

## SUPPLEMENTARY MATERIAL

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

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#### Table of contents

#### Supplemental methods.

#### Reference list of included studies.

**Table S1.** Criteria adopted to diagnose autonomous cortisol secretion (ACS).

**Table S2.** Clinical and biochemical parameters of the included patients.

**Figure S1.** Forest plot of the subgroup analysis of the prevalence of secreting tumours, according to the geographical area.

**Figure S2.** Meta-regression analysis for the publication year on the prevalence of functioning adenomas.

**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**).

**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.

**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**).

**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.

**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**).

**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.

**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.

**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.

**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).

## Supplemental methods

### Pubmed search

((adrenal incidentaloma [Title/abstract] OR adrenal incidentalomas [Title/abstract] OR adrenal mass [Title/abstract]) AND (aldosterone OR hyperaldosteronism OR Conn's syndrome OR aldosteronism)) OR ((adrenal incidentaloma [Title/abstract] OR adrenal incidentalomas [Title/abstract] OR adrenal mass [Title/abstract]) AND (cortisol OR hypercortisolism OR Cushing syndrome)) OR ((adrenal incidentaloma [Title/abstract] OR adrenal incidentalomas [Title/abstract] OR adrenal mass [Title/abstract]) AND (cortisol OR hypercortisolism OR Cushing syndrome)) OR ((adrenal incidentaloma [Title/abstract] OR adrenal incidentalomas [Title/abstract] OR adrenal mass [Title/abstract]) AND (subclinical hypercortisolism OR subclinical Cushing syndrome)) OR ((adrenal incidentaloma [Title/abstract] OR adrenal incidentalomas [Title/abstract] OR adrenal mass [Title/abstract]) AND (pheochromocytoma OR metanephrines OR normetanephrine OR catecholamines)). Items found: 1752

### Ovid MEDLINE search

#1 incidentaloma\* Results: 2326  
#2 exp hyperaldosteronism Results: 9401  
#3 exp pheochromocytoma Results: 15494  
#4 exp hypercortisolism Results: 12394  
#5 1 and 2 Results: 98  
#6 1 and 3 Results: 297  
#7 1 and 4 Results: 298  
#8 5 or 6 or 7 Results: 572

### Web of Science

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

### Modified Newcastle-Ottawa risk of bias scoring guide

**(1) Selection**

Is the definition of adrenal incidentaloma adequate?

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

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

Sample representativeness

1 point: consecutive or obviously representative series of cases

0 point: potential for selection biases or not stated

**(2) Sample size**

1 point: sample size was greater than or equal to 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.
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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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21. **Kastelan D**, Kraljevic I, Dusek T, et al. The clinical course of patients with adrenal incidentaloma: is it time to reconsider the current recommendations?. *Eur J Endocrinol*. 2015;173(2):275-282.
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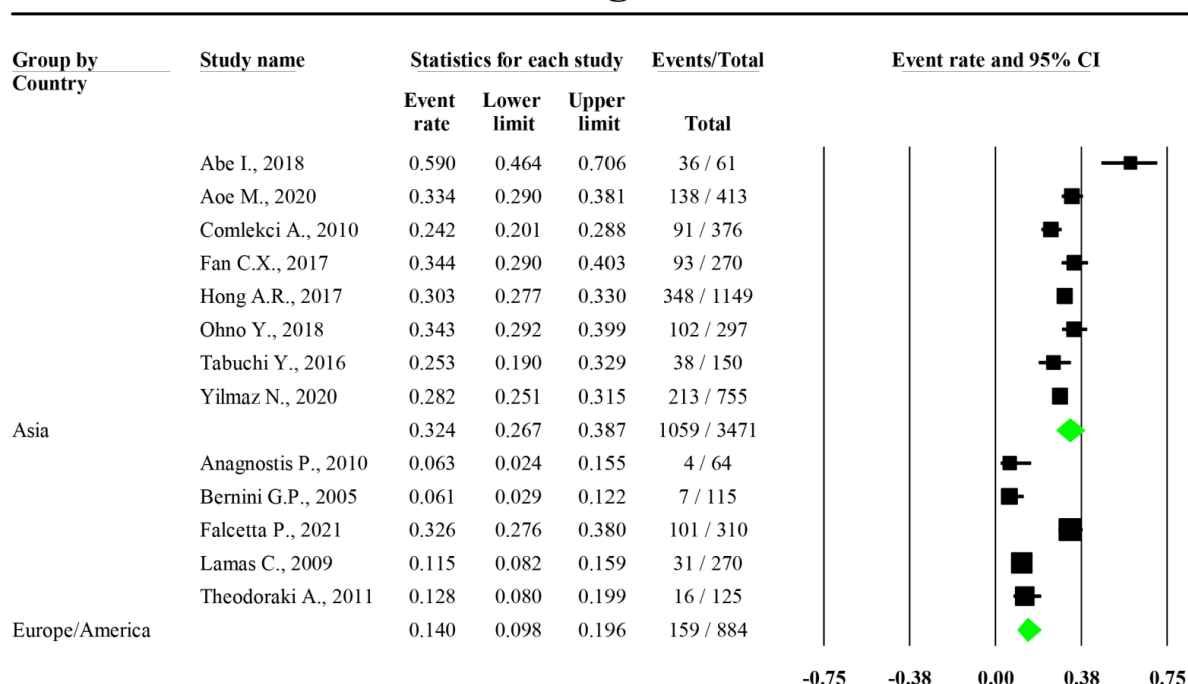
Profile 1	Profile 2	Profile 3
Abe I., 2018 Akkuş G., 2017 Anagnostis P., 2010 Aoe M., 2020 Cho Y.Y., 2013 Comlekci A., 2010 Cyranska-Chyrek E., 2019 Dennedy M.C., 2017 Falcetta P., 2021 Fan C.X., 2017 Giordano R., 2010 Goh Z., 2018 Hong A.R., 2017 Lamas C., 2009 Li L., 2017 Moraes A.B., 2020 Nunes M.L., 2009 Šojat A.S., 2021 Theodoraki A., 2011 Yeomans H., 2015 Yilmaz N., 2020	Bondanelli M., 1997 Kastelan D., 2015 Ohno Y., 2018 Tabuchi Y., 2016	Ahn S.H., 2018 Barzon L., 2002 Bernini G.P., 2005 Caplan R.H., 1994 Chrisoulidou A., 2019 Flecchia D., 1995 Libè R., 2002 Mantero F., 2000 Reincke M., 1992 Valli N., 2001

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

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

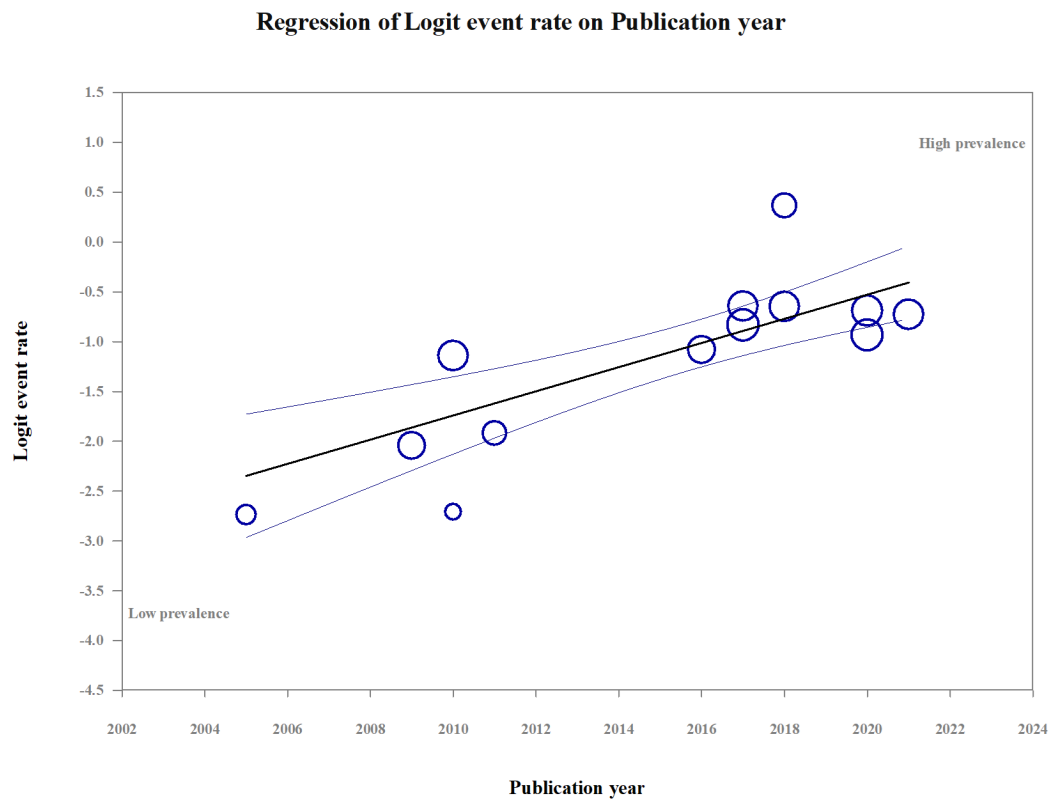
**Table S2. Clinical and biochemical parameters of the included patients.** Data are expressed as median [IQR]. In round brackets the number of studies in which the datum is available. BMI = body mass index; SBP = systolic blood pressure; DBP = diastolic blood pressure.

## Functioning adenomas



**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;  $I^2=93.71$ ;  $\tau^2=0.82$ .

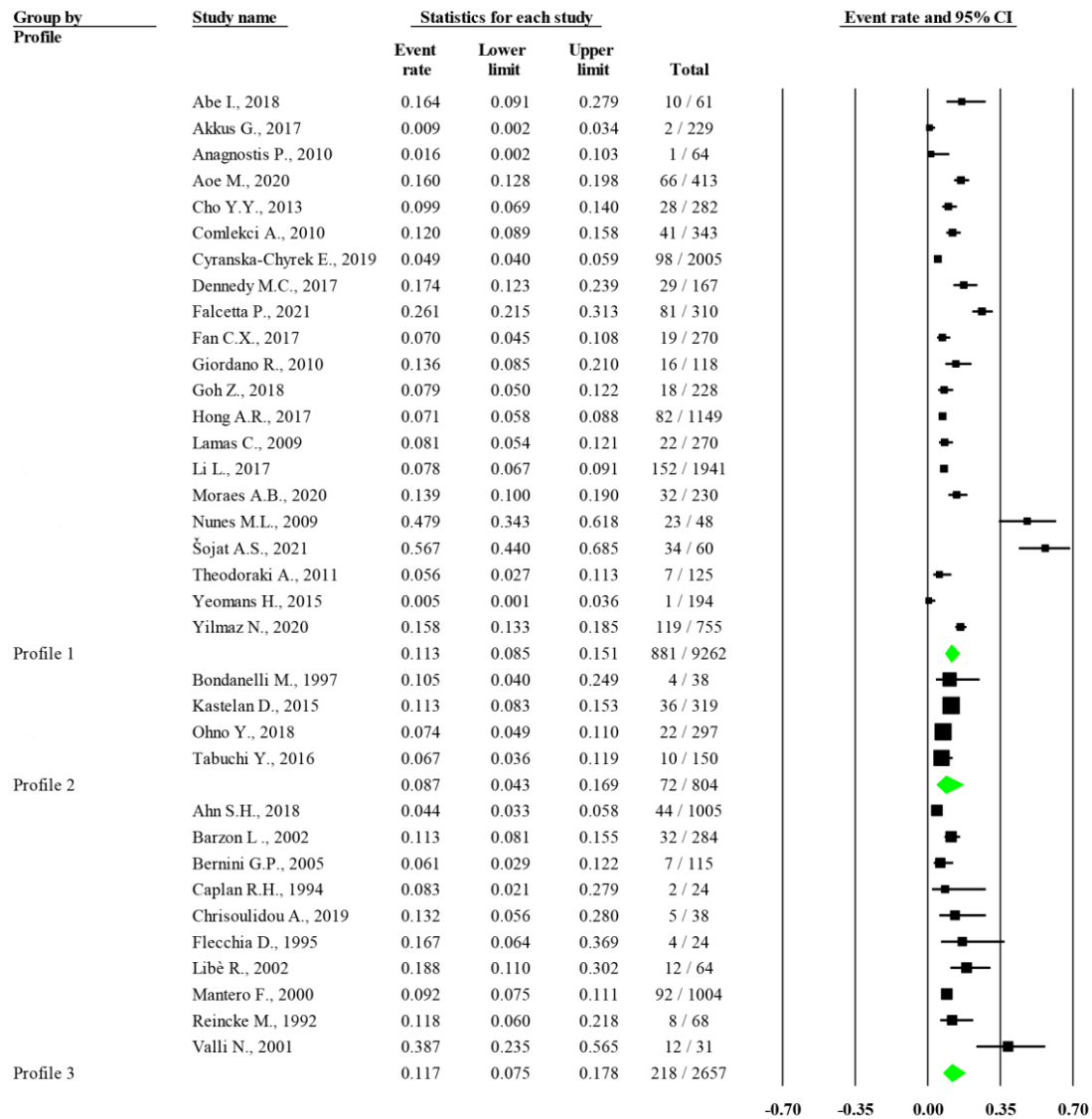




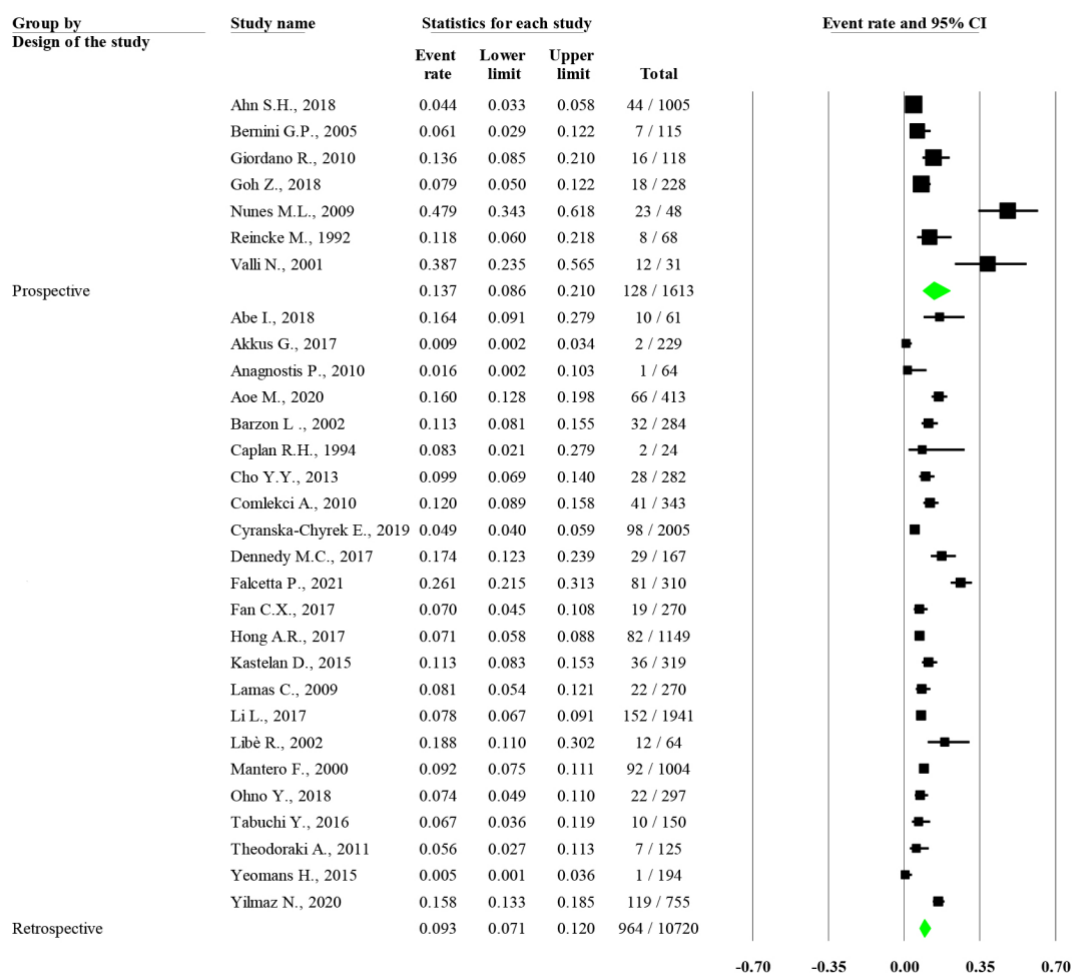
**Figure S2.** Meta-regression analysis for the publication year on the prevalence of functioning adenomas. The analysis showed that the covariates had a statically significant impact on the results: coefficient 0.121 [0.079; 0.164],  $p < 0.001$ .

A)

## Autonomous cortisol secretion

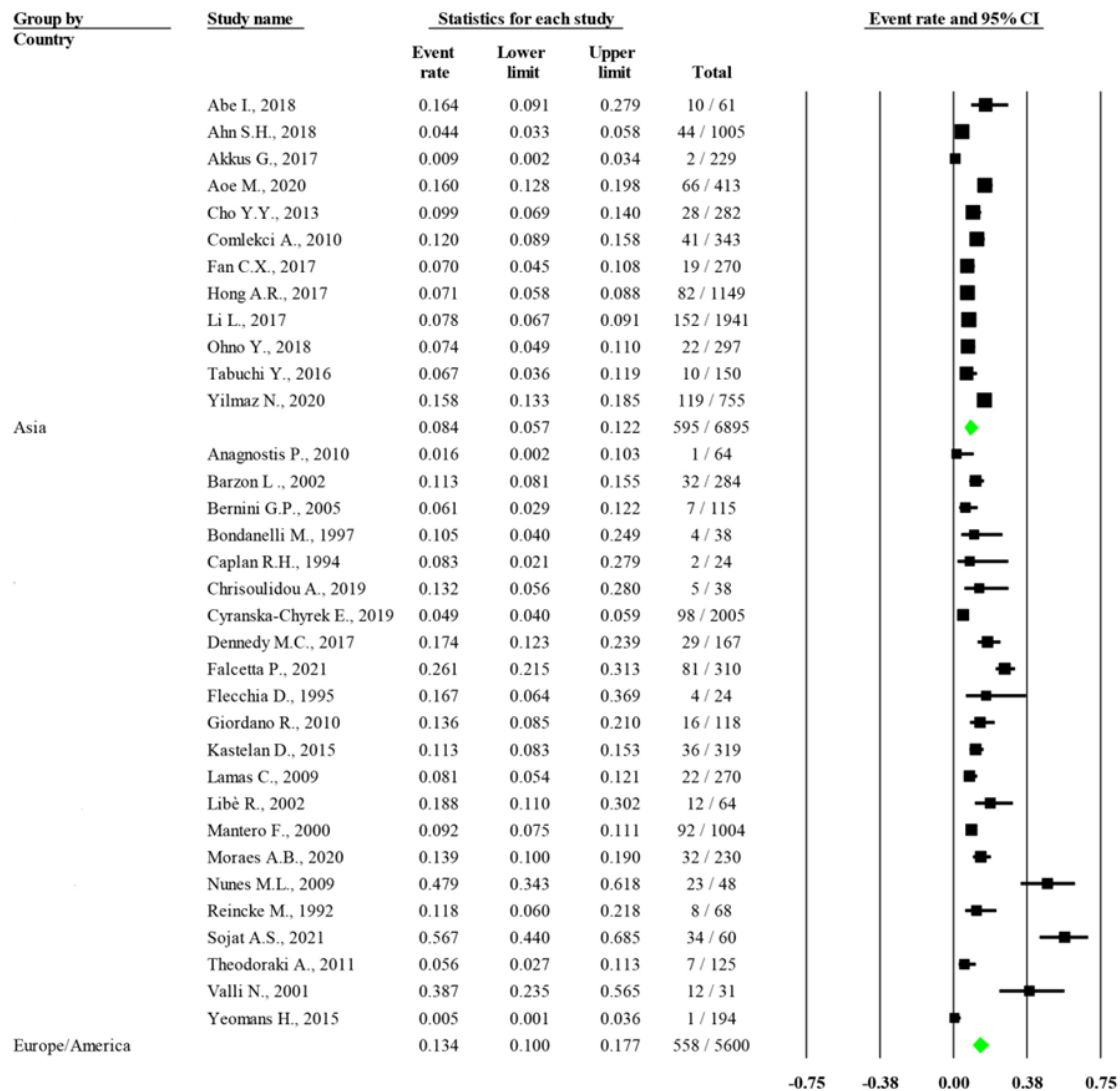


## B) Autonomous cortisol secretion



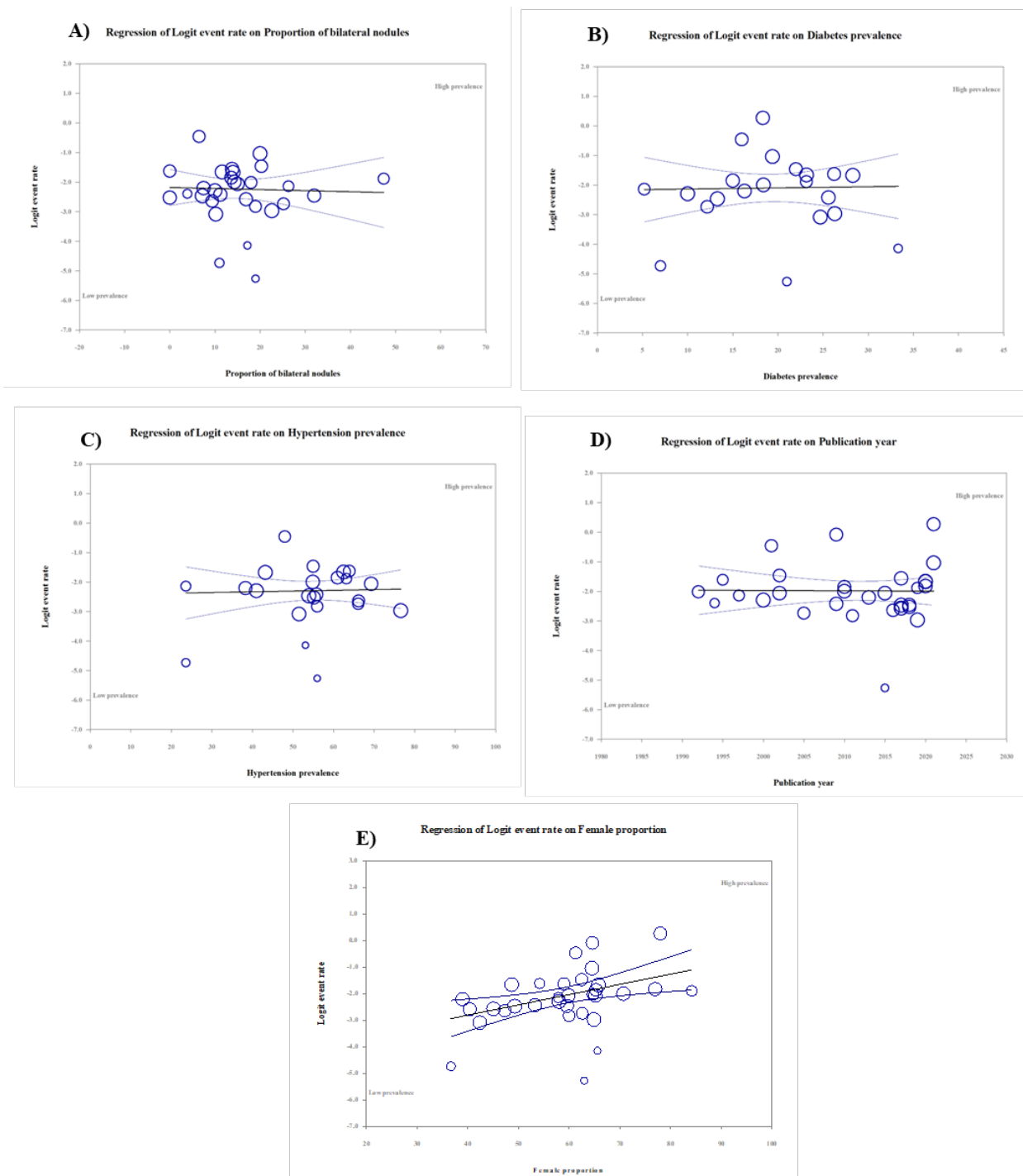
C)

## Autonomous cortisol secretion



**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  $<0.001$ ;  $I^2=93.51$ ;  $\tau^2=0.74$ .

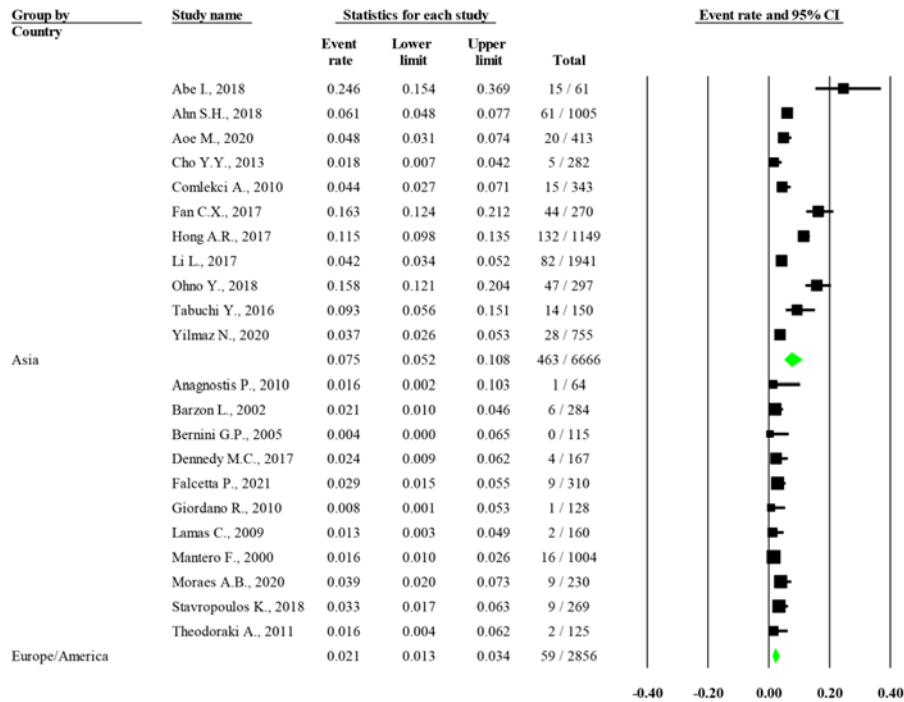
Central squares of each horizontal line represent the prevalence for each study. The area of each square is proportional to that study's weight in the analysis. Horizontal lines indicate the 95% confidence interval.



**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],  $p < 0.001$ .

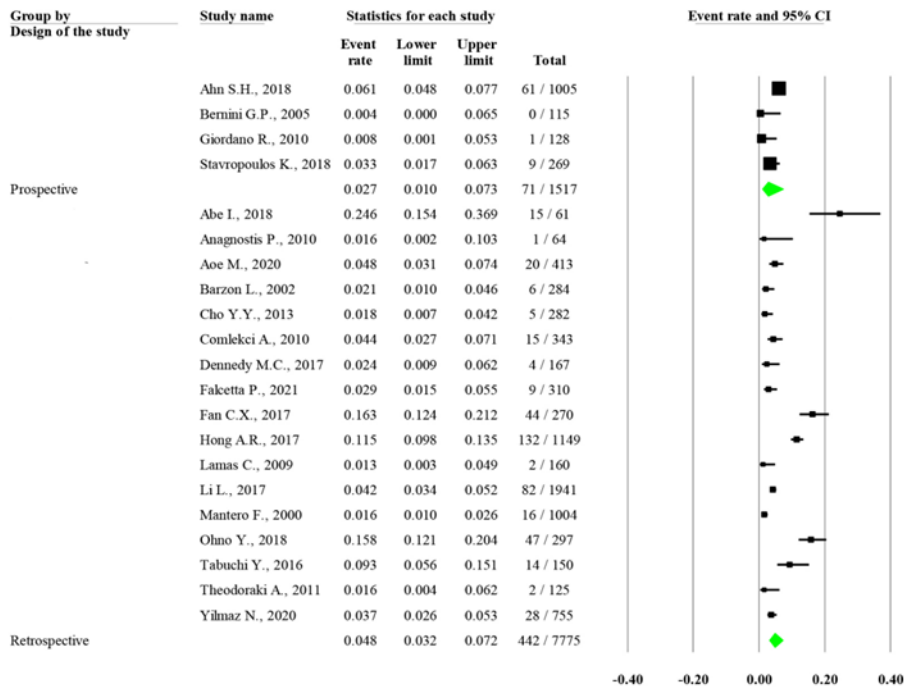
A)

## Primary aldosteronism

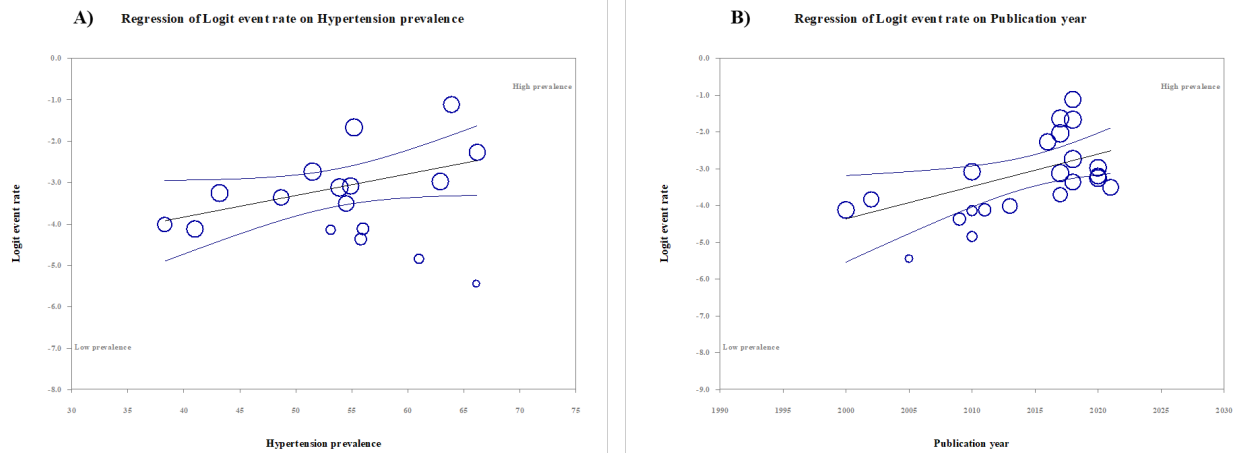


B)

## Primary aldosteronism



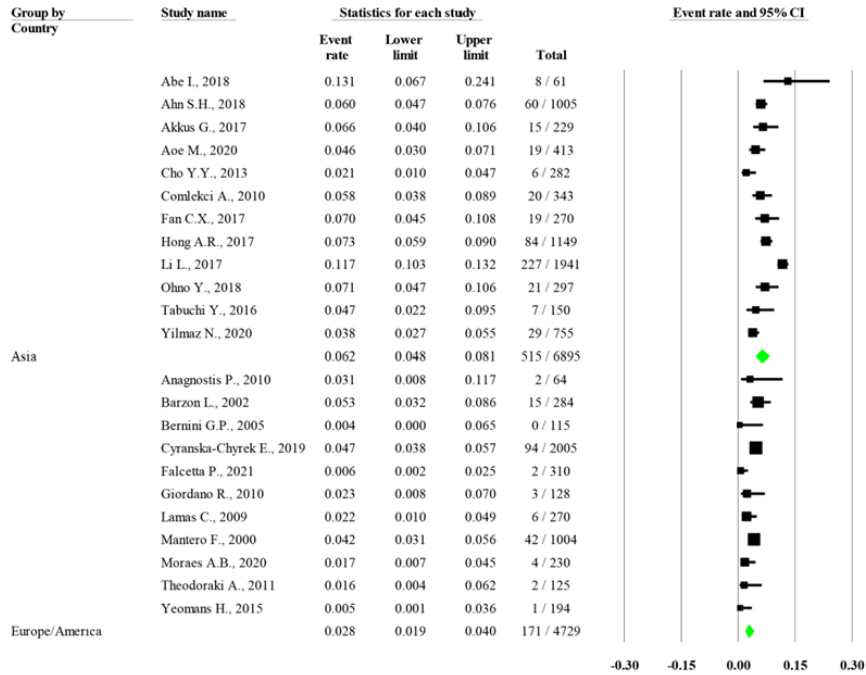
**Figure S5.** Forest plot of the subgroup analysis of the prevalence of primary aldosteronism in patients with adrenal incidentaloma, comparing studies according to the geographical area where they were conducted **(A)** and to their either retrospective or prospective design **(B)**. Central squares 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:  $Q=10.44$ ;  $df(Q)=10$ ,  $p$ -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],  $p = 0.003$ .

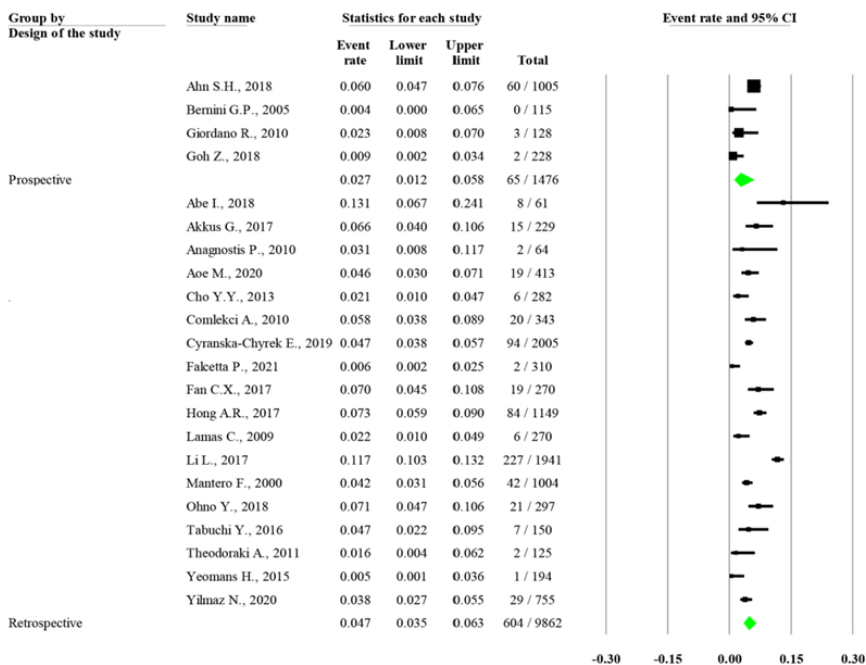
A)

## Pheochromocytoma



B)

## Pheochromocytoma



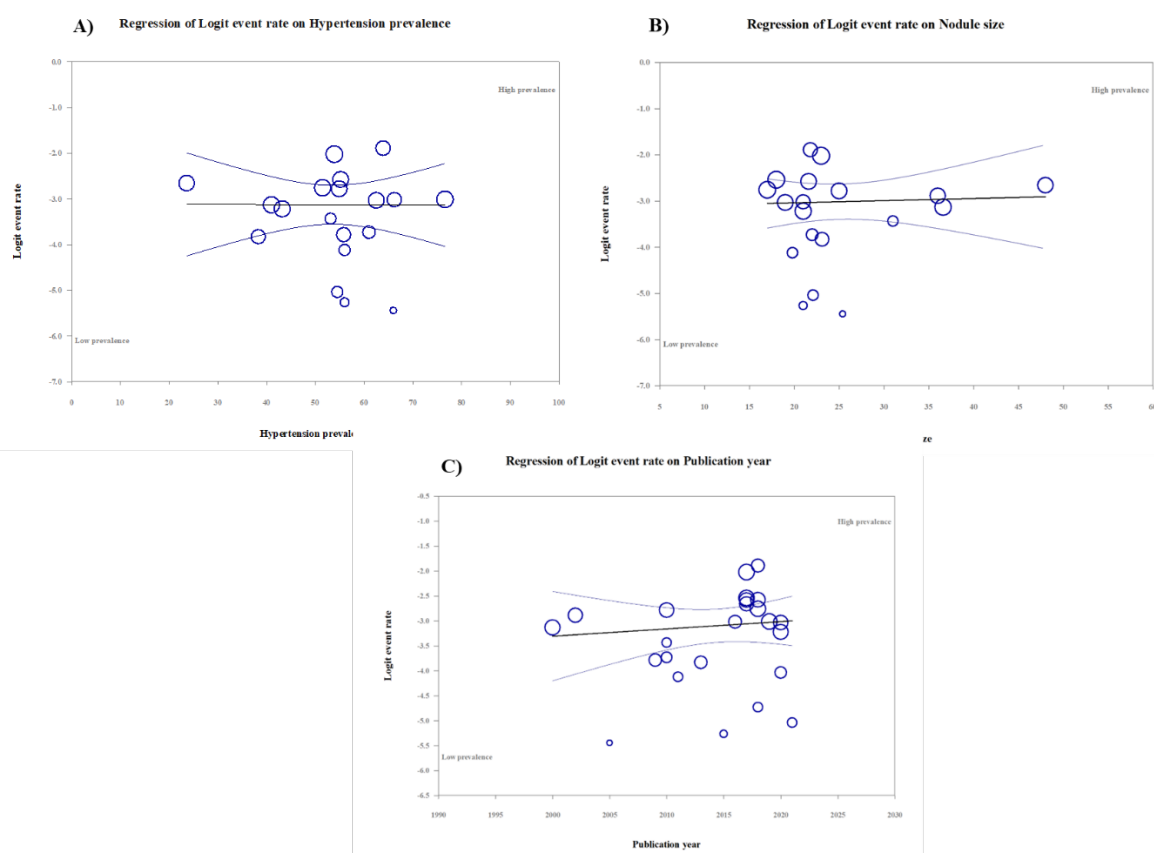
**Figure S7.** Forest plot of the subgroup analysis of the prevalence of pheochromocytoma in patients with adrenal incidentaloma, comparing studies according to the geographical area where they were



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.

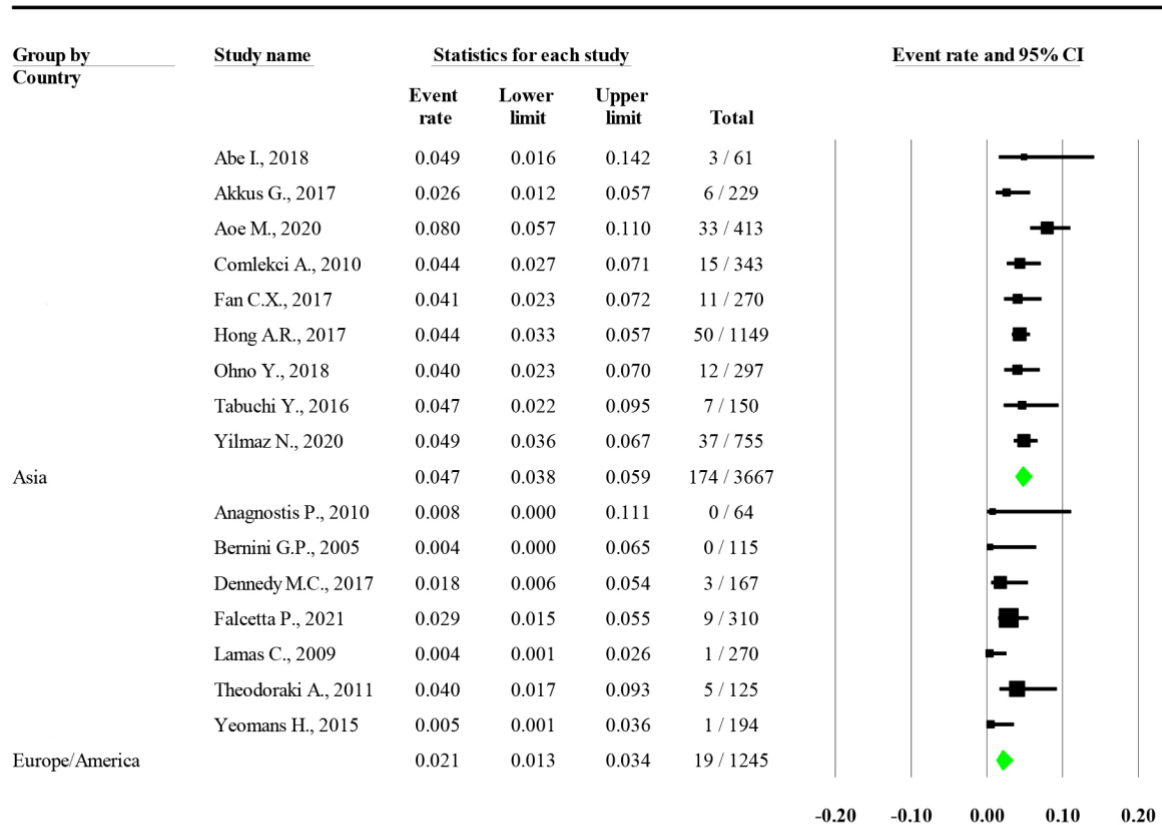
**(A)** Subgroup Asia:  $Q=84.06$ ,  $df(Q)=11$ ,  $p\text{-value} < 0.001$ ;  $I^2=86.91$ ;  $\tau^2=0.20$ . Subgroup Europe/America:  $Q=25.24$ ,  $df(Q)=10$ ,  $p\text{-value} 0.005$ ;  $I^2=60.39$ ;  $\tau^2=0.15$ . **(B)** Subgroup Prospective:  $Q=13.00$ ,  $df(Q)=3$ ,  $p\text{-value} 0.005$ ;  $I^2=76.93$ ;  $\tau^2=0.99$ . Subgroup Retrospective:  $Q=155.03$ ,  $df(Q)=17$ ,  $p\text{-value} < 0.001$ ;  $I^2=89.03$ ;  $\tau^2=0.31$ .

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.



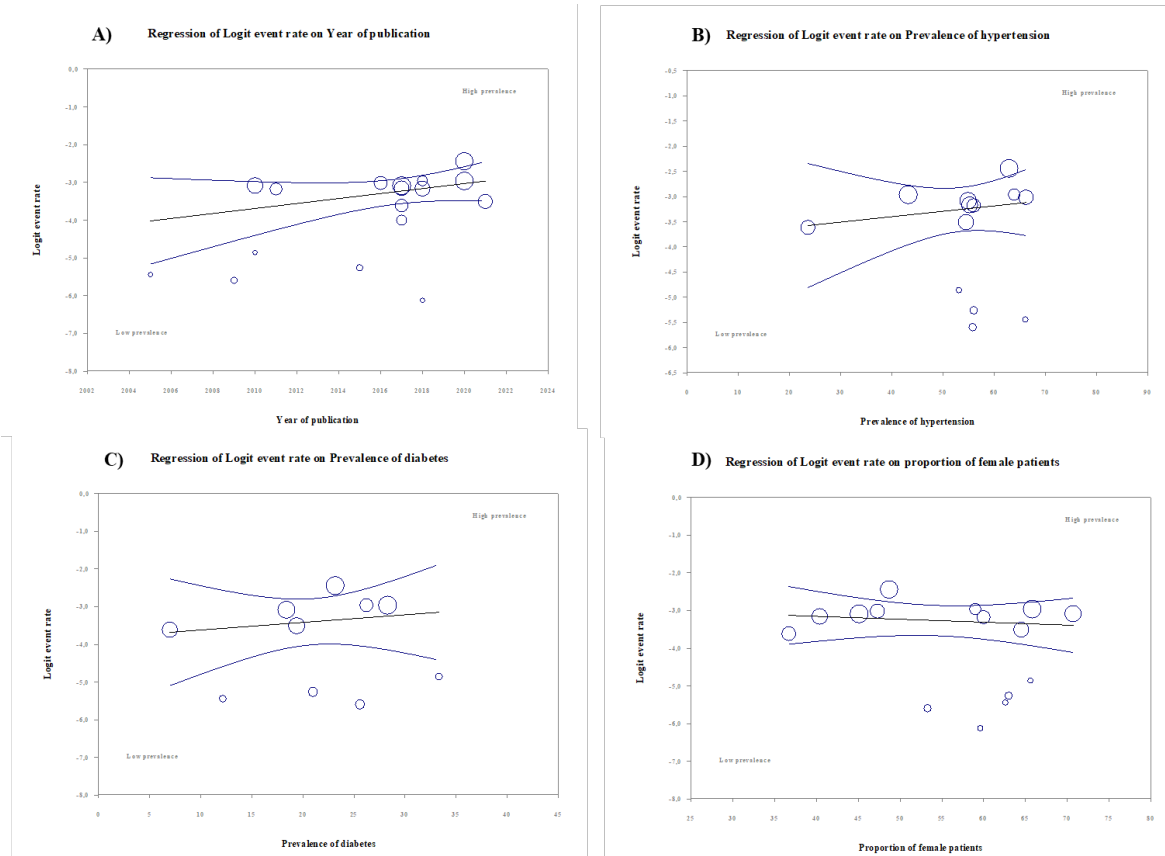
**Figure S8.** Meta-regression analysis for the proportion of hypertension **(A)**, the mean nodule size **(B)** and **(C)** the year of publication on the prevalence of pheochromocytoma in patients with adrenal incidentaloma. The analysis showed that the covariates did not impact significantly on the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

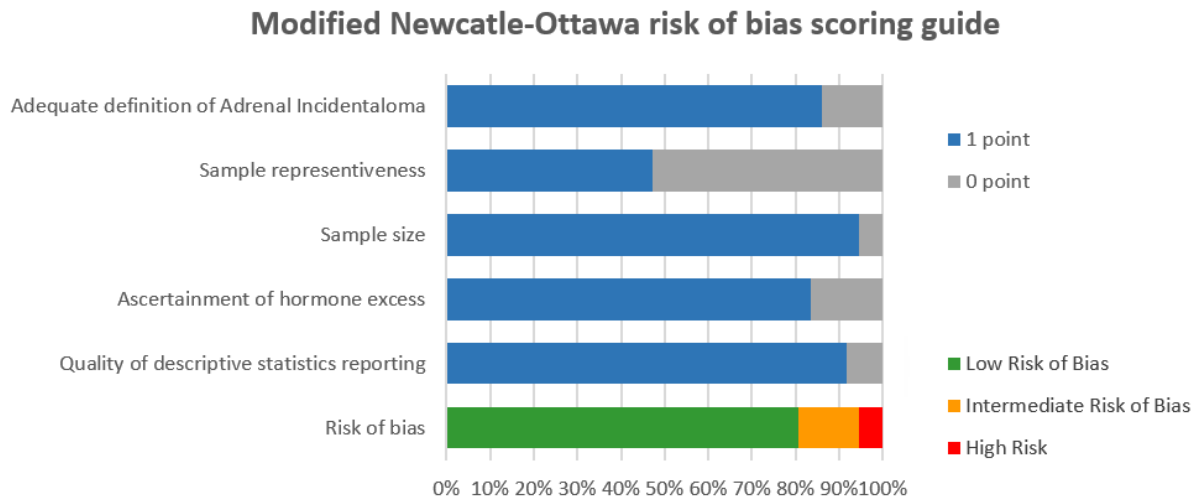


**Figure S9.** Forest plot of the subgroup analysis of the prevalence of Cushing syndrome in patients with adrenal incidentaloma, comparing studies according to the geographical area where they were conducted. The only study performed in New Zealand (Goh Z., 2018) was excluded from the analysis. Central squares of each horizontal line represent the prevalence for each study. Subgroup Asia:  $Q=12.57$ ,  $df(Q)=8$ ,  $p\text{-value } 0.128$ ;  $I^2=36.34$ ;  $\tau^2=0.03$ . Subgroup Europe/America:  $Q=9.94$ ,  $df(Q)=6$ ,  $p\text{-value } 0.127$ ;  $I^2=39.66$ ;  $\tau^2=0.29$

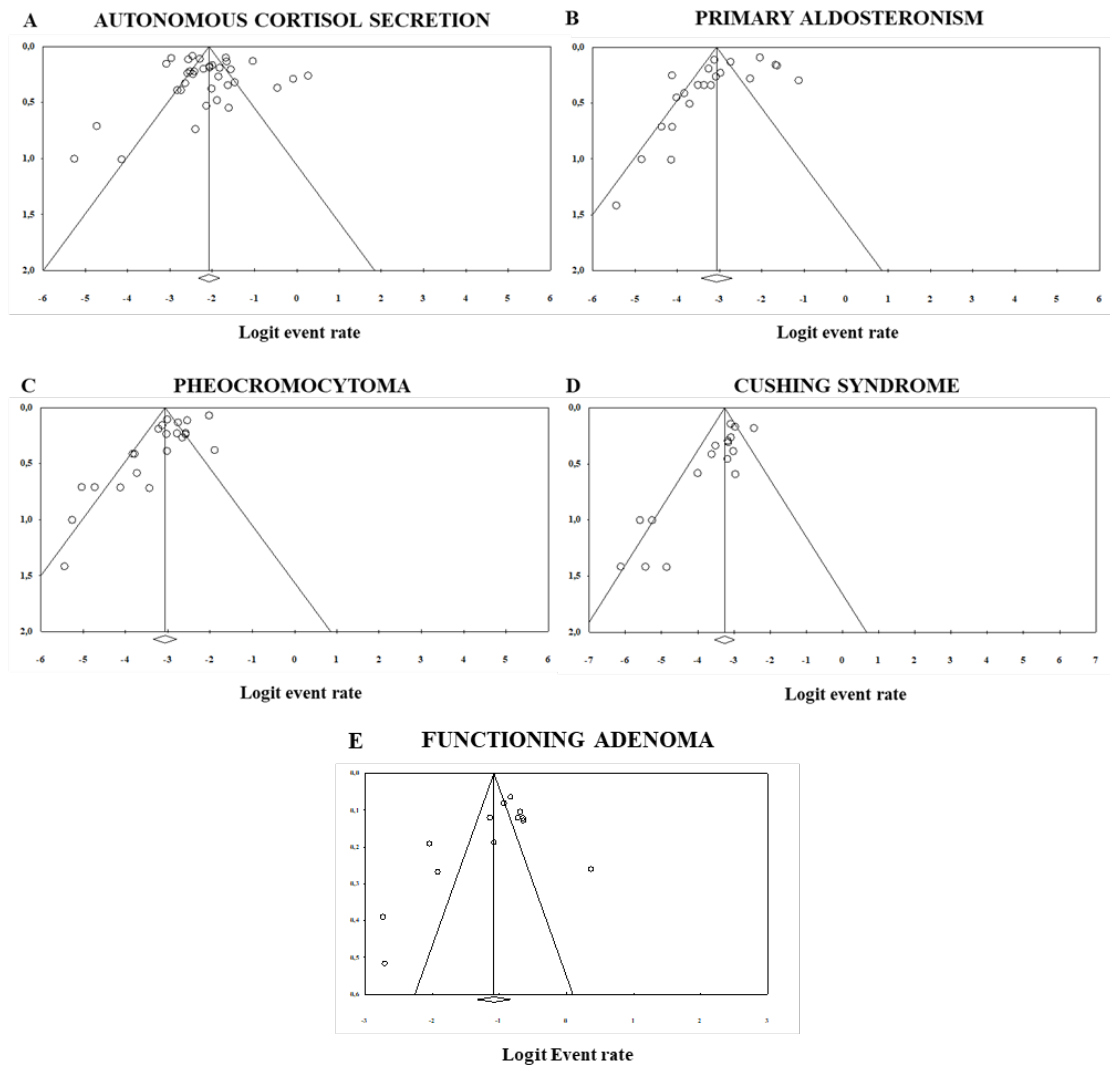
The area of each square is proportional to that study's weight in the analysis. Horizontal lines indicate the 95% confidence interval.



**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.



**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).