Renal damage in primary aldosteronism: a systematic review and meta-analysis

ONLINE SUPPLEMENT

Renal damage in primary aldosteronism: a sistematic review and meta-analysis

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Supplementary methods

Search strategy and selection criteria.

Despite being an exclusion criterion, five pairs of duplicate or partially duplicated reports were retained for the final analysis (Catena C., 2007, Sechi L.A., 2006 and Sechi L.A., 2009; Iwakura Y., 2014 and Iwakura Y., 2016; Kimura G., 1987 and Kimura G., 1996; Pimenta E., 2011 (1) and Pimenta E., 2011 (2)) since different outcomes were investigated. For each pair of duplicated studies, only the study with a greater number of patients was considered to calculate the total number of included patients and the clinical parameters (see Table S1).

Supplementary references

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Study	Parameters of matching
Catena C., 2007	Age, sex, BMI, duration of hypertension
Freel M., 2012	Age, sex, blood pressure, duration of hypertension
Galetta F., 2009	Blood pressure, duration of hypertension
Halimi J., 1995	Age, BMI, mean arterial pressure, renal function, known duration of hypertension
Jiang Y., 2016	Sex, age
Liu G., 2014	Age, sex, blood pressure, duration of hypertension
Muiesan M.L., 2008	Age, sex, blood pressure
Mulatero P., 2013	Age, sex, blood pressure, duration of hypertension, BMI, smoking habits, type 2 diabetes mellitus
Pimenta E., 2011	Age, sex, duration of hypertension, and 24-h systolic and diastolic blood pressure
Reincke M., 2009	Age, sex, BMI
Ribstein J., 2005	Age, sex, BMI, duration of hypertension
Savard S., 2013	Age, sex, blood pressure
Sechi L.A., 2009	Age, sex, BMI, duration of hypertension
Somloova Z., 2010	Age
Takeda R., 1995	Age, sex
Turchi F., 2014	Age, gender, duration of hypertension

Table S1. Parameters chosen for clinical matching of patients affected by PA with non-PA hypertensive patients across the studies. BMI = body mass index

Parameter	**Primary aldosteronism (n of patients)**	**Non-primary aldosteronism (n of patients)**
Total number of studies (patients)	44 (4,467)	35 (8,234)
Age (years)	50.0 [48.7-52.0] (4,214)	51.0 [49.4-55.5] (7,992)
Female gender (%)	45.9 [36.4-53.8] (4,374)	44.3 [35.8-53.0] (7,744)
BMI (Kg/m^2)	27.1 [24.4-28.5] (4,188)	26.8 [25.1-28.4] (7,992)
Duration of hypertension (years)	8.5 [7.2-10.0] (3,300)	6.8 [5.6-8.5] (6,476)
SBP (mmHg)	153 [150-163] (4,467)	150 [145-157] (8,216)
DBP (mmHg)	94 [90-97] (4,467)	92 [87-95] (8,216)
Plasma K^+ (mmoL/L)	3.5 [3.1-3.7] (4,164)	4.1 [3.9-4.2] (7,554)
Plasma aldosterone (ng/dL)	31.0 [26.2-41.7] (3,977)	15.4 [11.3-18.4] (6,755)
PRA (ng/ml/h)	0.3 [0.2-0.5] (2,876)	1.6 [1.2-2.3] (4,512)
DRC (mU/L)	4.9 [4.4-5.3] (637)	10.9 [10.2-28.4] (1,764)
Diabetes mellitus (%)	15.7 [6.5-24.3] (2,795)	10.5 [4.8-15.0] (5,832)
Duration of follow-up after PA treatment (months)	12 [6-24] (1,096)	n.app.

Table S2. Clinical and biochemical parameters of the included patients. BMI = body mass index; SBP = systolic blood pressure; DBP = diastolic blood pressure; PRA = plasma renin activity; DRC = direct renin concentration; n.app=not applicable

Study	Method to estimate or measure GFR
Catena C., 2007	24h creatinine clearance normalized for body surface area
Chiang W.F., 2013	Abbreviated MDRD formula[1]
Florczak E., 2013	n.a.
Fourkiotis V., 2013	Abbreviated MDRD formula[1]
Freel M., 2012	24h creatinine clearance
Iwakura Y., 2014	$194 \times \text{serum creatinine}^{-1.094} \times \text{age}^{-0.287}$ (× 0.739 women)[2]
Iwakura Y., 2016	$194 \times \text{serum creatinine}^{-1.094} \times \text{age}^{-0.287}$ (× 0.739 women)[2]
Kimura G., 1987	n.a.
Kimura G., 1996	Standard clearance techniques using para-amino hippurate and endogenous creatinine
Kobayashi H., 2017	n.a.
Kramers B.J., 2017	CKD-EPI[3]
Liu G., 2014	Abbreviated MDRD formula[1]
Luo Q., 2015	Abbreviated MDRD formula[1]
Monticone S., 2017	Abbreviated MDRD formula[1]
Muiesan M.L., 2008	Abbreviated MDRD formula[1]
Mulatero P., 2013	Cockroft- Gault formula[4]
Murase K., 2013	n.a.
Murata M., 2017	n.a.
Park K.S., 2017	n.a.
Pimenta E., 2011 (1)	24h creatinine clearance
Pimenta E., 2011 (2)	24h creatinine clearance
Pilz S., 2014	Abbreviated MDRD formula[1]
Reincke M., 2009	Abbreviated MDRD formula[1]
Ribstein J., 2005	Urinary clearance of technetium-labeled diethylene triiaminopentaacetic acid (^{99m}Tc-DTPA)
Rosa J., 2012	Creatinine clearance
Rossi G.P., 2006	Abbreviated MDRD formula[1]
Savard S., 2013	Abbreviated MDRD formula[1]
Sechi L.A., 2009	24h creatinine clearance normalized for body surface area
Tanase-Nakao K., 2014	$194 \times \text{Serum creatinine}^{-1.094} \times \text{Age}^{-0.287} \times 0.739$ (if female)[2]
Utsumi T., 2017	$194 \times \text{Serum creatinine}^{-1.094} \times \text{Age}^{-0.287} \times 0.739$ (if female)[2]
Wu V.C., 2011	Abbreviated MDRD formula[1]

Table S3. Criteria adopted to evaluate glomerular filtration rate (GFR) across the included studies. MDRD = modification of diet in renal disease; CKD-EPI = chronic kidney disease epidemiology collaboration; n.a.= not available.

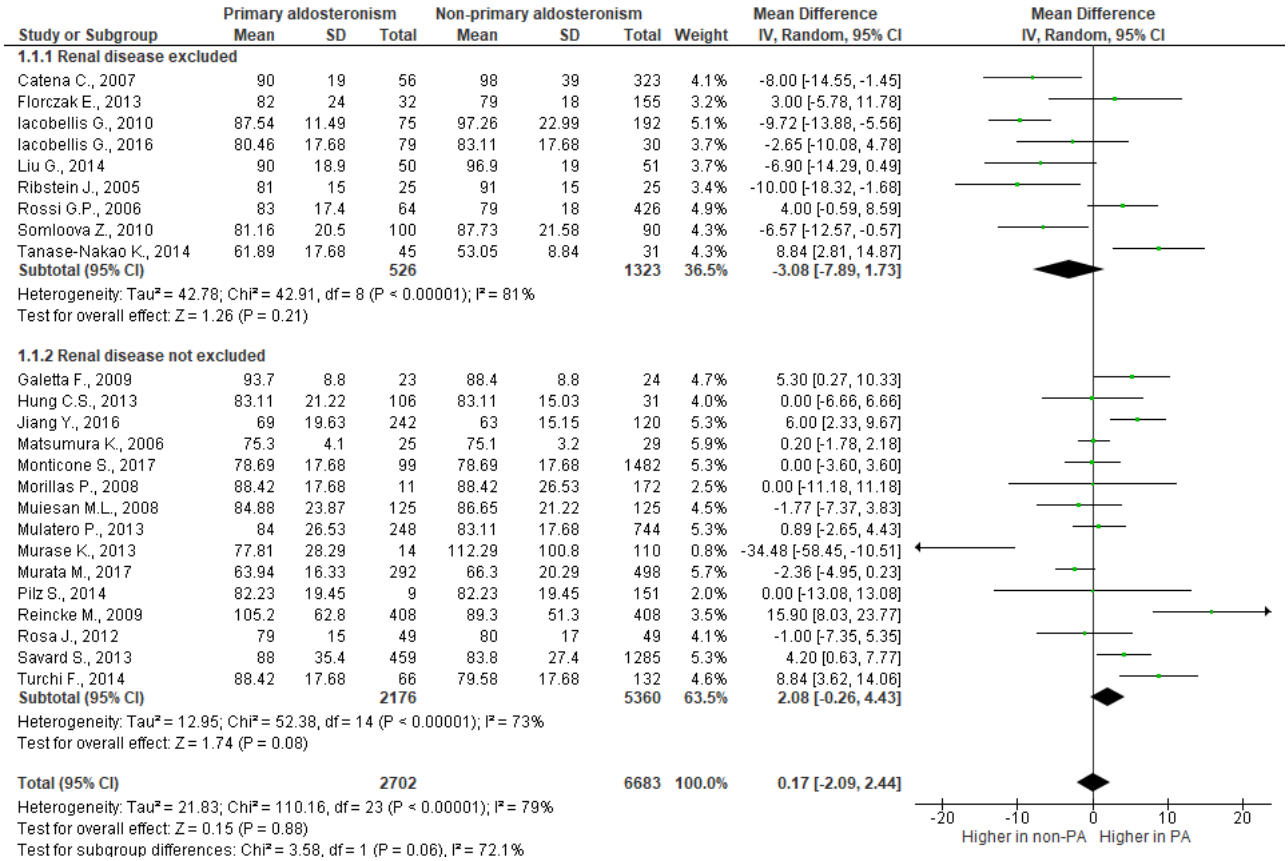

Figure S1. Forest plot of serum creatinine (µmol/L) in patients affected by PA and non-PA hypertensive patients. Central squares of each horizontal line represent the mean difference for each study. Horizontal lines indicate the range of the 95% confidence interval and the vertical line at zero indicates no difference between groups.

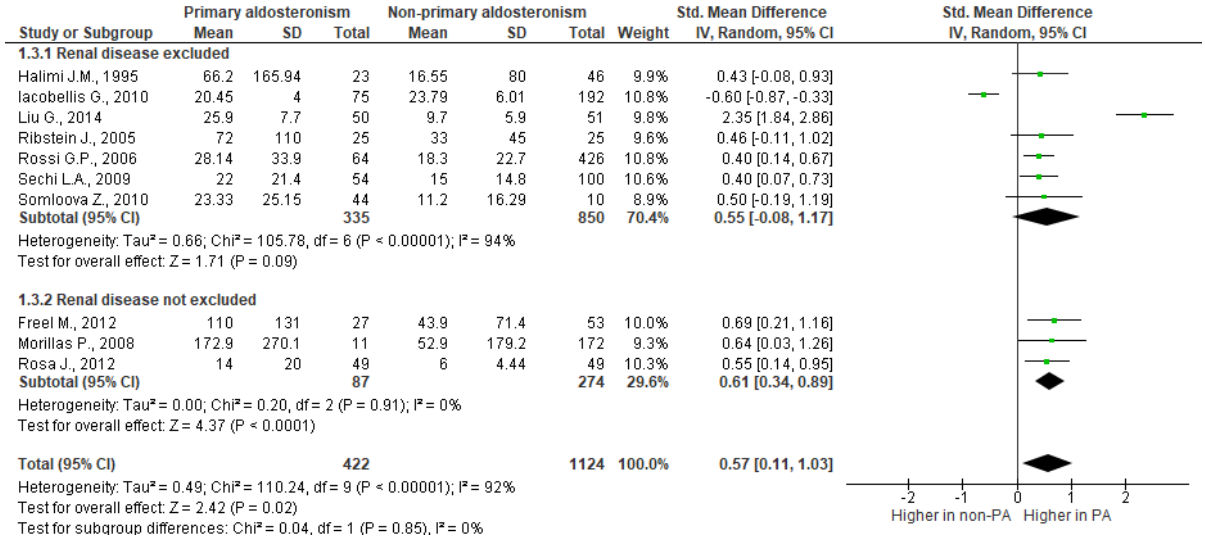

Figure S2. Forest plot of albuminuria in patients affected by PA and patients affected by non-PA hypertensive patients. Central squares of each horizontal line represent the standard mean difference for each study. Horizontal lines indicate the range of the 95% confidence interval and the vertical line at zero indicates no difference between groups.

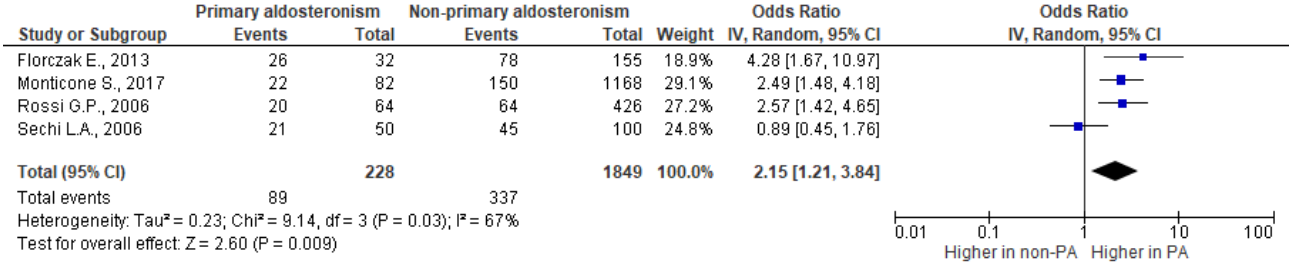

Figure S3. Forest plot of the odds ratio of microalbuminuria in patients with PA and non-PA hypertensive patients. Central squares of each horizontal line represent the odds ratio for each study. Horizontal lines indicate the range of the 95% confidence interval and the vertical line indicates the odds ratio of 1.0 (which indicates no differences in the odds ratio between patients with PA and non-PA hypertensive patients).

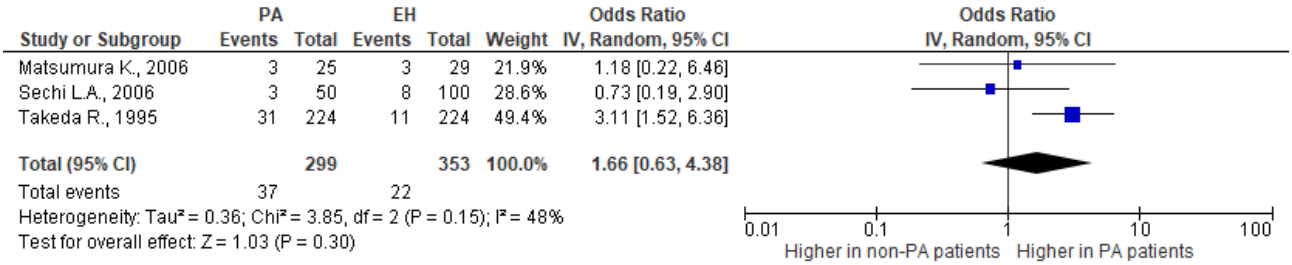

Figure S4. Forest plot of the odds ratio of proteinuria in patients with PA and non-PA hypertensive patients. Central squares of each horizontal line represent the odds ratio for each study. Horizontal lines indicate the range of the 95% confidence interval and the vertical line indicates the odds ratio

of 1.0 (which indicates no differences in the odds ratio between patients with PA and patients with EH).

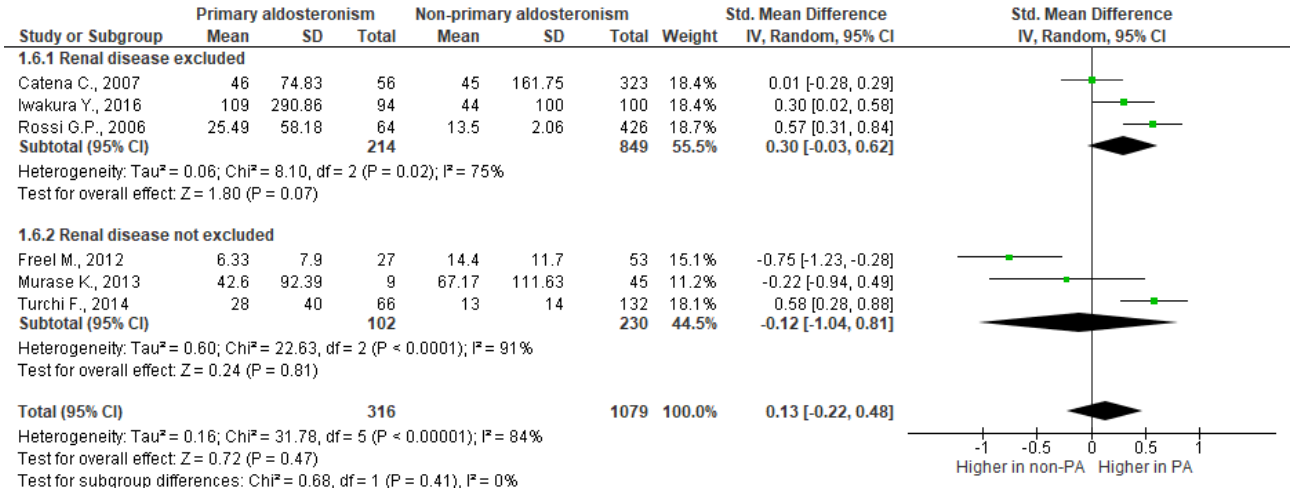

Figure S5. Forest plot of uAC ratio in patients with PA and non-PA hypertensive patients. Central squares of each horizontal line represent standard mean difference for each study. Horizontal lines indicate the range of the 95% confidence interval and the vertical line at zero indicates no difference between groups.

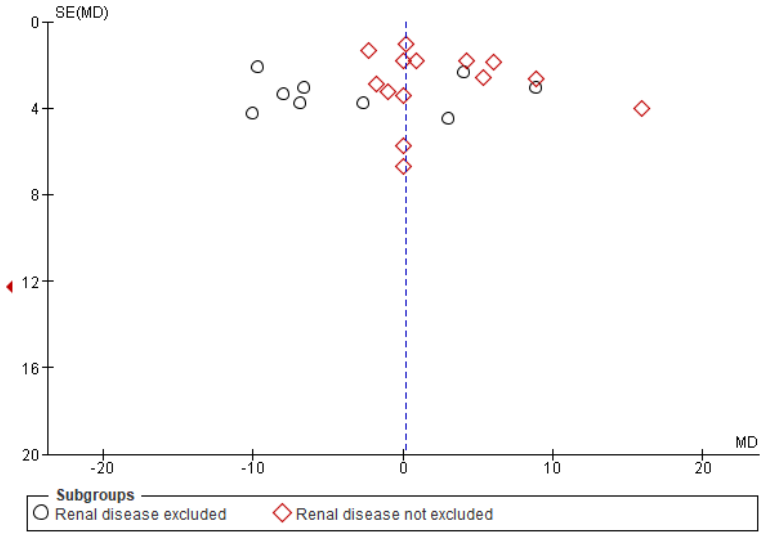

Figure S6. Funnel plot analysis for serum creatinine in patients affected by PA compared with non-PA hypertensive patients. The plots represent the visual graphical assessment of publication bias.

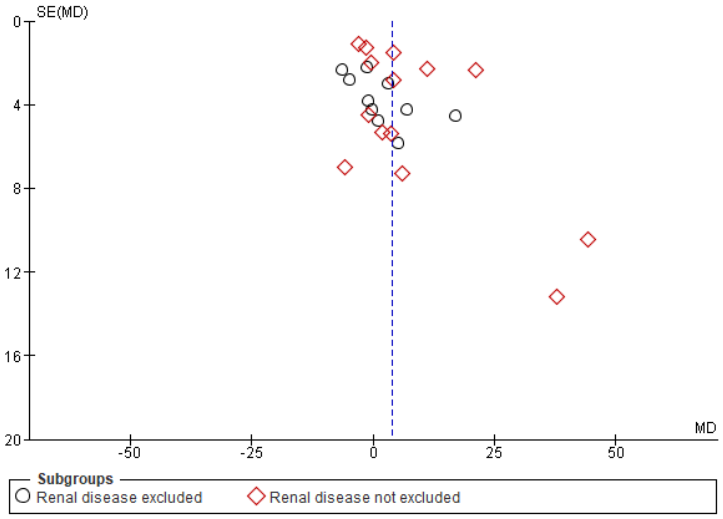

Figure S7. Funnel plot analysis for GFR in patients affected by PA compared with non-PA hypertensive patients. The plots represent the visual graphical assessment of publication bias.

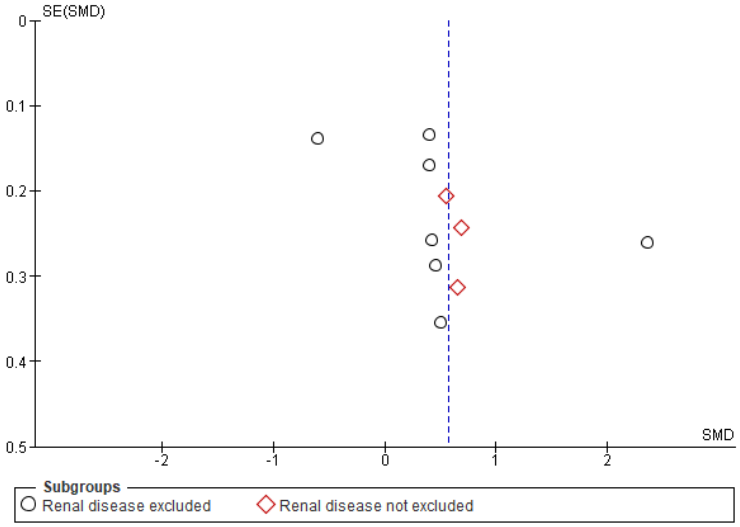

Figure S8. Funnel plot analysis for quantitative albuminuria in patients affected by PA compared with non-PA hypertensive patients. The plots represent the visual graphical assessment of publication bias.

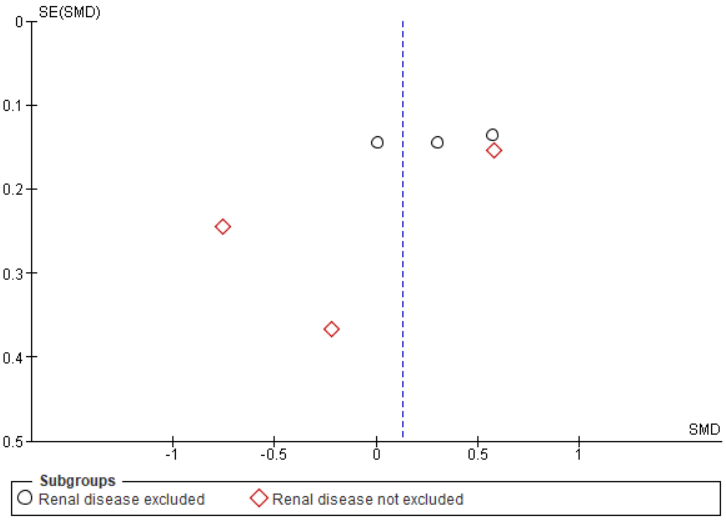

Figure S9. Funnel plot analysis for uAC ratio in patients affected by PA compared with hypertensive non-PA patients. The plots represent the visual graphical assessment of publication bias.

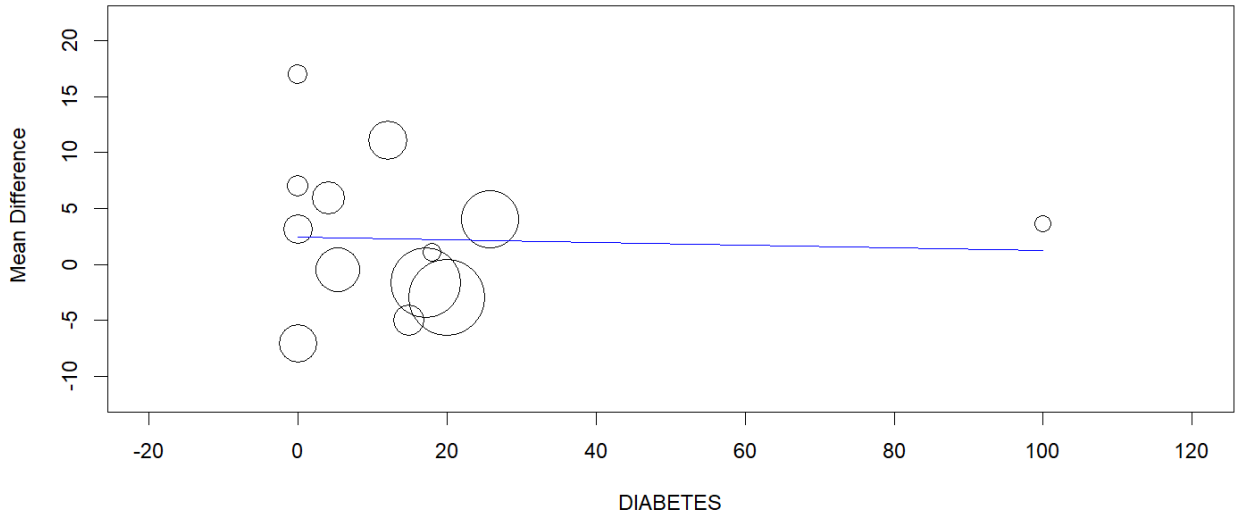

Figure S10. Meta-regression analysis for the prevalence of patients with diabetes on mean difference in GFR between patients affected by PA and non-PA patients, showing that the covariate did not impact significantly on the results (beta -0.011 [-0.163; 0.142])

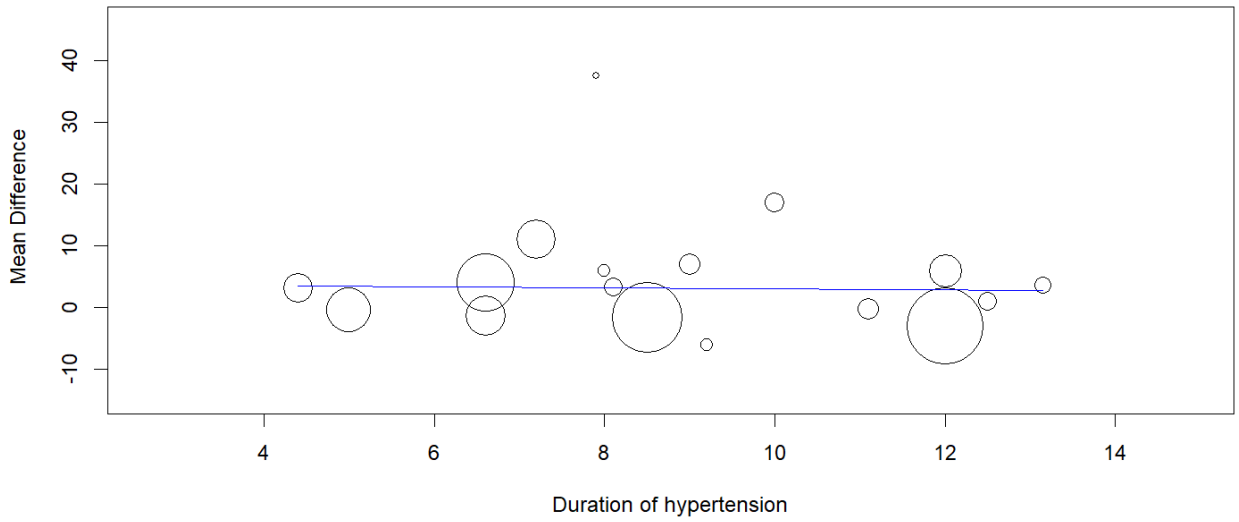

Figure S11. Meta-regression analysis for duration of hypertension on mean difference in GFR between patients affected by PA and patients affected by non-PA, showing that the covariate did not impact significantly the results (beta -0.154 [-1.224; 0.916]).

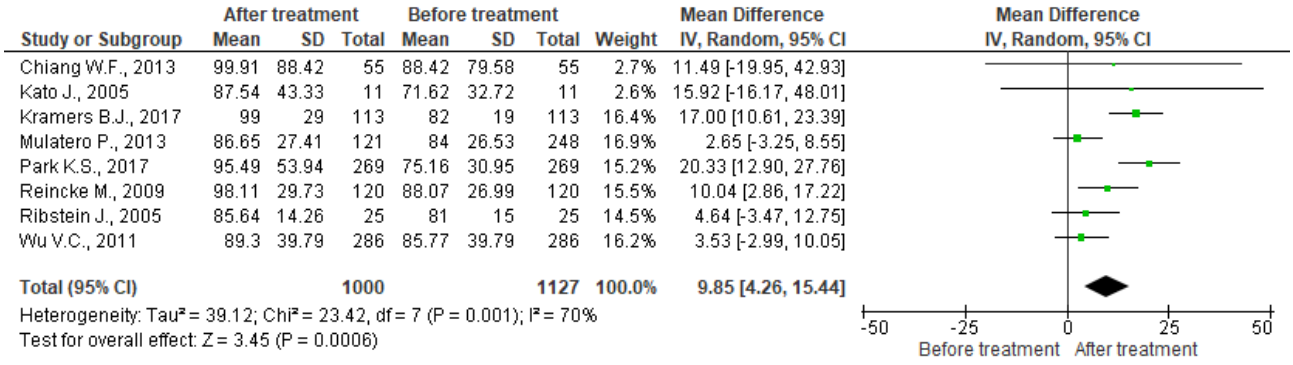

Figure S12. Forest plot of serum creatinine in patients affected by PA before and after specific treatment (either adrenalectomy or medical treatment). Central squares of each horizontal line represent the mean difference for each study. Horizontal lines indicate the range of the 95% confidence interval and the vertical line at zero indicates no difference between groups.

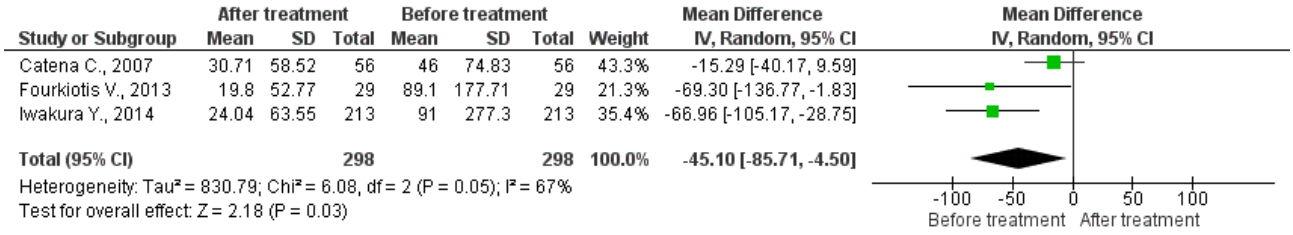

Figure S13. Forest plot of uACR in patients affected by PA before and after specific treatment (either adrenalectomy or medical treatment). Central squares of each horizontal line represent the mean difference for each study. Horizontal lines indicate the range of the 95% confidence interval and the vertical line at zero indicates no difference between groups.

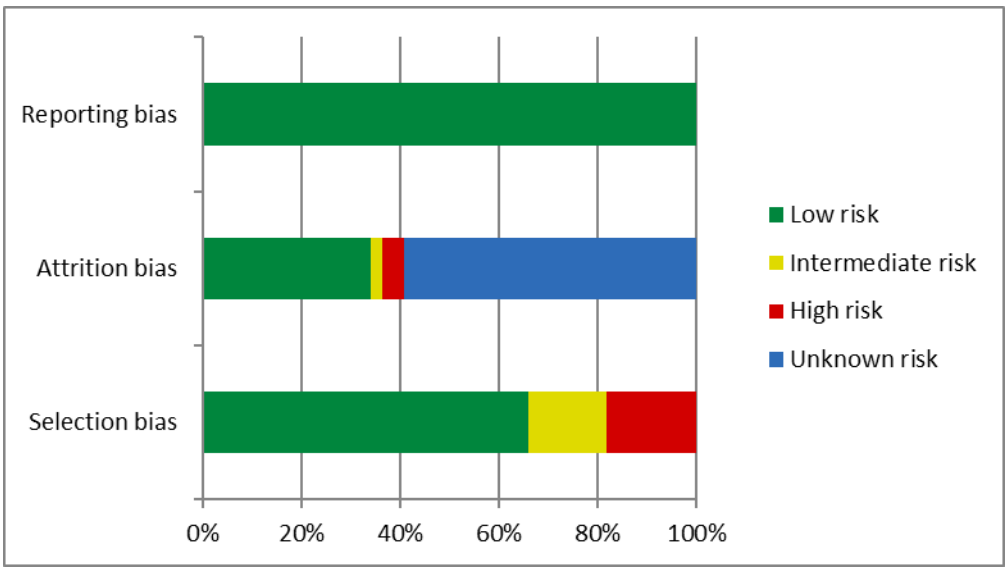

Figure S14. Qualitative evaluation of studies and risk of bias.