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: 1752

Ovid MEDLINE search

#1 incidentaloma* Results: 2326
#2 exp hyperaldosteronism Results: 9401
#3 exp pheochromocytoma Results: 15494
#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 200 participants

0 points: sample size was less than 200 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.

Study	Biochemical tests	Profile
Abe I., 2018	Serum cortisol after 1 mg DST >50 nmol/L (or 1.8 µg/dL) and at least one of the following: 1. ACTH level <10 pg/mL 2. Loss of diurnal serum cortisol rhythm 3. Low serum DHEA-S level (with respect to the patient's age and sex)	1
Ahn S.H., 2018*	At least two abnormalities among: 1. Lack of suppression in the 1 mg DST (cortisol >138 nmol/L) 2. UFC levels higher than the upper normal limit 3. ACTH levels <10 pg/mL	3
Akkuş G., 2017	Serum cortisol after 1 mg DST >50 nmol/L (or 1.8 µg/dL) and at least one of the following: 1. 24-h UFC levels >300 µg/d in 2 of the 3 consecutive collections 2. ACTH values <10 pg/mL 3. Decreased DHEAS levels	1
Anagnostis P., 2010*	Serum cortisol >1.8 µg/dL or urinary cortisol <20 µg/24h, after 1 mg DST and at least one of the following: 1. UFC >120 µg/d 2. Loss of diurnal rhythm of cortisol (levels at 8 p.m. <25% of those at 8 a.m. in normal subjects)	1
Aoe M., 2020*	Serum cortisol after 1 mg DST >50 nmol/L	1
Barzon L., 2002	Serum cortisol after 1 mg DST >138 nmol/L (>5µg/dL) and at least of the following: 1. Abnormal plasma cortisol rhythm 2. Urinary cortisol 3. Plasma ACTH	3
Bernini G.P., 2005	Serum cortisol after 1 mg DST >138 nmol/L (>5µg/dL)	3
Bondanelli M., 1997*	Serum cortisol after 1 mg DST >0.09 µmol/L, followed by high-dose DST with 8 mg/d for 2 days	2
Caplan R.H., 1994	Serum cortisol after 1 mg DST >138 nmol/L (>5µg/dL)	3
Cho Y.Y., 2013*	Serum cortisol after 1 mg DST >2.0 µg/dL	1
Chrisoulidou A., 2019	Serum cortisol after 1 mg DST >138 nmol/L (>5µg/dL) followed by a 2-day LDDST (0.5 mg of dexamethasone every 6 h for 48 h) and 24-h UFC	3
Comlekci A., 2010	Serum cortisol after 1 mg DST >50 nmol/L (or 1.8 µg/dL) and at least one of the following: 1. ACTH <5 pg/mL 2. UFC >110 µg/d 3. Midnight cortisol >7.5 µg/dL	1
Cyranska-Chyrek E., 2019*	1. ACTH suppression <7.20 pg/mL 2. Disturbed circadian rhythm of cortisol secretion (lack of decrease in cortisol level by at least 50% at 6 p.m. in comparison to 8 a.m.) 3. Increased 24 h urinary cortisol excretion (by at least two times above upper normal limit)	1

	4. Lack of cortisol suppression during 1 mg dexamethasone test (cortisol level at 8 a.m. >50 nmol/L) Patients were diagnosed with "possible autonomous cortisol secretion" if at least three out of four mentioned features were present and with "autonomous cortisol secretion" if all four features mentioned above were present.	
Dennedy M.C., 2017*	At least 2 of the following: 1. Failure to suppress serum cortisol after DST <1.8 µg/dL 2. Sleeping midnight serum cortisol >1.8 µg/dL 3. Awake midnight serum cortisol >7.5 µg/dL 4. Raised UFC	1
Falcetta P., 2021	Post-DST cortisol level >5 µg/dl (autonomous cortisol secretion) or >1.8 and ≤5 µg/dl (possible cortisol secretion) combined with an abnormal result in a least one of the following: 1. UFC values ≥405 µg/24h (1117.8 mmol/24h) 2. Absence of cortisol rhythm (midnight serum cortisol >7.5 µg/dL (220 nmol/L) 3. ACTH levels <10 pg/mL (2.2 pmol/L) 4. Post-LDDST (dexamethasone 0.5mg p.o. every 6h for 2 days) cortisol level >1.8 µg/dL (50 nmol/L)	1
Fan C.X., 2017	Serum cortisol after 1 mg DST or LDDST >50 nmol/L (or 1.8 µg/dL) and at least one of the following: 1. 24h-UFC 2. Abnormal serum cortisol rhythm	1
Flecchia D., 1995	Serum cortisol after 1 mg DST >138 nmol/L (>5µg/dL)	3
Giordano R., 2010	Serum cortisol after 1 mg DST >50 nmol/L (or 1.8 µg/dL) and at least one of the following: 1. Post-LDDST cortisol levels >1.8 mg/dl (50 nmol/l) 2. Absence of cortisol rhythm (midnight serum cortisol >7.5 mg/dl (220 nmol/L)) 3. Low ACTH levels (<5 pg/ml (1.1 pmol/l)) 4. High UFC (>100 mg/24 h (275 mmol/24 h)),	1
Goh Z., 2018*	If the 24h UFC (n.v. 100–400 nmol) was elevated, a 1 mg DST (reference range < 50 nmol/L) was performed. At least two biochemical abnormalities of the hypothalamic–pituitary–adrenal axis were required for the diagnosis (not specified).	1
Hong A.R., 2017*	Serum cortisol after 1 mg DST >50 nmol/L (or 1.8 µg/dL)	1
Kastelan D., 2015	Serum cortisol after 1 mg DST >83 nmol/L (>3.0 µg/dL) and at least one of the following: 1. 24h-UFC >379 nmol/d 2. Plasma ACTH <2.2 pmol/L	2
Lamas C., 2009*	At least two of the following: 1. Serum cortisol after 1 mg DST >50 nmol/L (or 1.8 µg/dL) 2. Absence of cortisol rhythm (midnight serum cortisol >7.5 mg/dL) 3. Raised UFC 4. ACTH <10 pg/mL	1

Li L., 2017*	Serum cortisol after 1 mg DST >50 nmol/L (or 1.8 µg/dL), confirmed by post-LDDST (4 mg/48 h) cortisol levels ≥ 50 nmol/L	1
Libè R., 2002*	At least two of the following criteria: 1. Inadequate cortisol inhibition after 1 mg DST (cortisol >138 nmol/L) 2. High or high–normal UFC excretion (≥ 275nmol/24 h) 3. Low or low–normal plasma ACTH levels (<0.7 pmol/l) 4. Blunted ACTH increase after CRH test (<4.4 pmol/l) 5. Lack of cortisol suppression after opioid agonist loperamide administration (≥138nmol/l).	3
Mantero F., 2000*	Two or more basal or dynamic tests of the HPA axis function abnormal: 1. UFC 2. Plasma ACTH 3. Serum DHEA-S 4. Serum 17-OHP 5. Serum cortisol at night 6. Serum cortisol after 1 mg DST >138 nmol/L (>5µg/dL) 7. 100-mg CRH test 8. 250-mg ACTH test	3
Moraes A.B., 2020*	Serum cortisol after 1 mg DST between 1.9-5.0 µg/dL	1
Nunes M.L., 2009	Serum cortisol after 1 mg DST >60 nmol/L and at least of the following: 1. Low 8-h plasma ACTH (<2.2 pmol/L) 2. Disruption of plasma cortisol circadian rhythm (0 h/8 h serum cortisol ratio >0.5)	1
Ohno Y., 2018*	Serum cortisol after 1 mg and 8 mg DST >83 nmol/L (>3.0 µg/dL)	2
Reincke M., 1992	Failure to suppress serum cortisol below 140 nmol/L after 1 mg DST plus serum cortisol levels repeatedly not suppressible below 90 nmol/L (3 µg/dL) by low dose and high dose DST	3
Šojat A.S., 2021*	Post-DST cortisol level >138 nmol/L (autonomous cortisol secretion) or between 51–138 nmol/L (possible cortisol secretion)	1
Tabuchi Y., 2016	Serum cortisol after 1 mg DST >3.0 µg/dL and after 8 mg DST >1.0 µg/dL and at least of the following: 1. Plasma ACTH <10 pg/mL 2. Decreased ACTH response after CRH stimulation 3. Loss of diurnal cortisol rhythm 4. Decreased DHEA-S levels	2
Theodoraki A., 2011	Serum cortisol after 1 mg DST or 2 mg LDDST >50 nmol/L (or 1.8 µg/dL) and at least of the following: 1. ACTH <10 ng/L 2. Midnight serum cortisol >50 nmol/L (when individual asleep)	1
Valli N., 2001*	At least one of the following criteria: 1. Abnormal serum cortisol rhythm (normal range 200 – 700 nmol/l) 2. Low plasma ACTH (normal range 2 – 14 pmol/l) 3. DHEAS >1 mmol/L (for subjects younger than 60 years) and >0.5 mmol/L (for subjects older than 60 years)	3

	4. 17-OHP (normal range 1.8-6.2 nmol/L in males and 0.5-2.6 nmol/L in postmenopausal females or during the follicular phase) 5. Midnight serum cortisol concentration >228 nmol/L 6. High 24h-UFC (normal range 20 – 100 mg/24h) 7. Determination of the diurnal variation in serum cortisol concentration by the ratio of the mean of 4 measurements at 30-min intervals 8. Serum cortisol after 1 mg DST >138 nmol/L 9. Measurement of serum cortisol during an i.v. 4 mg DST (normal range <27 – 66 nmol/l)	
Yeomans H., 2015*	A cortisol hypersecretion was defined as any two of the following tests being abnormal: 1. Serum cortisol post 1 mg DST >50 nmol/L 2. 24-hour urine collection of cortisol (normal range 40 nmol/d–170 nmol/24 h) 3. Morning plasma ACTH <2 pmol/L 4. Circadian rhythm of serum cortisol (normal when midnight cortisol value <50 nmol/L)	1
Yilmaz N., 2020	Patients with ACTH levels <10 pg/mL and cortisol level after 1 mg DST >1.8 µg/dL, plus one more positive test result: 1. High cortisol level after 2 days-2 mg DST 2. High 24-hour UFC level (above reference value) 3. Low DHEA-S 4. High late night salivary cortisol >0.27 µg/dL or midnight serum cortisol level >7.5 µg/dL	1

Table S1. Criteria adopted in each study to diagnose autonomous /possible autonomous cortisol secretion. In subgroup analysis, three different hormonal profiles were used to classify autonomous/possible autonomous cortisol secretion 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. *Studies in which the criteria used to define the profiles were partially modified and the diagnosis was supported by additional biochemical tests.

Study ID	ARR cut-off for PA diagnosis (with aldosterone in ng/dL and plasma renin activity in ng/mL/h)
Abe I., 2018	> 20
Ahn S.H., 2018	> 30
Anagnostis P., 2010	> 30
Aoe M., 2020	> 20
Barzon L., 2002	> 40 (Authors' personal communication)
Bernini G.P., 2005	> 70
Cho Y.Y., 2013	> 30
Comlekci A., 2010	> 25
Dennedy M.C., 2017	The specific cut-off was not indicated. The authors adopted Endocrine Society guidelines for the diagnosis of PA, using locally-derived thresholds for screening with ARR
Falcetta P., 2021	> 30 (3.7 with DRC in mU/L)
Fan C.X., 2017	> 30
Giordano R., 2010	Not specified. According with Rossi GP, Pessina AC & Heagerty AM. Primary aldosteronism: an update on screening, diagnosis and treatment. Journal of Hypertension 2008
Hong A.R., 2017	> 30
Lamas C., 2009	> 20
Li L., 2017	> 20
Mantero F., 2000	> 40
Moraes A.B., 2020	> 30
Ohno Y., 2018	> 20
Stavropoulos K., 2018	> 30
Tabuchi Y., 2016	> 20
Theodoraki A., 2011	> 30
Yilmaz N., 2020	> 20

Table S2. Cut-offs adopted to define a positive aldosterone-to-renin ratio (ARR) in patients with suspected primary aldosteronism.

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 S3. 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.

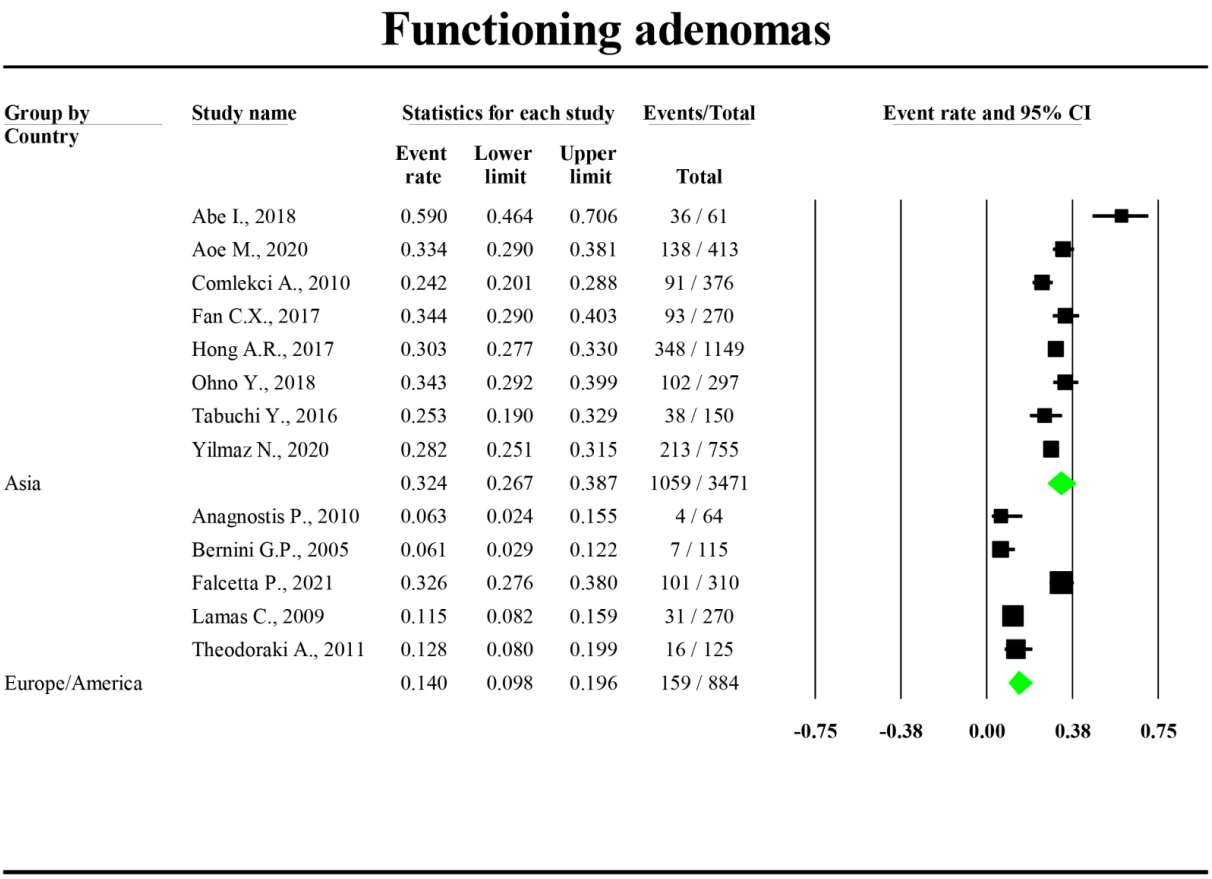


Figure S1. Forest plot of the subgroup analysis of the prevalence of secreting tumours, according to the geographical area. Central squares of each horizontal line represent the prevalence for each study. The area of each square is proportional to that study's weight in the analysis. Horizontal lines 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.

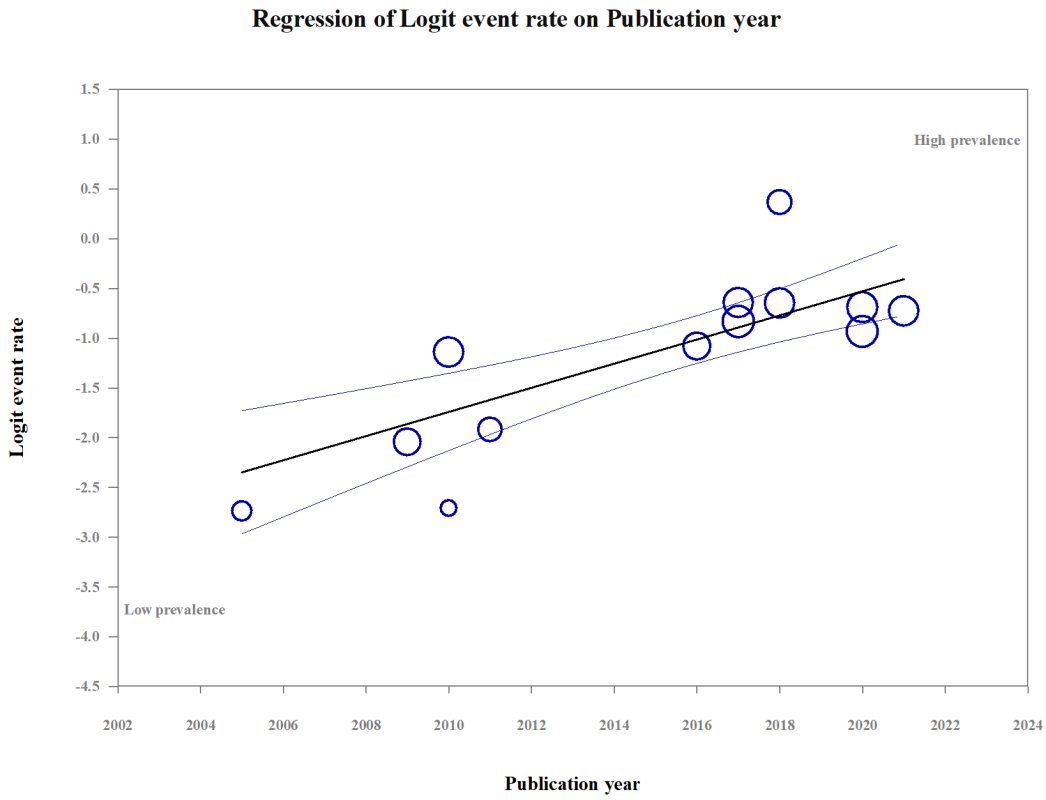
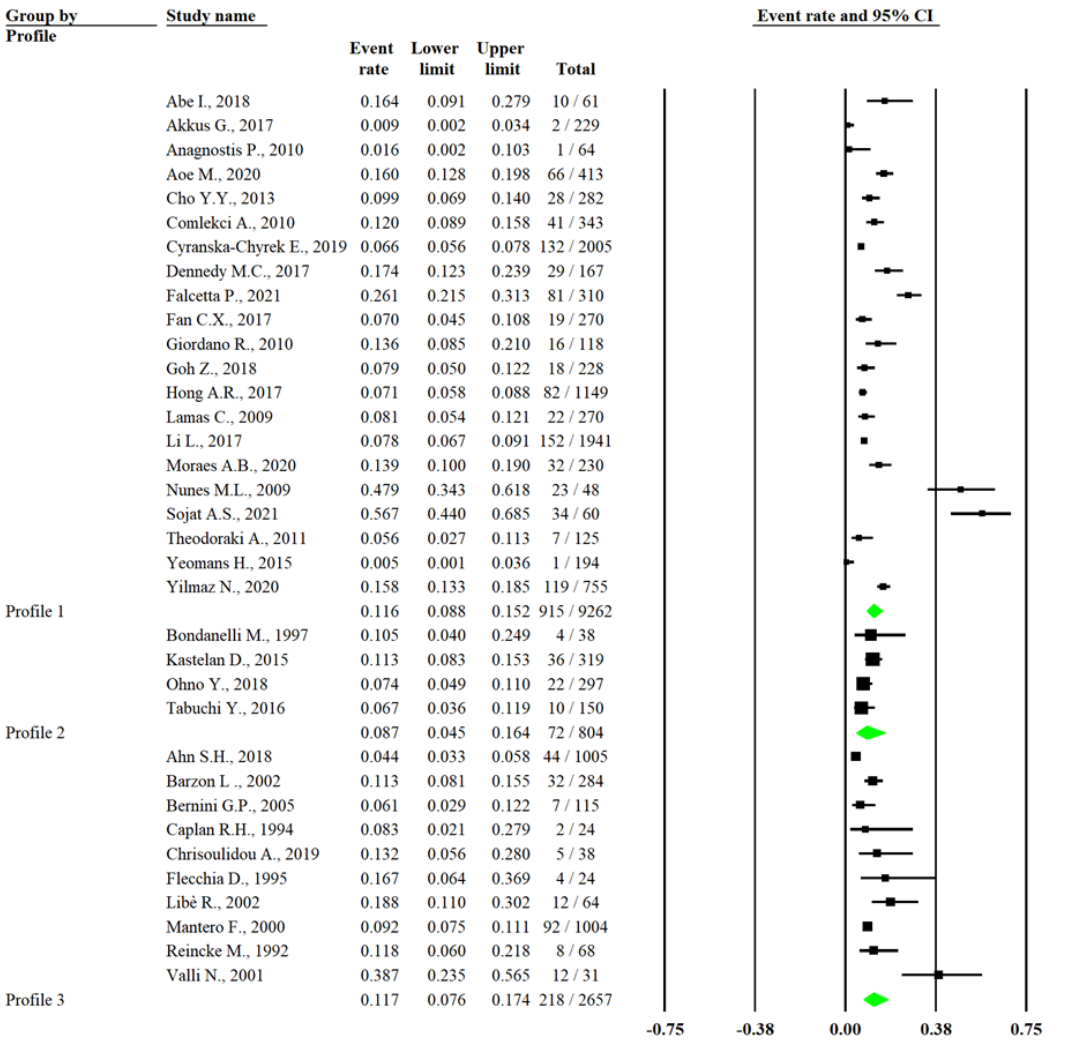


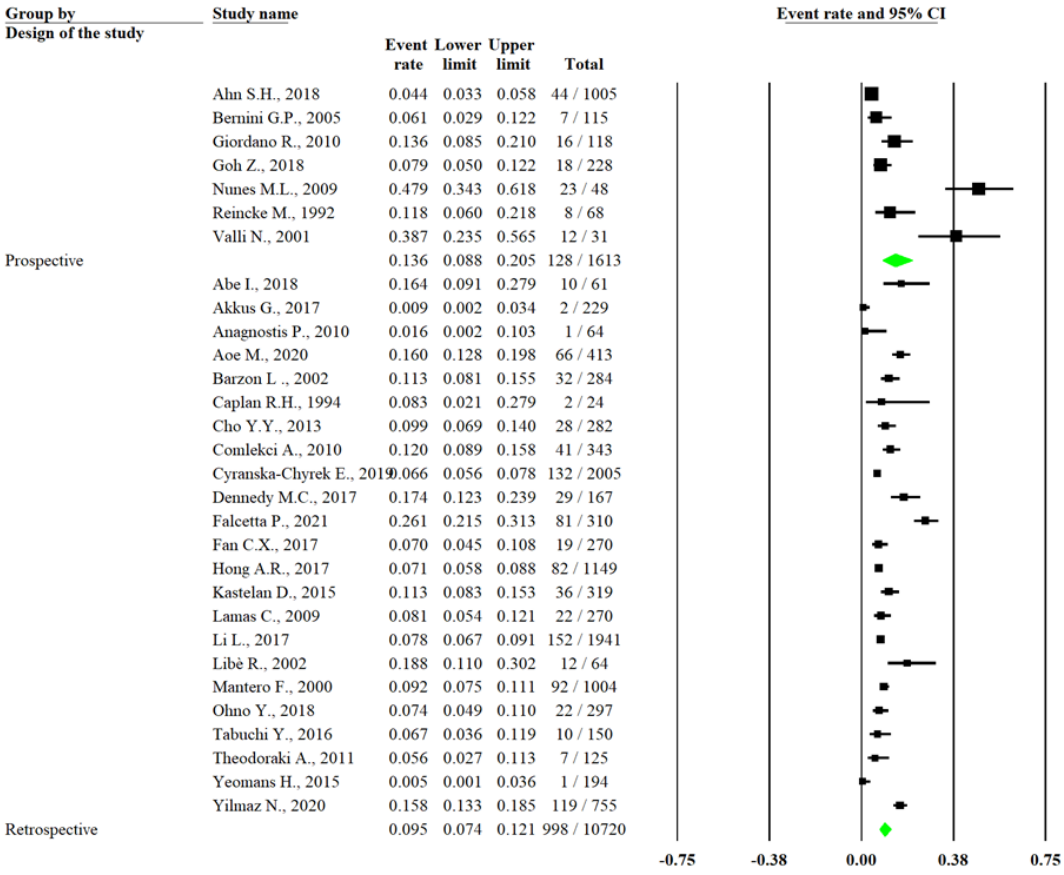
Figure S2. Meta-regression analysis for the publication year on the prevalence of functioning adenomas. The analysis showed that the covariates had a statically significant impact on the results: coefficient 0.121 [0.079; 0.164], $p < 0.001$.

A) **Possible autonomous cortisol secretion / Autonomous cortisol secretion**



Group by Profile	Study name	Event rate	Lower limit	Upper limit	Total
	Abe I., 2018	0.164	0.091	0.279	10 / 61
	Akkus G., 2017	0.009	0.002	0.034	2 / 229
	Anagnostis P., 2010	0.016	0.002	0.103	1 / 64
	Aoe M., 2020	0.160	0.128	0.198	66 / 413
	Cho Y.Y., 2013	0.099	0.069	0.140	28 / 282
	Comlekci A., 2010	0.120	0.089	0.158	41 / 343
	Cyranska-Chyrek E., 2019	0.066	0.056	0.078	132 / 2005
	Dennedy M.C., 2017	0.174	0.123	0.239	29 / 167
	Falcetta P., 2021	0.261	0.215	0.313	81 / 310
	Fan C.X., 2017	0.070	0.045	0.108	19 / 270
	Giordano R., 2010	0.136	0.085	0.210	16 / 118
	Goh Z., 2018	0.079	0.050	0.122	18 / 228
	Hong A.R., 2017	0.071	0.058	0.088	82 / 1149
	Lamas C., 2009	0.081	0.054	0.121	22 / 270
	Li L., 2017	0.078	0.067	0.091	152 / 1941
	Moraes A.B., 2020	0.139	0.100	0.190	32 / 230
	Nunes M.L., 2009	0.479	0.343	0.618	23 / 48
	Sojat A.S., 2021	0.567	0.440	0.685	34 / 60
	Theodoraki A., 2011	0.056	0.027	0.113	7 / 125
	Yeomans H., 2015	0.005	0.001	0.036	1 / 194
	Yilmaz N., 2020	0.158	0.133	0.185	119 / 755
Profile 1		0.116	0.088	0.152	915 / 9262
	Bondanelli M., 1997	0.105	0.040	0.249	4 / 38
	Kastelan D., 2015	0.113	0.083	0.153	36 / 319
	Ohno Y., 2018	0.074	0.049	0.110	22 / 297
	Tabuchi Y., 2016	0.067	0.036	0.119	10 / 150
Profile 2		0.087	0.045	0.164	72 / 804
	Ahn S.H., 2018	0.044	0.033	0.058	44 / 1005
	Barzon L ., 2002	0.113	0.081	0.155	32 / 284
	Bernini G.P., 2005	0.061	0.029	0.122	7 / 115
	Caplan R.H., 1994	0.083	0.021	0.279	2 / 24
	Chrisoulidou A., 2019	0.132	0.056	0.280	5 / 38
	Flecchia D., 1995	0.167	0.064	0.369	4 / 24
	Libè R., 2002	0.188	0.110	0.302	12 / 64
	Mantero F., 2000	0.092	0.075	0.111	92 / 1004
	Reincke M., 1992	0.118	0.060	0.218	8 / 68
	Valli N., 2001	0.387	0.235	0.565	12 / 31
Profile 3		0.117	0.076	0.174	218 / 2657

B) **Possible autonomous cortisol secretion / Autonomous cortisol secretion**



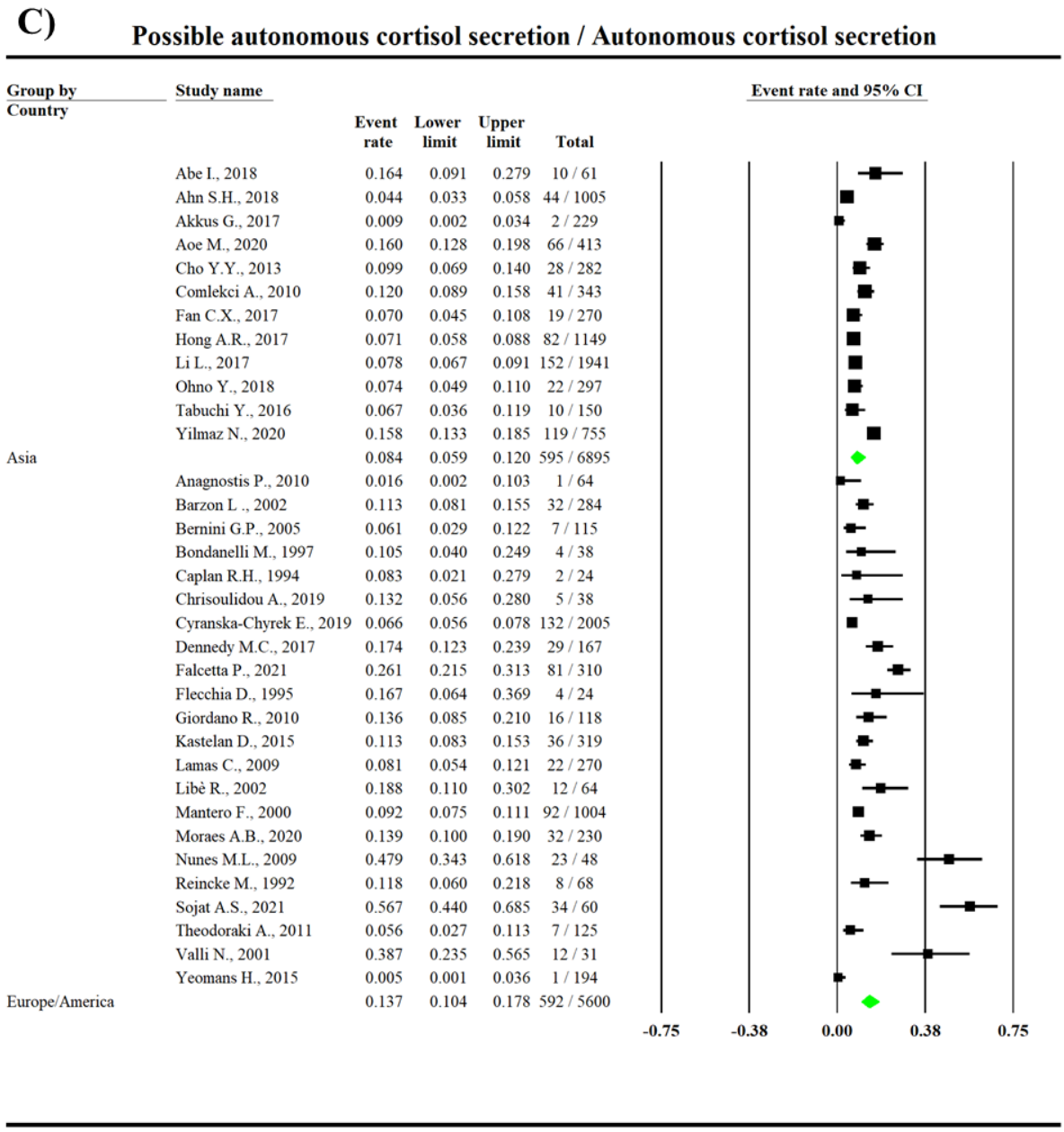


Figure S3. Forest plot of the subgroup analysis of the prevalence of autonomous/possible autonomous cortisol secretion in patients with adrenal incidentaloma, comparing studies according to the cut-off of cortisol post-dexamethasone suppression test used **(A)**, according to their either retrospective 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=351.39, df(Q)=20, p-value <0.001; I^2=94.31; τ^2=0.47. 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=225.74, df(Q)=22, p-value <0.001; I^2=90.25; τ^2=0.25. **(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=288.25, df(Q)=21, p-value < 0.001; I^2=92.72; τ^2=0.62.
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.

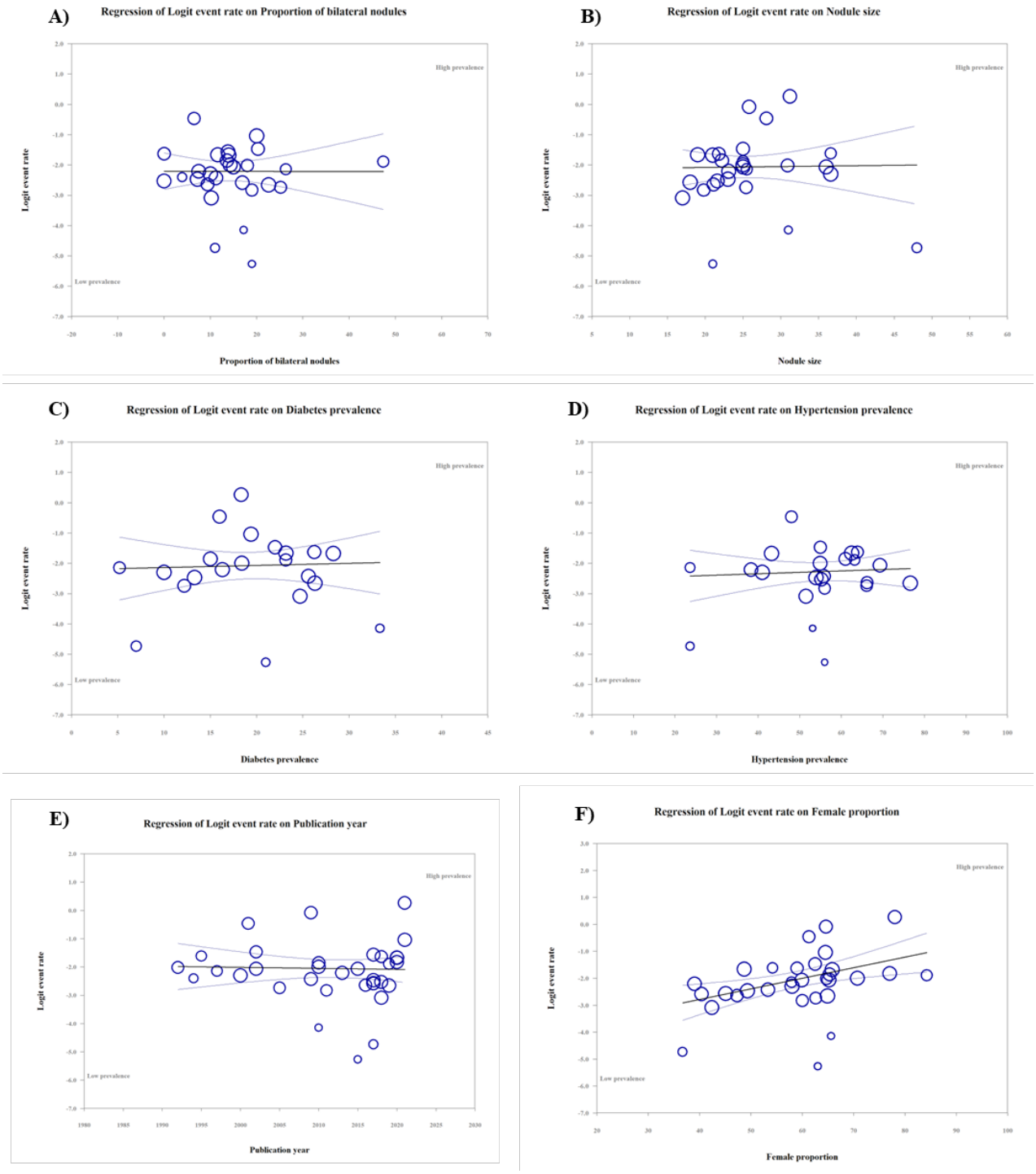
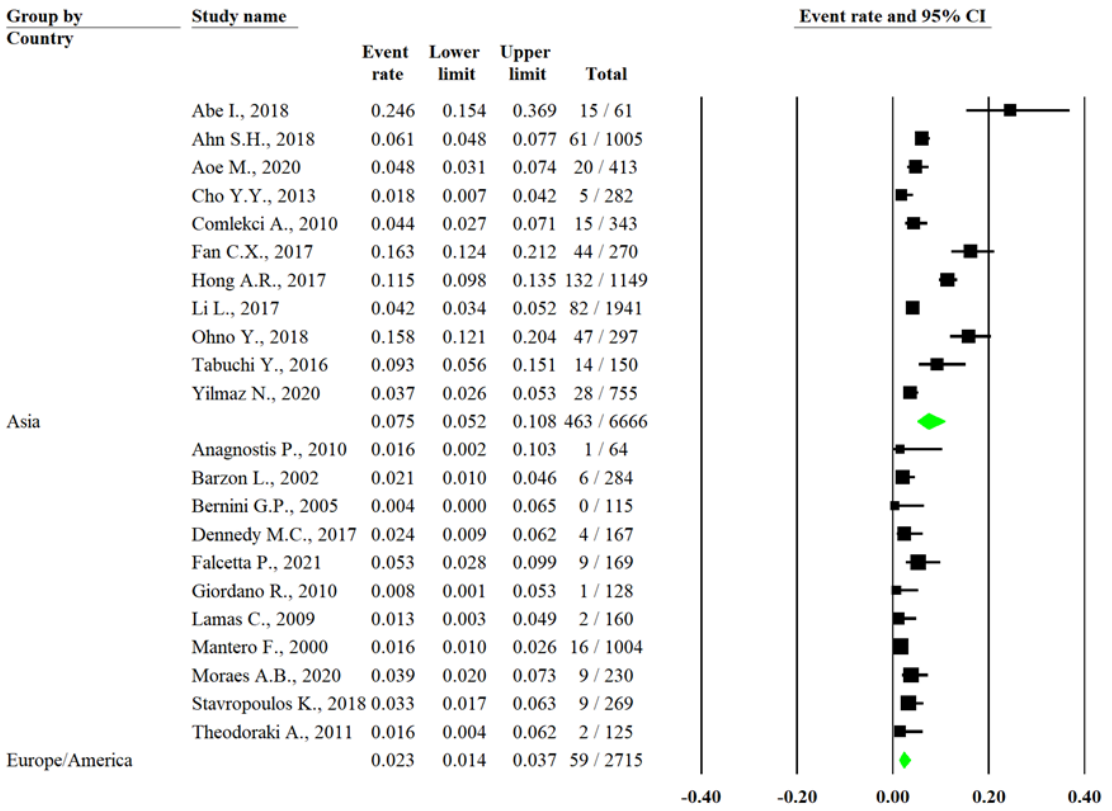


Figure S4. Meta-regression analysis for the proportion of bilateral nodules **(A)**, the size of the nodule **(B)**, the proportion of diabetes **(C)** and of hypertension **(D)** the year of publication **(E)** and the proportion of female patients **(F)** on the prevalence of autonomous/possible autonomous cortisol secretion in patients with adrenal incidentaloma. The analysis showed that the covariates A-D did not impact significantly on the results: **A)** coefficient -0.0003 [-0.029; 0.029], p = 0.983; **B)** coefficient 0.003 [-0.042; 0.047], p = 0.903; **C)** coefficient 0.007 [-0.047; 0.060, p = 0.800; **D)** coefficient 0.005 [-0.016; 0.025], p = 0.656; **E)** coefficient -0.004 [-0.034; 0.027], p = 0.812; while the proportion of female patients (E) had a significant impact on the results: **F)** coefficient 0.039 [0.018; 0.060], p = <0.001.

A) Primary aldosteronism



B) Primary aldosteronism

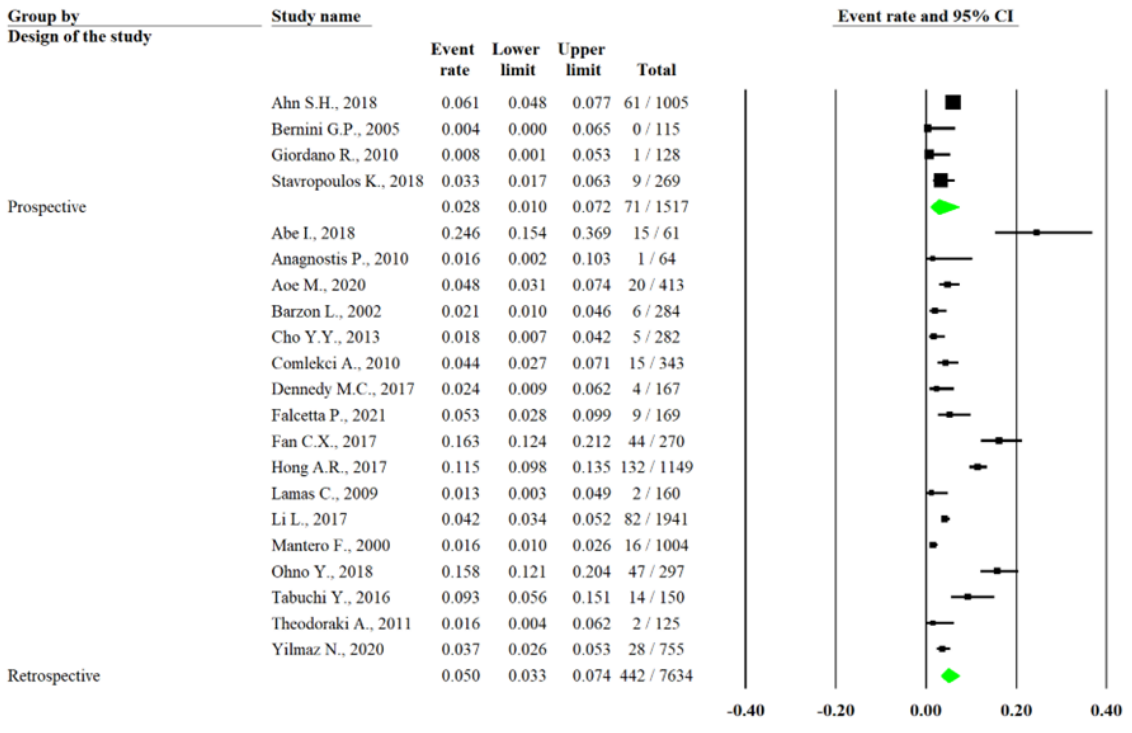


Figure S5. Forest plot of the subgroup analysis of the prevalence of primary aldosteronism in patients with adrenal incidentaloma, comparing studies according to the geographical area where they were conducted **(A)** and to their either retrospective or prospective design **(B).** Central squares of 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=15.98; df(Q)=10, p-value 0.10; I^2=37.41; τ^2=0.123 **(B)** Subgroup Prospective: Q=10.26, df(Q)=3, p-value 0.016; I^2=70.76; τ^2=0.41. Subgroup Retrospective: Q=241.052, df(Q)=16, p-value <0.001; I^2=93.36; τ^2=0.66.
The area of each square is proportional to that study's weight in the analysis. Horizontal lines indicate the 95% confidence interval.

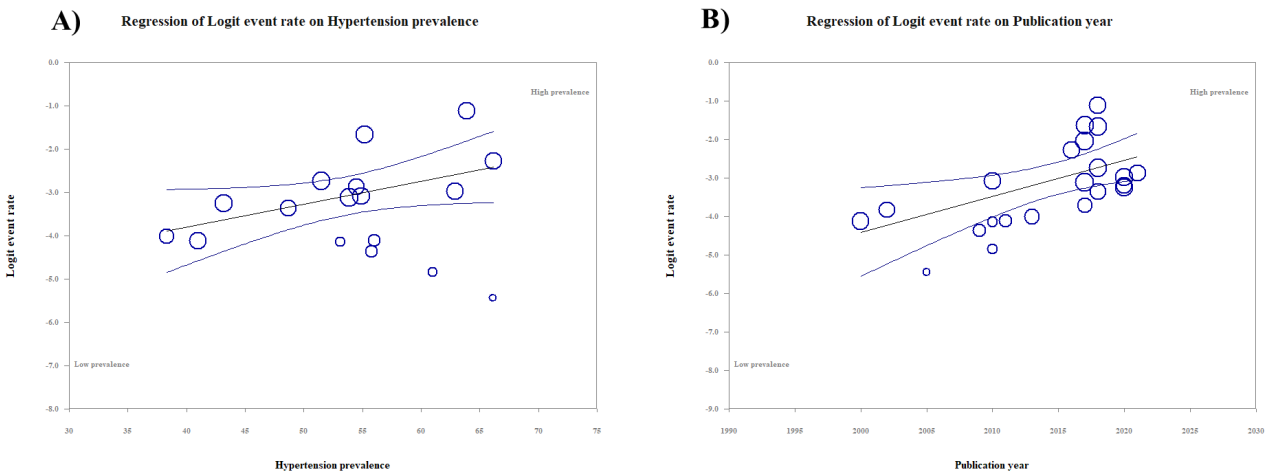
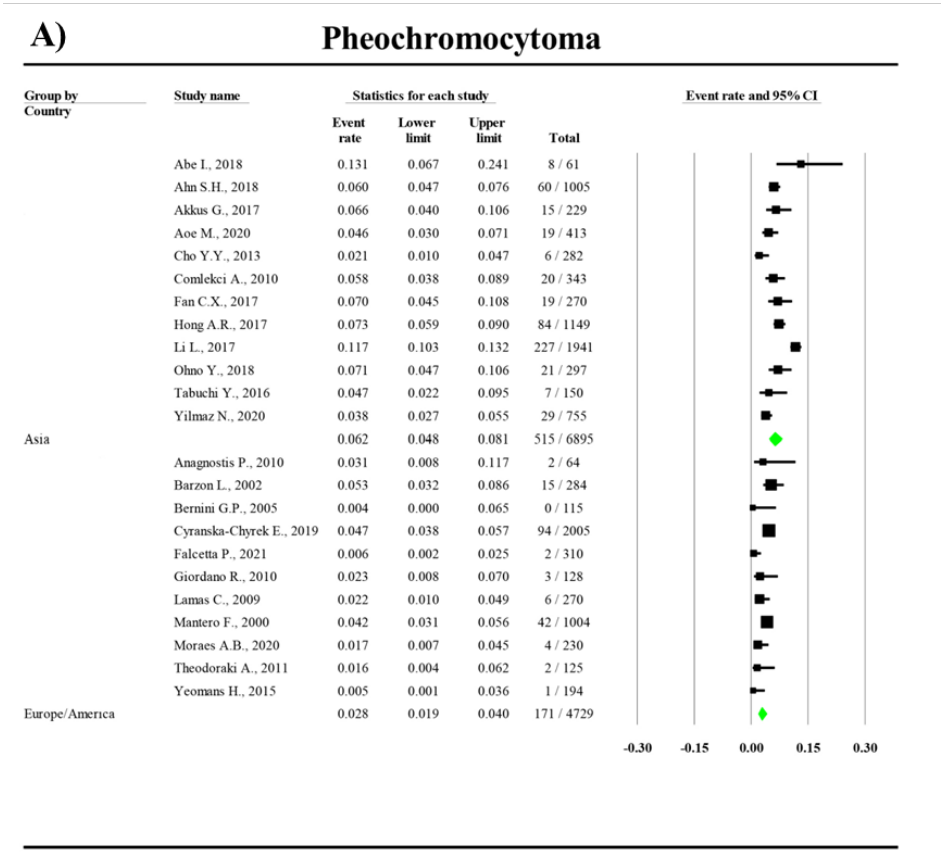


Figure S6. Meta-regression analysis for the proportion of hypertension **(A)** and the year of publication **(B)** on the prevalence of primary aldosteronism in patients with adrenal incidentaloma. The analysis showed that the factors have a significant impact on the results: **A)** coefficient 0.053 [0.001; 0.098], p = 0.019; B) coefficient 0.093 [0.029; 0.151], p = 0.002.



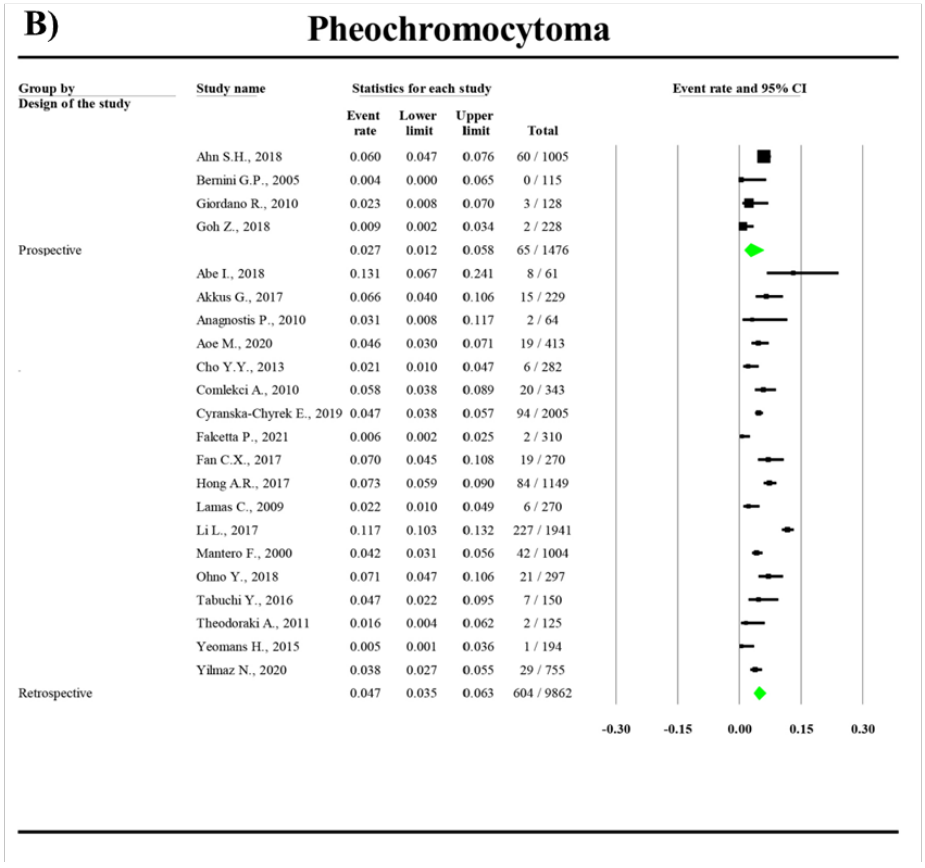


Figure S7. Forest plot of the subgroup analysis of the prevalence of pheochromocytoma in patients with adrenal incidentaloma, comparing studies according to the geographical area where they were

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.

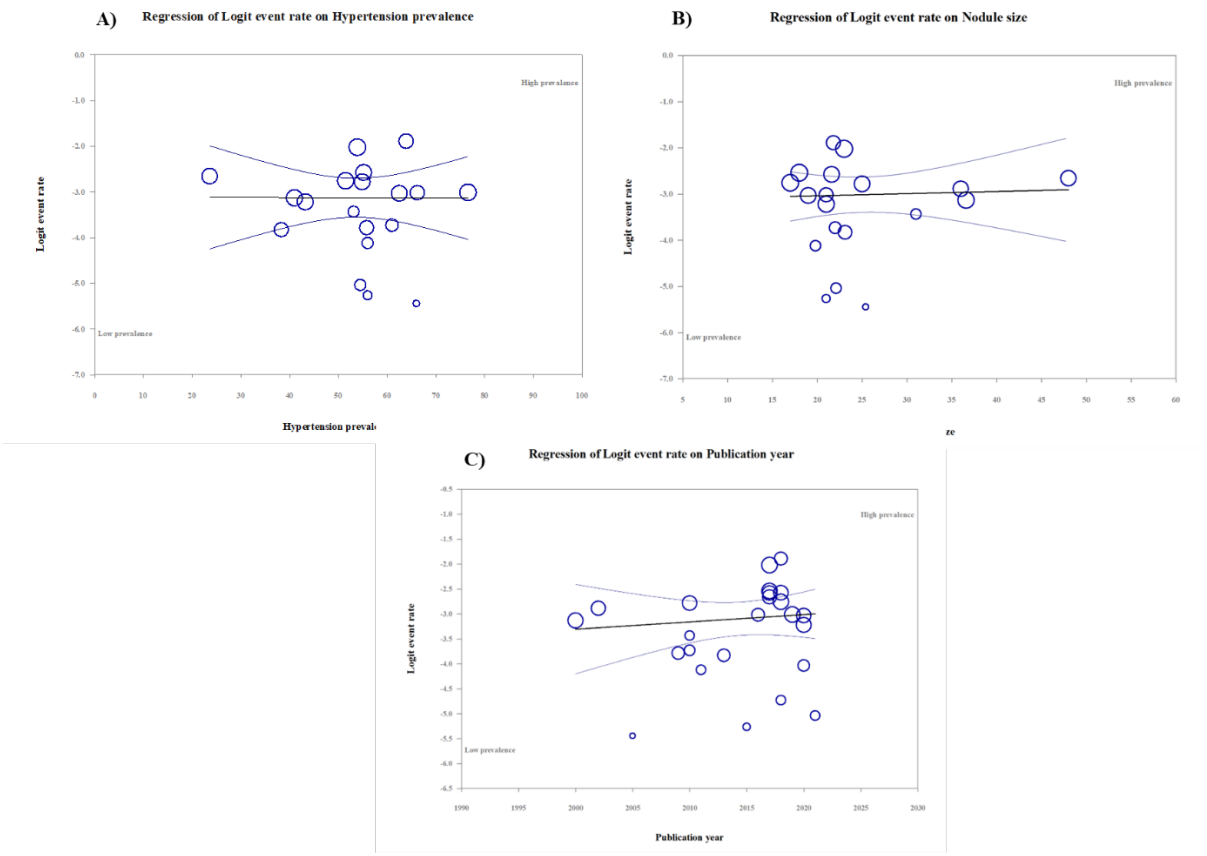


Figure S8. Meta-regression analysis for the proportion of hypertension **(A)**, the mean nodule size **(B)** and **(C)** the year of publication on the prevalence of pheochromocytoma in patients with adrenal incidentaloma. The analysis showed that the covariates did not impact significantly on the results: **(A)** coefficient -0.0003 [-0.028; 0.028], p = 0.986; **(B)** coefficient 0.005 [-0.032; 0.042], p = 0.806; **(C)** coefficient 0.015 [-0.031; 0.060], p = 0.531.

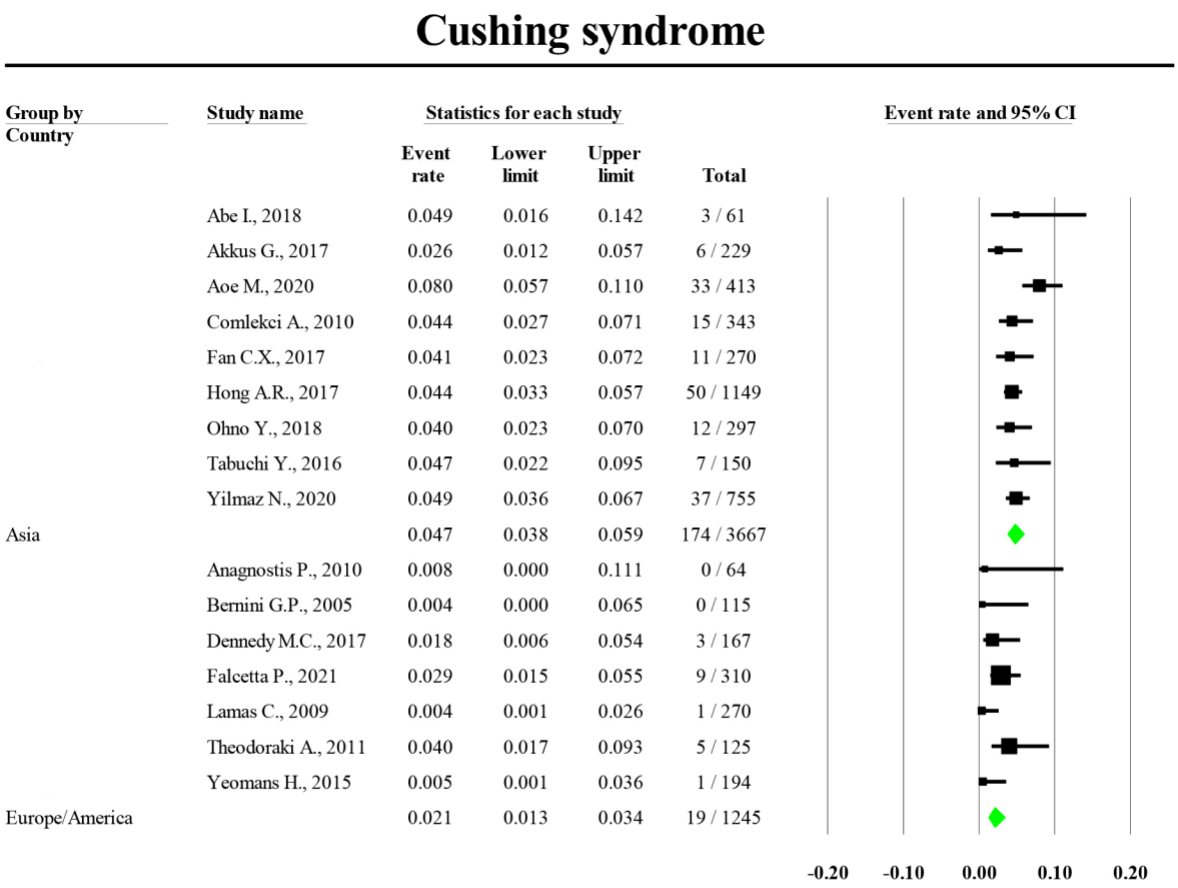


Figure S9. Forest plot of the subgroup analysis of the prevalence of Cushing syndrome in patients with adrenal incidentaloma, comparing studies according to the geographical area where they were conducted. The only study performed in New Zealand (Goh Z., 2018) was excluded from the analysis. Central 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.

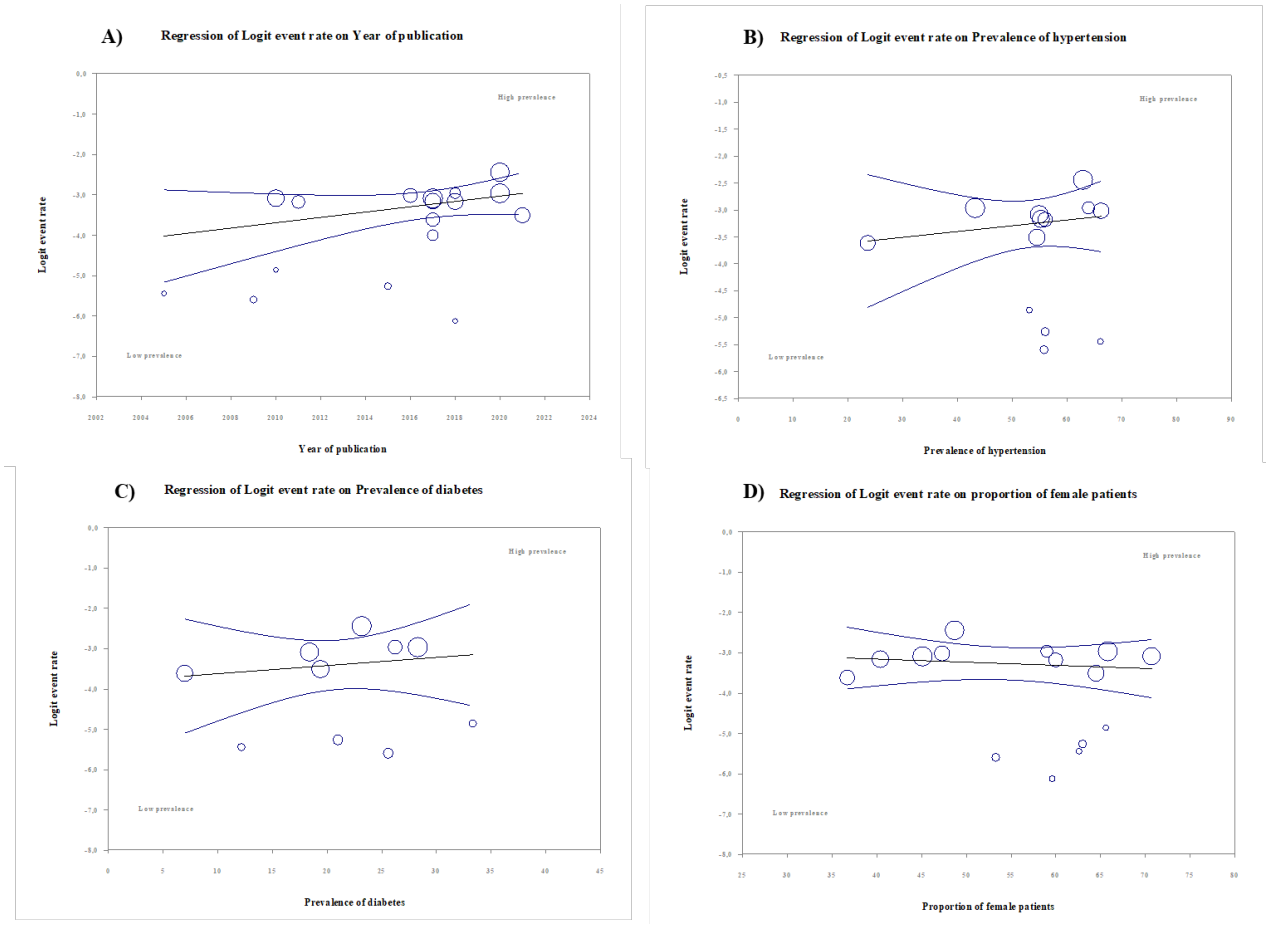


Figure S10. Meta-regression analysis for the year of study publication **(A)**, the proportion of hypertension **(B)** and of diabetes **(C)** and the proportion of female patients **(D)** on the prevalence of Cushing syndrome in patients with adrenal incidentaloma. The analysis showed that the covariates 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.

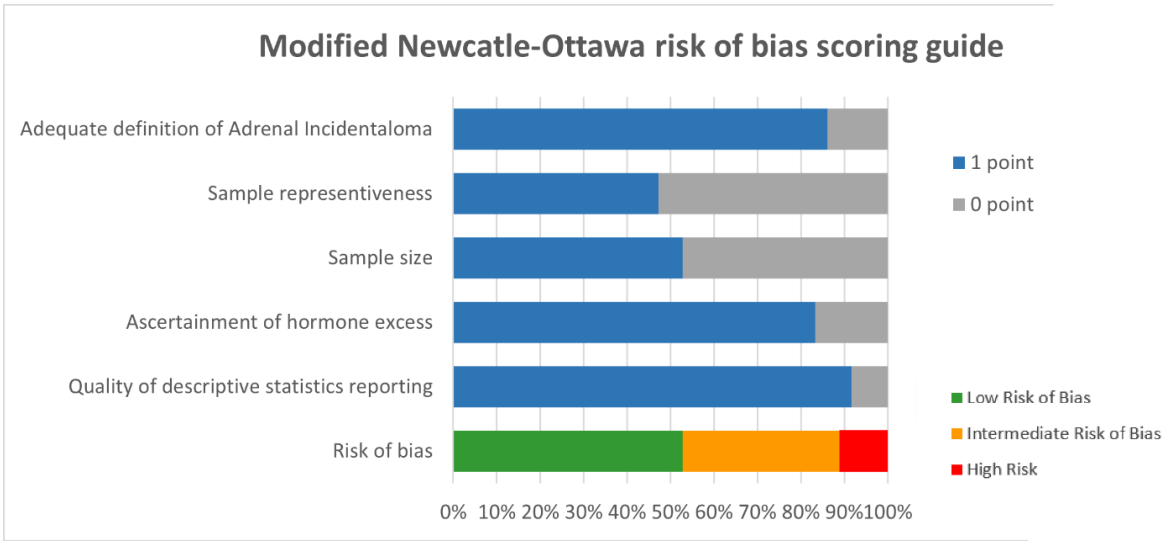
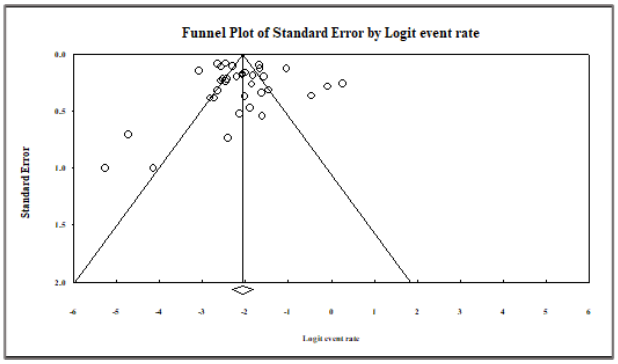
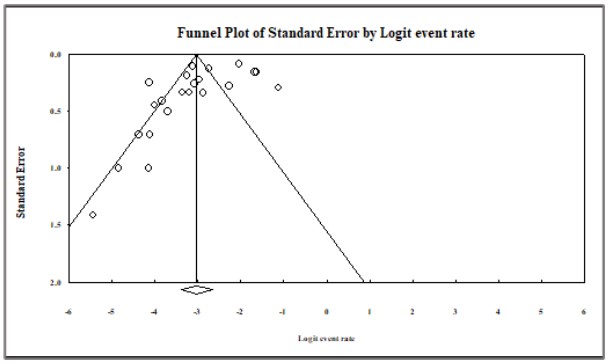


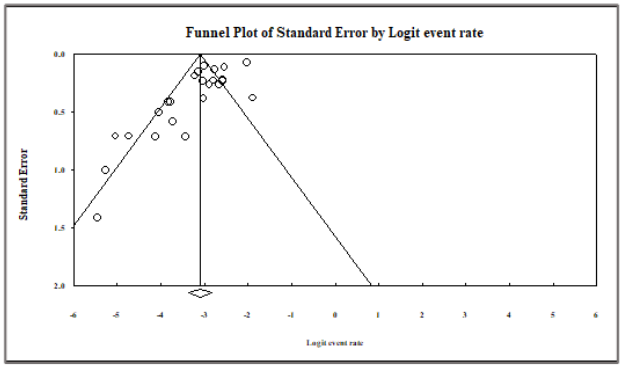
Figure S11. Qualitative evaluation of studies and risk of bias using modified Newcastle-Ottawa risk of bias scoring.



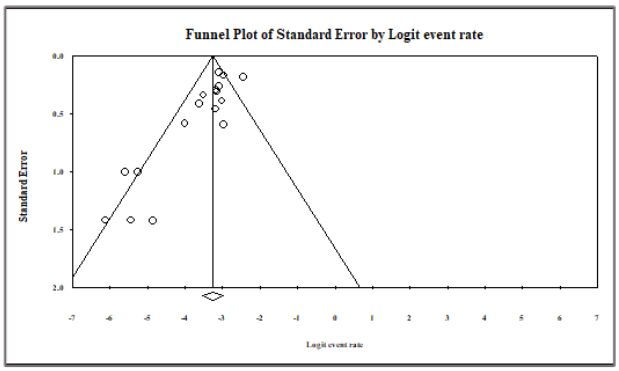
A. Autonomous cortisol secretion



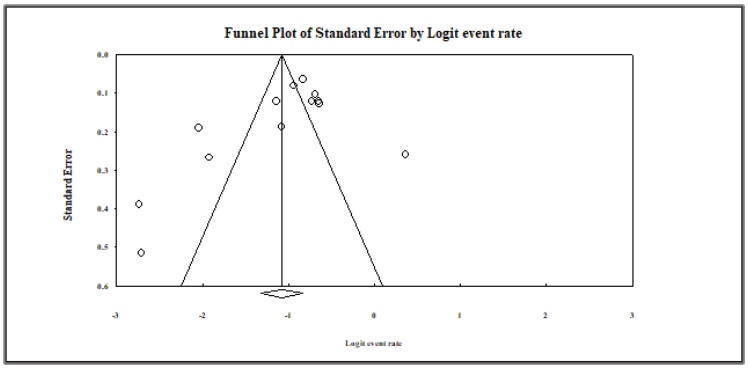
B. Primary aldosteronism



C. Pheochromocytoma



D. Cushing syndrome



E. Functioning adenomas

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