SUPPLEMENTARY MATERIAL

Prevalence of functioning adrenal incidentalomas: a systematic review and meta-analysis

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Supplemental methods

Pubmed search
((adrenal incidentaloma [Title/abstract] OR adrenal incidentalomas [Title/abstract] OR adrenal mass [Title/abstract]) AND (aldosterone OR hyperaldosteronism OR Conn's syndrome OR aldosteronism)) OR ((adrenal incidentaloma [Title/abstract] OR adrenal incidentalomas [Title/abstract] OR adrenal mass [Title/abstract]) AND (cortisol OR hypercortisolism OR Cushing syndrome)) OR ((adrenal incidentaloma [Title/abstract] OR adrenal incidentalomas [Title/abstract] OR adrenal mass [Title/abstract]) AND (cortisol OR hypercortisolism OR Cushing syndrome)) OR ((adrenal incidentaloma [Title/abstract] OR adrenal incidentalomas [title/abstract] OR adrenal mass [Title/abstract]) AND (subclinical hypercortisolism OR subclinical Cushing syndrome)) OR ((adrenal incidentaloma [Title/abstract] OR adrenal incidentalomas [Title/abstract] OR adrenal mass [Title/abstract]) AND (pheochromocytoma OR metanephrines OR normetanephrine OR catecholamines)). Items found: 1651

Ovid MEDLINE search
#1 incidentaloma* Results: 2323
#2 exp hyperaldosteronism Results: 8941
#3 exp pheochromocytoma Results: 15894
#4 exp hypercortisolism Results: 12394
#5 1 and 2 Results: 98
#6 1 and 3 Results: 297
#7 1 and 4 Results: 298
#8 5 or 6 or 7 Results: 572

Web of Science
#1 topic=incidentaloma* Results: 2921
#2 topic=hyperaldosteronism or aldosterone Results: 33839
#3 topic=pheochromocytoma Results: 16971
#4 topic=hypercortisolism Results: 2681
#5 1 and 2 Results: 231
#6 1 and 3 Results: 484
#7 1 and 4 Results: 363
#8 5 or 6 or 7 Results: 926

Modified Newcastle-Ottawa risk of bias scoring guide

(1) Selection

Is the definition of adrenal incidentaloma adequate?

1 point: an adrenal mass detected on imaging not performed for suspected adrenal disease.

0 point: an adrenal mass discovered on an imaging study performed during tumour evaluation or diagnostic work-up for patients affected by arterial hypertension or not clearly stated

Sample representativeness

1 point: consecutive or obviously representative series of cases

0 point: potential for selection biases or not stated

(2) Sample size

1 point: sample size was greater than or equal to 30 participants

0 points: sample size was less than 30 participants

(3) Ascertainment of hormone excess

1 point: the diagnosis was made according with the available scientific recommendations. Diagnostic criteria and cut-off to define hormone excess were clearly stated

0 point: the diagnosis was made according with the available scientific recommendations or guidelines, but the diagnostic criteria and cut-off were not clearly stated

(4) Quality of descriptive statistics reporting

1 point: the study reported descriptive statistics to describe the population, with proper measures of dispersion

0 point: the study did not report descriptive statistics, incompletely reported descriptive statistics or did not report measures of dispersion

Legend: the individual components listed above are summed to generate a total modified Newcastle-Ottawa risk of bias score for each study, ranging from 0 to 5. Studies were judged to be at low risk of bias when ≥ 4 points were scored, at intermediate risk of bias when 3 points were scored and at high risk of bias if ≤ 2 points were scored.

Reference list of included studies

1. **Abe I**, Sugimoto K, Miyajima T, et al. Clinical Investigation of Adrenal Incidentalomas in Japanese Patients of the Fukuoka Region with Updated Diagnostic Criteria for Sub-clinical Cushing's Syndrome. *Intern Med*. 2018;57(17):2467-2472.
2. **Ahn SH**, Kim JH, Baek SH, et al. Characteristics of Adrenal Incidentalomas in a Large, Prospective Computed Tomography-Based Multicenter Study: The COAR Study in Korea. *Yonsei Med J*. 2018;59(4):501-510.
3. **Akkuş G**, Evran M, Sert M, Ok F, Tetiker T. Multidisciplinary approach for patients with functional and non-functional adrenal masses and review of the literature. *Health Sci Rep*. 2017;1(3):e22.
4. **Anagnostis P**, Efstathiadou Z, Polyzos SA, et al. Long term follow-up of patients with adrenal incidentalomas--a single center experience and review of the literature. *Exp Clin Endocrinol Diabetes*. 2010;118(9):610-616.
5. **Aoe M**, Okada A, Usui T, Manaka K, Nangaku M, Makita N. Comparison between the clinical characteristics of patients with adrenal incidentalomas and those with hypertension-associated adrenal tumors in a single center in Japan. *Endocr J*. 2020;67(6):645-654.
6. **Barzon L**, Fallo F, Sonino N, Boscaro M. Development of overt Cushing's syndrome in patients with adrenal incidentaloma. *Eur J Endocrinol*. 2002;146(1):61-66.
7. **Bernini GP**, Moretti A, Oriandini C, Bardini M, Taurino C, Salvetti A. Long-term morphological and hormonal follow-up in a single unit on 115 patients with adrenal incidentalomas. *Br J Cancer*. 2005;92(6):1104-1109.
8. **Bondanelli M**, Campo M, Trasforini G, et al. Evaluation of hormonal function in a series of incidentally discovered adrenal masses. *Metabolism*. 1997;46(1):107-113.
9. **Caplan RH**, Strutt PJ, Wickus GG. Subclinical hormone secretion by incidentally discovered adrenal masses. *Arch Surg*. 1994;129(3):291-296.
10. **Cho YY**, Suh S, Joung JY, et al. Clinical characteristics and follow-up of Korean patients with adrenal incidentalomas. *Korean J Intern Med*. 2013;28(5):557-564.

11. **Chrisoulidou A**, Rakitzi P, Boudina M, et al. Patients with extra-adrenal malignancies and adrenal lesions have similar rates of subclinical hypercortisolism compared with patients with true adrenal incidentalomas. *Hormones (Athens)*. 2019;18(1):85-89.
12. **Comlekci A**, Yener S, Ertilav S, et al. Adrenal incidentaloma, clinical, metabolic, follow-up aspects: single centre experience. *Endocrine*. 2010;37(1):40-46.
13. **Cyranska-Chyrek E**, Szczepanek-Parulska E, Olejarz M, Ruchala M. Malignancy Risk and Hormonal Activity of Adrenal Incidentalomas in a Large Cohort of Patients from a Single Tertiary Reference Center. *Int J Environ Res Public Health*. 2019;16(10):1872.
14. **Dennedy MC**, Annamalai AK, Prankerd-Smith O, et al. Low DHEAS: A Sensitive and Specific Test for the Detection of Subclinical Hypercortisolism in Adrenal Incidentalomas. *J Clin Endocrinol Metab*. 2017;102(3):786-792.
15. **Falcetta P**, Orsolini F, Benelli E, et al. Clinical features, risk of mass enlargement, and development of endocrine hyperfunction in patients with adrenal incidentalomas: a long-term follow-up study. *Endocrine*. 2021;71(1):178-188.
16. **Fan CX**, Zhang JJ, Cai YY, et al. *Nan Fang Yi Ke Da Xue Xue Bao*. 2017;37(8):1054-1059.
17. **Flecchia D**, Mazza E, Carlini M, et al. Reduced serum levels of dehydroepiandrosterone sulphate in adrenal incidentalomas: a marker of adrenocortical tumour. *Clin Endocrinol (Oxf)*. 1995;42(2):129-134.
18. **Giordano R**, Marinazzo E, Berardelli R, et al. Long-term morphological, hormonal, and clinical follow-up in a single unit on 118 patients with adrenal incidentalomas. *Eur J Endocrinol*. 2010;162(4):779-785.
19. **Goh Z**, Phillips I, Hunt PJ, Soule S, Cawood TJ. Characteristics of adrenal incidentalomas in a New Zealand centre. *Intern Med J*. 2018;48(2):173-178.
20. **Hong AR**, Kim JH, Park KS, et al. Optimal follow-up strategies for adrenal incidentalomas: reappraisal of the 2016 ESE-ENSAT guidelines in real clinical practice. *Eur J Endocrinol*. 2017;177(6):475-483.
21. **Kastelan D**, Kraljevic I, Dusek T, et al. The clinical course of patients with adrenal incidentaloma: is it time to reconsider the current recommendations?. *Eur J Endocrinol*. 2015;173(2):275-282.
22. **Lamas C**, Palma M, Martín D, de Frutos VA, López M, Marco A. Incidentalomas suprarrenales: experiencia clínica en los hospitales de Castilla-La Mancha [Adrenal incidentalomas: clinical experience in the hospitals of Castilla-La Mancha (Spain)]. *Endocrinol Nutr*. 2009;56(8):392-399.
23. **Li L**, Yang G, Zhao L, et al. Baseline Demographic and Clinical Characteristics of Patients with Adrenal Incidentaloma from a Single Center in China: A Survey. *Int J Endocrinol*. 2017;2017:3093290.
24. **Libè R**, Dall'Asta C, Barbetta L, Baccarelli A, Beck-Peccoz P, Ambrosi B. Long-term follow-up study of patients with adrenal incidentalomas. *Eur J Endocrinol*. 2002;147(4):489-494.
25. **Mantero F**, Terzolo M, Arnaldi G, et al. A survey on adrenal incidentaloma in Italy. Study Group on Adrenal Tumors of the Italian Society of Endocrinology. *J Clin Endocrinol Metab*. 2000;85(2):637-644.
26. **Moraes AB**, de Paula MP, de Paula Paranhos-Neto F, et al. Bone Evaluation by High-Resolution Peripheral Quantitative Computed Tomography in Patients With Adrenal Incidentaloma. *J Clin Endocrinol Metab*. 2020;105(8):dgaa263.
27. **Nunes ML**, Vattaut S, Corcuff JB, et al. Late-night salivary cortisol for diagnosis of overt and subclinical Cushing's syndrome in hospitalized and ambulatory patients. *J Clin Endocrinol Metab*. 2009;94(2):456-462.
28. **Ohno Y**, Sone M, Taura D, et al. Evaluation of quantitative parameters for distinguishing pheochromocytoma from other adrenal tumors. *Hypertens Res*. 2018;41(3):165-175.

29. **Reincke M**, Nieke J, Krestin GP, Saeger W, Allolio B, Winkelmann W. Preclinical Cushing's syndrome in adrenal "incidentalomas": comparison with adrenal Cushing's syndrome. *J Clin Endocrinol Metab*. 1992;75(3):826-832.
30. **Šojat AS**, Dunjić-Kostić B, Marina LV, et al. Depression: another cortisol-related comorbidity in patients with adrenal incidentalomas and (possible) autonomous cortisol secretion [published online ahead of print, 2021 Feb 2]. *J Endocrinol Invest*. 2021;10.1007/s40618-021-01509-4.
31. **Stavropoulos K**, Imprialos KP, Katsiki N, et al. Primary aldosteronism in patients with adrenal incidentaloma: Is screening appropriate for everyone?. *J Clin Hypertens (Greenwich)*. 2018;20(5):942-948.
32. **Tabuchi Y**, Otsuki M, Kasayama S, et al. Clinical and endocrinological characteristics of adrenal incidentaloma in Osaka region, Japan. *Endocr J*. 2016;63(1):29-35.
33. **Theodoraki A**, Khoo B, Hamda A, et al. Outcomes in 125 individuals with adrenal incidentalomas from a single centre. a retrospective assessment of the 1 mg overnight and low dose dexamethasone suppression tests. *Horm Metab Res*. 2011;43(13):962-969.
34. **Valli N**, Catargi B, Ronci N, et al. Biochemical screening for subclinical cortisol-secreting adenomas amongst adrenal incidentalomas. *Eur J Endocrinol*. 2001;144(4):401-408.
35. **Yeomans H**, Calissendorff J, Volpe C, Falhammar H, Mannheimer B. Limited value of long-term biochemical follow-up in patients with adrenal incidentalomas-a retrospective cohort study. *BMC Endocr Disord*. 2015;15:6.
36. **Yilmaz N**, Avsar E, Tazegul G, Sari R, Altunbas H, Balci MK. Clinical Characteristics and Follow-Up Results of Adrenal Incidentaloma [published online ahead of print, 2020 Jan 20]. *Exp Clin Endocrinol Diabetes*. 2020;10.1055/a-1079-4915.

Profile 1	Profile 2	Profile 3
Abe I., 2018	Bondanelli M., 1997	Ahn S.H., 2018
Akkuş G., 2017	Kastelan D., 2015	Barzon L., 2002
Anagnostis P., 2010	Ohno Y., 2018	Bernini G.P., 2005
Aoe M., 2020	Tabuchi Y., 2016	Caplan R.H., 1994
Cho Y.Y., 2013		Chrisoulidou A., 2019
Comlekci A., 2010		Flecchia D., 1995
Cyranska-Chyrek E., 2019		Libè R., 2002
Dennedy M.C., 2017		Mantero F., 2000
Falcetta P., 2021		Reincke M., 1992
Fan C.X., 2017		Valli N., 2001
Giordano R., 2010		
Goh Z., 2018		
Hong A.R., 2017		
Lamas C., 2009		
Li L., 2017		
Moraes A.B., 2020		
Nunes M.L., 2009		
Šojat A.S., 2021		
Theodoraki A., 2011		
Yeomans H., 2015		
Yilmaz N., 2020		

Table S1. Criteria adopted to diagnose autonomous cortisol secretion (ACS). Three different hormonal profiles were used to describe ACS associated with adrenal incidentalomas. **Profile 1**: serum cortisol >50 nmol/L (>1.8 μg/dL) after 1, 2 or 8 mg overnight dexamethasone suppression tests, or 2-day low-dose dexamethasone test, and one of the following additional endocrine alterations: increased 24-h urinary-free cortisol (UFC), low plasma ACTH, elevated midnight serum or salivary cortisol. **Profile 2**: serum cortisol >83 nmol/L (>3.0 μg/ dL) after 1 mg overnight dexamethasone test and one additional endocrine alteration (same as above). **Profile 3**: cortisol >138 nmol/L (>5μg/dL) after 1 mg overnight dexamethasone test as sole criterion. In case one study did not fit completely with the profiles described, yet specific criteria were used to diagnose autonomous cortisol secretion, the study was included in the analysis.

Characteristics	
Total number of studies	36
Total number of patients	13,763
Age (years) (studies)	58 [56 – 62] (33)
Female gender (n%) (studies)	58.4% (34)
BMI (kg/m^2) (studies)	28.5 [26.1 – 28.9] (11)
SBP (mmHg) (studies)	128 [126 – 132] (6)
DBP (mmHg) (studies)	80 [78 – 80] (6)
Prevalence of hypertension (n%) (studies)	54.3% (26)
Prevalence of diabetes (%) (studies)	19.3% (18)
Nodule size (mm) (studies)	25.0 [21.0 – 28.1] (29)
Location of the tumor	
Left (n%) (studies)	48.7% (19)
Right (n%) (studies)	37.3% (20)
Bilateral (n%) (studies)	17.0% (30)

Table S2. Clinical and biochemical parameters of the included patients. Data are expressed as median [IQR]. In round brackets the number of studies in which the datum is available. BMI = body mass index; SBP = systolic blood pressure; DBP = diastolic blood pressure.

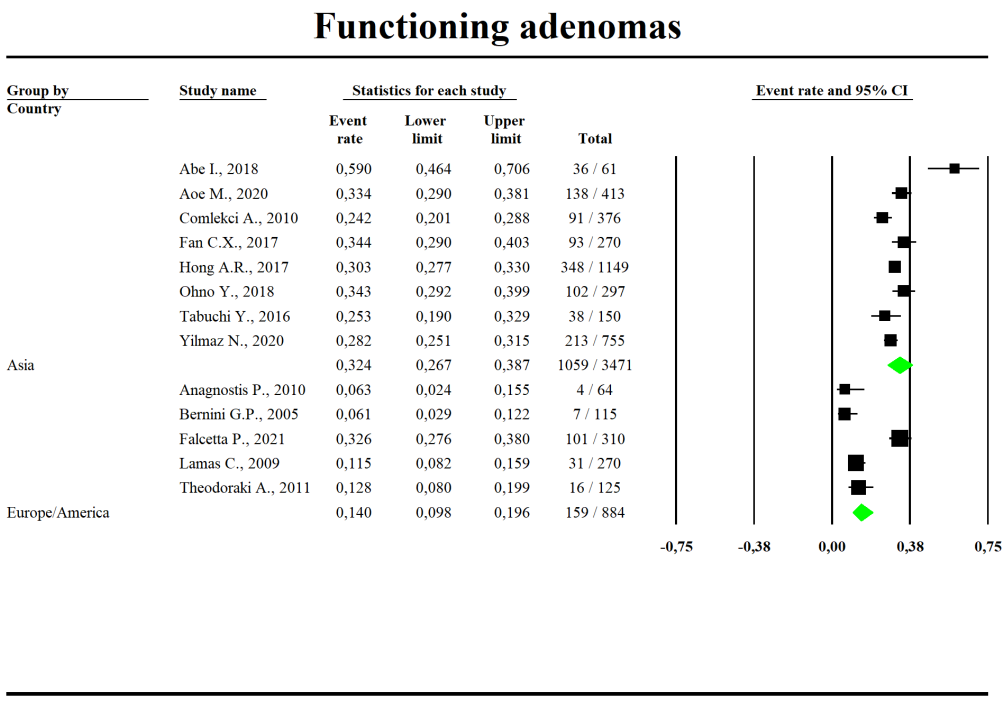

Figure S1. Forest plot of the subgroup analysis of the prevalence of secreting tumours, according to the geographical area. Central squares of each horizontal line represent the prevalence for each study. The area of each square is proportional to that study's weight in the analysis. Horizontal lines indicate the 95% confidence interval. Subgroup Asia: Q-value 37.24, df(Q)=7, p-value <0.001; I^2=81.21; τ^2=0.052. Subgroup Europe/America: Q-value 63.62, df(Q)=4, p-value<0.001; I^2=93.71; τ^2=0.82.

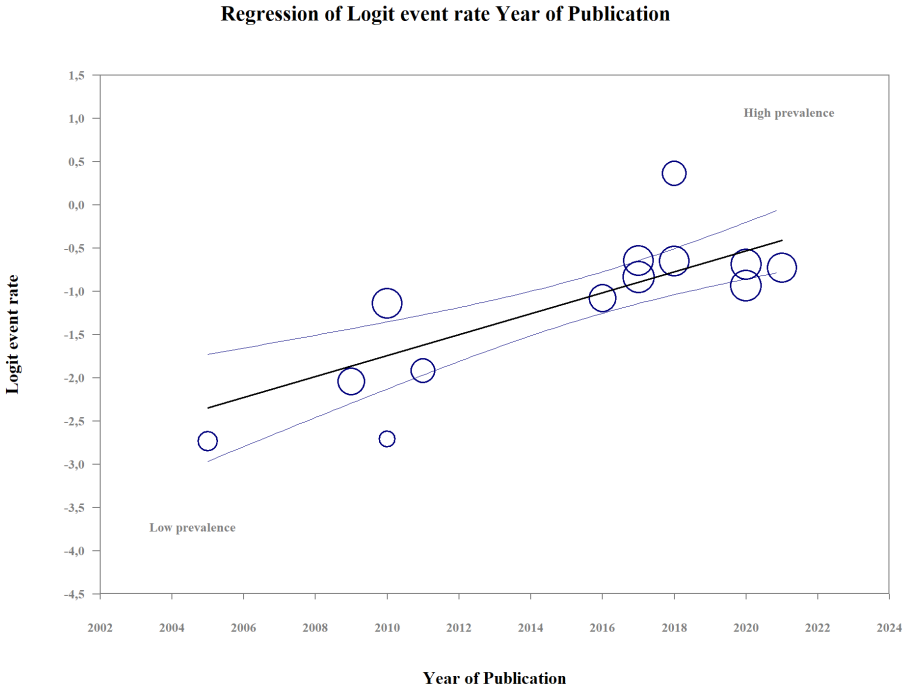

Figure S2. Meta-regression analysis for the publication year on the prevalence of functioning adenomas. The analysis showed that the covariates had a statically significant impact on the results: coefficient 0.121 [0.079; 0.164], p < 0.001.

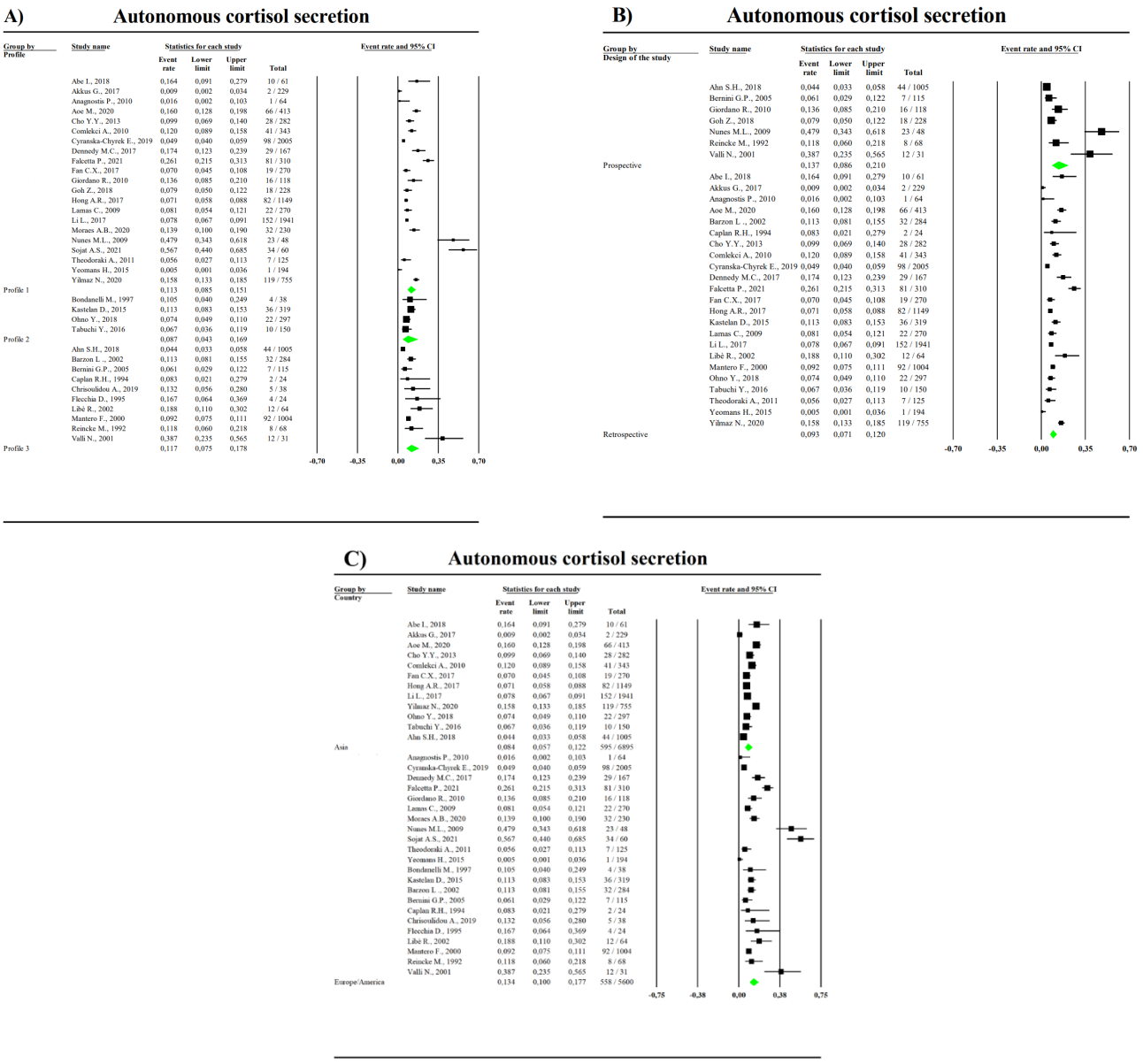

Figure S3. Forest plot of the subgroup analysis of the prevalence of autonomous cortisol secretion in patients with adrenal incidentaloma, comparing studies according to the cut-off of cortisol post-dexamethasone suppression test used **(A)** to their either retrospective or prospective design **(B)** and to the geographical area where they were conducted **(C).** The only study performed in New Zealand (Goh Z., 2018) was excluded from the last analysis. **(A)** Subgroup Profile 1: Q=384.71, df(Q)=20, p-value <0.001; I^2=94.80; τ^2=0.54. Subgroup Profile 2: Q=4.01, df(Q)=3, p-value=0.26; I^2=25.19; τ^2=0.024. Subgroup Profile 3: Q=63.29, df(Q)=9, p-value <0.001; I^2=85.78; τ^2=0.38. **(B)** Subgroup Prospective: Q=113.70, df(Q)=6, p-value <0.001; I^2=94.72; τ^2=1.32. Subgroup Retrospective: Q=256.28, df(Q)=22, p-value <0.001; I^2=91.42; τ^2=0.30. **(C)** Subgroup Asia: Q=118.37 df(Q)=11, p-value <0.001; I^2=90.71; τ^2=0.24. Subgroup Europe/America: Q=323.56, df(Q)=21, p-value < 0.001; I^2=93.51; τ^2=0.74.

Central squares of each horizontal line represent the prevalence for each study. The area of each square is proportional to that study's weight in the analysis. Horizontal lines indicate the 95% confidence interval.

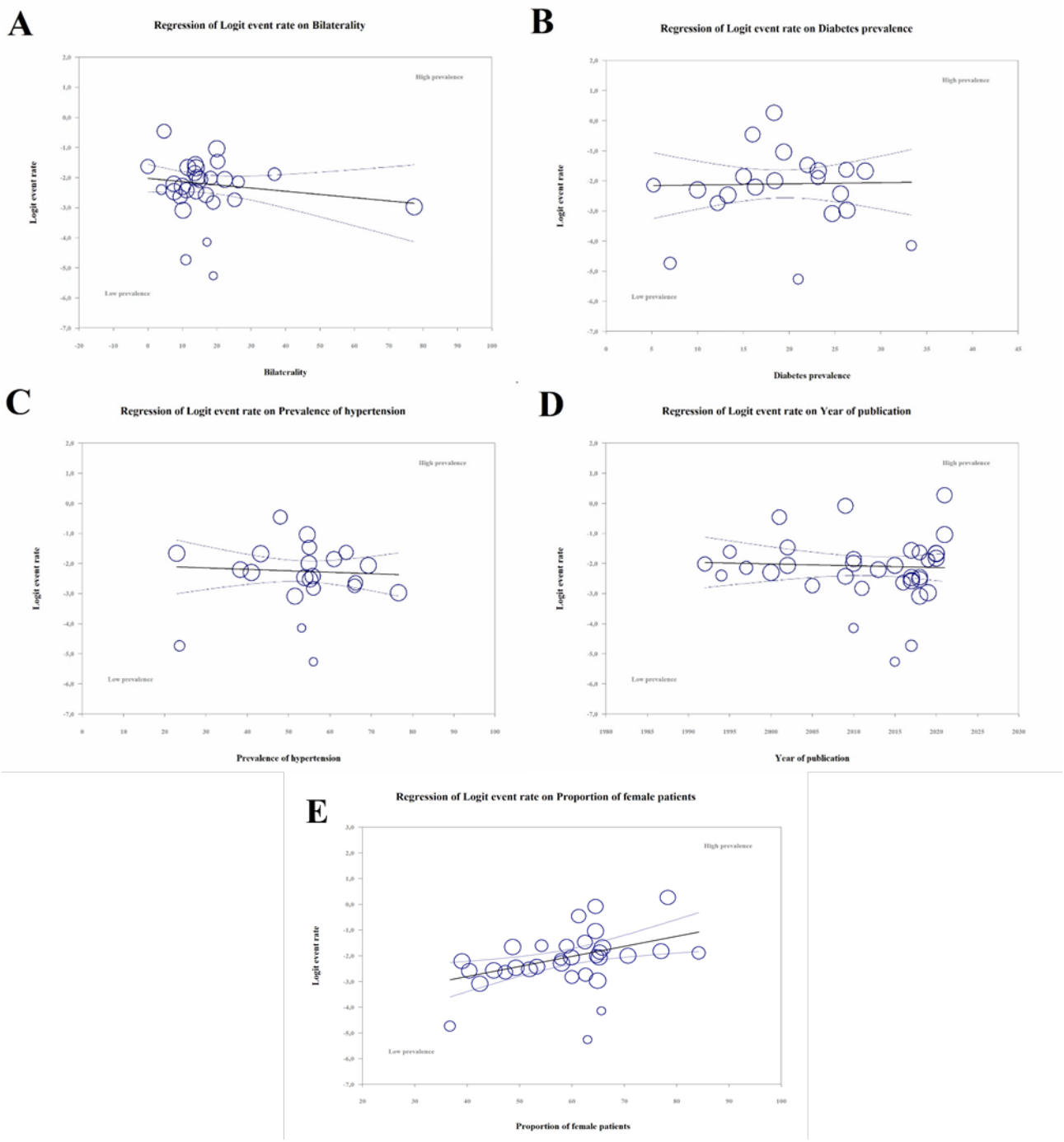

Figure S4. Meta-regression analysis for the proportion of bilateral nodules **(A)**, the proportion of diabetes **(B)** and of hypertension **(C)** the year of publication **(D)** and the proportion of female patients **(E)** on the prevalence of autonomous cortisol secretion in patients with adrenal incidentaloma. The analysis showed that the covariates A-D did not impact significantly on the results: **A)** coefficient -0.009 [-0.026; 0.007], p = 0.256; **B)** coefficient 0.004 [-0.052; 0.060, p = 0.891; **C)** coefficient -0.005 [-0.026; 0.015], p = 0.611; **D)** coefficient -0.006 [-0.037; 0.025], p = 0.706; while the proportion of female patients (E) had a significant impact on the results: **E)** coefficient 0.039 [0.017; 0.061], p = <0.001

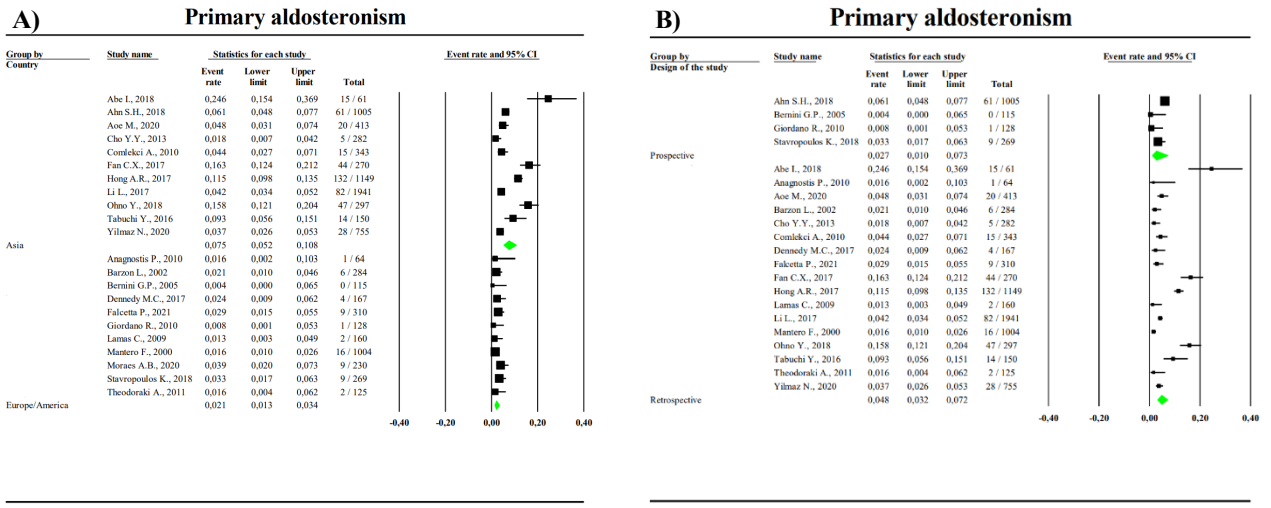

Figure S5. Forest plot of the subgroup analysis of the prevalence of primary aldosteronism in patients with adrenal incidentaloma, comparing studies according to the geographical area where they were conducted **(A)** and to their either retrospective or prospective design **(B).** Central squares of each horizontal line represent the prevalence for each study. **(A)** Subgroup Asia: Q=168.90, df(Q)=10, p-value <0.001; I^2=94.08; τ^2=0.451. Subgroup Europe/America: Q=10.44; df(Q)=10, p-value 0.40; I^2=4.25; τ^2=0.01 **(B)** Subgroup Prospective: Q=10.26, df(Q)=3, p-value 0.016; I^2=70.78; τ^2=0.41. Subgroup Retrospective: Q=248.46, df(Q)=16, p-value <0.001; I^2=93.56; τ^2=0.69.
The area of each square is proportional to that study's weight in the analysis. Horizontal lines indicate the 95% confidence interval.

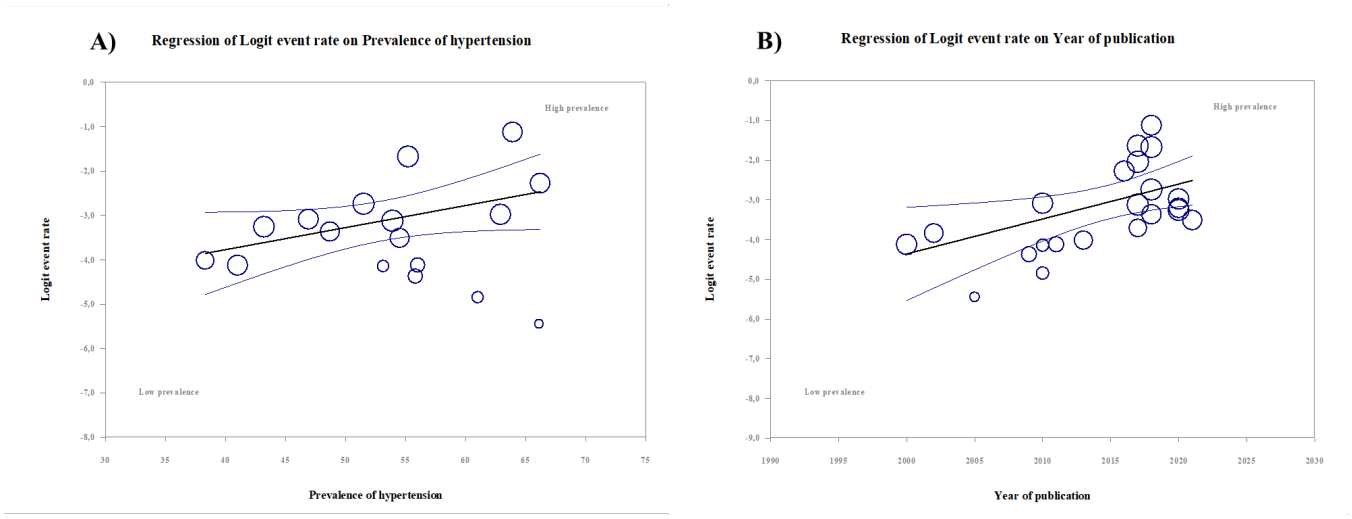

Figure S6. Meta-regression analysis for the proportion of hypertension **(A)** and the year of publication **(B)** on the prevalence of primary aldosteronism in patients with adrenal incidentaloma. The analysis showed that the factors have a significant impact on the results: A) coefficient 0.050 [0.006; 0.094], p = 0.027; B) coefficient 0.088 [0.029; 0.147], p = 0.003.

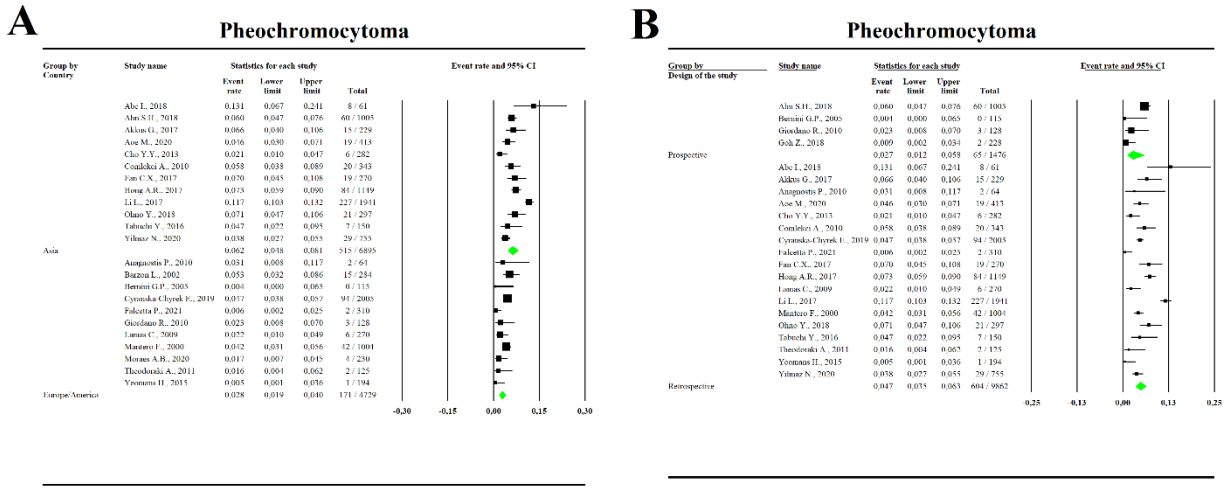

Figure S7. Forest plot of the subgroup analysis of the prevalence of pheochromocytoma in patients with adrenal incidentaloma, comparing studies according to the geographical area where they were conducted **(A)** and to their either retrospective or prospective design **(B).** The only study performed in New Zealand (Goh Z., 2018) was excluded from the first analysis.
(A) Subgroup Asia: Q=84.06, df(Q)=11, p-value <0.001; I^2=86.91; τ^2=0.20. Subgroup Europe/America: Q=25.24, df(Q)=10, p-value 0.005; I^2=60.39; τ^2=0.15. **(B)** Subgroup Prospective: Q=13.00, df(Q)=3, p-value 0.005; I^2=76.93; τ^2=0.99. Subgroup Retrospective: Q=155.03, df(Q)=17, p-value <0.001; I^2=89.03; τ^2=0.31.
Central squares of each horizontal line represent the prevalence for each study. The area of each square is proportional to that study's weight in the analysis. Horizontal lines indicate the 95% confidence interval.

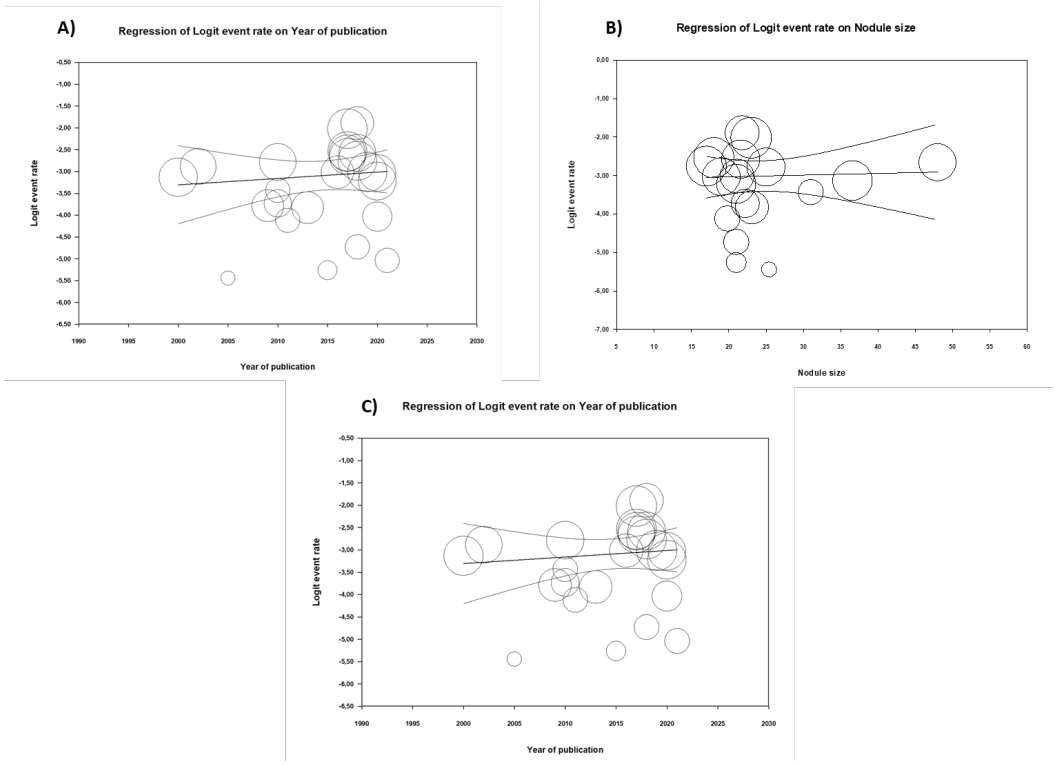

Figure S8. Meta-regression analysis for the proportion of hypertension **(A)**, the mean nodule size **(B)** and **(C)** the year of publication on the prevalence of pheochromocytoma in patients with adrenal incidentaloma. The analysis showed that the covariates did not impact significantly on the results: **(A)** coefficient -0,0003 [-0.028; 0.028], p = 0.986; **(B)** coefficient 0.004 [-0.036; 0.044], p = 0.832; **(C)** coefficient 0.015 [-0.031; 0.060], p = 0.531.

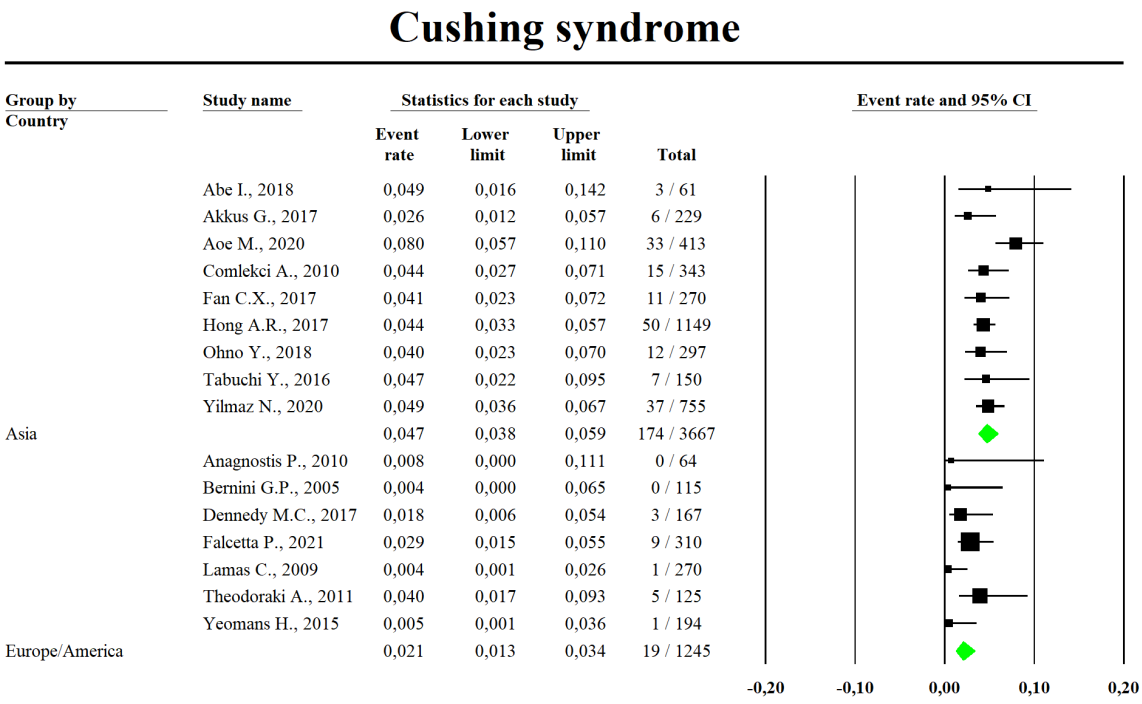

Figure S9. Forest plot of the subgroup analysis of the prevalence of Cushing syndrome in patients with adrenal incidentaloma, comparing studies according to the geographical area where they were conducted. The only study performed in New Zealand (Goh Z., 2018) was excluded from the analysis. Central squares of each horizontal line represent the prevalence for each study. Subgroup Asia: Q=12.57, df(Q)=8, p-value 0.128 ; I^2=36.34; τ^2=0.03. Subgroup Europe/America: Q=9.94, df(Q)=6, p-value 0.127; I^2=39.66; τ^2=0.29
The area of each square is proportional to that study's weight in the analysis. Horizontal lines indicate the 95% confidence interval.

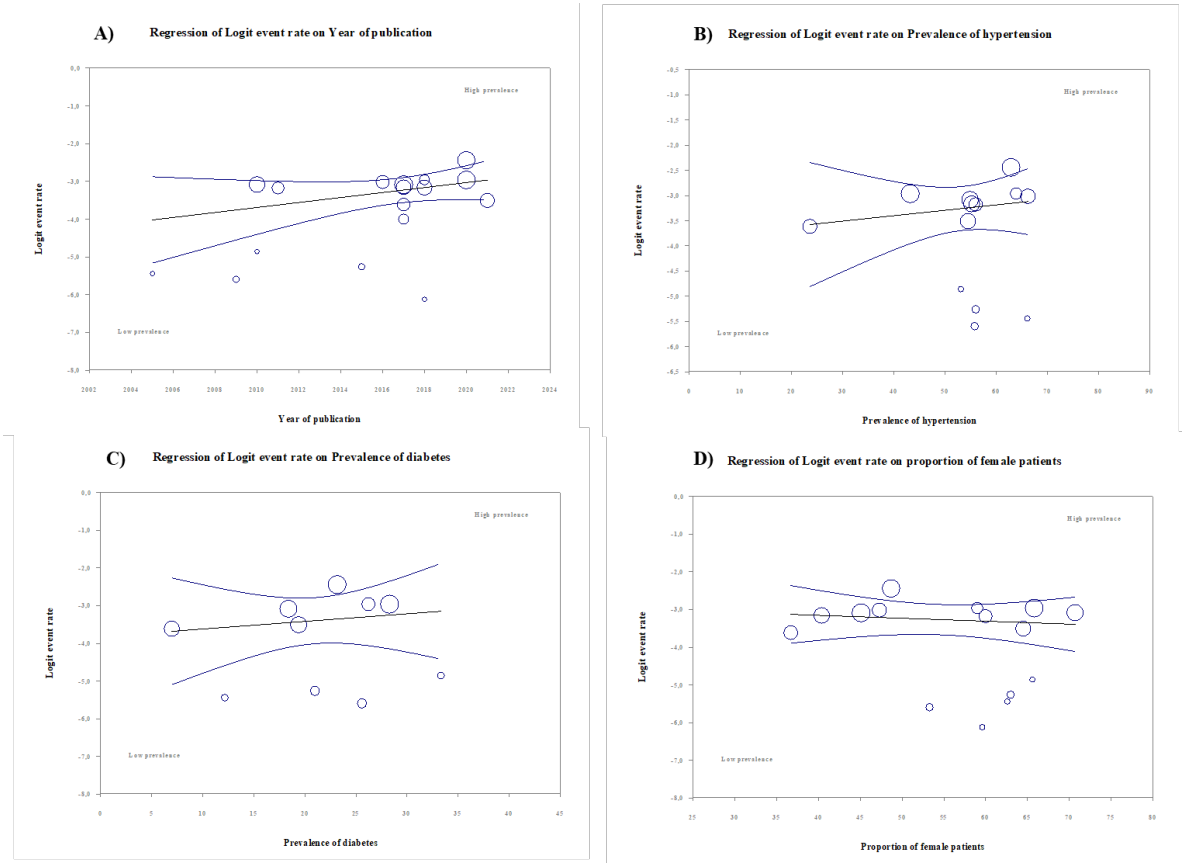

Figure S10. Meta-regression analysis for the year of study publication **(A)**, the proportion of hypertension **(B)** and of diabetes **(C)** and the proportion of female patients **(D)** on the prevalence of Cushing syndrome in patients with adrenal incidentaloma. The analysis showed that the covariates did not impact significantly on the results (**A)** coefficient 0.066 [-0.009; 0.141], p = 0.083; **(B)** coefficient 0.011 [-0.020; 0.042], p = 0.496; **(C)** coefficient 0.020 [-0.053; 0.093], p = 0.586; **(D)** coefficient -0.008 [-0.037; 0.022], p = 0.605.

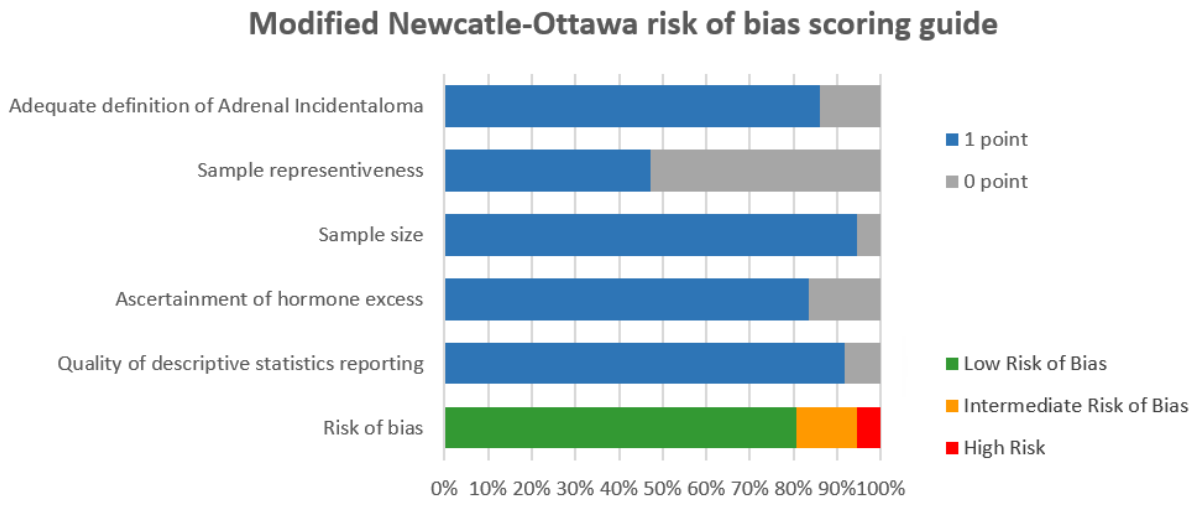

Figure S11. Qualitative evaluation of studies and risk of bias using modified Newcastle-Ottawa risk of bias scoring.

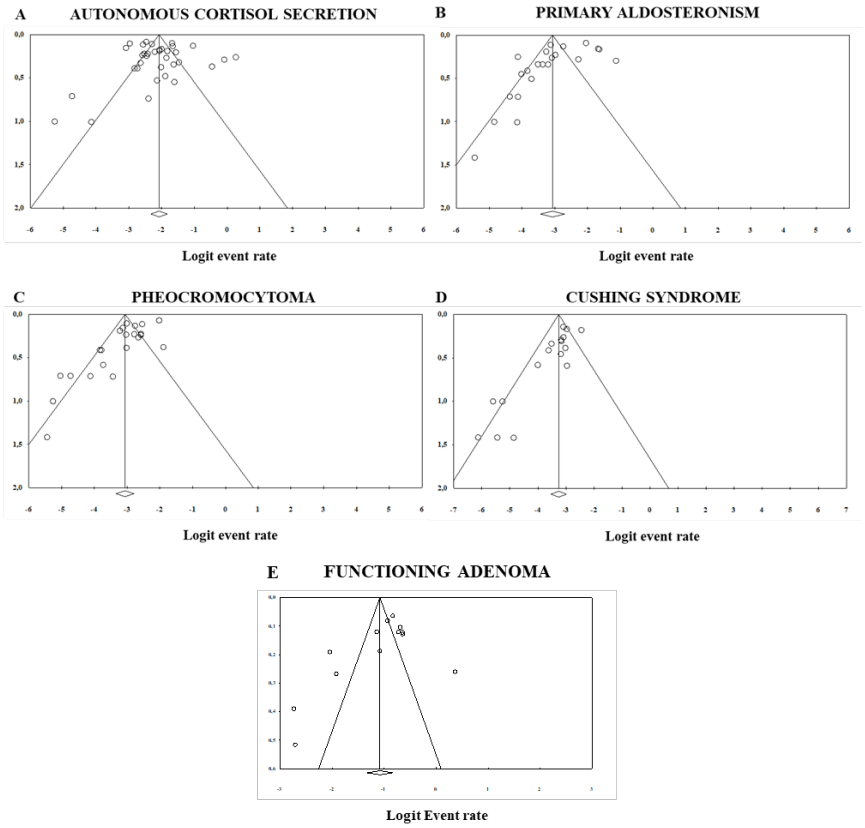

Figure S12. Assessment of potential bias secondary to small study effects by funnel plot for autonomous cortisol secretion **(A)**, primary aldosteronism **(B)**, pheochromocytoma **(C)** and Cushing syndrome **(D)** and functioning adenomas **(E).**