#### 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]]

#### **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

<u>Is the definition of adrenal incidentaloma adequate?</u>

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  $\geq 4$  points were scored, at intermediate risk of bias when 3 points were scored and at high risk of bias if  $\leq 2$  points were scored.

Study	Biochemical tests	Profile
Abe I., 2018	Serum cortisol after 1 mg DST >50 nmol/L (>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	1
	3. Low serum DHEA-S level (with respect to the patient's age and	
	sex)	
Ahn S.H., 2018*	At least two abnormalities among:	
	1. Lack of suppression in the 1 mg DST (cortisol >138 nmol/L)	3
	2. UFC levels higher than the upper normal limit	5
	3. ACTH levels <10 pg/mL	
Akkuş G., 2017	Serum cortisol after 1 mg DST >50 nmol/L (>1.8 μg/dL) and at least	
	one of the following:	
	1. 24-h UFC levels $>300 \mu g/d$ in 2 of the 3 consecutive collections	1
	2. ACTH values <10 pg/mL	
	3. 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:	
	1. UFC > 120 $\mu$ g/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
		1
Bancos I., 2020*	Serum cortisol after 1 mg DST >50 nmol/L (1.8 μg/dL)	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	3
	2. Urinary cortisol	
	3. Plasma ACTH	
Bernini G.P.,	Serum cortisol after 1 mg DST >138 nmol/L (>5µg/dL)	3
2005		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	2
Caplan R.H.,	Serum cortisol after 1 mg DST >138 nmol/L (>5µg/dL)	2
1994		3
Cho Y.Y., 2013*	Serum cortisol after 1 mg DST >2.0 μg/dL	1
Chrisoulidou A.,	Serum cortisol after 1 mg DST >138 nmol/L (>5µg/dL) followed	
2019	by a 2-day LDDST (0.5 mg of dexamethasone every 6 h for 48 h)	3
	and 24-h UFC	
Comlekci A.,	Serum cortisol after 1 mg DST >50 nmol/L (>1.8 μg/dL) and at least	
2010	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	1
	to 8 a.m.)	
	10 0 u.m.)	

	3. Increased 24 h urinary cortisol excretion (by at least two times	
	<ul><li>above upper normal limit)</li><li>4. Lack of cortisol suppression during 1 mg dexamethasone test</li></ul>	
	(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.	
Falcetta P., 2021	Post-DST cortisol level >5 μg/dl (autonomous cortisol secretion) or	
	>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 ≥405 µg/24h (1117.8 mmol/24h)	
	2. Absence of cortisol rhythm (midnight serum cortisol >7.5 μg/dL	1
	(220 nmol/L)	1
	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	
	$\mu g/dL$ ) and at least one of the following:	1
	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)	1
	2. Absence of cortisol rhythm (midnight serum cortisol >7.5 mg/dl (220 nmol/L))	1
	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*		1
Kjellbom A., 2021*	Serum cortisol after 1 mg DST >50 nmol/L (or 1.8 μg/dL)	1
Lamas C., 2009*	At least two of the following:	
Lamas C., 2007	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)	1
	3. Raised UFC	
	4. ACTH <10 pg/mL	
Li L., 2017*	Serum cortisol after 1 mg DST >50 nmol/L (or 1.8 µg/dL),	1
	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	3
	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).	
Mantero F.,	Two or more basal or dynamic tests of the HPA axis function	
2000*	abnormal:	
	1. UFC	
	2. Plasma ACTH	
	3. Serum DHEA-S	
	4. Serum 17-OHP	3
	5. Serum cortisol at night	
	6. Serum cortisol after 1 mg DST >138 nmol/L (>5μg/dL)	
	, , , , ,	
	7. 100-mg CRH test	
M A D	8. 250-mg ACTH test	
Moraes A.B.,	Serum cortisol after 1 mg DST between 1.9-5.0 μg/dL	1
2020*		
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)	1
	2. Disruption of plasma cortisol circadian rhythm (0 h/8 h serum	
	cortisol ratio >0.5)	
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	3
	90 nmol/L (3 μg/dL) by low dose and high dose DST	
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	
14040111 1., 2010	μg/dL and at least of the following:	
	1. Plasma ACTH <10 pg/mL	
	2. Decreased ACTH response after CRH stimulation	2
	3. Loss of diurnal cortisol rhythm	
	Loss of diurnal cortisol rhythin     Decreased DHEA-S levels	
Theodorels: A		
Theodoraki A.,	Serum cortisol after 1 mg DST or 2 mg LDDST >50 nmol/L (or 1.8	
2011	$\mu$ g/dL) and at least of the following:	1
	1. ACTH <10 ng/L	
Y 11' > Y 200' '	2. Midnight serum cortisol >50 nmol/L (when individual asleep)	
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.,	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— 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	
	4. High late night salivary cortisol >0.27 μg/dL or midnight serum cortisol level >7.5 μg/dL	

**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  $\mu$ g/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  $\mu$ g/ dL) after 1 mg overnight dexamethasone test and one additional endocrine alteration (same as above). **Profile 3**: cortisol >138 nmol/L (>5 $\mu$ g/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
Bancos I., 2020	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
Barzon L., 2002	> 40 (Authors' personal communication)
Bernini G.P., 2005	> 70
Cho Y.Y., 2013	> 30
Comlekci A., 2010	> 25
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
Kjellbom A., 2021	The specific cut-off was not indicated. The authors used
	locally-derived thresholds for screening with ARR.
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	
<b>Total number of studies</b>	36
<b>Total number of patients</b>	16,158
Age (years)	58 [56 – 62]
(studies)	(31)
Female gender (n%)	58.2%
(studies)	(33)
BMI (kg/m <sup>2</sup> )	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%)	53.7%
(studies)	(25)
Prevalence of diabetes (%)	19.3%
(studies)	(18)
Nodule size (mm)	24.1 [21.0 – 28.8]
(studies)	(28)
Location of the tumor	
Left (n%)	48.7%
(studies)	(19)
Right (n%)	37.3%
(studies)	(19)
Bilateral (n%)	16.9%
(studies)	(28)

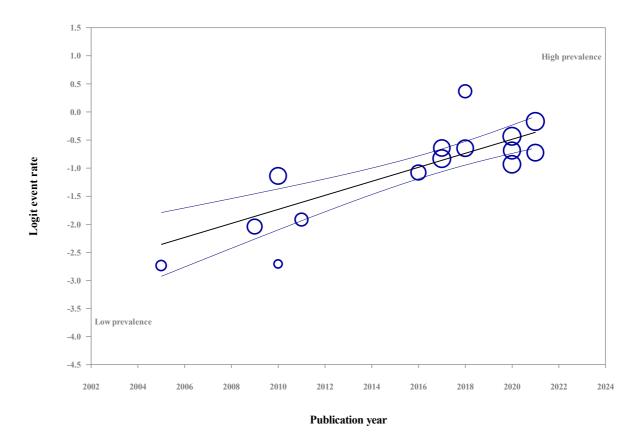
**Table S3. Clinical and biochemical parameters of the included patients.** Data are expressed as median [IQR]. In round brackets the number of studies in which the datum is available. BMI = body mass index; SBP = systolic blood pressure; DBP = diastolic blood pressure.

# **Functioning adenomas**

Country	Abe I., 2018	Event rate 0.590	Lower limit	Upper limit					
	,	0.590		шш	Total				
		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			-	
sia		0.326	0.261	0.399	1059 / 3471			•	
	Anagnostis P., 2010	0.063	0.024	0.155	4 / 64				
	Bancos I, 2020	0.393	0.370	0.416	662 / 1686				
	Bernini G.P., 2005	0.061	0.029	0.122	7 / 115		-		
	Falcetta P., 2021	0.326	0.276	0.380	101 / 310			-	
	Kjellbom A., 2021	0.457	0.429	0.485	547 / 1197				
	Lamas C., 2009	0.115	0.082	0.159	31 / 270		■		
	Theodoraki A., 201	1 0.128	0.080	0.199	16 / 125		=	-	
Europe/America		0.216	0.160	0.284	1368 / 3767			•	

**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;  $\tau^2$ =0.052. Subgroup Europe/America: Q-value 180.93, df(Q)=6, p-value<0.001;  $I^2$ =96.68;  $\tau^2$ =0.345.

## Regression of Logit event rate on Publication year

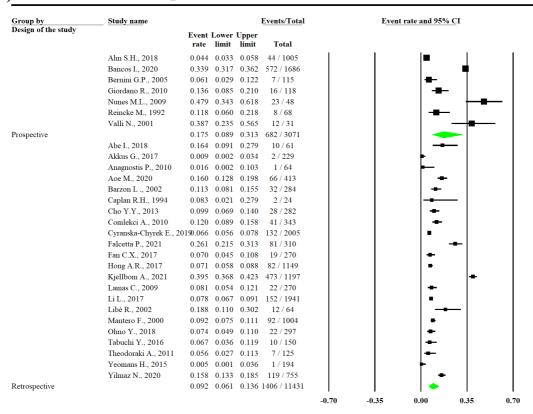


**Figure S2.** Meta-regression analysis for the publication year on the prevalence of functioning adenomas. The analysis showed that the covariate had a statically significant impact on the results: coefficient 0.125 [0.089; 0.161], p < 0.001.

# A) <u>Autonomous/possible</u> autonomous cortisol secretion

	Study name						E
Profile		Event	Lower	Upper			
		rate	limit	limit	Total		
1	Abe I., 2018	0.164	0.091	0.279	10 / 61	- 1	1
	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		
	Bancos I., 2020	0.339	0.317	0.362			
	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		0.056	0.078	132 / 2005		
	alcetta P., 2021	0.261	0.215	0.313	81 / 310		
	an C.X., 2017	0.070	0.045	0.108	19 / 270		
	Giordano R., 2010	0.136	0.085	0.210	16 / 118		
	Hong A.R., 2017	0.071	0.058	0.088	82 / 1149		
	Kjellbom A., 2021	0.395	0.368	0.423	473 / 1197		
	amas C., 2009	0.081	0.054	0.121	22 / 270		
	i 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	0.139	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	0.003	7 / 125		
	Yeomans H., 2015	0.005	0.027	0.036	1 / 194		
	ilmaz N., 2020	0.003	0.133	0.030	119 / 755		
ile 1	i iiiiaz iv., 2020	0.136	0.133		1913 / 11750		
	Bondanelli M., 1997	0.126	0.040	0.181	4/38		
	Ohno Y., 2018	0.103	0.040	0.249	22 / 297		
		0.074	0.049	0.110	10 / 150		
le 2	Sabuchi Y., 2016						
	1 CH 2010	0.079	0.027	0.211	36 / 485		
	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		
	/alli N., 2001	0.387	0.235	0.565	12 / 31		
file 3		0.118	0.067	0.200	218 / 2657		
						I	I
						-0.70	-0.35

## B) Autonomous/possible autonomous cortisol secretion

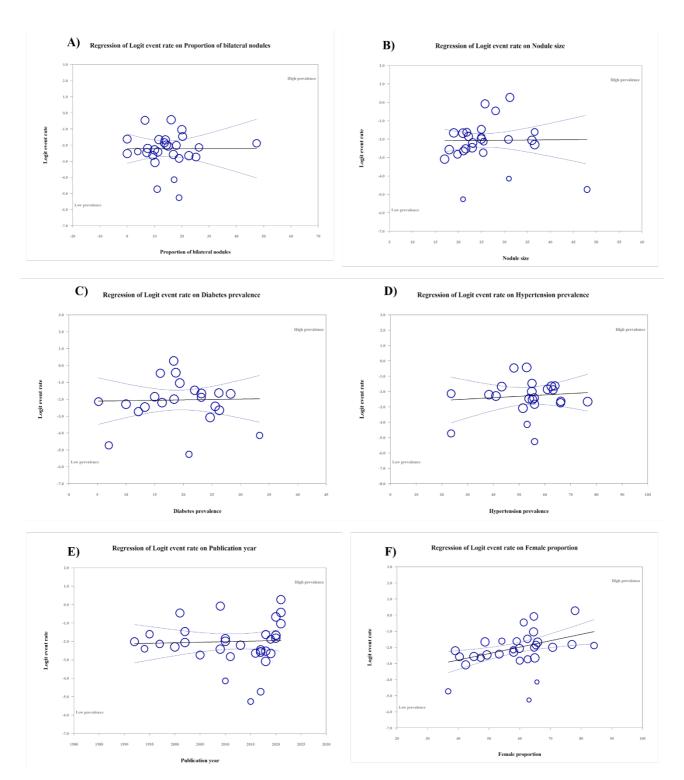


## C) Autonomous/possible autonomous cortisol secretion

Group by	Study name						Event	rate and 95	% CI
Country		Event	Lower	Upper					
		rate	limit	limit	Total				
	Abe I., 2018	0.164	0.091	0.279	10 / 61		1	-■	<b>—</b> 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			4	<b>.</b>
	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			■	
	Tabuchi Y., 2016	0.067	0.036	0.119	10 / 150				
	Yilmaz N., 2020	0.158	0.133	0.185	119 / 755				.
Asia		0.083	0.052	0.129	595 / 6895			•	
	Anagnostis P., 2010	0.016	0.002	0.103	1 / 64			▶—	
	Bancos I., 2020	0.339	0.317	0.362	572 / 1686				-
	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				
	Falcetta P., 2021	0.261	0.215	0.313	81 / 310				-
	Flecchia D., 1995	0.167	0.064	0.369	4 / 24			<b>-</b>	_
	Giordano R., 2010	0.136	0.085	0.210	16 / 118			-	-
	Kjellbom A., 2021	0.395	0.368	0.423	473 / 1197				
	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			<b>-</b>	
	Valli N., 2001	0.387	0.235	0.565	12 / 31				$\dashv$
	Yeomans H., 2015	0.005	0.001	0.036	1 / 194			•	
Europe/America		0.150	0.107	0.205	1572 / 7997			4	•
						-0.70	-0.35	0.00	0.3

**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=1150.29, df(Q)=20, p-value <0.001;  $I^2$ =98.26;  $\tau^2$ =0.94. Subgroup Profile 2: Q=0.65, df(Q)=2, p-value=0.723;  $I^2$ =0.00;  $\tau^2$ =0.00. Subgroup Profile 3: Q=63.29, df(Q)=9, p-value <0.001;  $I^2$ =85.78;  $\tau^2$ =0.38. **(B)** Subgroup Prospective: Q=272.93, df(Q)=6, p-value <0.001;  $I^2$ =97.80;  $\tau^2$ =1.71. Subgroup Retrospective: Q=876.321, df(Q)=21, p-value <0.001;  $I^2$ =97.60;  $\tau^2$ =0.88. **(C)** Subgroup Asia: Q=118.37 df(Q)=11, p-value <0.001;  $I^2$ =90.71;  $\tau^2$ =0.24. Subgroup Europe/America: Q=825.109, df(Q)=21, p-value <0.001;  $I^2$ =97.46;  $\tau^2$ =0.93.

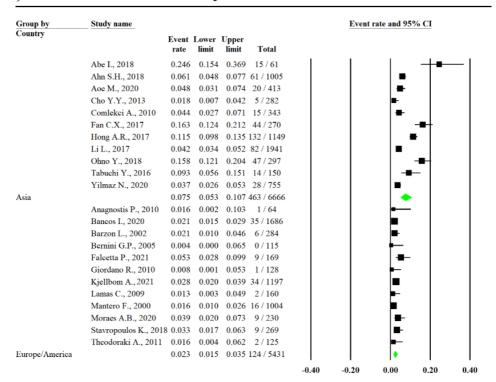
Central squares of each horizontal line represent the prevalence for each study. The area of each square is proportional to that study's weight in the analysis. Horizontal lines indicate the 95% confidence interval.



**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-E did not impact significantly on the results: **A**) coefficient 0.0001 [-0.043; 0.043], p = 0.998; **B**) coefficient 0.002 [-0.043; 0.047], p = 0.928; **C**) coefficient 0.005 [-0.067; 0.076], p = 0.897; **D**) coefficient 0.009 [-0.028; 0.046], p = 0.631; **E**) coefficient 0.006 [-0.032; 0.044], p = 0.763; while the proportion of female patients (**F**) had a significant impact on the results: **F**) coefficient 0.040 [0.018; 0.061], p = <0.001.

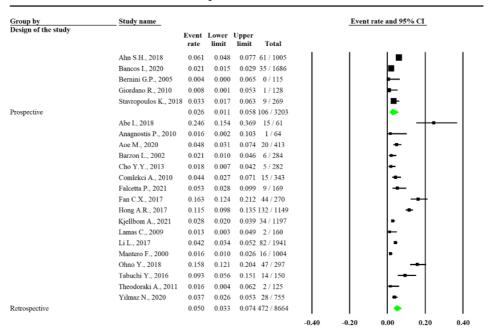
## A)

## Primary aldosteronism

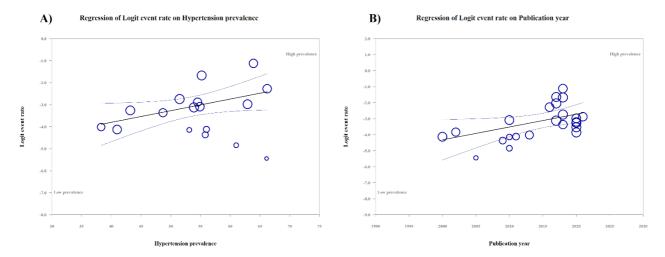


## B)

## 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;  $\tau^2$ =0.451. Subgroup Europe/America: Q=17.75; df(Q)=11, p-value 0.088;  $I^2$ =38.02;  $I^2$ =0.069 **(B)** Subgroup Prospective: Q=32.23, df(Q)=4, p-value <0.001;  $I^2$ =87.59;  $I^2$ =0.49. Subgroup Retrospective: Q=267.56, df(Q)=16, p-value <0.001;  $I^2$ =94.02;  $I^2$ =0.68. 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 [0.009; 0.098], p = 0.019; **B)** coefficient 0.080 [0.018; 0.142], p = 0.011.

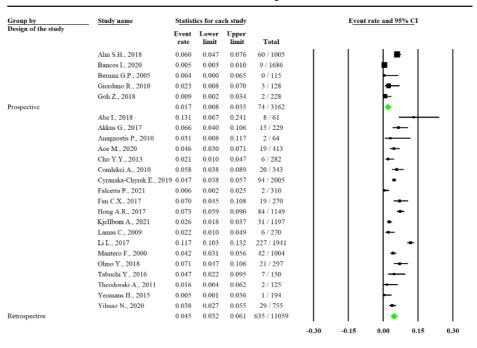
## **A**)

# Pheochromocytoma

Group by Country	Study name						Event	rate and 95	70 (.1
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				۱
	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			-	
Asia		0.062	0.046	0.083	515 / 6895			•	.
	Anagnostis P., 2010	0.031	0.008	0.117	2 / 64				-
	Bancos I., 2020	0.005	0.003	0.010	9 / 1686			•	
	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			-	
	Kjellbom A., 2021	0.026	0.018	0.037	31 / 1197			■	
	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			-	
Europe/America		0.023	0.016	0.033	211 / 7612			•	
						-0.30	-0.15	0.00	0.1

## B)

# Pheochromocytoma



**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;  $\tau^2$ =0.20. Subgroup Europe/America: Q=64.92, df(Q)=12, p-value <0.001;  $I^2$ =81.52;  $\tau^2$ =0.35. (B) Subgroup Prospective: Q=55.81, df(Q)=4, p-value <0.001;  $I^2$ =92.83;  $\tau^2$ =2.12. Subgroup Retrospective: Q=186.29, df(Q)=18, p-value <0.001;  $I^2$ =90.34;  $\tau^2$ =0.35.

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.

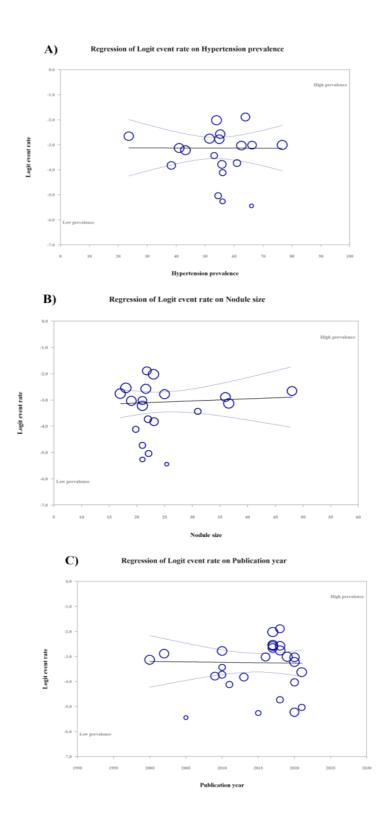


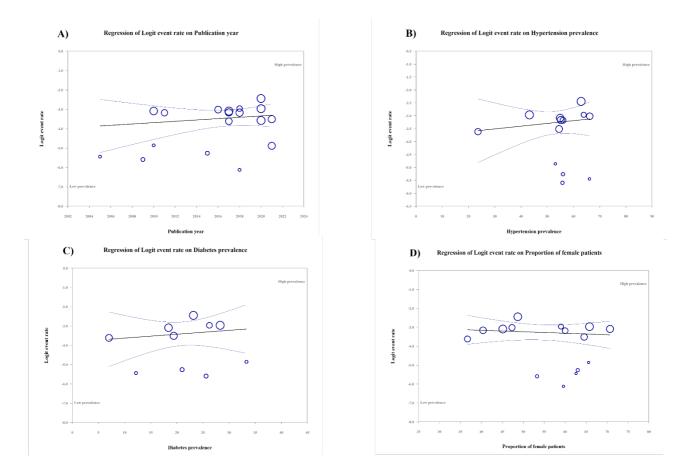
Figure S8. Meta-regression analysis for the proportion of hypertension (A), the mean nodule size (B) and (C) the year of publication on the prevalence of pheochromocytoma in patients with adrenal incidentaloma. The analysis showed that the covariates did not impact significantly on the results: (A) coefficient -0.003 [-0.028; 0.028], p = 0.986; (B) coefficient 0.008 [-0.030; 0.048], p = 0.681; (C) coefficient -0.004 [-0.055; 0.048], p = 0.888.

# **Cushing syndrome**

roup by	Study name						Event	rate and 95
ountry		Event rate	Lower limit	Upper limit	Total			
	Abe I., 2018	0.049	0.016	0.142	3 / 61	- [		I —
	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			4
		0.047	0.035	0.061	174 / 3667			
	Anagnostis P., 2010	0.008	0.000	0.111	0 / 64			<del>-</del>
	Bancos I., 2020	0.027	0.020	0.036	46 / 1686			■
	Bernini G.P., 2005	0.004	0.000	0.065	0 / 115			<b> </b>
	Falcetta P., 2021	0.029	0.015	0.055	9 / 310			
	Kjellbom A., 2021	0.008	0.004	0.014	9 / 1197			
	Lamas C., 2009	0.004	0.001	0.026	1 / 270			-
	Theodoraki A., 201	0.040	0.017	0.093	5 / 125			
	Yeomans H., 2015	0.005	0.001	0.036	1 / 194			
rope/America		0.018	0.012	0.027	71 / 3961			•
						-0.20	-0.10	0.00

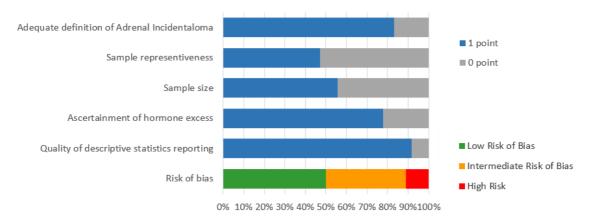
**Figure S9.** Forest plot of the subgroup analysis of the prevalence of Cushing syndrome in patients with adrenal incidentaloma, comparing studies according to the geographical area where they were conducted. The only study performed in New Zealand (Goh Z., 2018) was excluded from the analysis. Central 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=22.57, df(Q)=7, p-value 0.002;  $I^2=68.98$ ;  $\tau^2=0.40$ .

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

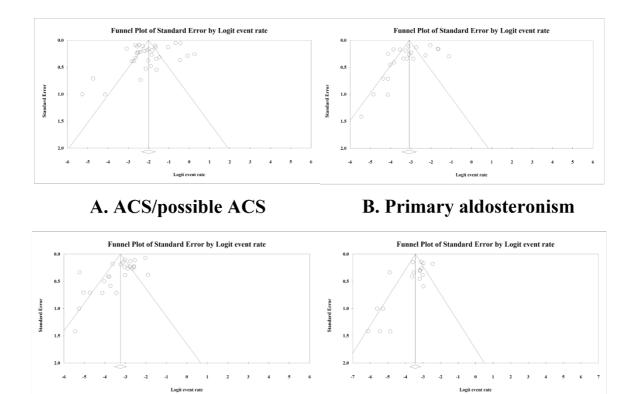


**Figure S10.** Meta-regression analysis for the year of study publication (**A**), the proportion of hypertension (**B**) and of diabetes (**C**) and the proportion of female patients (**D**) on the prevalence of Cushing syndrome in patients with adrenal incidentaloma. The analysis showed that the covariates did not impact significantly on the results (**A**) coefficient 0.035 [-0.052; 0.121], p = 0.436; (**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.

## Modified Newcatle-Ottawa risk of bias scoring guide

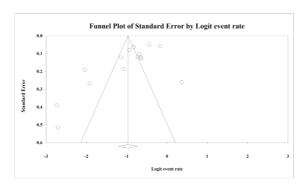


**Figure S11.** Qualitative evaluation of studies and risk of bias using modified Newcastle-Ottawa risk of bias scoring.



## C. Pheochromocytoma

## D. Cushing syndrome



## E. Functioning adenomas

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