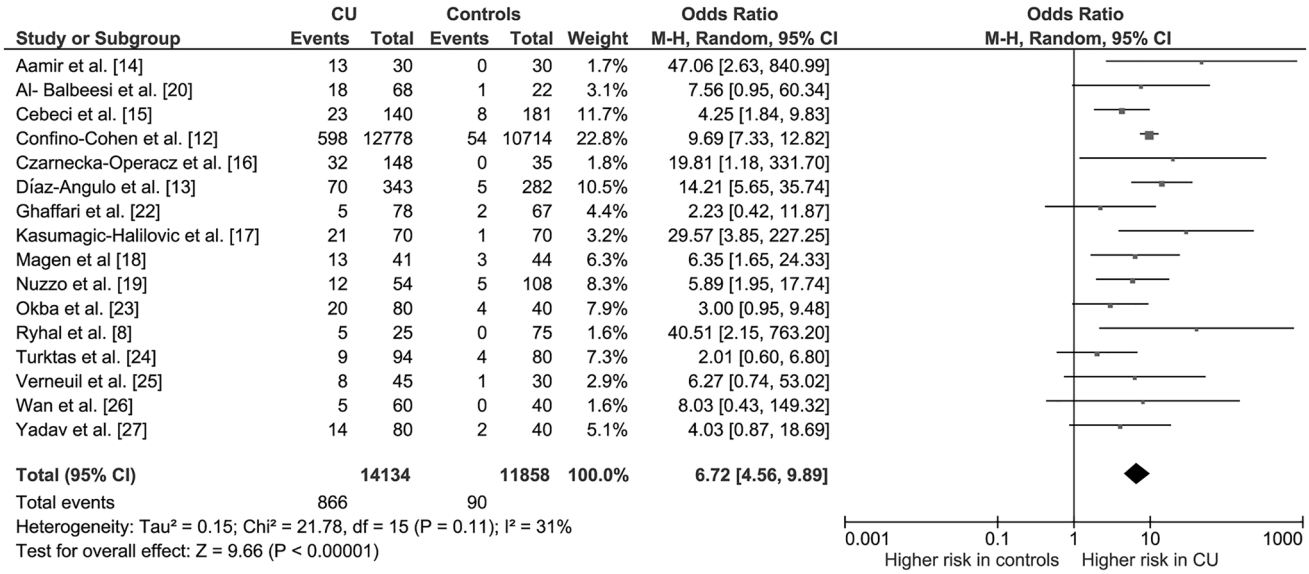


Fig. 4 Sensitivity analysis based on the quality score at the Newcastle–Ottawa Scale (NOS): only studies with NOS score ≥ 7 were included. Forest plot of odds ratios for thyroid autoimmunity in subjects with and without CU. Diamond indicates the overall estimate (diamond width represents 95% CI). Boxes indicate the weight of individual studies in the pooled result. *CI* confidence interval, *CU* chronic urticaria, *df* degrees of freedom, *M–H* Mantel–Haenszel

have shown that IL6 increases endothelial permeability, a key mechanism in the pathogenesis of urticaria [47]. The levels of this cytokine are indeed higher in patients with CU than in healthy controls and decrease with remission of urticaria [48]. Interestingly, high circulating levels of IL6 have been also reported in Hashimoto's thyroiditis where they positively correlate with the number of Th22 lymphocytes, which in turn is related to the TPOAbs titre [49, 50]. Another possible immunopathologic link underlying the association between autoimmune thyroiditis and CU could lie in a defective activity of regulatory T cells (Tregs). Tregs are T lymphocytes with suppressor properties on effector immune cells, and a decrease in number and/or functionality of Tregs was associate with a variety of autoimmune disorders [51]. Interestingly, decreased percentage and activity of Tregs have been demonstrated both in CU [52–54] and autoimmune thyroid diseases [55, 56]. Unfortunately, the lack of information on these immuno-molecular factors hindered quantitative analyses to clarify their possible pathogenic role.

This meta-analysis has some limitations. First, some potentially relevant studies were not included because of incomplete or unsuitable data. In this regard, only articles published in English language retrievable from well-recognized electronic databases were screened for eligibility. Nevertheless, when the analysis was restricted to TPOAbs, we included more studies than in the only other previously published meta-analysis on the topic [57]. Second, different criteria for the diagnosis of thyroid dysfunction could have made it difficult to compare the studies when the rate of hypothyroidism and hyperthyroidism was analyzed in meta-regression. Moreover, although TPOAbs represent a sensitive marker of autoimmune thyroid disease, their positivity is not a sufficient criterion for the diagnosis of chronic autoimmune thyroiditis and there may be also cases of autoimmune thyroid disease with negative TPOAbs [58]. On the other hand, TPOAbs positivity can be found also in subacute thyroiditis, as well as in non-thyroid autoimmune disorders. Unfortunately, available studies were largely lacking in information about thyroid ultrasonographic features that could have helped in the correct diagnostic framing. As another major limitation, many of the included studies may not be fully comparable due to the different assay methods and cut-offs used to identify TPOAbs positivity (Table 1). These differences may have affected the accuracy of the overall estimate. Finally, unadjusted data were extracted and pooled in our quantitative synthesis: availability of point estimates corrected for confounders would have made it possible to produce a more representative pooled estimate of the true association between CU and thyroid autoimmunity. To partially overcome this limitation, meta-regressions were conducted that did not demonstrate a significant role as a source of heterogeneity of several possible confounding factors, except for the methodological quality, highlighting that the studies with lower risk of bias found the strongest associations.

In conclusion, people with CU have a five-to-nearly sevenfold higher odd of exhibiting TPOAbs positivity. From a clinical point of view, independently of the pathogenesis underlying such an association, this finding points to the opportunity to perform a screening for thyroid autoimmunity in the presence of CU. This approach could allow identification of patients with chronic autoimmune thyroiditis still in euthyroidism who could benefit from monitoring of TSH levels over time.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s40618-022-01761-2.

Author contributions Conceptualization: AB and DT. Methodology: AB, DT, CC, and MM. Formal analysis and investigation: DT, FDG, LS, CC, MT, and AB. Writing—original draft preparation: DT. Writing—review and editing: AB, SF, and MGB. Supervision: AB and MGB.

Funding The authors did not receive support from any organization for the submitted work.

Declarations

Conflict of interest The authors declare they have no financial interests. Marco Giorgio Baroni and Arcangelo Barbonetti are members of the Editorial Board of the J Endocrinol Invest.

Ethical approval Not applicable.

Research involving human participants and/or animals This is a systematic review with meta-analysis of data produced from studies already published in the literature. Forthis type of study is not required approval of the ethics committee not involving neither animals nor people.

Informed consent For this type of study, formal consent is not required.

Open Access This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if changes were made. The images or other third party material in this article are included in the article's Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit http://creativecommons.org/licenses/by/4.0/.

References

1. Powell RJ, Du Toit GL, Siddique N, Leech SC, Dixon TA, Clark AT, Mirakian R, Walker SM, Huber PA, Nasser SM, British

Society for Allergy and Clinical Immunology (BSACI) (2007) BSACI guidelines for the management of chronic urticaria and angio-oedema. Clin Exp Allergy 37:631–650
2. Grattan CE (2007) Towards rationalizing the nomenclature and classification of urticaria: some guidance on guidelines. Clin Exp Allergy 37:625–626
3. Kulthanan K, Jiamton S, Thumpimukvatana N, Pinkaew S (2007) Chronic idiopathic urticaria: prevalence and clinical course. J Dermatol 34:294–301
4. Rottem M (2003) Chronic urticaria and autoimmune thyroid disease: is there a link? Autoimmun Rev 2:69–72
5. Dreskin SC, Andrews KY (2005) The thyroid and urticaria. Curr Opin Allergy Clin Immunol 5:408–412
6. Leznoff A, Josse RG, Denburg J, Dolovich J (1983) Association of chronic urticaria and angioedema with thyroid autoimmunity. Arch Dermatol 119:636–640
7. Gaig P, García-Ortega P, Enrique E, Richart C (2000) Successful treatment of chronic idiopathic urticaria associated with thyroid autoimmunity. J Investig Allergol Clin Immunol 10:342–345
8. Ryhal B, DeMera RS, Shoenfeld Y, Peter JB, Gershwin ME (2001) Are autoantibodies present in patients with subacute and chronic urticaria? J Investig Allergol Clin Immunol 11:16–20
9. Gangemi S, Saitta S, Lombardo G, Patafi M, Benvenga S (2009) Serum thyroid autoantibodies in patients with idiopathic either acute or chronic urticaria. J Endocrinol Invest 32:107–110
10. Fusari A, Colangelo C, Bonifazi F, Antonicelli L (2005) The autologous serum skin test in the follow-up of patients with chronic urticaria. Allergy 60:256–258
11. Palma-Carlos AG, Palma-Carlos ML (2005) Chronic urticaria and thyroid autoimmunity. Eur Ann Allergy Clin Immunol 37:143–146
12. Confino-Cohen R, Chodick G, Shalev V, Leshno M, Kimhi O, Goldberg A (2012) Chronic urticaria and autoimmunity: associations found in a large population study. J Allergy Clin Immunol 129:1307–1313
13. Díaz-Angulo S, López-Hoyos M, Muñoz Cacho P, Fernández M, López-Escobar M, Rodríguez F, González-López MA (2016) Prevalence of thyroid autoimmunity in spanish patients with chronic idiopathic urticaria: a case-control study involving 343 subjects. J Eur Acad Dermatol Venereol 30:692–693
14. Aamir IS, Tauheed S, Majeed F, Atif A (2008) Serum antithyroid antibodies in female patients with chronic urticaria. J Coll Physicians Surg Pak 18:498–501
15. Cebeci F, Tanrikut A, Topcu E, Onsun N, Kurtulmus N, Uras AR (2006) Association between chronic urticaria and thyroid autoimmunity. Eur J Dermatol 16:402–405
16. Czarnecka-Operacz M, Sadowska-Przytocka A, Jenerowicz D, Szeliga A, Adamski Z, Łącka K (2017) Thyroid function and thyroid autoantibodies in patients with chronic spontaneous urticaria. Postepy Dermatol Alergol 34:566–572
17. Kasumagic-Halilovic E, Beslic N, Ovcina-Kurtovic N (2017) Thyroid autoimmunity in patients with chronic urticaria. Med Arch 71:29–31
18. Magen E, Zueva E, Mishal J, Schlesinger M (2016) The clinical and laboratory characteristics of acute spontaneous urticaria and its progression to chronic spontaneous urticaria. Allergy Asthma Proc 37:394–399
19. Nuzzo V, Tauchmanova L, Colasanti P, Zuccoli A, Colao A (2011) Idiopathic chronic urticaria and thyroid autoimmunity: experience of a single center. Dermatoendocrinol 3:255–258
20. Al-Balbeesi AO (2011) Significance of antithyroid antibodies and other auto-antibodies in Saudi patients with chronic urticaria. Possible parameters in predicting chronic over three years disease. J Saudi Soc Dermatol Dermatologic Surg 15:47–51
21. Alpay A, Solak Tekin N, Tekin IÖ, Altinyazar HC, Koca R, Cınar S (2013) Autologous serum skin test versus autologous plasma skin test in patients with chronic spontaneous urticaria. Dermatol Res Pract. https://doi.org/10.1155/2013/267278
22. Ghaffari J, Khademloo M, Mohammadzadeh I, Golpoor M (2013) Chronic urticaria: the necessity of laboratory examination. Zahedan J Res Med Sci 15:66–68
23. Okba AM, Sheha DS, Moustafa AS, El-Sherbeny AA, Mohamed NA, Aglan MF (2015) Association between thyroid autoimmunity and chronic urticaria in patients versus healthy controls. Egypt J Obes Diabetes Endocrinol 1:84–89
24. Turktas I, Gokcora N, Demirsoy S, Cakir N, Onal E (1997) The association of chronic urticaria and angioedema with autoimmune thyroiditis. Int J Dermatol 36:187–190
25. Verneuil L, Leconte C, Ballet JJ, Coffin C, Laroche D, Izard JP, Reznik Y, Leroy D (2004) Association between chronic urticaria and thyroid autoimmunity: a prospective study involving 99 patients. Dermatology 208:98–103
26. Wan KS, Wu CS (2013) The essential role of anti-thyroid antibodies in chronic idiopathic urticaria. Endocr Res 38:85–88
27. Yadav S, Kanwar A, Parsad D, Minz R (2013) Chronic idiopathic urticaria and thyroid autoimmunity: perplexing association. Indian J Dermatol 58:325
28. Cho CB, Stutes SA, Altrich ML, Ardoin SP, Phillips G, Ogbogu PU (2013) Autoantibodies in chronic idiopathic urticaria and non-urticarial systemic autoimmune disorders. Ann Allergy Asthma Immunol 110:29–33
29. Ferrari SM, Fallahi P, Santaguida G, Virili C, Ruffilli I, Ragusa F, Centanni M, Antonelli A (2017) Circulating CXCL10 is increased in non-segmental vitiligo, in presence or absence of autoimmune thyroiditis. Autoimmun Rev 16:946–950
30. Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart LA, PRISMA-P Group (2015) Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ 350:g7647
31. Stroup DF, Berlin JA, Morton SC, Olkin I, Williamson GD, Rennie D, Moher D, Becker BJ, Sipe TA, Thacker SB (2000) Meta analysis of observational studies in epidemiology: a proposal for reporting. JAMA 283:2008–2012
32. Deeks JJ, Dinnes J, D'Amico R, Sowden AJ, Sakarovitch C, Song F, Petticrew M, Altman DG, International Stroke Trial Collaborative Group; European Carotid Surgery Trial Collaborative Group (2003) Evaluating non-randomised intervention studies. Health Technol Assess 7(27):1–173
33. Mantel N, Haenszel W (1959) Statistical aspects of the analysis of data from retrospective studies of disease. J Natl Cancer Inst 22:719–748
34. Greenland S, Robins JM (1985) Confounding and misclassification. Am J Epidemiol 122:495–506
35. Sterne JA, Egger M (2001) Funnel plots for detecting bias in meta-analysis: guidelines on choice of axis. J Clin Epidemiol 54:1046–1055
36. Egger M, Davey Smith G, Schneider M, Minder C (1997) Bias in meta-analysis detected by a simple, graphical test. BMJ 315:629–634
37. Duval S, Tweedie R (2000) Trim and fill: a simple funnel-plot-based method of testing and adjusting for publication bias in meta-analysis. Biometrics 56:455–463
38. Barbonetti A, Martorella A, Minaldi E, D'Andrea S, Bardhi D, Castellini C, Francavilla F, Francavilla S (2019) Testicular cancer in infertile men with and without testicular microlithiasis: a systematic review and meta-analysis of case-control studies. Front Endocrinol (Lausanne) 10:164
39. Di Lorenzo G, Leto-Barone MS, La Piana S, Seidita A, Rini GB (2013) Chronic spontaneous urticaria: an autoimmune disease? A revision of the literature. Clin Exp Med 13:159–164

40. Berghi NO (2017) Immunological mechanisms implicated in the pathogenesis of chronic urticaria and hashimoto thyroiditis. Iran J Allergy Asthma Immunol 16:358–366
41. Gonzalez-Diaz SN, Sanchez-Borges M, Rangel-Gonzalez DM, Guzman-Avilan RI, Canseco-Villarreal JI, Arias-Cruz A (2020) Chronic urticaria and thyroid pathology. World Allergy Organ J 13:100101
42. Aversano M, Caiazzo P, Iorio G, Ponticiello L, Laganá B, Leccese F (2005) Improvement of chronic idiopathic urticaria with L-thyroxine: a new TSH role in immune response? Allergy 60:489–493
43. Koh CK, Hew FL, Chiu CL (2000) Treatment of chronic urticaria with thyroxine in an euthyroid patient with thyroglobulin and microsomal antibodies. Ann Acad Med Singap 29:528–530
44. Kiyici S, Gul OO, Baskan EB, Hacioglu S, Budak F, Erturk E, Imamoglu S (2010) Effect of levothyroxine treatment on clinical symptoms and serum cytokine levels in euthyroid patients with chronic idiopathic urticaria and thyroid autoimmunity. Clin Exp Dermatol 35:603–607
45. Magen E, Mishal J (2012) The effect of L-thyroxine treatment on chronic idiopathic urticaria and autoimmune thyroiditis. Int J Dermatol 51:94–97
46. Eckman JA, Hamilton RG, Gober LM, Sterba PM, Saini SS (2008) Basophil phenotypes in chronic idiopathic urticaria in relation to disease activity and autoantibodies. J Invest Dermatol 128:1956–1963
47. Tanaka T, Kishimoto T (2014) The biology and medical implications of interleukin-6. Cancer Immunol Res 2:288–294
48. Kasperska-Zajac A, Sztylc J, Machura E (2011) Plasma IL-6 concentration correlates with clinical disease activity and serum C-reactive protein concentration in chronic urticaria patients. Clin Exp Allergy 41:1386–1391
49. Bai X, Sun J, Wang W, Shan Z, Zheng H, Li Y, Zhao Y, Gong M, Teng W (2014) Increased differentiation of Th22 cells in Hashimoto's thyroiditis. Endocr J 61:1181–1190
50. Al-Jameil N, Khan MF, Al-Rashid M, Tabassum H (2015) Thyroid dysfunction: an autoimmune aspect. Int J Clin Exp Med 8(5):6677
51. Valencia X, Lipsky PE (2007) CD4+ CD25+ FoxP3+ regulatory T cells in autoimmune diseases. Nat Clin Pract Rheumatol 3(11):619–626
52. Arshi S, Babaie D, Nabavi M, Tebianian M, Ghalehbaghi B, Jalali F, Ahmadvand A, Gholami R (2014) Circulating level of CD4+ CD25+ FOXP3+ T cells in patients with chronic urticaria. Int J Dermatol 53:e561–e566
53. Sun RS, Sui JF, Chen XH, Ran XZ, Yang ZF, Guan WD, Yang T (2011) Detection of CD4+ CD25+ FOXP3+ regulatory T cells in peripheral blood of patients with chronic autoimmune urticaria. Australas J Dermatol 52:e15–e18
54. Chen WC, Chiang BL, Liu HE, Leu SJ, Lee YL (2008) Defective functions of circulating CD4+CD25+ and CD4+CD25- T cells in patients with chronic ordinary urticaria. J Dermatol Sci 51:121–130
55. Glick AB, Wodzinski A, Fu P, Levine AD, Wald DN (2013) Impairment of regulatory T-cell function in autoimmune thyroid disease. Thyroid 23:871–878
56. Xue H, Yu X, Ma L, Song S, Li Y, Zhang L, Yang T, Liu H (2015) The possible role of $CD4^{+}CD25(high)Foxp3^{+}/CD4^{+}IL\text{-}17A^{+}$ cell imbalance in the autoimmunity of patients with Hashimoto thyroiditis. Endocrine 50:665–673
57. Pan XF, Gu JQ, Shan ZY (2015) The prevalence of thyroid autoimmunity in patients with urticaria: a systematic review and meta-analysis. Endocrine 48:804–810
58. Rotondi M, Coperchini F, Magri F, Chiovato L (2014) Serum-negative autoimmune thyroiditis: what's in a name? J Endocrinol Invest 37:589–591

Publisher's Note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Supplemental Table 1: PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist

Section and topic	Item No	Checklist item	Reported section
ADMINISTRATIVE INFORMATION			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	See PROSPERO registration number in section "Materials and Methods.
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	NA
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	See PROSPERO registration number in section "Materials and Methods (CRD42021274422).
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	See title page
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	See sections: "Systematic search strategy", "Inclusion and exclusion criteria" and "Assessment of study reporting quality"
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	NA
Support:			
Sources	5a	Indicate sources of financial or other support for the review	NA
Sponsor	5b	Provide name for the review funder and/or sponsor	NA
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	NA
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	See "Introduction"

Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	See the last sentence of the introduction
METHODS			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	See "Inclusion and exclusion criteria" in the section "materials and methods"
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	See "Systematic search strategy" in the section "materials and methods"
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	See "Systematic search strategy" in the section "materials and methods" and Figure 1
Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	See "Data extraction" in the section "materials and methods"
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	See "Inclusion and exclusion criteria" in the section "materials and methods"
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	See "Data extraction" in the section "materials and methods"
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	See "Inclusion and exclusion criteria" and "Data extraction" in the section "materials and methods"
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	See "Inclusion and exclusion criteria" in the section "materials and methods"
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	See "Assessment of study reporting quality" and "Statistical analysis" in the section "materials and methods", Figure 3, Figure 4 and Table 2

Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	See "Statistical analysis" and Figure 2
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)	See "Statistical analysis", "synthesis of results" and Figure 2
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	See the section "Heterogeneity analysis" in the results, Supplementary Figure 1 and Figure 4
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	NA
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	See "statistical analysis" in "materials and methods" and "Publication bias" and Figure 3 in the results
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	NA

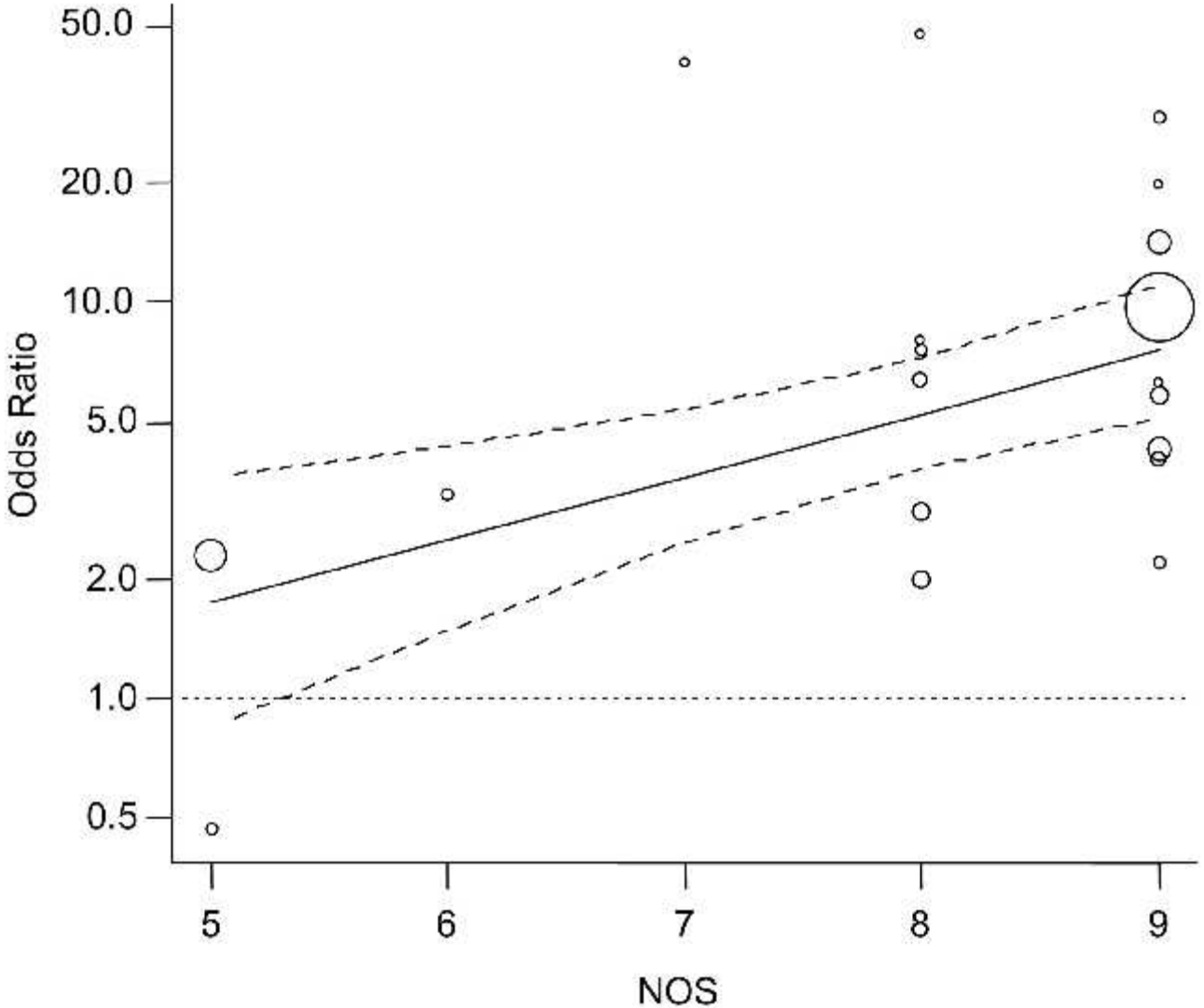
From: Shamseer et al. (29)

Supplementary Table 2. MOOSE Checklist for Meta-analyses of Observational Studies

Item No	Recommendation	Reported section
Reporting of background should include		
1	Problem definition	Introduction
2	Hypothesis statement	Introduction
3	Description of study outcome(s)	Introduction/Material and methods
4	Type of exposure or intervention used	Material and methods
5	Type of study designs used	Material and methods
6	Study population	Material and methods: Inclusion and exclusion criteria
Reporting of search strategy should include		
7	Qualifications of searchers (eg, librarians and investigators)	Material and methods
8	Search strategy, including time period included in the synthesis and key words	Material and methods: Systematic search strategy
9	Effort to include all available studies, including contact with authors	Material and methods: Systematic search strategy and data extraction
10	Databases and registries searched	Material and methods: Systematic search strategy
11	Search software used, name and version, including special features used (eg, explosion)	Statistical analysis
12	Use of hand searching (eg, reference lists of obtained articles)	Figure 1
13	List of citations located and those excluded, including justification	Figure 1
14	Method of addressing articles published in languages other than English	NA
15	Method of handling abstracts and unpublished studies	NA
16	Description of any contact with authors	Data extraction
Reporting of methods should include		
17	Description of relevance or appropriateness of studies assembled for assessing the hypothesis to be tested	Material and methods: Quality assessment
18	Rationale for the selection and coding of data (eg, sound clinical principles or convenience)	Material and methods: Inclusion and exclusion criteria
19	Documentation of how data were classified and coded (eg, multiple raters, blinding and interrater reliability)	Material and methods: Quality assessment
20	Assessment of confounding (eg, comparability of cases and controls in studies where appropriate)	Material and methods: Quality assessment
21	Assessment of study quality, including blinding of quality assessors, stratification or regression on possible predictors of study results	Material and methods: Quality assessment
22	Assessment of heterogeneity	“Heterogeneity analysis” in section Results, Supplementary Fig. 1 and Fig. 4

23	Description of statistical methods (eg, complete description of fixed or random effects models, justification of whether the chosen models account for predictors of study results, dose-response models, or cumulative meta-analysis) in sufficient detail to be replicated	Material and methods: Statistical analysis
24	Provision of appropriate tables and graphics	Table 1, Table 2, Figures 1, 2, 3, 4 and Supplementary Figure 1
Reporting of results should include		
25	Graphic summarizing individual study estimates and overall estimate	Summary of results: Figure 2
26	Table giving descriptive information for each study included	Table 1
27	Results of sensitivity testing (eg, subgroup analysis)	Figure 4
28	Indication of statistical uncertainty of findings	Table 1
Reporting of discussion should include		
29	Quantitative assessment of bias (eg, publication bias)	Figure 3
30	Justification for exclusion (eg, exclusion of non-English language citations)	Figure 1
31	Assessment of quality of included studies	Table 2
Reporting of conclusions should include		
32	Consideration of alternative explanations for observed results	Discussion
33	Generalization of the conclusions (ie, appropriate for the data presented and within the domain of the literature review)	Discussion
34	Guidelines for future research	Discussion
35	Disclosure of funding source	NA

From: Stroup DF, Berlin JA, Morton SC, et al, for the Meta-analysis Of Observational Studies in Epidemiology (MOOSE) Group. Meta-analysis of Observational Studies in Epidemiology. A Proposal for Reporting. *JAMA*. 2000;283(15):2008-2012. doi: 10.1001/jama.283.15.2008.


50.0
20.0
10.0
5.0
2.0
1.0
0.5
Odds Ratio
5
6
7
8
9
NOS