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 incidentalomas [Title/abstract]) 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	1
	2. Loss of diurnal serum cortisol rhythm 2. Loss of diurnal serum cortisol (with respect to the notice), and and	
	3. Low serum DHEA-S level (with respect to the patient's age and sex)	
Ahn S.H., 2018*	At least two abnormalities among:	
7 mm 2.111, 2010	1. Lack of suppression in the 1 mg DST (cortisol >138 nmol/L)	0
	2. UFC levels higher than the upper normal limit	3
	3. ACTH levels < 10 pg/mL	
Akkuş G., 2017	Serum cortisol after 1 mg DST >50 nmol/L (or 1.8 μg/dL) and at	
	least one of the following:	<u></u>
	1. 24-h UFC levels >300 μg/d in 2 of the 3 consecutive collections	1
	2. ACTH values <10 pg/mL3. Decreased DHEAS levels	
Anagnostis P.,	Serum cortisol >1.8 μg/dL or urinary cortisol <20 μg/24h, after 1	
2010*	mg DST and at least one of the following:	
2010	1. UFC >120 μg/d	1
	2. Loss of diurnal rhythm of cortisol (levels at 8 p.m. <25% of	
	those at 8 a.m. in normal subjects)	
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	<mark>3</mark>
	2. Urinary cortisol	
D ' ' C D	3. Plasma ACTH	
Bernini G.P., 2005	Serum cortisol after 1 mg DST >138 nmol/L (>5μg/dL)	3
Bondanelli M.,	Serum cortisol after 1 mg DST >0.09 μmol/L, followed by high-	2
1997*	dose DST with 8 mg/d for 2 days	<u> </u>
<mark>Caplan R.H.,</mark>	Serum cortisol after 1 mg DST >138 nmol/L (>5μg/dL)	3
1994	DOTE OF THE	
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)	3
2019	and 24-h UFC	<u> </u>
Comlekci A.,	Serum cortisol after 1 mg DST >50 nmol/L (or 1.8 µg/dL) and at	
2010	least one of the following:	
	1. ACTH <5 pg/mL	1
	2. UFC >110 μg/d	
	3. Midnight cortisol >7.5 μg/dL	
Cyranska-Chyrek	1. ACTH suppression <7.20 pg/mL	
E., 2019*	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.)	1
	3. Increased 24 h urinary cortisol excretion (by at least two times	
1	above upper normal limit)	
	5	

	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.,	At least 2 of the following:	
2017*	1. Failure to suppress serum cortisol after DST <1.8 μg/dL	
2017	 Sleeping midnight serum cortisol >1.8 μg/dL 	1
	3. Awake midnight serum cortisol >7.5 μg/dL	<u> </u>
	4. Raised UFC	
Falcetta P., 2021	Post-DST cortisol level >5 μg/dl (autonomous cortisol secretion) or	
1 4100114 1 ., 2021	>1.8 and \leq 5 µg/dl (possible cortisol secretion) combined with an	
	abnormal result in a least one of the following:	
	1. UFC values $\geq 405 \mu \text{g}/24\text{h}$ (1117.8 mmol/24h)	
	2. Absence of cortisol rhythm (midnight serum cortisol >7.5 μg/dL	1
	(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)	
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	1
	2. Abnormal serum cortisol rhythm	
Flecchia D., 1995	Serum cortisol after 1 mg DST >138 nmol/L (>5μg/dL)	3
Giordano R.,	Serum cortisol after 1 mg DST >50 nmol/L (or 1.8 μg/dL) and at	
2010	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	1
	(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)),	
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-	1
	pituitary-adrenal axis were required for the diagnosis (not	
	specified).	
Hong A.R.,	Serum cortisol after 1 mg DST >50 nmol/L (or 1.8 μg/dL)	1
2017*		<u>*</u>
Kastelan D., 2015	Serum cortisol after 1 mg DST >83 nmol/L (>3.0 μg/dL) and at least	
	one of the following:	2
	1. 24h-UFC >379 nmol/d	_
T	2. Plasma ACTH <2.2 pmol/L	
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	1
	mg/dL)	
	3. Raised UFC	
	4. ACTH <10 pg/mL	

Li L., 2017*	Serum cortisol after 1 mg DST >50 nmol/L (or 1.8 μ g/dL), confirmed by post-LDDST (4 mg/48 h) cortisol levels \geq 50 nmol/L	1
Libè R., 2002*	 At least two of the following criteria: Inadequate cortisol inhibition after 1 mg DST (cortisol >138 nmol/L) High or high–normal UFC excretion (≥ 275nmol/24 h) Low or low–normal plasma ACTH levels (<0.7 pmol/l) Blunted ACTH increase after CRH test (<4.4 pmol/l) 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	
XZ XX	range <27 – 66 nmol/l)	
Yeomans H.,	A cortisol hypersecretion was defined as any two of the following	
2015*	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-	1
	170 nmol/24 h)	1
	3. Morning plasma ACTH <2 pmol/L	
	4. Circadian rhythm of serum cortisol (normal when midnight	
	cortisol value <50 nmol/L)	
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)	1
	3. Low DHEA-S	<u>*</u>
	4. High late night salivary cortisol >0.27 μg/dL or midnight serum	
	cortisol level >7.5 μg/dL	
	cornsor rever / 1.3 µg/aL	

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	<u>>40</u>
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.

Total number of studies36Total number of patients13,763Age (years)58 [56 - 62]	
Age (years) 58 [56 – 62]	
(studies) (33)	
Female gender (n%) 58.4%	
(studies) (34)	
BMI (kg/m^2) 28.5 [26.1 – 28.9]	
(studies) (11)	
SBP (mmHg) 128 [126 – 132]	
(studies) (6)	
DBP (mmHg) 80 [78 – 80]	
(studies) (6)	
Prevalence of hypertension (n%) 54.3%	
(studies) (26)	
Prevalence of diabetes (%) 19.3%	
(studies) (18)	
Nodule size (mm) 25.0 [21.0 – 28.1]	
(studies) (29)	
Location of the tumor	
Left (n%) 48.7%	
(studies) (19)	
Right (n%) 37.3%	
(studies) (20)	
Bilateral (n%) 17.0%	
(studies) (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.

Functioning adenomas

Group by	Study name	Statist	ics for eac	ch study	Events/Total	Event rate and 95% CI
Country		Event rate	Lower limit	Upper limit	Total	
	Abe I., 2018	0.590	0.464	0.706	36 / 61	
	Aoe M., 2020	0.334	0.290	0.381	138 / 413	=
	Comlekci A., 2010	0.242	0.201	0.288	91 / 376	=
	Fan C.X., 2017	0.344	0.290	0.403	93 / 270	📥
	Hong A.R., 2017	0.303	0.277	0.330	348 / 1149	
	Ohno Y., 2018	0.343	0.292	0.399	102 / 297	
	Tabuchi Y., 2016	0.253	0.190	0.329	38 / 150	-
	Yilmaz N., 2020	0.282	0.251	0.315	213 / 755	
Asia		0.324	0.267	0.387	1059 / 3471	
	Anagnostis P., 2010	0.063	0.024	0.155	4 / 64	
	Bernini G.P., 2005	0.061	0.029	0.122	7 / 115	
	Falcetta P., 2021	0.326	0.276	0.380	101 / 310	
	Lamas C., 2009	0.115	0.082	0.159	31 / 270	
	Theodoraki A., 2011	0.128	0.080	0.199	16 / 125	
Europe/America		0.140	0.098	0.196	159 / 884	•

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.

Regression of Logit event rate on Publication year

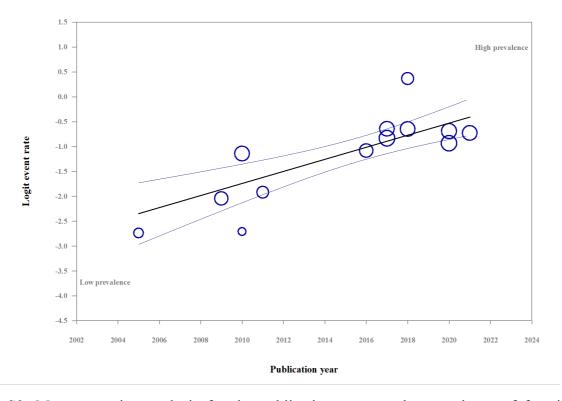


Figure S2. Meta-regression analysis for the publication year on the prevalence of functioning adenomas. The analysis showed that the covariates had a statically significant impact on the results: coefficient 0.121 [0.079; 0.164], p < 0.001.

A) Possible autonomous cortisol secretion / Autonomous cortisol secretion

Group by	Study name					Ev	ent
Profile		Event	Lower	Upper			
		rate	limit	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		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		119 / 755		
e l	1111112 11., 2020	0.116	0.088		915 / 9262		
. 1	Bondanelli M., 1997	0.110	0.040	0.249	4/38		
	Kastelan D., 2015	0.113	0.040	0.153	36 / 319		
	Ohno Y., 2018	0.074	0.049	0.110	22 / 297		
	Tabuchi Y., 2016	0.074	0.049	0.110	10 / 150		
le 2	1abucii 1., 2010	0.087					
ie Z	Ab., C.H. 2019		0.045	0.164	72 / 804		
	Ahn S.H., 2018	0.044	0.033		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		92 / 1004		
	Reincke M., 1992	0.118	0.060		8 / 68		
	Valli N., 2001	0.387	0.235		12 / 31		
file 3		0.117	0.076	0.174	218 / 2657		

B) Possible autonomous cortisol secretion / Autonomous cortisol secretion

Group by	Study name						Event	t rate and 95	<u>% C</u> I
Design of the study		Event	Lower	Upper					
		rate	limit	limit	Total				
	Ahn S.H., 2018	0.044	0.033	0.058	44 / 1005		- 1		
	Bernini G.P., 2005	0.061	0.029	0.122	7 / 115			-	
	Giordano R., 2010	0.136	0.085	0.210	16 / 118			-	-
	Goh Z., 2018	0.079	0.050	0.122	18 / 228				
	Nunes M.L., 2009	0.479	0.343	0.618	23 / 48				+-
	Reincke M., 1992	0.118	0.060	0.218	8 / 68			-	-
	Valli N., 2001	0.387	0.235	0.565	12 / 31				
Prospective		0.136	0.088	0.205	128 / 1613				.
-	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				.
	Barzon L ., 2002	0.113	0.081	0.155	32 / 284			-	
	Caplan R.H., 1994	0.083	0.021	0.279	2 / 24				_
	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., 20	190.066	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			-	
	Hong A.R., 2017	0.071	0.058	0.088	82 / 1149			•	
	Kastelan D., 2015	0.113	0.083	0.153	36 / 319			-	
	Lamas C., 2009	0.081	0.054	0.121	22 / 270			-	
	Li L., 2017	0.078			152 / 1941				
	Libè R., 2002	0.188	0.110	0.302	12 / 64			-	-
	Mantero F., 2000	0.092	0.075	0.111	92 / 1004			-	
	Ohno Y., 2018	0.074	0.049	0.110	22 / 297			-	
	Tabuchi Y., 2016	0.067		0.119	10 / 150			-	
	Theodoraki A., 2011	0.056		0.113	7 / 125			-	
	Yeomans H., 2015	0.005		0.036	1 / 194			-	
	Yilmaz N., 2020	0.158			119 / 755				
Retrospective	.,	0.095			998 / 10720			•	
						-0.75	-0.38	0.00	0.38

Group by	Study name						Even	t rate and 95%	% CI
Country		Event rate	Lower limit	Upper limit	Total				
	Abe I., 2018	0.164	0.091	0.279	10 / 61			-	- 1
	Ahn S.H., 2018	0.044	0.033	0.058	44 / 1005				
	Akkus G., 2017	0.009	0.002	0.034	2 / 229			+	
	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			-	
	Fan C.X., 2017	0.070	0.045	0.108	19 / 270				
	Hong A.R., 2017	0.071	0.058	0.088	82 / 1149				-
	Li L., 2017	0.078	0.067	0.091	152 / 1941				
	Ohno Y., 2018	0.074	0.049	0.110	22 / 297				- 1
	Tabuchi Y., 2016	0.067	0.036	0.119	10 / 150				
	Yilmaz N., 2020	0.158	0.133	0.185	119 / 755				
Asia		0.084	0.059	0.120	595 / 6895			•	
	Anagnostis P., 2010	0.016	0.002	0.103	1 / 64			 - -	
	Barzon L ., 2002	0.113	0.081	0.155	32 / 284			-	
	Bernini G.P., 2005	0.061	0.029	0.122	7 / 115			-	
	Bondanelli M., 1997	0.105	0.040	0.249	4/38			 -	-
	Caplan R.H., 1994	0.083	0.021	0.279	2 / 24			-	-
	Chrisoulidou A., 2019	0.132	0.056	0.280	5 / 38				_
	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				-
	Flecchia D., 1995	0.167	0.064	0.369	4 / 24				
	Giordano R., 2010	0.136	0.085	0.210	16 / 118			-= -	
	Kastelan D., 2015	0.113	0.083	0.153	36 / 319			-	
	Lamas C., 2009	0.081	0.054	0.121	22 / 270			-	
	Libè R., 2002	0.188	0.110	0.302	12 / 64				_
	Mantero F., 2000	0.092	0.075	0.111	92 / 1004			■	
	Moraes A.B., 2020	0.139	0.100	0.190	32 / 230			-	
	Nunes M.L., 2009	0.479	0.343	0.618	23 / 48				-
	Reincke M., 1992	0.118	0.060	0.218	8 / 68			-■	
	Sojat A.S., 2021	0.567	0.440	0.685	34 / 60				
	Theodoraki A., 2011	0.056	0.027	0.113	7 / 125			-	
	Valli N., 2001	0.387	0.235	0.565	12 / 31				\rightarrow
	Yeomans H., 2015	0.005	0.001	0.036	1 / 194			+	- 1
Europe/America		0.137	0.104	0.178	592 / 5600	- 1	- 1		

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.

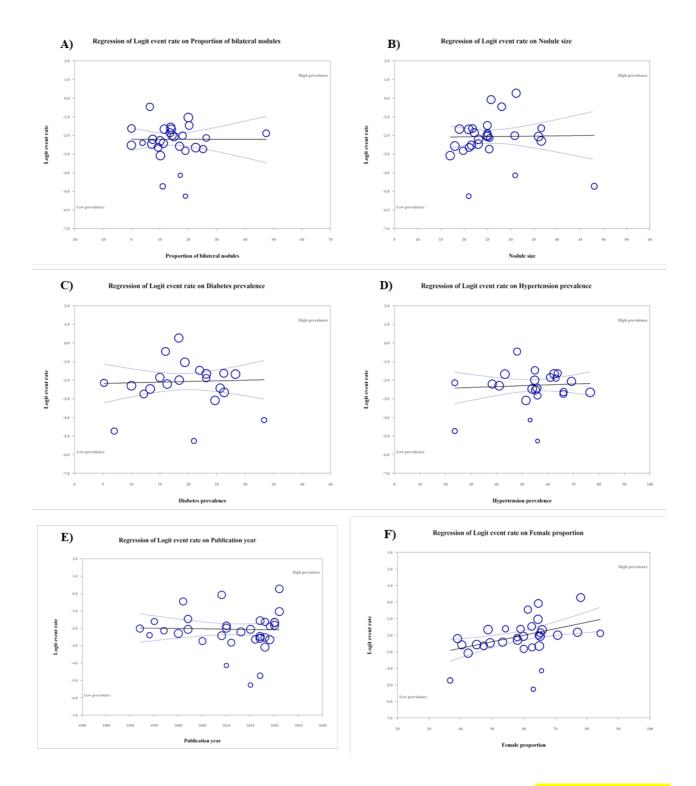
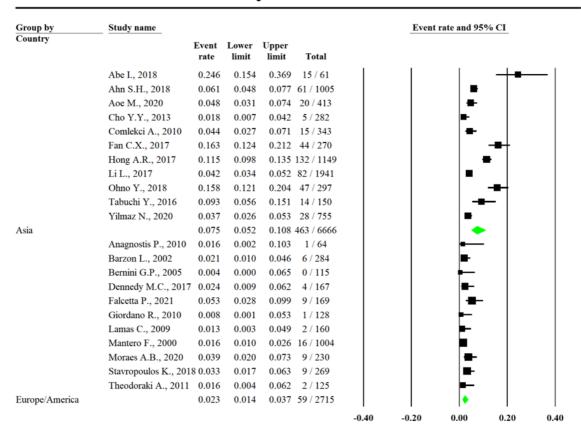


Figure S4. Meta-regression analysis for the proportion of bilateral nodules (**A**), the size of the nodule (**B**), the proportion of diabetes (**C**) and of hypertension (**D**) the year of publication (**E**) and the proportion of female patients (**F**) on the prevalence of autonomous/possible autonomous 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.

Primary aldosteronism



B)

Primary aldosteronism

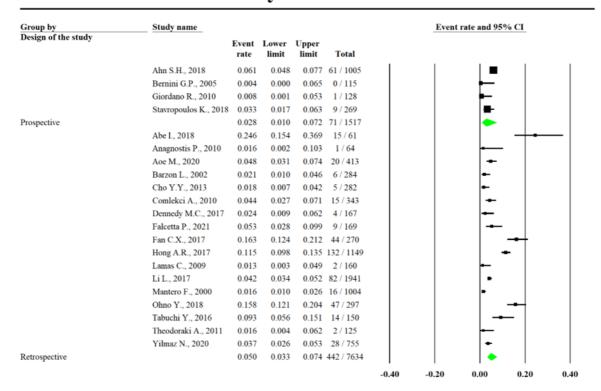


Figure S5. Forest plot of the subgroup analysis of the prevalence of primary aldosteronism in patients with adrenal incidentaloma, comparing studies according to the geographical area where they were conducted (**A**) and to their either retrospective or prospective design (**B**). Central squares of 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.

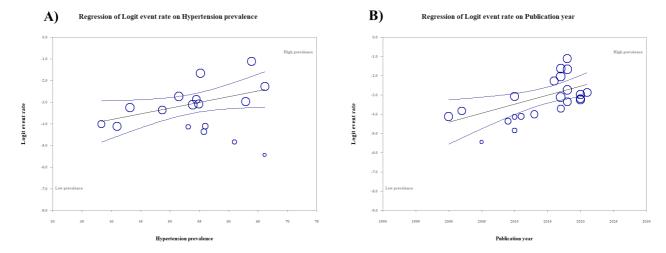


Figure S6. Meta-regression analysis for the proportion of hypertension **(A)** and the year of publication **(B)** on the prevalence of primary aldosteronism in patients with adrenal incidentaloma. The analysis showed that the factors have a significant impact on the results: **A)** coefficient 0.053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

roup by	Study name	Statis	Event rate and 95% C						
Country		Event rate	Lower limit	Upper limit	Total				
	Abe I., 2018	0.131	0.067	0.241	8 / 61		•	-	-
	Ahn S.H., 2018	0.060	0.047	0.076	60 / 1005		-	.	
	Akkus G., 2017	0.066	0.040	0.106	15 / 229		-	-	
	Aoe M., 2020	0.046	0.030	0.071	19 / 413				
	Cho Y.Y., 2013	0.021	0.010	0.047	6 / 282		-		
	Comlekci A., 2010	0.058	0.038	0.089	20 / 343			-	
	Fan C.X., 2017	0.070	0.045	0.108	19 / 270		-	-	
	Hong A.R., 2017	0.073	0.059	0.090	84 / 1149		•	•	
	Li L., 2017	0.117	0.103	0.132	227 / 1941			-	
	Ohno Y., 2018	0.071	0.047	0.106	21 / 297		•	⊢	
	Tabuchi Y., 2016	0.047	0.022	0.095	7 / 150		-	-	
	Yilmaz N., 2020	0.038	0.027	0.055	29 / 755				
ia		0.062	0.048	0.081	515 / 6895		•	•	
	Anagnostis P., 2010	0.031	0.008	0.117	2 / 64		-	-	
	Barzon L., 2002	0.053	0.032	0.086	15 / 284			-	
	Bernini G.P., 2005	0.004	0.000	0.065	0 / 115		⊢		
	Cyranska-Chyrek E., 2019	0.047	0.038	0.057	94 / 2005				
	Falcetta P., 2021	0.006	0.002	0.025	2 / 310		-		
	Giordano R., 2010	0.023	0.008	0.070	3 / 128		-		
	Lamas C., 2009	0.022	0.010	0.049	6 / 270				
	Mantero F., 2000	0.042	0.031	0.056	42 / 1004				
	Moraes A.B., 2020	0.017	0.007	0.045	4 / 230		■-		
	Theodoraki A., 2011	0.016	0.004	0.062	2 / 125		-		
	Yeomans H., 2015	0.005	0.001	0.036	1 / 194		-		
rope/America		0.028	0.019	0.040	171 / 4729		•		

S.H., 2018 ini G.P., 2005 lano R., 2010 Z., 2018 G., 2018 G., 2017 nostis P., 2010 M., 2020 Y.Y., 2013 lekci A., 2010 nska-Chyrek E., 2019 tta P., 2021 Z.X., 2017 A.A.R., 2017	0.060 0.004 0.023 0.009 0.027 0.131 0.066 0.031 0.046 0.021 0.058 0.047 0.006	Lower limit 0.047 0.000 0.008 0.002 0.012 0.067 0.040 0.008 0.030 0.010 0.038 0.038	Upper limit 0.076 0.065 0.070 0.034 0.058 0.241 0.106 0.117 0.071 0.047 0.089 0.057	Total 60 / 1005 0 / 115 3 / 128 2 / 228 65 / 1476 8 / 61 15 / 229 2 / 64 19 / 413 6 / 282 20 / 343 94 / 2005			•	- - -	-
ini G.P., 2005 dano R., 2010 Z., 2018 L., 2018 L., 2018 L., 2017 nostis P., 2010 M., 2020 Y.Y., 2013 dekci A., 2010 nska-Chyrek E., 2019 tta P., 2021 C.X., 2017	0.004 0.023 0.009 0.027 0.131 0.066 0.031 0.046 0.021 0.058 0.047	0.000 0.008 0.002 0.012 0.067 0.040 0.008 0.030 0.010 0.038	0.065 0.070 0.034 0.058 0.241 0.106 0.117 0.071 0.047 0.089	0 / 115 3 / 128 2 / 228 65 / 1476 8 / 61 15 / 229 2 / 64 19 / 413 6 / 282 20 / 343 94 / 2005				- - -	-
lano R., 2010 Z., 2018 L., 2018 L., 2018 L., 2018 L., 2017 nostis P., 2010 M., 2020 Y.Y., 2013 lekci A., 2010 nska-Chyrek E., 2019 tta P., 2021 C.X., 2017	0.023 0.009 0.027 0.131 0.066 0.031 0.046 0.021 0.058 0.047 0.006	0.008 0.002 0.012 0.067 0.040 0.008 0.030 0.010 0.038	0.070 0.034 0.058 0.241 0.106 0.117 0.071 0.047 0.089	3 / 128 2 / 228 65 / 1476 8 / 61 15 / 229 2 / 64 19 / 413 6 / 282 20 / 343 94 / 2005			•	 - -	-
Z., 2018 L., 2018 s. G., 2017 mostis P., 2010 M., 2020 Y.Y., 2013 lekci A., 2010 nska-Chyrek E., 2019 tta P., 2021 C.X., 2017	0.009 0.027 0.131 0.066 0.031 0.046 0.021 0.058 0.047 0.006	0.002 0.012 0.067 0.040 0.008 0.030 0.010 0.038 0.038	0.034 0.058 0.241 0.106 0.117 0.071 0.047 0.089 0.057	2 / 228 65 / 1476 8 / 61 15 / 229 2 / 64 19 / 413 6 / 282 20 / 343 94 / 2005			-		-
L., 2018 Is G., 2017 nostis P., 2010 M., 2020 Y.Y., 2013 lekci A., 2010 nska-Chyrek E., 2019 tta P., 2021 C.X., 2017	0.027 0.131 0.066 0.031 0.046 0.021 0.058 0.047 0.006	0.012 0.067 0.040 0.008 0.030 0.010 0.038 0.038	0.058 0.241 0.106 0.117 0.071 0.047 0.089 0.057	65 / 1476 8 / 61 15 / 229 2 / 64 19 / 413 6 / 282 20 / 343 94 / 2005			-	<u>-</u> - -	-
is G., 2017 mostis P., 2010 M., 2020 Y.Y., 2013 dekci A., 2010 mska-Chyrek E., 2019 tta P., 2021 C.X., 2017	0.131 0.066 0.031 0.046 0.021 0.058 0.047	0.067 0.040 0.008 0.030 0.010 0.038 0.038	0.241 0.106 0.117 0.071 0.047 0.089 0.057	8 / 61 15 / 229 2 / 64 19 / 413 6 / 282 20 / 343 94 / 2005			-	-	-
is G., 2017 mostis P., 2010 M., 2020 Y.Y., 2013 dekci A., 2010 mska-Chyrek E., 2019 tta P., 2021 C.X., 2017	0.066 0.031 0.046 0.021 0.058 0.047 0.006	0.040 0.008 0.030 0.010 0.038 0.038	0.106 0.117 0.071 0.047 0.089 0.057	15 / 229 2 / 64 19 / 413 6 / 282 20 / 343 94 / 2005			-	-	-
nostis P., 2010 M., 2020 Y.Y., 2013 lekci A., 2010 nska-Chyrek E., 2019 tta P., 2021 C.X., 2017	0.031 0.046 0.021 0.058 0.047 0.006	0.008 0.030 0.010 0.038 0.038	0.117 0.071 0.047 0.089 0.057	2 / 64 19 / 413 6 / 282 20 / 343 94 / 2005			-	<u>-</u>	
M., 2020 Y.Y., 2013 lekci A., 2010 nska-Chyrek E., 2019 tta P., 2021 C.X., 2017	0.046 0.021 0.058 0.047 0.006	0.030 0.010 0.038 0.038	0.071 0.047 0.089 0.057	19 / 413 6 / 282 20 / 343 94 / 2005			-	-	
Y.Y., 2013 lekci A., 2010 nska-Chyrek E., 2019 tta P., 2021 C.X., 2017	0.021 0.058 0.047 0.006	0.010 0.038 0.038	0.047 0.089 0.057	6 / 282 20 / 343 94 / 2005			-		
lekci A., 2010 nska-Chyrek E., 2019 tta P., 2021 C.X., 2017	0.058 0.047 0.006	0.038 0.038	0.089 0.057	20 / 343 94 / 2005			-		
nska-Chyrek E., 2019 tta P., 2021 C.X., 2017	0.047	0.038	0.057	94 / 2005			-	-	
tta P., 2021 C.X., 2017	0.006								
C.X., 2017		0.002	0.025	2/210			•		
	0.070		0.023	2/310			-		
A D 2017		0.045	0.108	19 / 270			-	-	
; A.K., 2017	0.073	0.059	0.090	84 / 1149			-	-	
as C., 2009	0.022	0.010	0.049	6 / 270			-		
, 2017	0.117	0.103	0.132	227 / 1941				-	
ero F., 2000	0.042	0.031	0.056	42 / 1004			-		
Y., 2018	0.071	0.047	0.106	21 / 297			-	-	
chi Y., 2016	0.047	0.022	0.095	7 / 150				-	
doraki A., 2011	0.016	0.004	0.062	2 / 125			-		
nans H., 2015	0.005	0.001	0.036	1 / 194			-		
az N., 2020	0.038	0.027	0.055	29 / 755			-		
	0.047	0.035	0.063	604 / 9862			•		
					-0.30	-0.15	0.00	0.15	0.30
	ero F., 2000 Y., 2018 chi Y., 2016 doraki A., 2011 nans H., 2015	ero F., 2000 0.042 Y., 2018 0.071 chi Y., 2016 0.047 doraki A., 2011 0.016 ans H., 2015 0.005 z N., 2020 0.038	ro F., 2000 0.042 0.031 Y., 2018 0.071 0.047 shi Y., 2016 0.047 0.022 doraki A., 2011 0.016 0.004 ans H., 2015 0.005 0.001 z N., 2020 0.038 0.027	ro F., 2000 0.042 0.031 0.056 Y., 2018 0.071 0.047 0.106 shi Y., 2016 0.047 0.022 0.095 doraki A., 2011 0.016 0.004 0.062 ans H., 2015 0.005 0.001 0.036 z N., 2020 0.038 0.027 0.055	ro F., 2000 0.042 0.031 0.056 42 / 1004 Y., 2018 0.071 0.047 0.106 21 / 297 thi Y., 2016 0.047 0.022 0.095 7 / 150 doraki A., 2011 0.016 0.004 0.062 2 / 125 ans H., 2015 0.005 0.001 0.036 1 / 194 z N., 2020 0.038 0.027 0.055 29 / 755	ro F., 2000 0.042 0.031 0.056 42 / 1004 Y., 2018 0.071 0.047 0.106 21 / 297 hi Y., 2016 0.047 0.022 0.095 7 / 150 fornki A., 2011 0.016 0.004 0.062 2 / 125 ans H., 2015 0.005 0.001 0.036 1 / 194 z N., 2020 0.038 0.027 0.055 29 / 755 0.047 0.035 0.063 604 / 9862	ro F., 2000 0.042 0.031 0.056 42 / 1004 Y., 2018 0.071 0.047 0.106 21 / 297 shi Y., 2016 0.047 0.022 0.095 7 / 150 foraki A., 2011 0.016 0.004 0.062 2 / 125 ans H., 2015 0.005 0.001 0.036 1 / 194 z N., 2020 0.038 0.027 0.055 29 / 755 0.047 0.035 0.063 604 / 9862	Pro F., 2000 0.042 0.031 0.056 42 / 1004 Y., 2018 0.071 0.047 0.106 21 / 297	ro F., 2000 0.042 0.031 0.056 42 / 1004 Y., 2018 0.071 0.047 0.106 21 / 297

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; I²=86.91; τ^2 =0.20. Subgroup Europe/America: Q=25.24, df(Q)=10, p-value 0.005; I²=60.39; τ^2 =0.15. (B) Subgroup Prospective: Q=13.00, df(Q)=3, p-value 0.005; I²=76.93; τ^2 =0.99. Subgroup Retrospective: Q=155.03, df(Q)=17, p-value <0.001; I²=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.

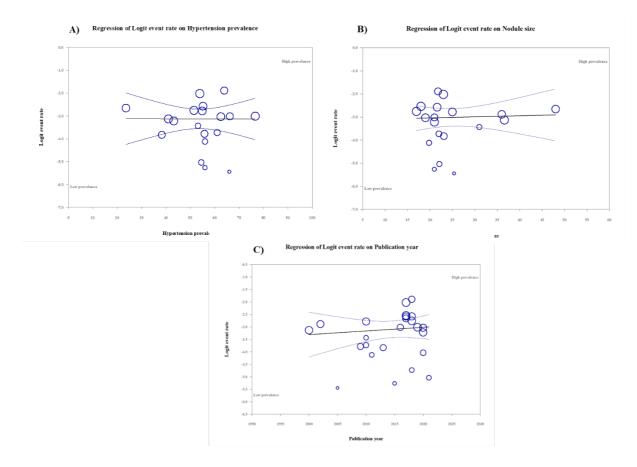


Figure S8. Meta-regression analysis for the proportion of hypertension (A), the mean nodule size (B) and (C) the year of publication on the prevalence of pheochromocytoma in patients with adrenal incidentaloma. The analysis showed that the covariates did not impact significantly on the results: (A) coefficient -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.

Cushing syndrome

Group by Country	Study name	Statistics for each study				Event rate and 95% CI		
		Event rate	Lower limit	Upper limit	Total			
	Abe I., 2018	0.049	0.016	0.142	3 / 61			
	Akkus G., 2017	0.026	0.012	0.057	6 / 229	-		
	Aoe M., 2020	0.080	0.057	0.110	33 / 413	-		
	Comlekci A., 2010	0.044	0.027	0.071	15 / 343			
	Fan C.X., 2017	0.041	0.023	0.072	11 / 270			
	Hong A.R., 2017	0.044	0.033	0.057	50 / 1149			
	Ohno Y., 2018	0.040	0.023	0.070	12 / 297			
	Tabuchi Y., 2016	0.047	0.022	0.095	7 / 150			
	Yilmaz N., 2020	0.049	0.036	0.067	37 / 755	-		
Asia		0.047	0.038	0.059	174 / 3667	→		
	Anagnostis P., 2010	0.008	0.000	0.111	0 / 64	-		
	Bernini G.P., 2005	0.004	0.000	0.065	0 / 115	—		
	Dennedy M.C., 2017	0.018	0.006	0.054	3 / 167	-		
	Falcetta P., 2021	0.029	0.015	0.055	9 / 310			
	Lamas C., 2009	0.004	0.001	0.026	1 / 270	⊢		
	Theodoraki A., 2011	0.040	0.017	0.093	5 / 125	-		
	Yeomans H., 2015	0.005	0.001	0.036	1 / 194	 -		
Europe/America		0.021	0.013	0.034	19 / 1245			

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; $I^2=36.34$; $\tau^2=0.03$. Subgroup Europe/America: Q=9.94, df(Q)=6, p-value 0.127; $I^2=39.66$; $\tau^2=0.29$

The area of each square is proportional to that study's weight in the analysis. Horizontal lines indicate the 95% confidence interval.

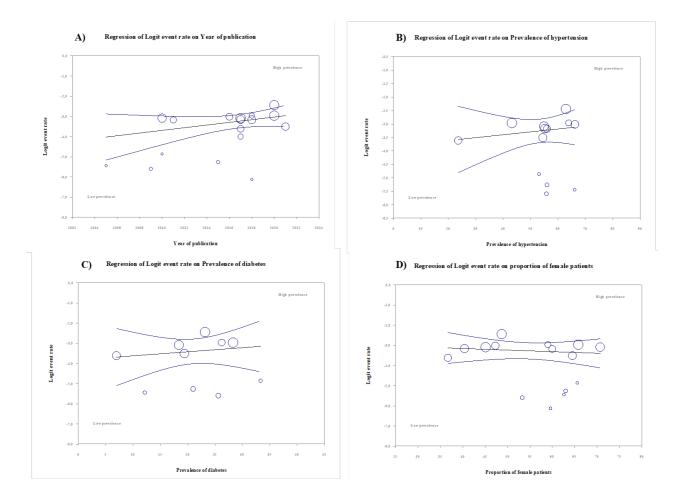


Figure S10. Meta-regression analysis for the year of study publication (**A**), the proportion of hypertension (**B**) and of diabetes (**C**) and the proportion of female patients (**D**) on the prevalence of Cushing syndrome in patients with adrenal incidentaloma. The analysis showed that the covariates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

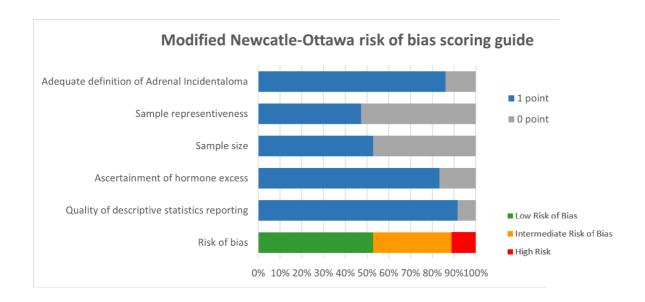
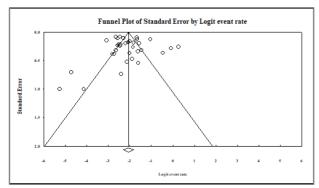
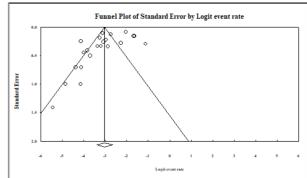


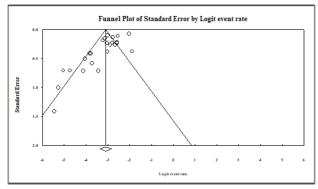
Figure S11. Qualitative evaluation of studies and risk of bias using modified Newcastle-Ottawa risk of bias scoring.

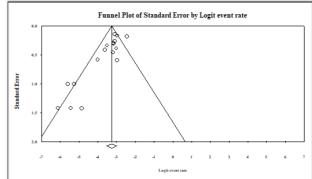




A. Autonomous cortisol secretion

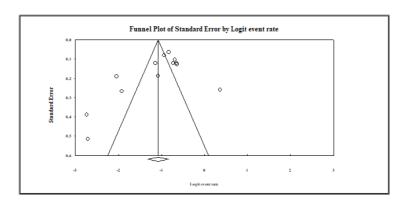
B. Primary aldosteronism





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).