#### SUPPLEMENTARY MATERIAL

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

Elisa Sconfienza<sup>1</sup>, Martina Tetti<sup>1</sup>, Vittorio Forestiero<sup>1</sup>, Franco Veglio<sup>1</sup>, Paolo Mulatero<sup>1</sup>, Silvia Monticone<sup>1</sup>

<sup>1</sup> Division of Internal Medicine and Hypertension Unit, Department of Medical Sciences, University of Torino, Via Genova 3, 10126 Torino, Italy.

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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

#### (1) Selection

Is the definition of adrenal incidentaloma adequate?

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

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

1 point: consecutive or obviously representative series of cases

0 point: potential for selection biases or not stated

## (2) Sample size

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

0 points: sample size was less than 30 participants

### (3) Ascertainment of hormone excess

1 point: the diagnosis was made according with the available scientific recommendations.

Diagnostic criteria and cut-off to define hormone excess were clearly stated

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

### (4) Quality of descriptive statistics reporting

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

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

**Legend**: the individual components listed above are summed to generate a total modified Newcastle-Ottawa risk of bias score for each study, ranging from 0 to 5. Studies were judged to be at low risk of bias when  $\geq 4$  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.

#### Reference list of included studies

- 1. **Abe I**, Sugimoto K, Miyajima T, et al. Clinical Investigation of Adrenal Incidentalomas in Japanese Patients of the Fukuoka Region with Updated Diagnostic Criteria for Sub-clinical Cushing's Syndrome. *Intern Med.* 2018;57(17):2467-2472.
- 2. **Ahn SH**, Kim JH, Baek SH, et al. Characteristics of Adrenal Incidentalomas in a Large, Prospective Computed Tomography-Based Multicenter Study: The COAR Study in Korea. *Yonsei Med J.* 2018;59(4):501-510.
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- 5. **Aoe M**, Okada A, Usui T, Manaka K, Nangaku M, Makita N. Comparison between the clinical characteristics of patients with adrenal incidentalomas and those with hypertension-associated adrenal tumors in a single center in Japan. *Endocr J.* 2020;67(6):645-654.
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- 15. **Falcetta P**, Orsolini F, Benelli E, et al. Clinical features, risk of mass enlargement, and development of endocrine hyperfunction in patients with adrenal incidentalomas: a long-term follow-up study. *Endocrine*. 2021;71(1):178-188.
- 16. Fan CX, Zhang JJ, Cai YY, et al. Nan Fang Yi Ke Da Xue Xue Bao. 2017;37(8):1054-1059.
- 17. **Flecchia D**, Mazza E, Carlini M, et al. Reduced serum levels of dehydroepiandrosterone sulphate in adrenal incidentalomas: a marker of adrenocortical tumour. *Clin Endocrinol (Oxf)*. 1995;42(2):129-134.
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- 31. **Stavropoulos K**, Imprialos KP, Katsiki N, et al. Primary aldosteronism in patients with adrenal incidentaloma: Is screening appropriate for everyone?. *J Clin Hypertens (Greenwich)*. 2018;20(5):942-948.
- 32. **Tabuchi Y**, Otsuki M, Kasayama S, et al. Clinical and endocrinological characteristics of adrenal incidentaloma in Osaka region, Japan. *Endocr J.* 2016;63(1):29-35.
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Profile 1	Profile 2	Profile 3
Abe I., 2018	Bondanelli M., 1997	Ahn S.H., 2018
Akkuş G., 2017	Kastelan D., 2015	Barzon L., 2002
Anagnostis P., 2010	Ohno Y., 2018	Bernini G.P., 2005
Aoe M., 2020	Tabuchi Y., 2016	Caplan R.H., 1994
Cho Y.Y., 2013		Chrisoulidou A., 2019
Comlekci A., 2010		Flecchia D., 1995
Cyranska-Chyrek E., 2019		Libè R., 2002
Dennedy M.C., 2017		Mantero F., 2000
Falcetta P., 2021		Reincke M., 1992
Fan C.X., 2017		Valli N., 2001
Giordano R., 2010		
Goh Z., 2018		
Hong A.R., 2017		
Lamas C., 2009		
Li L., 2017		
Moraes A.B., 2020		
Nunes M.L., 2009		
Šojat A.S., 2021		
Theodoraki A., 2011		
Yeomans H., 2015		
Yilmaz N., 2020		

Table S1. Criteria adopted to diagnose autonomous cortisol secretion (ACS). Three different hormonal profiles were used to describe ACS associated with adrenal incidentalomas. Profile 1: serum cortisol >50 nmol/L (>1.8  $\mu$ 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. In case one study did not fit completely with the profiles described, yet specific criteria were used to diagnose autonomous cortisol secretion, the study was included in the analysis.

Characteristics	
<b>Total number of studies</b>	36
<b>Total number of patients</b>	13,763
Age (years)	58 [56 – 62]
(studies)	(33)
Female gender (n%)	58.4%
(studies)	(34)
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%)	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)

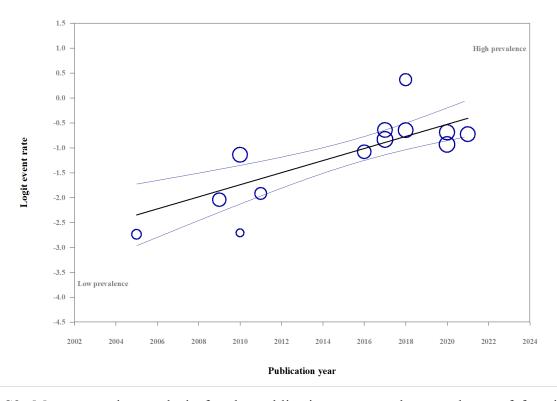
**Table S2. Clinical and biochemical parameters of the included patients.** Data are expressed as median [IQR]. In round brackets the number of studies in which the datum is available. BMI = body mass index; SBP = systolic blood pressure; DBP = diastolic blood pressure.

# **Functioning adenomas**

Group by	Study name	Statist	ics for eac	ch study	Events/Total		Event 1	rate and 9	5% 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			•	.	
						-0.75	-0.38	0.00	0.38	0.7

**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 63.62, df(Q)=4, p-value<0.001;  $I^2$ =93.71;  $\tau^2$ =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.

# **Autonomous cortisol secretion**

Group by	Study name	Statis	tics for each	study		Ev	ent rate and 9	5% CI	
Profile		Event rate	Lower limit	Upper limit	Total				
	Abe I., 2018	0.164	0.091	0.279	10 / 61		-	<b>-</b>	
	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	0.049	0.040	0.059	98 / 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			<b>⊢</b> •	
	Šojat 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		<b>+</b>		
	Yilmaz N., 2020	0.158	0.133	0.185	119 / 755		•	.	
rofile 1		0.113	0.085	0.151	881 / 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	0.043	0.169	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		-	<b>-</b>	
	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	0.075	0.178	218 / 2657		•	.	
						' '		'	

# **Autonomous cortisol secretion**

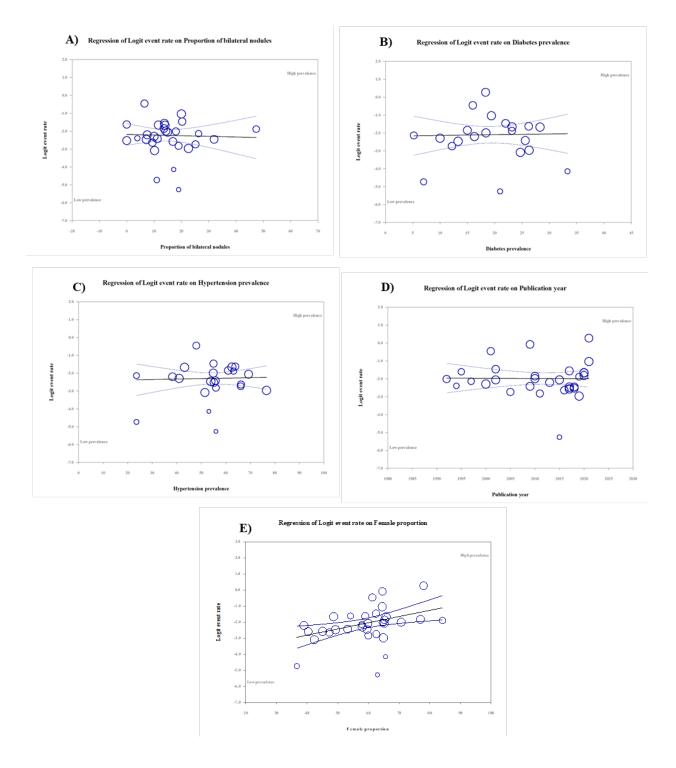
Group by	Study name	Statist	ics for eac	h study		Event	rate and 9	5% CI	
Design of the study		Event rate	Lower limit	Upper limit	Total				
	Ahn S.H., 2018	0.044	0.033	0.058	44 / 1005				
	Bernini G.P., 2005	0.061	0.029	0.122	7 / 115		■-		
	Giordano R., 2010	0.136	0.085	0.210	16 / 118		-	-	
	Goh Z., 2018	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			_=	-
rospective		0.137	0.086	0.210	128 / 1613		4		
-	Abe I., 2018	0.164	0.091	0.279	10 / 61		-	<b>-</b> - ∣	
	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., 2019	0.049	0.040	0.059	98 / 2005		-		
	Dennedy M.C., 2017	0.174	0.123	0.239	29 / 167		- 4	-	
	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				
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	Li L., 2017	0.078	0.067	0.091	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	0.036	0.119	10 / 150		-		
	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				
etrospective		0.093	0.071	0.120	964 / 10720		•		

## C) Autonomous cortisol secretion

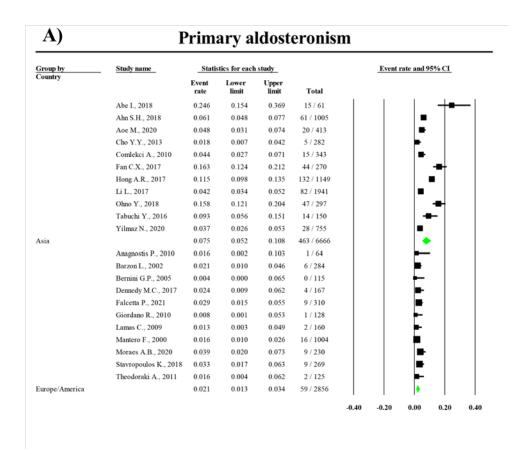
Group by	Study name	Statis	stics for each	study	Event rate a			% CI
Country		Event rate	Lower limit	Upper limit	Total			
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	Ahn S.H., 2018	0.044	0.033	0.058	44 / 1005			
	Akkus G., 2017	0.009	0.002	0.034	2 / 229		•	
	Aoe M., 2020	0.160	0.128	0.198	66 / 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		■	
	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	0.057	0.122	595 / 6895		•	
	Anagnostis P., 2010	0.016	0.002	0.103	1 / 64		<b>⊨</b> -	
	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		- <del>-</del> -	.
	Caplan R.H., 1994	0.083	0.021	0.279	2 / 24		-	-
	Chrisoulidou A., 2019	0.132	0.056	0.280	5 / 38		- <del>-</del> -	-
	Cyranska-Chyrek E., 2019	0.049	0.040	0.059	98 / 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		-	$\dashv$
	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		<del></del> -	
	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			<del>-</del>
	Yeomans H., 2015	0.005	0.001	0.036	1 / 194		÷	
Europe/America		0.134	0.100	0.177	558 / 5600		•	

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

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



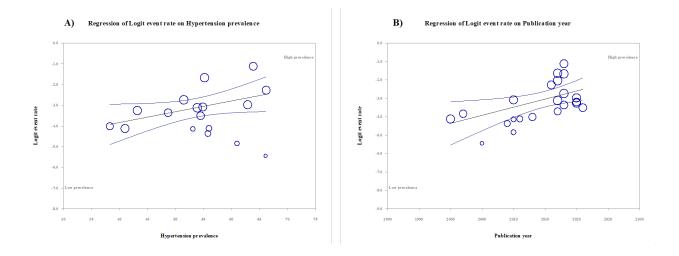
**Figure S4.** Meta-regression analysis for the proportion of bilateral nodules (**A**), the proportion of diabetes (**B**) and of hypertension (**C**) the year of publication (**D**) and the proportion of female patients (**E**) on the prevalence of autonomous cortisol secretion in patients with adrenal incidentaloma. The analysis showed that the covariates A-D did not impact significantly on the results: **A**) coefficient -0.004 [-0.032; 0.025], p = 0.800; **B**) coefficient 0.004 [-0.052; 0.060, p = 0.891; **C**) coefficient 0.002 [-0.019; 0.024], p = 0.821; **D**) coefficient -0.006 [-0.037; 0.025], p = 0.706; while the proportion of female patients (E) had a significant impact on the results: **E**) coefficient 0.039 [0.017; 0.061], p = <0.001.



#### B) Primary aldosteronism Group by Design of the study Study name Event rate and 95% CI Ahn S.H., 2018 0.061 0.048 0.077 61 / 1005 Bernini G.P., 2005 0.004 0.000 0.065 Giordano R., 2010 0.008 0.001 0.053 1/128Stavropoulos K., 2018 0.033 0.017 0.063 9 / 269 0.027 0.010 0.073 71 / 1517 Prospective Abe I., 2018 0.246 0.154 0.369 15 / 61 Anagnostis P., 2010 0.016 0.002 0.103 Aoe M., 2020 0.048 0.031 0.074 20 / 413 Barzon L., 2002 0.021 0.010 0.046 6 / 284 Cho Y.Y., 2013 0.018 0.007 0.042 5 / 282 Comlekci A., 2010 0.027 0.071 15 / 343 0.044 Dennedy M.C., 2017 0.024 0.009 0.062 4 / 167 Faketta P., 2021 Fan C.X., 2017 0.212 44 / 270 0.163 0.124 Hong A.R., 2017 0.115 0.098 0.135 132 / 1149 Lamas C., 2009 0.013 Li L., 2017 0.042 0.034 0.052 82 / 1941 Mantero F., 2000 0.016 0.010 0.026 16 / 1004 Ohno Y., 2018 0.158 Tabuchi Y., 2016 0.093 0.056 0.151 14 / 150 Theodoraki A., 2011 0.016 0.004 0.062 2 / 125 Yilmaz N., 2020 0.037 0.026 0.053 28 / 755 Retrospective 0.048 0.032 0.072 442 / 7775 -0.20 0.00 0.20 0.40

**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=10.44; df(Q)=10, p-value 0.40;  $I^2$ =4.25;  $\tau^2$ =0.01 (**B**) Subgroup Prospective: Q=10.26, df(Q)=3, p-value 0.016;  $I^2$ =70.78;  $\tau^2$ =0.41. Subgroup Retrospective: Q=248.46, df(Q)=16, p-value <0.001;  $I^2$ =93.56;  $\tau^2$ =0.69.

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



**Figure S6**. Meta-regression analysis for the proportion of hypertension **(A)** and the year of publication **(B)** on the prevalence of primary aldosteronism in patients with adrenal incidentaloma. The analysis showed that the factors have a significant impact on the results: A) coefficient 0.0521 [0.070; 0.097], p = 0.024; B) coefficient 0.088 [0.029; 0.147], p = 0.003.

Group by	Study name	Study name Statistics for each study							
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	■			
sia		0.062	0.048	0.081	515 / 6895	•			
	Anagnostis P., 2010	0.031	0.008	0.117	2 / 64	- I			
	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	<b>  -</b>			
	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				

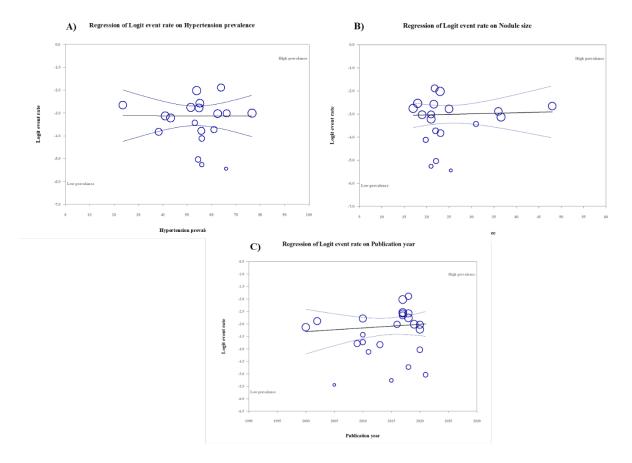
Group by	Study name	Statist	ics for eac	h study			Event	rate and 9	5% CI	
Design of the study		Event rate	Lower limit	Upper limit	Total					
	Ahn S.H., 2018	0.060	0.047	0.076	60 / 1005					
	Bernini G.P., 2005	0.004	0.000	0.065	0 / 115			-		
	Giordano R., 2010	0.023	0.008	0.070	3 / 128			-		
	Goh Z., 2018	0.009	0.002	0.034	2 / 228			-		
rospective		0.027	0.012	0.058	65 / 1476			•		
	Abe I., 2018	0.131	0.067	0.241	8 / 61					-
	Akkus G., 2017	0.066	0.040	0.106	15 / 229			-	-	
	Anagnostis P., 2010	0.031	0.008	0.117	2 / 64				_	
	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			-	-	
	Cyranska-Chyrek E., 2019	0.047	0.038	0.057	94 / 2005			•		
	Falcetta P., 2021	0.006	0.002	0.025	2/310			-		
	Fan C.X., 2017	0.070	0.045	0.108	19 / 270			-	_	
	Hong A.R., 2017	0.073	0.059	0.090	84 / 1149			٠.	-	
	Lamas C., 2009	0.022	0.010	0.049	6 / 270			-		
	Li L., 2017	0.117	0.103	0.132	227 / 1941				-	
	Mantero F., 2000	0.042	0.031	0.056	42 / 1004			-		
	Ohno Y., 2018	0.071	0.047	0.106	21 / 297			-	_	
	Tabuchi Y., 2016	0.047	0.022	0.095	7 / 150				-	
	Theodoraki A., 2011	0.016	0.004	0.062	2 / 125			-		
	Yeomans H., 2015	0.005	0.001	0.036	1 / 194			-		
	Yilmaz N., 2020	0.038	0.027	0.055	29 / 755			-		
Retrospective		0.047	0.035	0.063	604 / 9862			•		
						1	,	1	'	
						-0.30	-0.15	0.00	0.15	0.30

**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=25.24, df(Q)=10, p-value 0.005;  $I^2$ =60.39;  $\tau^2$ =0.15. (B) Subgroup Prospective: Q=13.00, df(Q)=3, p-value 0.005;  $I^2$ =76.93;  $\tau^2$ =0.99. Subgroup Retrospective: Q=155.03, df(Q)=17, p-value <0.001;  $I^2$ =89.03;  $\tau^2$ =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.



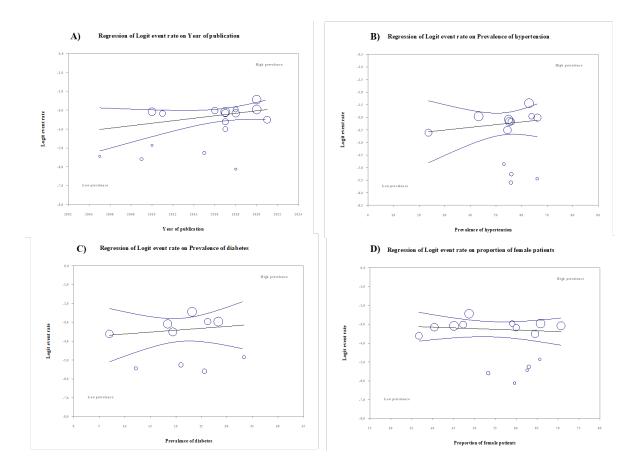
**Figure S8.** Meta-regression analysis for the proportion of hypertension (A), the mean nodule size (B) and (C) the year of publication on the prevalence of pheochromocytoma in patients with adrenal incidentaloma. The analysis showed that the covariates did not impact significantly on the results: (A) 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	Study name	Statis	tics for eacl	n study		$\mathbf{E}$	vent rate an	d 95% CI
Country		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			<b>-</b>
	Hong A.R., 2017	0.044	0.033	0.057	50 / 1149			-
	Ohno Y., 2018	0.040	0.023	0.070	12 / 297			<b>-</b>
	Tabuchi Y., 2016	0.047	0.022	0.095	7 / 150			
	Yilmaz N., 2020	0.049	0.036	0.067	37 / 755			-
sia		0.047	0.038	0.059	174 / 3667			•
	Anagnostis P., 2010	0.008	0.000	0.111	0 / 64		-	<del></del>
	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			

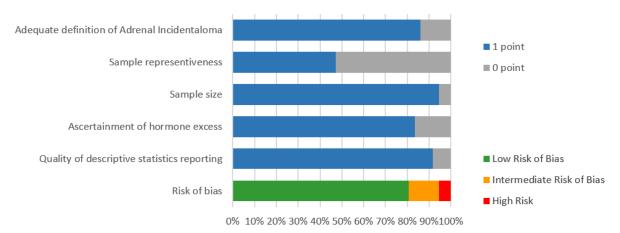
**Figure S9.** Forest plot of the subgroup analysis of the prevalence of Cushing syndrome in patients with adrenal incidentaloma, comparing studies according to the geographical area where they were conducted. The only study performed in New Zealand (Goh Z., 2018) was excluded from the analysis. Central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

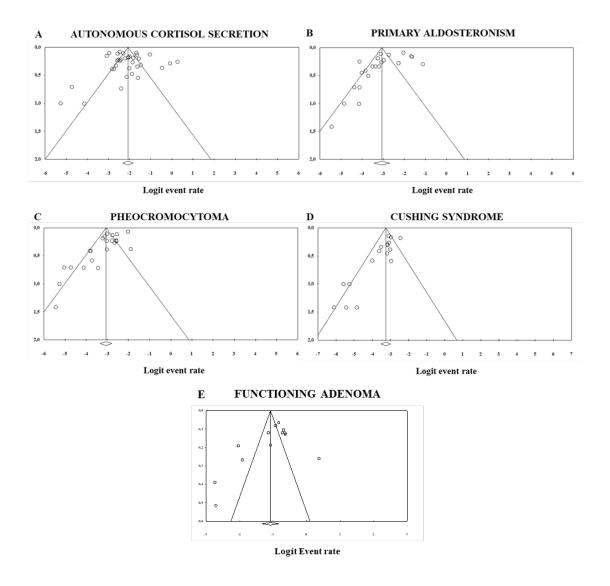


**Figure S10.** Meta-regression analysis for the year of study publication (**A**), the proportion of hypertension (**B**) and of diabetes (**C**) and the proportion of female patients (**D**) on the prevalence of Cushing syndrome in patients with adrenal incidentaloma. The analysis showed that the covariates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

# 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.



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