No difference between Hashimoto's thyroiditis and Graves' disease in the association of other autoimmune conditions - systematic review and meta-analysis

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Author contributions

Gréta Pham-Dobor and Emese Mezősi conceptualized and designed the study in cooperation with Péter Hegyi and Katalin Márta; Gréta Pham-Dobor, Marin Gergics and Katalin Márta constructed the forms to be filled with patient data; Gréta Pham-Dobor and Marin Gergics performed the data extraction from the articles. Gréta Pham-Dobor wrote the article; Emese Mezősi supervised the study. Emese Mezősi, Péter Hegyi, Patrícia Sarlós, Bálint Erőss, Katalin Márta, Andrea Párniczky, Marin Gergics and Lilla Hanák provided valuable feedback after critically reviewing the first drafts of the manuscript. Lilla Hanák carried out the statistical analysis. All the authors reviewed and approved the final manuscript for publication.

Completing Interests

The authors declare that they have no completing interests.

Data Availability Statement

Since the article is a meta-analysis, the data is publicly available in the original articles.

Statement of Ethics

An ethics statement is not applicable because this study is based exclusively on published literature.

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Abbreviations: AD- Addison's disease; AITD- autoimmune thyroid disorder; aTg- thyroglobulin antibody; aTPO- thyroid peroxidase antibody; APS- autoimmune polyglandular syndrome; CI- confidence interval; CTLA-4- cytotoxic T-lymphocyte antigen-4; FCRL3- Fc receptor-like protein 3 gene; GD- Graves' disease; HLA- human leukocyte antigen; HT- Hashimoto's thyroiditis; MS- multiple sclerosis; POF- premature ovarian syndrome; PTPN-22- protein tyrosine phosphatase, non-receptor type 22 gene; RA- rheumatoid arthritis; SLE- systemic lupus erythematosus, TSHR- thyroid stimulating hormone receptor antibodies T1DM- type I diabetes mellitus

Abstract

Objective: In autoimmune polyglandular syndromes (APS) both types of Autoimmune Thyroid Disorders (AITDs), i.e. Hashimoto's thyroiditis (HT) and Graves' disease (GD) can be manifested.

Design: In this meta-analysis, the differences between HT and GD in APS II and III were investigated.

Methods: A comprehensive search in MEDLINE and Embase databases identified 479 studies with the keywords of APS II and APS III. Eighteen records containing a total of 1312 patients fulfilled the criteria of the study (original studies reporting at least 10 cases and containing the combination of other autoimmune disorders) and were selected for analysis. Meta-analysis was performed using the random-effects model. Results of each meta-analysis were displayed graphically using forest plots.

Results: AITDs were detected in 87.8% of APS patients. HT and GD were distinguished in 279 and 151 cases, respectively. In the remaining 309 cases, the diagnosis was AITDs, without any further characterization. The prevalence of HT, GD and AITD was not significantly different among APS patients. The pattern of co-associated endocrine, non-endocrine organ-specific and systemic autoimmune disorders was similar in HT and GD. T1DM and AD were found in larger proportion of patients, 70.7% and 18.5%, respectively. Other autoimmune conditions occurred in $\leq$4%. The majority of autoimmunities occurred in dual combinations (91.8%). The combination of four and more autoimmune disorders was published only in HT, in 0.1% of patients.

Conclusions: Using a meta-analysis, no difference in the prevalence of HT and GD among APS patients was found and no distinct pattern of co-associated autoimmunities was established.

Introduction

Autoimmune polyglandular syndromes (APS) are complex, heterogeneous disorders with the combination of autoimmune endocrinopathies and other organ-specific and systemic autoimmune disorders [1–4]. Antibodies against the endocrine and non-endocrine organs can develop [2,5,6]. Autoimmune thyroid disorders (AITDs) may occur in APS II and III. APS II is defined by the presence of Addison's disease (AD) and autoimmune thyroid diseases and/or diabetes mellitus (T1DM) [1]. APS III patients have AITDs and any other autoimmune conditions except AD [1–4]. The main important genes are common in APS II and III, the HLA, CTLA-4 and PTPN-22 genes [7].

AITDs are multifactorial diseases due to the combination of endogenous, environmental factors and genetic predisposition. There is a strong female preponderance among AITDs patients, with a female:male ratio ranging from 5:1 to 10:1[8].

Hashimoto's thyroiditis (HT) and Graves' disease (GD) are the autoimmune disorders of the thyroid gland. HT commonly pretends with hypothyroidism, whereas GD is a hyperthyroid condition [9]. Th1 pattern of autoimmune reaction is characteristic for HT, whereas the predominance of Th2 cytokines indicates a humoral pattern of immune reaction in GD. However, AITDs encompasses a spectrum of conditions ranging from HT at one end to GD at the other end [9].

A predominance of Th1-mediated immunity in HT may lead to the activation of apoptotic pathways with the consequence of thyroid cell destruction [10]. The thyroid gland is gradually destroyed resulting in reduced production of thyroid hormones. HT, also known as chronic lymphocytic thyroiditis is the most common autoimmune disease and is the most common cause of primary hypothyroidism in iodine-sufficient areas [11]. The presence of autoantibodies against thyroglobulin (aTg) and thyroid peroxidase (aTPO) is

the basic humoral immunological feature of HT [12]. HT affects more than 15 % of females over 60 years and 2 % of males [13].

Conversely, a predominance of Th2-mediated immune activity in GD results in the release of thyroid stimulating hormone receptor (TSHR) antibodies, causing thyroid cell hypertrophy and over-activity [10]. GD is typically characterized by a diffuse hyperfunctional goiter. TSHR antibodies appeared in GD are the most important diagnostic tools to differentiate between GD and HT [12,13].

The aim of this meta-analysis was to find differences between HT and GD in APS II and APS III patients regarding the associated autoimmune disorders. Here, we present a systematic review of literature and the first meta-analysis that includes retrospective and cohort studies to verify the differences between HT and GD in APS II and III.

Methods

This meta-analysis and systematic review was created in accordance with the recommendations of the Preferred Reporting Items for Systemic Reviews and Meta-Analyses (PRISMA) statement [14]. It was registered in the international prospective register of systematic reviews with number CRD42019126826. An other article was published from this meta-analyses in the Journal of Endocrinological Investigations in 2020 [15].

Search strategy

We searched the following electronic databases: MEDLINE, EMBASE and used only Human filter. There was no restriction for the language. The search was completed by 5th November 2018, and the following keywords were used for the search: “autoimmune polyglandular syndrome”, “autoimmune polyendocrinopathies”, “autoimmune polyglandular syndrome type II” and “autoimmune polyglandular syndrome type III”. The EndNote software (version: X 7.0.2., Clarivate Analytics, Philadelphia, PA, USA) was used to manage all references, to remove duplicates and to facilitate the selection process.

Inclusion and Exclusion criteria

For inclusion, publications had to demonstrate that (1) the study explained cases with two or more autoimmunities of endocrine and non-endocrine organs, (2) the study showed data of at least 10 patients. Publications were excluded if (1) a previous study was duplicated, (2) the study focused on patients only with systemic autoimmune disorders. Review articles were also excluded. The records were independently screened by two investigators for these criteria.

Data extraction

A standardized form of numeric data were extracted by two investigators and populated into an Excel 2016 sheet (Office 365, Microsoft, Redmond, WA, USA) containing the following information: year of publication, type of study, number of patients included and diagnosed with APS, average age of the patients, sex, main disorders (AD, AITDs, T1DM, POF, vitiligo, alopecia, coeliac disease, autoimmune hepatitis, pernicious anaemia, autoimmune bowel disease, haemolytic anaemia, SLE, psoriasis, Sjögren's syndrome, RA, myasthenia gravis, multiple sclerosis, hypoparathyroidism, hypophysitis) and the combinations of these diseases.

Statistical analysis

The methods recommended by the working group of the Cochrane Collaboration were used for the synthesis of data [16]. Event rates (in percentage distribution) were calculated for dichotomous outcomes. Random effect model was applied for all analysis with DerSimonian-Laird estimation [17]. Statistical heterogeneity was analysed using the I^2 and the χ^2 test to gain probability-values; $p<0.1$ was defined to indicate significant heterogeneity. Statistical analyses were performed with Stata 15 (Stata Corporation, College Station, TX, USA).

Assessment of the quality of the included studies

Two authors independently assessed the quality of the included studies as recommended by Murad et al. in 2018 [18] (Supplementary table 1.). Disagreements between the authors over the quality were resolved by discussion, with the involvement of a third review author if it was necessary.

Synthesis and analysis of the data (meta-analysis) and quality of evidence

Only the available data were used in the published articles, and when necessary, the authors of the original studies were contacted to obtain missing information. Publication biases of the included studies were checked by Egger's test and by visual assessment of funnel plots [18]. A significant test result ($p<0.1$) indicates the existence of bias. (Supplementary fig. 1-5.)

Results

Characteristics of the included studies

After the comprehensive searches of MEDLINE and Embase databases, 479 studies were found. After removing duplicates, we reviewed the remaining 454 studies for the eligibility criteria and identified 118 suitable papers for inclusion in our meta-analysis. Excluding case-reports, 18 articles containing a total of 1312 (10-254/papers) patients were selected for further analysis. Our PRISMA flow chart of the selection process is shown in Supplementary fig. 6. Caucasian, Asian and Hispanic ethnicities were included. Characteristics of the included studies in APS II and III are summarized in Supplementary table 2.

Characteristics of the patients

Distinction between APS II and APS III was made in 842 cases, of which 177 and 665 were APS II and III (21.1% vs 78.9%), respectively [3,19,28–34,20–27].

Prevalence of HT, GD and AITD in APS

Among all APS patients (1312 cases), thyroid autoimmune disorders were published in 739 cases (87.8%). The second and third most prevalent autoimmune diseases were T1DM and AD (523 and 137 cases, respectively) as it is expected from the definitions of APS. HT and GD were diagnosed in 279 and 151 cases, respectively. In 309 cases, the diagnosis was AITDs, without any further characterization. The prevalence of HT, GD and AITD was not significantly different among all APS patients (HT: 35%, 95% CI: 16% - 57% vs. GD: 10%, 95% CI: 1% - 22% vs. AITD: 10%, 95% CI: 0% - 31%, p=0.064). (Fig. 1.) [3,19,28–34,20–27]. No significant differences were found in APS II patients (HT: 10%, 95% CI: 0% - 35% vs. GD: 2%, 95% CI: 0% - 22% vs. AITD: 39%,

95% CI: 5% - 79%, p=0.183). (Fig. 2.) [20–22,28,30,31,33]. Among APS III patients, the prevalence of HT, GD and AITD also did not differ significantly (HT: 45%, 95% CI: 14% - 78% vs. GD: 9%, 95% CI: 0% - 27% vs. AITD: 30%, 95% CI: 1% - 72%, p=0.121) (Fig. 3.) [3,19,28–34,20–27].

Co-existence of other autoimmune disorders in HT, GD and AITD

In HT patients, three autoimmune endocrinopathies (T1DM, AD and POF), five non-endocrine organ-specific (autoimmune hepatitis, pernicious anaemia, vitiligo, multiple sclerosis and coeliac disease), and two systemic autoimmune diseases (RA and psoriasis) were reported.

In GD patients, three autoimmune endocrinopathies (T1DM, AD and POF), five non-endocrine organ-specific (autoimmune hepatitis, vitiligo, coeliac disease, myasthenia gravis and alopecia), and three systemic autoimmune diseases (SLE, RA and Sjögren's syndrome) were diagnosed.

In AITD patients, also three autoimmune endocrinopathies (T1DM, AD and POF), four non-endocrine organ-specific autoimmune disorders (autoimmune hepatitis, pernicious anaemia, vitiligo, and coeliac disease) were published and no systemic autoimmune diseases were found.

The evaluation of co-associated autoimmune disorders is further aggravated by the lack of proper classification of HT and GD. In this part of analysis, many cases were transported to the AITD group. The prevalence of the individual autoimmune conditions is demonstrated in Table 1. Only T1DM and AD were found in larger proportion of APS patients, 70.7 and 18.5%, respectively. The prevalence of autoimmune hepatitis, pernicious anaemia, vitiligo, POF, celiac disease and RA was between 1-4%, all the others were rare, <1%.

One, two and more than two other autoimmune disorders were combined with any kind of autoimmune thyroid abnormalities in 91.8%, 8% and 0,1% of cases, respectively.

HT, GD and AITDs were reported in dual combinations in 167, 92 and 419 cases (24.5%, 13.5% and 61.8%), respectively. The prevalence of dual combinations in HT, GD and AITD was not different (HT: 35%, 95% CI: 11% - 63% vs. GD: 10%, 95% CI: 0% - 26% vs. AITD: 29%, 95% CI: 3% - 63%, p=0.186). (Fig. 4.) [7,19,28–34,20–27].

Triple combinations were more sparse in GD and did not differed between HT and AITDs (GD: 3%, 95% CI: 0% - 18% vs. AITD: 77%, 95% CI: 21% - 100%, vs. HT: 14%, 95% CI: 0% - 66% p=0.028) (Fig. 5.) [20,23,28,31–34].

More than two other autoimmune disorders were never combined with GD and AITD, this clinical situation only occurred in HT but the low number of cases did not allow the relevant statistical analysis [27,28,34].

In HT patients, the most common associated disorders were T1DM, autoimmune hepatitis and pernicious anaemia, in 121, 23 and 19 cases, respectively. GD most commonly manifested together with T1DM, AD and vitiligo (64, 7 and 6 cases, respectively). In the not classified AITDs group, T1DM, AD and vitiligo were the most common combinations (282, 104 and 16 cases, respectively).

The pattern of non-endocrine dual combinations of autoimmune disorders was slightly different between GD and HT; systemic autoimmune disorders – SLE, Sjögren's syndrome and rheumatoid arthritis -, occurred in dual combinations only with GD. In HT patients, systemic autoimmune disorders (RA and psoriasis) were only the part of triple and even more combinations.

The non-endocrine organ-specific autoimmune disorders, myasthenia gravis and alopecia occurred in dual combinations only in GD, pernicious anaemia in AITD, vitiligo in HT.

Interestingly, triple combinations of any kind of autoimmune disorders occurred in GD only in APS II patients. Triple combinations in AITD patients were only detected when T1DM was one of the associated diseases.

Discussion

The combinations of autoimmune disorders are common but the manifestation of the second or third autoimmune conditions may be many years after the first presentation [35]. The prediction of the future autoimmune diseases is difficult; many attempts were done based on the screening of autoantibodies [36]. Regular screening procedures are expensive and their cost-effectivity is questionable. Both GD and HT are among the most common autoimmune diseases [36]. In this systematic review and meta-analysis we tried to establish typical patterns of co-associated conditions in HT and GD to help the better orientation of patients and physicians and to initiate a screening algorithm.

The best-characterized combinations of autoimmune disorders are the APS patients [1]. We did not find any difference in the prevalence of HT, GD and AITDs in APS patients, nor in APS II neither in APS III. Co-associated organ-specific endocrine and non-endocrine and systemic autoimmune disorders occurred in both HT and GD. Common co-morbidities were only T1DM and AD, the prevalence of other autoimmune disorders was $\leq$4%. This is taken into account regarding the development of cost-effective screening algorithms.

The occurrence of dual combinations was similar in HT, GD and AITDs but triple combinations were rarer in GD. Three or more autoimmune disorders were combined only with HT. Systemic autoimmune diseases were diagnosed with GD in dual combinations, with HT in triple or even more combinations.

Many systemic autoimmune diseases can be associated with AITDs [19,37]. Organ specific, non-endocrine autoimmunities (such as pernicious anaemia, coeliac disease, autoimmune hepatitis, multiple sclerosis, and myasthenia) are also common comorbidities with AITDs. This means that proper screening protocols for AITDs may

be useful in patients with systemic autoimmunities as well as with organ specific autoimmune diseases [37]. Unfortunately, studies investigating the association of non-endocrine autoimmune disorders did not specify HT and GD among AITD patients [19,37]. Probably these associations would be more interesting if there would be a proper distinction between HT and GD.

A previous review found that HT is significantly more frequent in individuals who suffer from other autoimmunities, such as AD, T1DM, RA or SLE [36]. In our meta-analysis, T1DM, autoimmune hepatitis, pernicious anaemia, POF, AD, vitiligo, coeliac disease, MS, RA and psoriasis were found in HT patients.

A recent study showed that in GD patients, the following autoimmune diseases were observed with a significantly higher prevalence: T1DM, celiac disease, autoimmune gastritis, vitiligo, RA, Sjögren's syndrome, SLE, sarcoidosis, hepatitis C virus - related mixed cryoglobulinemia, polymyalgia rheumatica and multiple sclerosis [38,39]. In our review, T1DM, POF, AD, autoimmune hepatitis, vitiligo, coeliac disease, myasthenia gravis, alopecia, SLE, RA and Sjögren's syndrome was diagnosed in GD patients. Interestingly, in GD patients, triple combinations occurred only when AD was one of the associated disorders.

HT and GD are both due to polymorphisms in the HLA DQ/DR regions [13]. Immune-regulatory genes such as HLA region, CD40, CTLA4, PTPN22, and FCRL3 are involved in the development of GD [39]. Protective genes are also identified like HLA-DRB1* 07, HLA-C03, and HLA-C*16. CTLA4 polymorphisms are associated with an increased risk of GD and HT [13]. HT has been found strongly associated with HLA haplotypes DRB1*03:01, -DR4, -DR5, and -DQB1*03:01 (DQ7) [40]. Identification of

polymorphisms in immune regulatory genes may be useful to estimate the risk of HT, GD and other combined autoimmunities in APS.

Limitations of the study

Unfortunately, publications in the field of APS are mainly case reports, only 18 retrospective and cohort studies were suitable for further analysis and the number of published APS patients was low. Although AITDs are the most common autoimmune disorders in APS (87.8%), only 739 AITDs patients were collected with known co-associations of other autoimmunities. Moreover, only 58% of patients were initially classified as HT or GD and even this classification became confused during the discussion of combinations, so only 39% of patients was available for analysis of autoimmune combinations. This markedly limits the potential conclusions and calls the attention of urgent need for better documentation.

Strengths of the study

This is the first systematic review and meta-analysis in the field of APS and the first attempt to establish typical patterns of co-associated autoimmune conditions in HT and GD. Relevant statistical analysis was done despite the incomplete clinical data.

Implications for clinicians

The combination of autoimmune disorders is common and the prediction of multi-organ involvement is desirable by the patients and clinicians. Better and uniform classification of clinical data and development of registries can help to improve the management of patients.

Implications for research

The lack of differences between HT and GD in the association of other autoimmune disorders indicates similarities in the immunological background. As the genetic

predisposing factors are seemingly heterogeneous, the investigation of genetic polymorphism may serve the classification of patients and have prognostic significance.

In conclusion, using a systematic review and meta-analysis, no difference in the prevalence of HT and GD was found in APS patients and the pattern of co-associated autoimmune disorders was also similar. Many organ-specific endocrine and non-endocrine and systemic autoimmune disorders may occur in patients with autoimmune thyroid disorders, however only T1DM and AD were found with high prevalence in APS patients.

References

1. Betterle C, Lazzarotto F, Presotto F. Autoimmune polyglandular syndrome Type 2: The tip of an iceberg? Clin Exp Immunol. 2004;137:225–33. doi:10.1111/j.1365-2249.2004.02561.x

2. Bain A, Stewart M, Mwamure P, Nirmalaraj K. Addison's disease in a patient with hypothyroidism: Autoimmune polyglandular syndrome type 2. BMJ Case Rep. 2015;2015:2–4. doi:10.1136/bcr-2015-210506

3. Renzullo A, Accardo G, Esposito D, De Bellis A, Bizzarro A, Romano M, et al. Hashimoto's thyroiditis and entero-chromaffin-like cell hyperplasia: Early detection and somatostatin analogue Treatment. Eur J Inflamm. 2013;11:863–70. doi:10.1177/1721727X1301100329

4. Cutolo M. Autoimmune polyendocrine syndromes. Autoimmun Rev [Internet]. Elsevier B.V.; 2014;13:85–9. Available from: http://dx.doi.org/10.1016/j.autrev.2013.07.006 doi:10.1016/j.autrev.2013.07.006

5. Anaya JM. The diagnosis and clinical significance of polyautoimmunity. Autoimmun Rev. 2014;13:423–6. doi:10.1016/j.autrev.2014.01.049

6. Arlt W, Allolio B. Adrenal insufficiency. Lancet. 2003;361:1881–93. doi:10.1016/S0140-6736(03)13492-7

7. Hansen MP. Type 1 diabetes and polyglandular autoimmune syndrome: A review. World J Diabetes. 2015;6:67. doi:10.4239/wjd.v6.i1.67

8. Effraimidis G, Wiersinga WM. Mechanisms in endocrinology: Autoimmune thyroid disease: Old and new players. Eur J Endocrinol. 2014;170. doi:10.1530/EJE-14-0047

9. Shao S, Yu X, Shen L. Autoimmune thyroid diseases and Th17/Treg lymphocytes. Life Sci [Internet]. Elsevier Inc; 2018;192:160–5. Available from: http://dx.doi.org/10.1016/j.lfs.2017.11.026 doi:10.1016/j.lfs.2017.11.026

10. Sasazuki T, Inoko H, Morishima S, Morishima Y. Gene Map of the HLA Region, Graves' Disease and Hashimoto Thyroiditis, and Hematopoietic Stem Cell Transplantation [Internet]. 1st ed. Adv. Immunol. Elsevier Inc.; 2016. Available from: http://dx.doi.org/10.1016/bs.ai.2015.08.003 doi:10.1016/bs.ai.2015.08.003

11. Rayman MP. Symposium 2: Nutrient interactions and their role in protection from chronic diseases: Multiple nutritional factors and thyroid disease, with particular reference to autoimmune thyroid disease. Proc Nutr Soc. 2019;78:34–44. doi:10.1017/S0029665118001192

12. Wémeau J louis, Klein M, Sadoul JL, Briet C, Vélayoudom-Céphise FL. Graves' disease: Introduction, epidemiology, endogenous and environmental pathogenic factors. Ann Endocrinol (Paris) [Internet]. Elsevier Masson SAS; 2018;79:599–607. Available from: https://doi.org/10.1016/j.ando.2018.09.002 doi:10.1016/j.ando.2018.09.002

13. Hu S, Rayman MP. Multiple Nutritional Factors and the Risk of Hashimoto's Thyroiditis. Thyroid. 2017;27:597–610. doi:10.1089/thy.2016.0635

14. Kamioka H. Preferred reporting items for systematic review and meta-analysis protocols (prisma-p) 2015 statement. Japanese Pharmacol Ther. 2019;47:1177–85.

15. Pham-Dobor G, Hanák L, Hegyi P, Márta K, Párniczky A, Gergics M, et al. Prevalence of other autoimmune diseases in polyglandular autoimmune syndromes type II and III. J Endocrinol Invest [Internet]. Springer International Publishing; 2020;43:1327–35. Available from: https://doi.org/10.1007/s40618-020-01229-1

doi:10.1007/s40618-020-01229-1

16. Higgins JPT GS editors. The Cochrane Collaboration. Cochrane Handbook for Systematic Rewievs of Interventions Version 5.1.0. Internet. 2011;

17. DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials. 1986;7:177–88. doi:10.1016/0197-2456(86)90046-2

18. Murad MH, Sultan S, Haffar S, Bazerbachi F. Methodological quality and synthesis of case series and case reports. Evid Based Med. 2018;23:60–3. doi:10.1136/bmjebm-2017-110853

19. Choudhuri G, Somani SK, Baba CS, Alexander G. Autoimmune hepatitis in India: Profile of an uncommon disease. BMC Gastroenterol. 2005;5:1–8. doi:10.1186/1471-230X-5-27

20. Cruz AAV, Akaishi PMS, Vargas MA, De Paula SA. Association between thyroid autoimmune dysfunction and non-thyroid autoimmune diseases. Ophthal Plast Reconstr Surg. 2007;23:104–8. doi:10.1097/IOP.0b013e318030b06b

21. Dittmar M, Kahaly GJ. Polyglandular autoimmune syndromes: Immunogenetics and long-term follow-up. J Clin Endocrinol Metab. 2003;88:2983–92. doi:10.1210/jc.2002-021845

22. Szadkowska A, Pietrzak I, Czerniawska E, Teodorczyk A, Bodalski J. Albuminuria in children and adolescents with type 1 diabetes mellitus [Albuminuria u dzieci I młodzieży z cukrzycą typu 1]. Prz Pediatryczny [Internet]. 2002;32:126–32. Available from: https://www.scopus.com/inward/record.uri?eid=2-s2.0-0036341184&partnerID=40&md5=b798b94e6cdee1f31e89a810b510b4ca

23. Papadopoulos KI, Hörnblad Y, Liljebladh H, Hallengren B. High frequency of endocrine autoimmunity in patients with sarcoidosis. Eur. J. Endocrinol. 1996. p. 331–6. doi:10.1530/eje.0.1340331

24. Kordonouri O, Klinghammer A, Lang EB, Grüters-Kieslich A, Grabert M, Holl RW. Thyroid autoimmunity in children and adolescents with type 1 diabetes: A multicenter survey. Diabetes Care. 2002;25:1346–50. doi:10.2337/diacare.25.8.1346

25. Storz SM, Wylenzek SAM, Matheis N, Weber MM, Kahaly GJ. Impaired psychometric testing in polyglandular autoimmunity. Clin Endocrinol (Oxf). 2011;74:394–403. doi:10.1111/j.1365-2265.2010.03952.x

26. Horie I, Kawasaki E, Ando T, Kuwahara H, Abiru N, Usa T, et al. Clinical and genetic characteristics of autoimmune polyglandular syndrome type 3 variant in the Japanese population. J Clin Endocrinol Metab. 2012;97:1043–50. doi:10.1210/jc.2011-3109

27. Ben-Skowronek I, Michalczyk A, Piekarski R, Wysocka-Łukasik B, Banecka B. Type III Polyglandular Autoimmune Syndromes in children with type 1 diabetes mellitus. Ann Agric Environ Med. 2013;20:140–6.

28. Suresh Kumar Angurana RSA. A very rare cohort of elderly patients with autoimmune polyglandular syndrome type 3b. Indian J Endocrinol Metab. 2014;18:429–30.

29. Efe C, Purnak T, Ozaslan E. Concurrent autoimmune thyroid diseases in patients with autoimmune hepatitis. J Clin Gastroenterol. 2010;44:660–1. doi:10.1097/MCG.0b013e3181d7b1ac

30. Betterle C, Dalpra C, Greggio N, Volpato M, Zanchetta R. Autoimmunity in isolated Addison's disease and in polyglandular autoimmune diseases type 1, 2 and 4. Ann Endocrinol (Paris). 2001;62:193–201.

31. Karagüzel G, Şimşek S, Değer O, Ökten A. Screening of diabetes, thyroid, and celiac diseases-related autoantibodies in a sample of Turkish children with type 1 diabetes and their siblings. Diabetes Res Clin Pract. 2008;80:238–43. doi:10.1016/j.diabres.2007.12.007

32. Karavanaki K, Kakleas K, Paschali E, Kefalas N, Konstantopoulos I, Petrou V, et al. Screening for associated autoimmunity in children and adolescents with Type 1 diabetes mellitus (T1DM). Horm Res. 2009;71:201–6. doi:10.1159/000201108

33. Handa S, Dogra S. Epidemiology of childhood vitiligo: A study of 625 patients from North India. Pediatr Dermatol. 2003;20:207–10. doi:10.1046/j.1525-1470.2003.20304.x

34. Papadopoulos KI, Hallengren B. Polyglandular autoimmune syndrome type II in patients with idiopathic Addison's disease. Acta Endocrinol. (Copenh). 1990. p. 472–8. doi:10.1530/acta.0.1220472

35. Kristensen B. Regulatory B and T cell responses in patients with autoimmune thyroid disease and healthy controls. Dan Med J. 2016;63:1–27.

36. Pyzik A, Grywalska E, Matyjaszek-Matuszek B, Roliński J. Immune disorders in Hashimoto's thyroiditis: What do we know so far? J Immunol Res. 2015;2015. doi:10.1155/2015/979167

37. Lazúrová I, Benhatchi K. Lazúrová 12 Thyroid disease and other AuImm disorders. :55–9.

38. Ferrari SM, Fallahi P, Ruffilli I, Elia G, Ragusa F, Benvenga S, et al. The association of other autoimmune diseases in patients with Graves' disease (with or without ophthalmopathy): Review of the literature and report of a large series. Autoimmun Rev. 2019;18:287–92. doi:10.1016/j.autrev.2018.10.001

39. De Leo S, Lee SY, Braverman LE. Hyperthyroidism. Lancet. 2016;388:906–18. doi:10.1016/S0140-6736(16)00278-6

40. Wémeau JL, Proust-Lemoine E, Ryndak A, Vanhove L. Thyroid autoimmunity and polyglandular endocrine syndromes. Hormones. 2013;12:39–45. doi:10.1007/bf03401285

Figure legends

Figure 1. Prevalence of Hashimoto's thyroiditis, Graves' disease and autoimmune thyroid disorders among autoimmune polyglandular syndrome patients; The prevalence of Hashimoto's thyroiditis, Graves' disease and autoimmune thyroid disorders was not significantly different among all autoimmune polyglandular syndrome patients, ES: effect size

Figure 2. Prevalence of Hashimoto's thyroiditis, Graves' disease and autoimmune thyroid disorder among autoimmune polyglandular syndrome type II patients; In autoimmune polygalndular syndrome type II patients, the difference between the prevalence of Hashimoto's thyroiditis, Graves' disease and autoimmune thyroid disorder did not reach the level of significance; ES: effect size

Figure 3. Prevalence of Hashimoto's thyroiditis, Graves' disease and autoimmune thyroid disorders among autoimmune polyglandular syndrome type III patients; Among autoimmune polyglandular syndrome type III patients, the prevalence of Hashimoto's thyroiditis, Graves' disease and autoimmune thyroid disorder did not reach the level of significance; ES: effect size

Figure 4. Prevalence of dual combinations in Hashimoto's thyroiditis, Graves' disease and autoimmune thyroid disorder patients; The prevalence of dual combinations in Hashimoto's thyroiditis, Graves' disease and autoimmune thyroid disorder did not reach the level of significance; ES: effect size

Figure 5. Prevalence of triple combinations in Hashimoto's thyroiditis, Graves' disease and autoimmune thyroid disorder patients; The difference in the number of two associated disorders between autoimmune thyroid disorders and Graves' disease was also

significant, however it did not reach the level of significance among Hashimoto's thyroiditis patients; ES: effect size

Table 1. The prevalence of other autoimmune disorders associated to any kind of autoimmune thyroid diseases in APS II and III

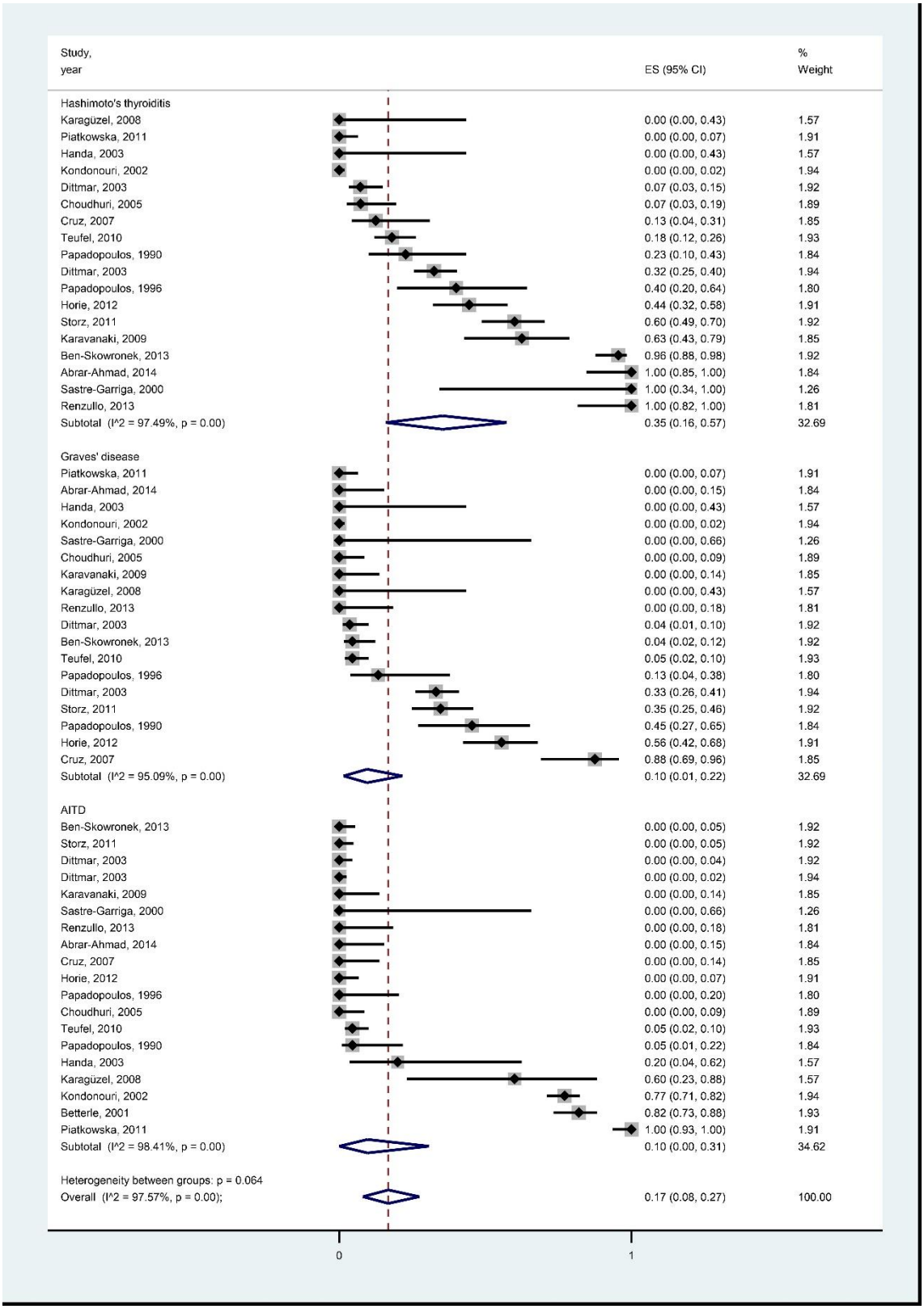


Figure 1 Prevalence of HT GD and AITD among APS patients

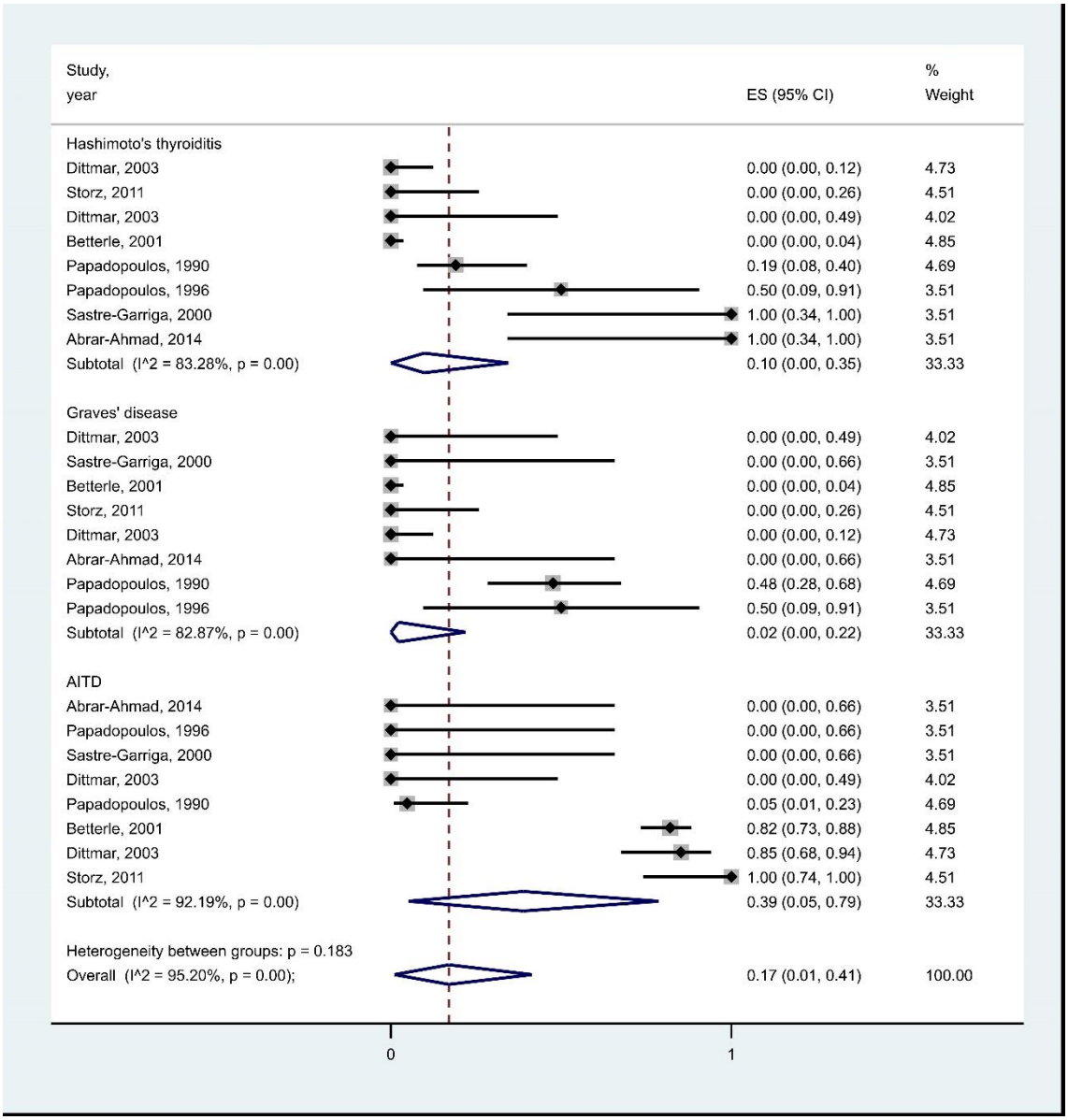


Figure 2 Prevalence of HT GD and AITD among APS II patients

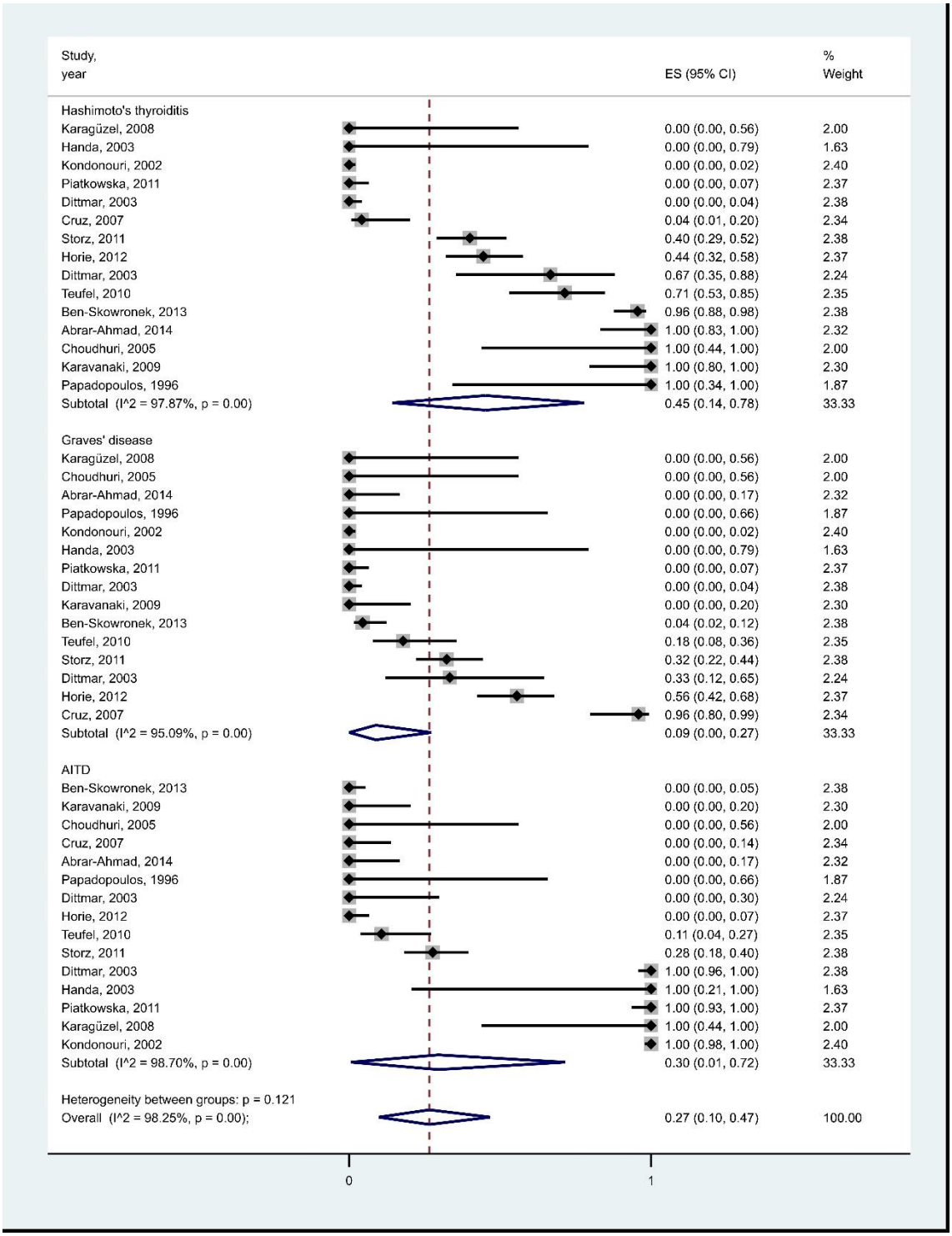


Figure 3 Prevalence of HT GD and AITD among APS III patients

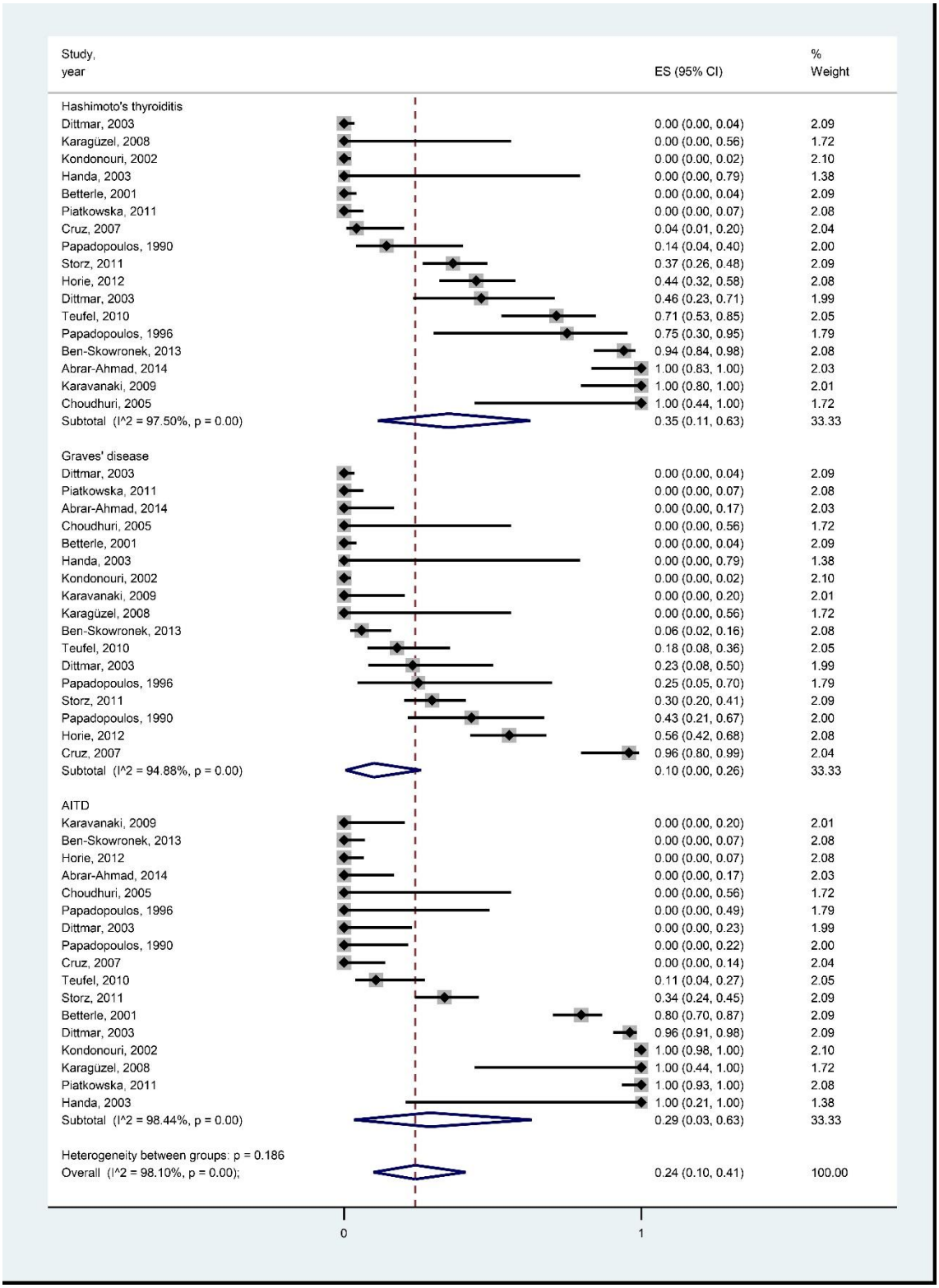


Figure 4 Prevalence of dual combinations in HT GD and AITD patients

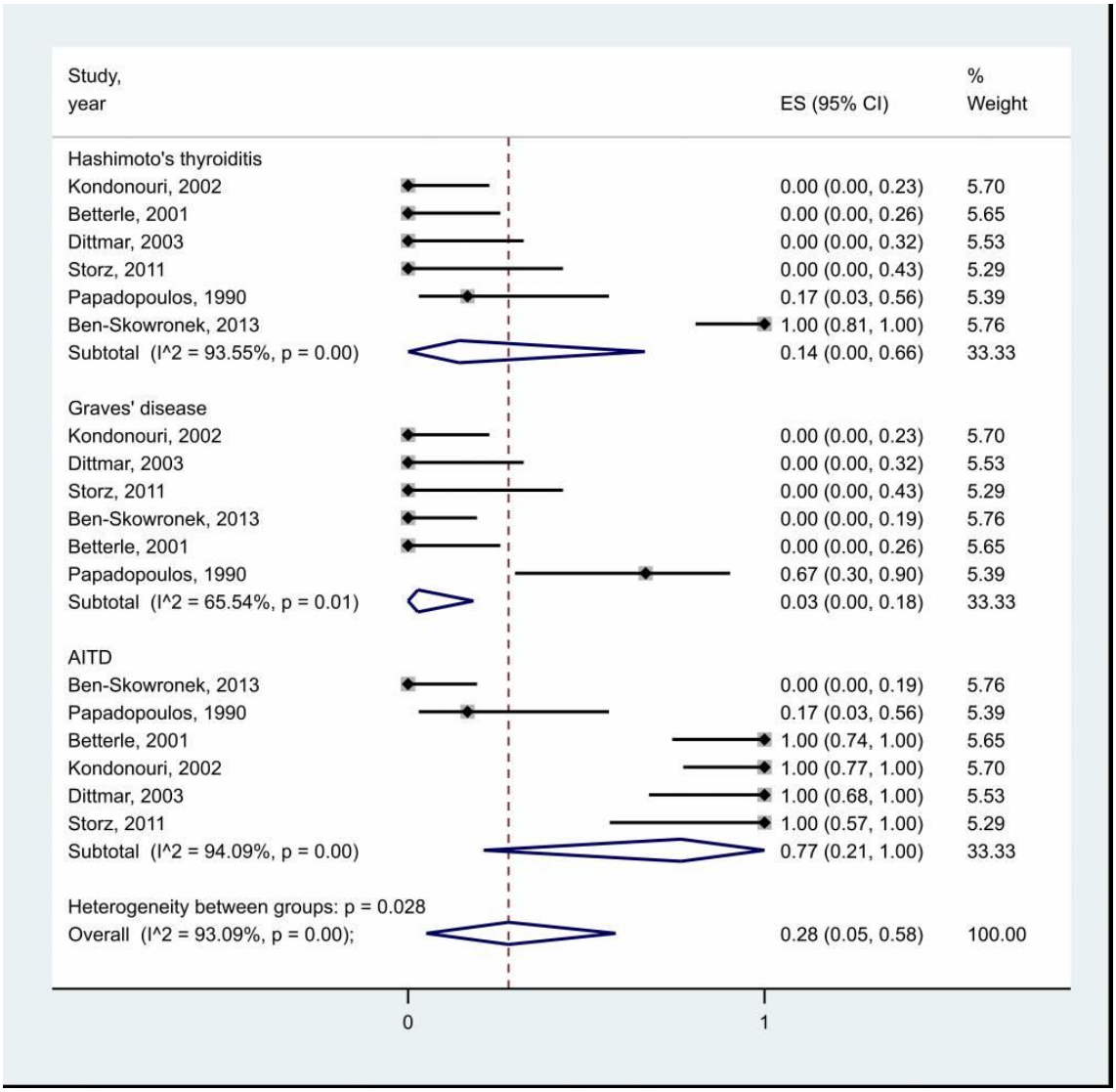


Figure 5 Prevalence of triple combinations in Hashimoto thyroiditis and Graves disease and autoimmune thyroid disorder patients

Autoimmune disorders	**Number of cases**	**Percentages**
Type I diabetes mellitus	523	70,7%
Addison's disease	137	18,5%
Autoimmune hepatitis	31	4%
Pernicious anaemia	28	3,7%
Vitiligo	25	3,4%
Premature ovarian syndrome	21	2,8%
Coeliac disease	20	2,7%
Rheumatoid arthritis	10	1,3%
Alopecia	4	0,5%
Multiple sclerosis	2	0,3%
Systemic lupus erythematosus	2	0,3%
Sjögren's syndrome	2	0,3%
Myasthenia gravis	2	0,3%
Psoriasis	1	0,1%

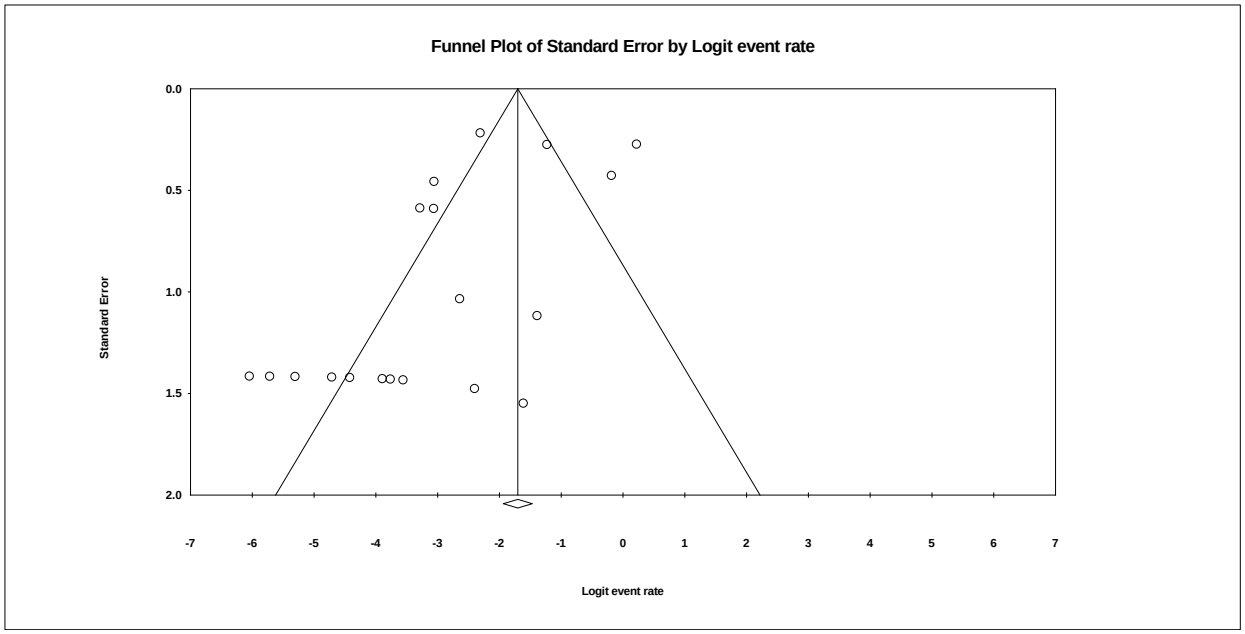
Table 1. The prevalence of other autoimmune disorders associated to any kind of autoimmune thyroid diseases in APS II and III

Supplementary material

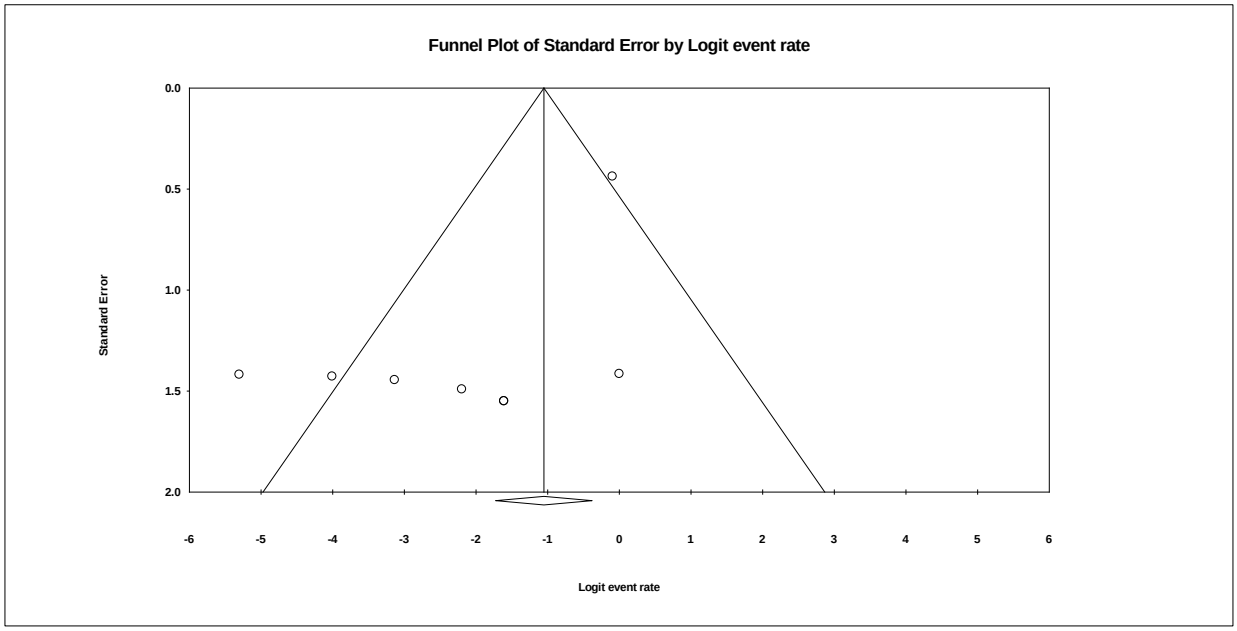
		Is the objective of the study stated clearly in the abstract, introduction, or methods section?	Are the characteristics of the participants included in the study described?	Were the cases collected in more than one centre?	Are the eligibility criteria (inclusion and exclusion criteria) for entry into the study explicit and appropriate?	Were participants recruited consecutively?	Did participants enter the study at a similar point in the disease?	Is the cases described with sufficient details to allow other investigators to replicate the research or to allow practitioners make inferences related to their own practice?
Abrar-Ahmad	2014	*	*	*	*	*		
Ben-Skowronek	2013	*	*		*	*	*	*
Betterle	2001	*	*		*	*	*	*
Choudhuri	2005		*		*	*		
Cruz	2007	*	*		*	*	*	*
Dittmar	2003	*	*		*	*		*
Handa	2003	*	*			*	*	*
Horie	2012	*	*		*		*	*
Karagüzel	2008	*	*		*	*		*
Karavanaki	2009	*	*		*	*	*	*
Kondonouri	2002	*	*	*	*	*		
Papadopoulos	1990	*	*		*	*	*	*
Papadopoulos	1996	*	*	*	*	*	*	
Piatkowska	2011	*	*			*		*
Renzullo	2013		*		*	*	*	*
Sastre-Garriga	2000	*			*	*	*	

Storz	2011	*	*	*	*	*		*
Teufel	2010	*	*		*	*	*	*

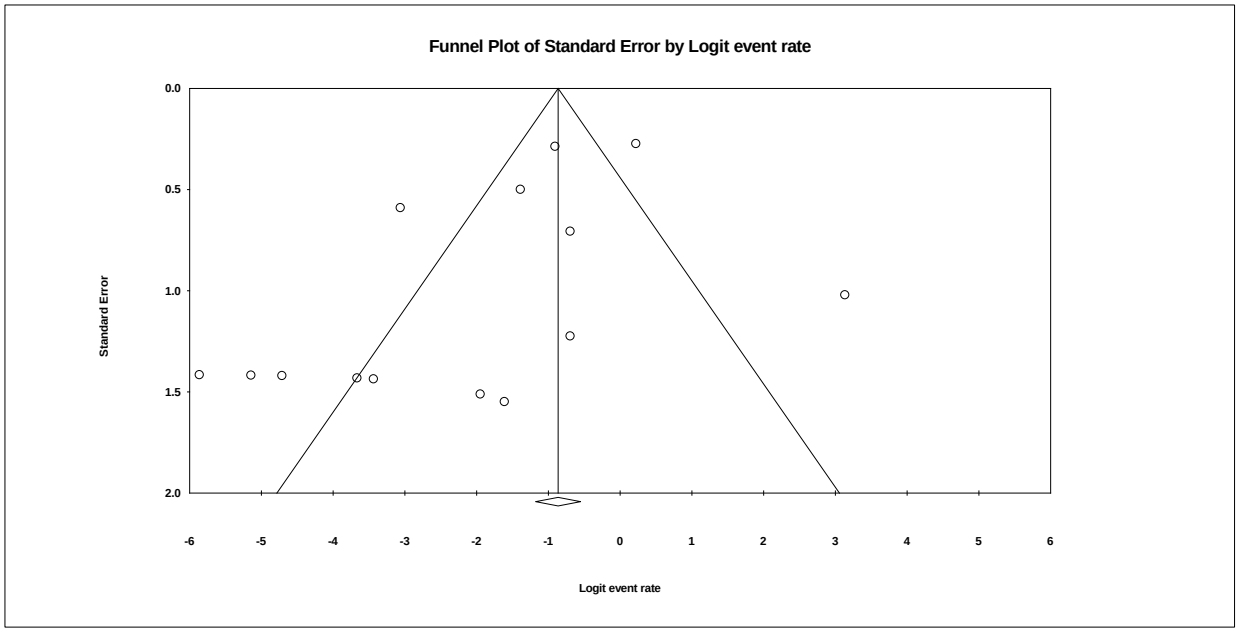
Supplementary table. 1. Quality assesment of the included studies



Supplementary fig. 1. Funnel plots of severity in terms of publication bias regarding the presence of Graves's disease in APS patients. Funnel plots represent the standard error (SE) plotted againts event rates (ES) for each study. The dotted line shows the 95% confidence limits.

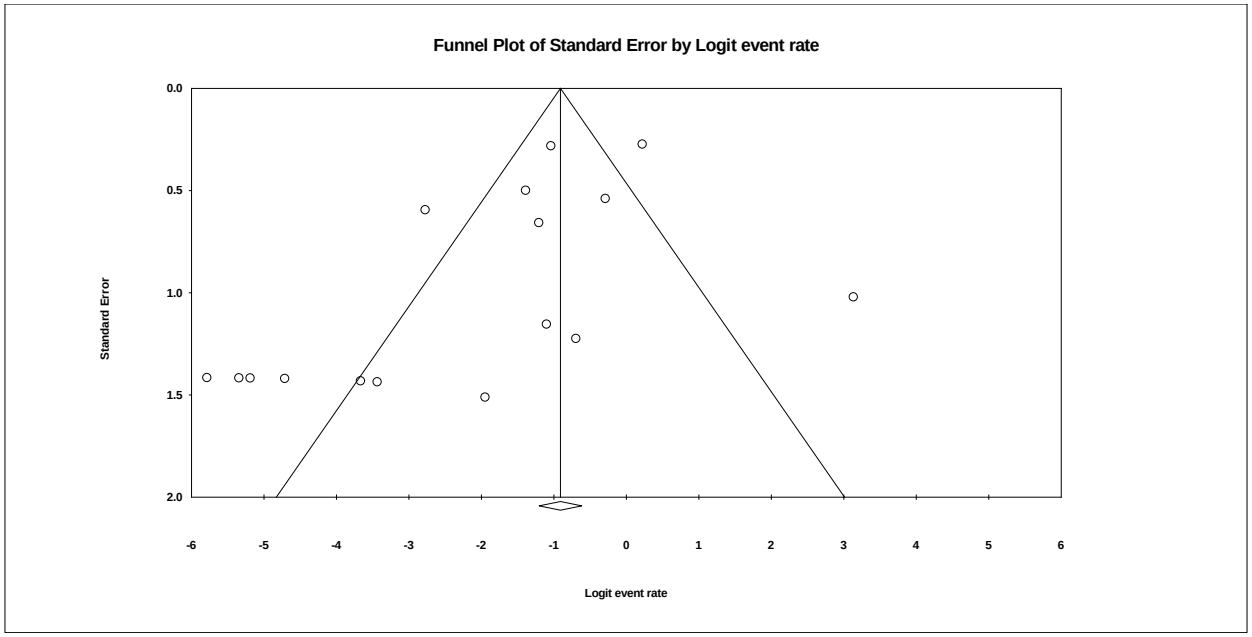


Supplementary fig. 2. Funnel plots of severity in terms of publication bias regarding the presence of Graves's disease in APS II patients. Funnel plots represent the standard error (SE) plotted againts event rates (ES) for each study. The dotted line shows the 95% confidence limits.

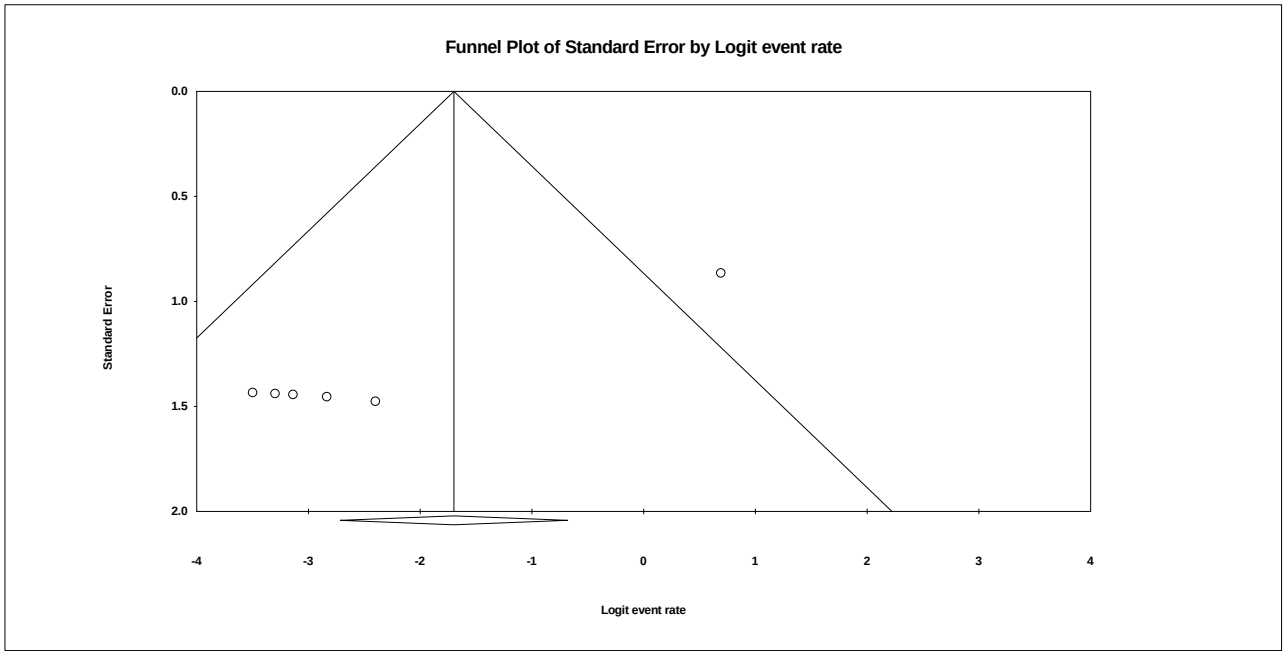


Supplementary fig. 3. Funnel plots of severity in terms of publication bias regarding the presence of Graves's disease in APS III patients. Funnel plots represent the standard error

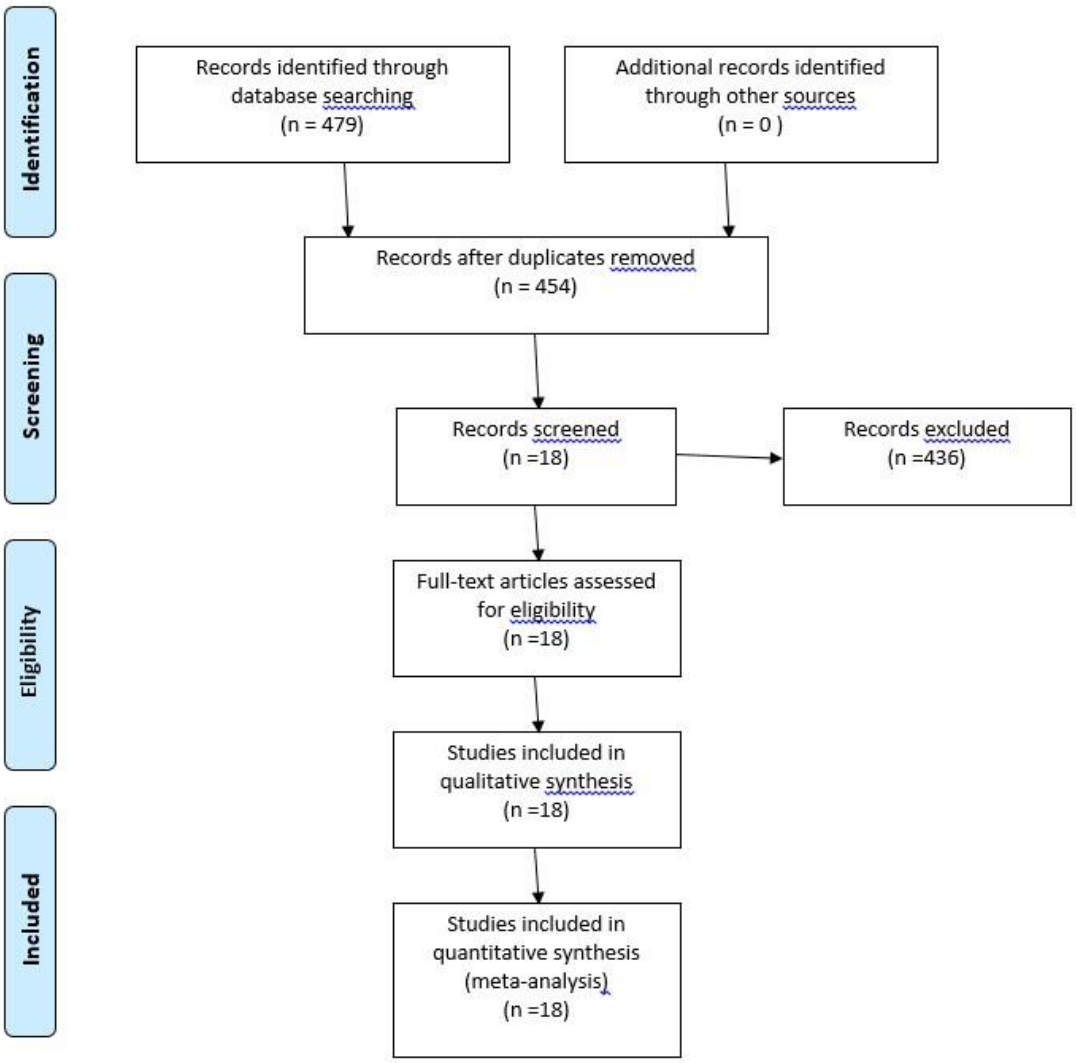
(SE) plotted againts event rates (ES) for each study. The dotted line shows the 95% confidence limits.



Supplementary fig. 4. Funnel plots of severity in terms of publication bias regarding the presence of dual combinations in Graves's disease patients. Funnel plots represent the standard error (SE) plotted againts event rates (ES) for each study. The dotted line shows the 95% confidence limits.



Supplementary fig. 5. Funnel plots of severity in terms of publication bias regarding the presence of triple combinations in Graves's disease patients. Funnel plots represent the standard error (SE) plotted againts event rates (ES) for each study. The dotted line shows the 95% confidence limits.



Supplementary figure 6. PRISMA flow diagram of the study

First Author	Year of publication	Design	Country	Number of patients		Age in APS			Sex in APS	
				APS	not APS	Mean	SD	range	Female	Male
Abrar-Ahmad	2014	Case series	France	21	7	NA	NA	NA	NA	NA
Ben-Skowronek	2013	Case series	Poland	67	394	NA	NA	NA	51	16
Betterle	2001	Retrospective review	Italy	100	147	NA	NA	NA	NA	NA
Choudhuri	2005	Retrospective review	India	41	0	36,3	2,6	7-68	34	7
Cruz	2007	Retrospective review	Brazil	254	0	39,32	13,48	NA	203	51
Dittmar	2003	Retrospective review	Germany	151	0	NA	NA	NA	114	37
				83	388	48,2	19,1	NA	53	30
Handa	2003	Retrospective review	India	5	620	NA	NA	NA	NA	NA
Horie	2012	Retrospective review	Japan	54	143	NA	NA	NA	44	10
Karagüzel	2008	Cohort study	Turkey	5	52	NA	NA	NA	NA	NA
Karavanaki	2009	Retrospective review	Greece	24	120	NA	NA	NA	NA	NA
Kondonouri	2002	Retrospective review	Germany and Austria	210	17539	13,6	3,8	NA	NA	NA
Papadopoulos	1990	Retrospective review	Sweden	22	22	35	NA	18-61	16	6
Papadopoulos	1996	Retrospective review	Sweden	15	63	57	NA	26-78	8	7
Piatkowska	2011	Retrospective review	Poland	55	327	11,31	3,74	NA	36	19
Renzullo	2013	Retrospective review	Italy	17	98	52	7	NA	17	0
Sastre-Garriga	2000	Retrospective review	Spain	2	1275	NA	NA	28-37	1	1
Storz	2011	Retrospective review	Germany	75	75	47,51	15,3	NA	49	26
Teufel	2010	Retrospective review	Germany	111	167	NA	NA	NA	NA	NA

Supplementary table 2. Characteristics of the included studies (NA= not available)