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

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19   **Short title:** Renal damage in primary aldosteronism

1 **Abstract**

2 **Objectives.** In experimental animal models, exogenous aldosterone excess has been linked to the  
3 progression of renal disease. However, the evidence of an increased risk of renal damage in patients  
4 affected by primary aldosteronism (PA) remains controversial. We aimed at evaluating the  
5 association between PA and renal damage through a meta-analysis.

6 **Methods.** We performed a quantitative review of studies evaluating parameters of renal function in  
7 patients affected by PA compared with patients affected by non-PA arterial hypertension and in  
8 patients affected by PA before and after specific treatment. We searched MEDLINE, EMBASE,  
9 and the Cochrane Central Register of Controlled Trials from January 1960 up to August 2017.

10 **Results.** 44 studies including 4,467 patients with PA and 8,234 patients affected by non-PA arterial  
11 hypertension were included. After 8.5 years from hypertension diagnosis, patients with PA had an  
12 increased glomerular filtration (GFR) rate compared with non-PA hypertensive patients (by  
13 3.93ml/min IQR [0.60; 7.26]) and a more severe albuminuria (Std. mean difference 0.57 [0.11-  
14 1.03]), resulting into a significant association with microalbuminuria (OR 2.15 [1.21; 3.84]).  
15 Following specific PA treatment, after a median follow-up of 12 months, a significant reduction in  
16 GFR was observed (by -10.91ml/min [-13.61; -8.21]) that was consistent in both patients surgically  
17 treated and patients treated with medical therapy. Similarly, a reduction in albumin excretion and an  
18 increase in serum creatinine were observed after treatment.

19 **Conclusions.** Patients affected by PA, compared with patients affected by non-PA arterial  
20 hypertension, display a more pronounced target organ damage, which can be mitigated by the  
21 specific treatment.

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## 1 **Introduction**

2 Aldosterone is the principal mineralocorticoid hormone in humans and plays a key role in  
3 water and electrolytes homeostasis and blood pressure regulation. According to the classical view of  
4 aldosterone actions, the distal nephron is its main target site: through the binding to the  
5 mineralocorticoid receptor (MR) aldosterone can promote sodium and water reabsorption and  
6 potassium excretion<sup>1</sup>.

7 A large body of evidence supports a pathophysiological link between aldosterone excess,  
8 vascular and perivascular inflammation<sup>2</sup>, oxidative stress<sup>3</sup> and fibrosis<sup>4</sup> in different animal models.  
9 Seminal studies indicate that exogenous administration of mineralocorticoids can induce thrombotic  
10 micro-angiopathy of both the medium-sized arteries and the arterioles, associated with ischemic  
11 modifications of the glomerular tufts with hyalinization and subsequent development of  
12 proteinuria<sup>5,6</sup>.

13 Primary aldosteronism (PA), affecting 6% of the general hypertensive population<sup>7</sup>, is the  
14 most frequent, but often overlooked<sup>8</sup> cause of secondary hypertension. Patients affected by PA (due  
15 to either an aldosterone producing adenoma – APA – or a bilateral adrenal hyperplasia – BAH -) are  
16 exposed to chronic aldosterone excess, which stimulates sodium reabsorption and volume  
17 expansion, thereby increasing renal perfusion pressure and stimulating glomerular hyperfiltration.  
18 Nonetheless, current evidence regarding a link between PA and an increased risk of renal damage is  
19 limited and controversial. In fact, while some old reports indicate a low prevalence of renal  
20 abnormalities in patients affected by PA<sup>9</sup> more recent studies point towards a partially reversible  
21 renal dysfunction<sup>10</sup>. Moreover, individual reports are often inadequate to assess this issue due to  
22 small sample size, to the different criteria to evaluate renal function and potential selection bias  
23 across studies.

1           Therefore, we performed a meta-analysis of observational epidemiological studies available  
2 in the literature, to ascertain the association between PA and renal damage and to evaluate the effect  
3 of a targeted treatment on the same parameters after an adequate follow-up.

#### 4   **Methods**

5           The present meta-analysis was performed according to the Preferred Reporting Items for  
6 Systematic reviews and Meta-Analyses (PRISMA) amendment<sup>11</sup> to the Quality of Reporting of  
7 Meta-analyses (QUOROM) statement<sup>12</sup>, and the Cochrane Collaboration and Meta-analysis Of  
8 Observational Studies in Epidemiology (MOOSE)<sup>13</sup>.

#### 9           **Search strategy and selection criteria.**

10           We sought MEDLINE, EMBASE, and the Cochrane Central Register of Controlled Trials  
11 with terms related to PA (e.g., “primary aldosteronism” “hyperaldosteronism”, “primary  
12 aldosteronism/hyperaldosteronism”) and the following terms: “renal damage”, “albuminuria”,  
13 “hyperfiltration” limited to human studies from January 1960 up to August 2017.

14           Two authors independently evaluated the titles and/or the abstracts (S.M., E.S.) with  
15 divergences resolved after consensus and discussion with a third author (P.M.). If potentially  
16 pertinent, they were evaluated, by the same authors, as full-text reports according to the following  
17 criteria. Studies were included if a) investigating patients with PA compared with non-PA  
18 hypertensive patients (as a control group) and/or b) patients with PA before and after targeted  
19 treatment, and c) including any data on renal function; while exclusion criteria were (i) duplicate  
20 reports (in which case the manuscript reporting the largest sample of patients was selected) (ii)  
21 missing control group and (iii) inappropriate report or missing outcome data. We considered for the  
22 analysis the following parameters of renal function: i) serum creatinine, ii) estimated glomerular  
23 filtration rate (eGFR) or creatinine clearance, iii) quantitative albuminuria, iv) urinary albumin  
24 creatinine (uAC) ratio and v) presence of microalbuminuria and proteinuria.

1           **Study selection**

2           **Data extraction and end-points**

3           Two unblinded independent reviewers (S.M., and E.S.) extracted the following data on pre-  
4 specified reports: authors, journal, year of publication, location of the study group, design of the  
5 study and baseline features of included patients.

6           The two co-primary end-points were the eGFR difference between patients affected by PA  
7 and non-PA hypertensive patients and the eGFR difference before and after specific treatment for  
8 PA; difference in serum creatinine, quantitative evaluation of albuminuria, prevalence of  
9 microalbuminuria, proteinuria and uACR ratio were evaluated as secondary end-points.

10          **Internal validity and quality appraisal**

11          Unblinded independent reviewers (S.M. and E.S.) evaluated the quality of the selected  
12 studies on pre-specified data collection forms using modified MOOSE criteria to take into account  
13 the specific features of included studies<sup>13</sup>. The independent reviewers separately appraised study  
14 design, setting, data source, and statistical methods for multivariable analysis, as well as risk of  
15 reporting, selection, and attrition bias (expressed as low, moderate, or high risk of bias).

16          **Data analysis and synthesis**

17          Continuous variables are reported as mean (standard deviation) or median (IQR).  
18 Categorical variables are expressed as n/N (%). Considering the high likelihood of between-study  
19 variance, statistical pooling was performed according to a random-effect model with generic  
20 inverse-variance weighting, computing risk estimates with 95% confidence intervals, using RevMan  
21 5 (The Cochrane Collaboration, The Nordic Cochrane Centre, and Copenhagen, Denmark). For  
22 albuminuria and uAC ratio, standard mean difference (SMD=mean difference between treatment  
23 groups divided by the standard deviation) was computed to account for the different Units across

1 studies. For interpreting the SMD the following indication can be used: small effect, SMD = 0.2;  
2 medium effect, SMD = 0.5; and large, SMD = 0.8<sup>14</sup>. A SMD of zero means no differences between  
3 the two evaluated treatments or groups. Publication bias was evaluated by graphical inspection of  
4 funnel plots. Standard hypothesis testing was set at the two-tailed 0.05 level. Null hypothesis of  
5 statistical homogeneity was refuted if  $p < 0.10$  at Cochran Q test, with I<sup>2</sup> values of around 25%,  
6 50%, and 75% representing, respectively, mild, moderate, and extensive statistical inconsistency. A  
7 meta-regression analysis with random effect model was performed to appraise the impact of the  
8 proportion of the diabetes and the duration of hypertension in each study on the eGFR difference  
9 between PA and non-PA hypertensive patients. This analysis was performed with Open meta  
10 analyst software.

## 11 **Results**

12 The electronic search yielded 9,575 citations that were first evaluated for eligibility at title  
13 and/or abstract level (Figure 1).

14 Of the 105 full text reports assessed, 34 were excluded because of duplicate reports, 22  
15 because not appropriate or with missing outcome data and 5 for lack of appropriate control group  
16 and. Finally, 44 studies were included in the analysis (Figure 1 and Supplemental material for  
17 complete references' list), to give a total of 4,467 patients with PA and 8,234 non-PA hypertensive  
18 patients. Characteristics of the studies included in the final meta-analysis are provided in Table 1.  
19 Thirty-five of the included studies investigated patients affected by PA compared with patients  
20 affected by non-PA hypertension, 16 investigated patients affected by PA (due to either APA or  
21 BAH) before and after targeted treatment and in 7 studies both investigations were available. In 14  
22 out of 44 studies patients with different degree of renal impairment were excluded (Table 1) and  
23 two subgroups have been generated (i.e. "Renal disease excluded" and "Renal disease not

1 excluded”). Additionally, in 16 studies patients with PA and patients affected by non-PA arterial  
2 hypertension were matched for potential confounding variables, as detailed in Table S1.

3 Clinical and biochemical parameters of patients affected by EH and patients affected by PA  
4 are detailed in Table S2. The median age of patients with PA and non-PA patients was 50.0 and  
5 51.0 years respectively, while the proportion of females were 45.9% and 44.3% respectively; the  
6 proportion of patients affected by diabetes mellitus was 15.7% and 10.5% and the median duration  
7 of hypertension were 8.5 and 6.8 years among patients affected by PA and non-PA patients.

### 8 **Primary aldosteronism and renal function**

9 To evaluate renal function in patients affected by PA compared to non-PA hypertensive  
10 patients we considered the following parameters: serum creatinine ( $\mu\text{mol/L}$ ), creatinine clearance or  
11 eGFR (the different methods used to calculate/estimate the GFR across studies are detailed in Table  
12 S3), albuminuria ( $\text{mg/day}$ ) and uAC ratio ( $\text{mg/g}$ ).

13 Twenty-four studies comparing 2,702 patients with PA and 6,683 non-PA hypertensive  
14 patients showed no difference in mean creatinine values between the two diagnoses (mean  
15 difference  $0.17 \mu\text{mol/L}$  [-2.09; 2.44 IQR]), consistently across studies in which patients with renal  
16 disease have been excluded or not, as depicted in Figure S1.

17 In 22 reports, including 2,740 patients with PA and 6,975 non-PA hypertensive patients,  
18 GFR data were available. When considering the clinical studies in which patients with renal disease  
19 were excluded, the mean GFR was not different between patients affected by PA and non-PA  
20 hypertensive patients (mean difference  $1.22 \text{ mL/min}$  [-3.37; 5.80]). However, when studies  
21 including patients with renal disease were considered, patients with PA showed a significantly  
22 higher mean GFR compared with non-PA hypertensive patients (by  $5.69 \text{ ml/min}$  [1.15; 10.22])  
23 (Figure 2), resulting in a significantly higher values in the overall cohort of PA patients (by  $3.93$   
24  $\text{ml/min}$  [0.60; 7.26]).

1           Notably, urinary albumin excretion, was increased in patients with PA (Std. mean difference  
2 0.57 [0.11;1.03] compared to patients with non-PA arterial hypertension (Figure S2), resulting into  
3 an increased risk of albuminuria (OR 2.15 [1.21-3.84]) (Figure S3) but not proteinuria (OR 1.66  
4 [0.63; 4.38]) (Figure S4). Similarly, the uAC ratio did not differ significantly between patients  
5 affected by PA and non-PA hypertensive patients (Std. mean difference 0.13 [-0.22; 0.48] (Figure  
6 S5), possibly for the relatively low number of studies included in these analyses.

7           At funnel plot analysis (Figures S6-S9) no small study bias was graphically assessed.

8           Proportion of patients affected by diabetes across the studies and the duration of  
9 hypertension, which might represent important confounding factors while evaluating renal function,  
10 did not have a significant impact on the observed effect on GFR as demonstrated by meta-  
11 regression analysis (beta -0.011 [-0.163; 0.142] and -0.154 [-1.224; 0.916] respectively) (Figure S10  
12 and S11).

### 13           **Renal function before and after PA treatment**

14           Given the increase in GFR and urinary albumin excretion, we aimed at evaluating the  
15 reversibility of the aldosterone-induced renal damage after institution of a targeted treatment for  
16 PA.

17           In an overall population of 1,504 PA patients, after a median follow-up of 12 months [6-24],  
18 we could observe a significant increase in serum creatinine (by 9.85  $\mu\text{mol/L}$  [4.26; 15.44]) (Figure  
19 S12) and reduction in both the eGFR (by -10.91 ml/min [-13.61; -8.21]) (Figure 3) and the urinary  
20 albumin excretion (by -45.10 mg/day [-85.71;-4.50] (Figure S13).

21           Of note, as indicated by subgroup analysis, the observed effect on GFR was consistent in  
22 both surgically and medically treated patients (Figure 3).

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## 1 **Assessment of publication bias and quality of the studies**

2           None of the included studies was randomized; risk of selection bias is judged to be high in  
3 17% of the studies and moderate in 15%, while the risk of reporting bias was low in 100% of the  
4 studies, as reported in Figure S14.

## 5 **Discussion**

6           The present meta-analysis, aimed at investigating the renal damage in patients affected by  
7 PA, extends our previous findings of a significant association between hyperaldosteronism, cardiac  
8 target organ damage, cardio- and cerebrovascular events and metabolic comorbidities<sup>15</sup>, further  
9 expanding the evidence of a detrimental role of aldosterone excess on the cardio-vascular system.

10           The main evidence gained from the present analysis is that patients with PA, compared with  
11 non-PA hypertensive patients, display a higher GFR (suggestive of glomerular hyperfiltration),  
12 which is significantly reduced by the specific treatment, either unilateral adrenalectomy or medical  
13 therapy with mineralocorticoid receptor antagonists.

14           Seminal studies reported that, in patients affected by PA, the renal function curve (pressure-  
15 natriuresis relationship) was shifted rightward, with a decrease in the slope<sup>16</sup>, changes comparable  
16 to those reported in animal models<sup>17</sup>. Patients with PA also showed glomerular hyperfiltration and  
17 glomerular capillary hypertension<sup>18</sup>, which might depend on a hemodynamic renal adaptation,  
18 based on the vasodilation of both afferent and efferent arterioles, as it has been described in renal  
19 micro puncture studies on experimental models of DOCA-salt hypertension rats<sup>19</sup>.

20           Consistently with experimental data, patients with PA exhibit a decreased intrarenal vascular  
21 resistance and this alteration can be reverted by the introduction of a specific treatment<sup>20</sup>. Sechi et  
22 al. suggested that the increased urinary albumin excretion observed in patients affected by PA is  
23 ascribable to the glomerular hyperfiltration induced by aldosterone excess; therefore, either

1 unilateral adrenalectomy in case of an adenoma or treatment with mineralocorticoid receptor  
2 antagonists in bilateral PA, might represent the strategy to correct these hemodynamic alterations<sup>20</sup>.

3 The hypothesis that the increased urinary albumin excretion in PA might be a consequence  
4 of the relative hyperfiltration, has been debated by some authors. Particularly, Rossi et al. suggested  
5 that the increased albuminuria might depend on endothelial dysfunction and the aldosterone-  
6 induced renal damage<sup>21</sup>, as previously described in experimental and clinical studies<sup>22,23</sup>. In the  
7 kidney, aldosterone promotes inflammation<sup>2</sup>, fibrosis<sup>4</sup>, mesangial cell proliferation<sup>24</sup>, podocyte  
8 injury<sup>25</sup> and endothelial dysfunction, which might be involved in the development of  
9 microalbuminuria<sup>26</sup>. Additionally, these data from experimental studies correlate with the findings  
10 from renal biopsies of glomerular damage in kidneys of patients with PA, associated with  
11 progressive glomerulosclerosis, tubulointerstitial inflammation and scarring, leading to proteinuria  
12 and progressive loss of renal function<sup>27</sup>.

13 In our study, subgroup analysis showed that the increase in GFR and urinary albumin  
14 excretion observed in patients with PA is limited to those studies in which patients with a certain  
15 degree of renal impairment were not excluded. This finding indicates that relative hyperfiltration in  
16 PA might represent a functional adaptive mechanism secondary to the nephron loss, similarly to  
17 what occurs in focal segmental glomerulosclerosis<sup>28</sup>. Therefore, a plausible explanation for the  
18 increased albuminuria in PA patients can be, in our view, a synergic action of both mechanisms  
19 (glomerular hyperfiltration and aldosterone-induced renal damage).

20 According with the currently available guidelines<sup>29,30</sup>, unilateral adrenalectomy and medical  
21 therapy with mineralocorticoid receptor antagonists are the recommended treatments for PA. The  
22 current study also aimed at evaluating the changes in renal function in patients with PA before and  
23 after the introduction of a specific treatment, showing a decrease in glomerular filtration, together  
24 with an increase in serum creatinine. On the basis of previous independent studies with similar  
25 results<sup>10,31</sup>, in the latest years it has been postulated that the treatment of PA could worsen renal

1 function. However, the most accepted explanation is that PA treatment, abolishing the relative  
2 hyperfiltration, might unveil a previously deteriorated renal function<sup>31,33</sup>. Furthermore, our analysis  
3 showed a decrease in urinary albumin excretion following specific PA treatment, indicating that  
4 patients undergoing an appropriate treatment for PA could witness a slower progression of  
5 aldosterone-induced renal damage.

6 A recent large cohort study showed that PA patients treated with MR antagonists, compared  
7 with patients affected by essential hypertension, remain at increased risk for annual decline in eGFR  
8 and hence incident chronic kidney disease, while unilateral adrenalectomy effectively mitigate this  
9 risk<sup>34</sup>. Similarly, patients with PA on MRA therapy had an augmented risk of cardiovascular events  
10 and incident mortality, compared to those with EH, that was circumscribed to the patients whose  
11 plasma renin activity remained suppressed on MR antagonists therapy<sup>35</sup>. In our analysis, both  
12 unilateral adrenalectomy and medical therapy with MR antagonists showed a similar short-term  
13 effect on GFR reduction, however the lack of long-term follow-up data did not allow to compare  
14 the effect of adrenalectomy to a long-term therapy with MR antagonists on renal outcomes. We  
15 acknowledge that the overall number of studies included for the evaluation of some end-points,  
16 such as the risk of proteinuria and albuminuria, was small, making it difficult to draw robust  
17 conclusions for these variables.

18 In conclusion, the results of this meta-analysis show that patients with PA, compared with  
19 non-PA hypertensive patients, display a more prominent renal damage, which can be mitigated by  
20 the specific treatment (either surgical or medical) through a reduction in glomerular hyperfiltration  
21 and urinary albumin excretion. These data provide further strong evidence in favor of the  
22 detrimental role of aldosterone excess on the cardio-vascular system, corroborating the results of  
23 previous studies and demonstrating that patients affected by PA display less favorable outcomes  
24 than patients affected by essential hypertension<sup>15,34,35</sup>. Additionally, long term follow-up studies on  
25 large number of patients, aimed at directly compared the impact of medical and surgical approaches

- 1 on specific outcomes, including renal function, would be important to further improve the clinical
- 2 management of patients affected by PA.
- 3

## 1 **Author contribution**

2 All the authors significantly contributed to the study. S.M. and P.M. devised the study concept;  
3 S.M., E.S. and F.D.A. extracted the data; F.B. and F.D.A. performed the statistical analysis, S.M.  
4 and E.S. drafted the manuscript; P.M., F.V., L.A.S. and F.S. contributed to the interpretation of the  
5 results and critically revised the manuscript. Each author contributed important intellectual content  
6 during manuscript drafting or revision and accepts accountability for the overall work by ensuring  
7 that questions pertaining to the accuracy or integrity of any portion of the work are appropriately  
8 investigated and resolved.

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10 There was no funding source for this study.

## 11 **Conflict of interest**

12 The authors declare no competing interests.

## 13 **References**

- 14 1. Booth RE, Johnson JP, Stockand JD. Aldosterone. *Adv Physiol Educ.* 2002; **26**(1-4):8-20.
- 15 2. Rocha R, Rudolph AE, Friedrich GE et al. Aldosterone induces a vascular inflammatory  
16 phenotype in the rat heart. *Am J Physiol Heart Circ Physiol.* 2002; **283**(5):H1802-810.
- 17 3. Kuster GM, Kotlyar E, Rude MK et al. Mineralocorticoid receptor inhibition ameliorates the  
18 transition to myocardial failure and decreases oxidative stress and inflammation in mice with  
19 chronic pressure overload. *Circulation.* 2005; **111**(4):420-427.
- 20 4. Blasi ER, Rocha R, Rudolph AE, Blomme EA, Polly ML, McMahon EG. Aldosterone/salt  
21 induces renal inflammation and fibrosis in hypertensive rats. *Kidney Int.* 2003; **63**(5):1791-  
22 1800.

- 1 5. Selye H, Hall CE, Rowley EM. Malignant hypertension produced by treatment with  
2 deoxycorticosterone acetate and sodium chloride. *Can Men Assoc J.* 1943; **49**(2):88-92.
- 3 6. Greene EL, Kren S, Hostetter TH. Role of aldosterone in the remnant kidney model in the rat. *J*  
4 *Clin Invest.* 1996; **98**(4):1063-1068.
- 5 7. Monticone S, Burrello J, Tizzani D et al. Prevalence and Clinical Manifestations of Primary  
6 Aldosteronism Encountered in Primary Care Practice. *J Am Coll Cardiol* 2017; **69**(14):1811-  
7 1820.
- 8 8. Mulatero P, Monticone S, Burrello J, Veglio F, Williams TA, Funder J. Guidelines for primary  
9 aldosteronism: uptake by primary care physicians in Europe. *J Hypertens.* 2016; **34**(11):2253-  
10 2257.
- 11 9. Beevers DG, Brown JJ, Ferriss JB, Fraser R, Lever AF, Robertson JI, Tree M. Renal  
12 abnormalities and vascular complications in primary hyperaldosteronism. Evidence on tertiary  
13 hyperaldosteronism. *Q J Med.* 1976; **45**(179):401-410.
- 14 10. Sechi LA, Novello M, Lapenna R et al. Long-term renal outcomes in patients with primary  
15 aldosteronism. *JAMA* 2006; **295**(2):2638-2645.
- 16 11. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic  
17 reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and  
18 elaboration. *BMJ* 2009; **339**:b2700.
- 19 12. Moher D, Cook DJ, Eastwood S, Olkin I, Rennie D, Stroup DF. Improving the quality of reports  
20 of meta-analyses of randomised controlled trials: the QUOROM statement. Quality of Reporting  
21 of Meta-analyses. *Lancet* 1999; **354**(9193):1896–1900.
- 22 13. Stroup DF, Berlin JA, Morton SC et al. Meta-analysis of observational studies in epidemiology:  
23 a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE)  
24 group. *JAMA* 2000; **283**(15):2008–2012.

- 1 14. Cohen J. Statistical Power Analysis for the Behavioral Sciences, 2<sup>nd</sup> ed. Hillsdale, NJ: Erlbaum;  
2 1988
- 3 15. Monticone S, D'Ascenzo F, Moretti C et al. Cardiovascular events and target organ damage in  
4 primary aldosteronism compared with essential hypertension: a systematic review and meta-  
5 analysis. hypertension: a systematic review and meta-analysis. *Lancet Diabetes Endocrinol.*  
6 2018; **6**(1):41-50.
- 7 16. Kimura G, Saito F, Kojima S, Yoshimi H, Abe H, Kawano Y, Yoshida K, Ashida T, Kawamura  
8 M, Kuramochi M, Ito K, Omae E. Renal function curve in patients with secondary forms of  
9 hypertension. *Hypertension.* 1987; **10**(1):11-15.
- 10 17. Sugai T, Nakagawa Y, Takeda K, Imai S. Arterial pressure-urinary output relationship in  
11 DOCA-saline hypertensive rats. *Am J Physiol.* 1983; **245**(5 Pt 1):R633-636.
- 12 18. Kimura G, Uzu T, Nakamura S, Inenaga T, Fujii T. High sodium sensitivity and glomerular  
13 hypertension/hyperfiltration in primary aldosteronism. *J Hypertens.* 1996; **14**(12):1463-1468.
- 14 19. Dworkin LD, Hostetter TH, Rennke HG, Brenner BM. Hemodynamic basis for glomerular  
15 injury in rats with desoxycorticosterone-salt hypertension. *J Clin Invest.* 1984; **73**(5):1448-1461.
- 16 20. Sechi LA, Di Fabio A, Bazzocchi M, Uzzau A, Catena C. Intrarenal hemodynamics in primary  
17 aldosteronism before and after treatment. *J Clin Endocrinol Metab.* 2009; **94**(4):1191-1197.
- 18 21. Rossi GP, Bernini G, Desideri G et al. PAPY Study Participants. Renal damage in primary  
19 aldosteronism: results of the PAPY Study. *Hypertension.* 2006; **48**(2):232-238.
- 20 22. Farquharson CA, Struthers AD. Aldosterone induces acute endothelial dysfunction in vivo in  
21 humans: evidence for an aldosterone-induced vasculopathy. *Clin Sci (Lond).* 2002; **103**(4):425-  
22 431.
- 23 23. Nishizaka MK, Zaman MA, Green SA, Renfro KY, Calhoun DA. Impaired endothelium-  
24 dependent flow-mediated vasodilation in hypertensive subjects with hyperaldosteronism.  
25 *Circulation* 2004; **109**(23):2857-61.

- 1 24. Huang S, Zhang A, Ding G, Chen R. Aldosterone-induced mesangial cell proliferation is  
2 mediated by EGF receptor transactivation. *Am J Physiol Renal Physiol*. 2009; **296**(6):F1323-  
3 1333.
- 4 25. Chen C, Liang W, Jia J, van Goor H, Singhal PC, Ding G. Aldosterone induces apoptosis in rat  
5 podocytes: role of PI3-K/Akt and p38MAPK signaling pathways. *Nephron Exp Nephrol*. 2009;  
6 **113**(1):e26-34.
- 7 26. Campese VM, Bianchi S, Bigazzi R. Is microalbuminuria a predictor of cardiovascular and  
8 renal disease in patients with essential hypertension? *Curr Opin Nephrol Hypertens*. 2000;  
9 **9**(2):143-147.
- 10 27. Grady RW, Kaylor WM, Lee JC, Bravo EL, Gephardt GN, Novick AC. Renal pathology in  
11 patients with primary hyperaldosteronism secondary to an adrenal cortical adenoma. *Urology*.  
12 1996; **48**(3):369-372.
- 13 28. Helal I, Fick-Brosnahan GM, Reed-Gitomer B, Schrier RW. Glomerular hyperfiltration:  
14 definitions, mechanisms and clinical implications. *Nat Rev Nephrol*. 2012; **8**(5):293-300.
- 15 29. Funder JW, Carey RM, Mantero F et al. The management of primary aldosteronism: case  
16 detection, diagnosis, and treatment: an endocrine society clinical practice guideline. *J Clin*  
17 *Endocrinol Metab*. 2016; **101**(5):1889-1916.
- 18 30. Nishikawa T, Omura M, Satoh F et al. Task Force Committee on Primary Aldosteronism, The  
19 Japan Endocrine Society. Guidelines for the diagnosis and treatment of primary aldosteronism--  
20 the Japan Endocrine Society 2009. *Endocr J*. 2011; **58**(9):711-721.
- 21 31. Ribstein J, Du Cailar G, Fesler P, Mimran A. Relative glomerular hyperfiltration in primary  
22 aldosteronism. *J Am Soc Nephrol*. 2005; **16**(5):1320-1325.
- 23 32. Catena C, Colussi G, Nadalini E et al. Relationships of plasma renin levels with renal function  
24 in patients with primary aldosteronism. *Clin J Am Soc Nephrol*. 2007; **2**(4):722-731.

- 1 33. Fourkiotis V, Vonend O, Diederich S et al. Mephisto Study Group. Effectiveness of eplerenone  
2 or spironolactone treatment in preserving renal function in primary aldosteronism. *Eur J*  
3 *Endocrinol.* 2012; **168**(1):75-81.
- 4 34. Hundemer GL, Curhan GC, Yozamp N, Wang M, Vaidya A. Renal Outcomes in Medically and  
5 Surgically Treated Primary Aldosteronism. *Hypertension.* 2018; **72**(3):658-666.
- 6 35. Hundemer GL, Curhan GC, Yozamp N, Wang M, Vaidya A. Cardiometabolic outcomes and  
7 mortality in medically treated primary aldosteronism: a retrospective cohort study. *Lancet*  
8 *Diabetes Endocrinol.* 2018; **6**(1):51-59.
- 9 36. Rossi GP, Bernini G, Caliumi C, et al; PAPY Study Investigators. A prospective study of the  
10 prevalence of primary aldosteronism in 1,125 hypertensive patients. *J Am Coll Cardiol.* 2006;  
11 **48**(11):2293-2300.
- 12 37. Rossi E, Perazzoli F, Negro A, Magnani A. Diagnostic rate of primary aldosteronism in Emilia-  
13 Romagna, Northern Italy, during 16 years (2000-2015). *J Hypertens.* 2017; **35**(8):1691-1697.
- 14 38. Olsen MH, Angell SY, Asma S, et al. A call to action and a lifecourse strategy to address the  
15 global burden of raised blood pressure on current and future generations: the Lancet  
16 Commission on hypertension. *Lancet.* 2016; **388**(1006):2665-2712.

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1 **Table 1.** Characteristics of the included studies.

<b>Study ID</b>	<b>Country / years</b>	<b>Design of the study</b>	<b>Number of patients Type of comparison</b>	<b>Exclusion of patients with impaired renal function</b>	<b>Diabetes prevalence (% PA/non-PA)</b>
Catena C., 2007	Italy 1994-2004	Observational prospective	56 PA compared with 323 matched non-PA hypertensive patients; 56 PA before and after treatment	Yes; if creatinine clearance <30 mL/min/1.73m <sup>2</sup> and/or proteinuria > 1 g	0/0 (excluded)
Chiang W.F., 2013	Taiwan 2002-2011	Retrospective	55 APA before and after treatment	No	16
Florczak E., 2013	Poland 2009-2011	Prospective	32 PA compared with 155 RHT	Yes; if GFR < 60 mL/min	18/10
Fourkiotis V., 2013	Germany 2008-2011	Prospective multicenter	29 PA before and after treatment	No	n.a.
Freel M., 2012	Scotland n.a.	n.a.	27 PA compared with 53 matched non-PA hypertensive patients	No	n.a.
Galetta F., 2009	Italy n.a.	n.a.	23 PA compared with 24 matched non-PA hypertensive patients	No	0/0
Halimi J.M., 1995	France n.a.	Retrospective	23 PA compared with 46 matched non-PA hypertensive patients	No. Patients were matched for renal function	n.a.
Hung C.S., 2013	Taiwan 2006-2010	Cross-sectional	106 PA compared with 31 non-PA hypertensive patients	No	n.a.
Iacobellis G., 2010	Italy 2002-2008	Prospective	75 PA compared with 192 non-PA hypertensive patients	Yes; patients with renal disease were excluded	0/0 (excluded)
Iacobellis G., 2016	Italy 2010-2014	Prospective	79 PA compared with 30 non-PA hypertensive patients	Yes; if serum creatinine > 133 μmol/L (1.5 mg/dl) or albuminuria > 300 mg/24 h)	0/0 (excluded)
Iwakura Y., 2014	Japan 2007-2010	Prospective	102 APA and 111 BAH before and after treatment	Yes; if primary renal diseases, diabetes with evident proteinuria, renal artery stenosis, renal cell carcinoma, or other urinary findings such as hematuria and urinary tract infection	33
Iwakura Y., 2016	Japan 2009-2012	Prospective	94 APA compared with 100 non-PA hypertensive patients 94 APA before and after treatment	See Iwakura Y., 2014	14.9/7
Jiang Y., 2016	China 2009-2012	Prospective	242 PA compared with 120 matched non-PA hypertensive patients	No	n.a.
Kato J., 2005	Japan	n.a.	11 APA before and after treatment	No	n.a.
Kimura G., 1987	Japan n.a.	n.a.	6 APA before and after adrenalectomy	No	n.a.
Kimura G., 1996	Japan n.a.	n.a.	6 APA compared with 18 non-PA hypertensive	No	n.a.

			patients		
Kobayashi H., 2017	Japan 2006-2016	Retrospective	73 PA compared with 24 non-PA hypertensive patients	No	n.a.
Kramers B.J., 2017	Netherlands 1972-2013	Retrospective	113 PA before and after treatment	No	n.a.
Liu G., 2014	China 2008-2013	n.a.	50 PA compared with 51 matched non-PA hypertensive patients	Yes; if with moderate severe renal disease	0/0 (excluded)
Luo Q., 2015	China 2009-2011	Prospective	216 PA compared with 657 non-PA hypertensive patients	Yes; if GFR < 60 mL/min	n.a.
Matsumura K., 2006	Japan n.a.	n.a.	25 APA compared with 29 non-PA hypertensive patients	No	n.a.
Monticone S., 2017	Italy 2009-2014	Prospective	99 PA compared with 1573 non-PA hypertensive patients	No	5.4/3.9
Morillas P., 2008	Spain 2005-2006	Prospective	11 PA compared with 172 non-PA hypertensive patients	No	27.3/9.4
Muiesan M.L., 2008	Italy 1988-2002	Retrospective	125 PA compared with 125 matched non-PA hypertensive patients	No	n.a.
Mulatero P., 2013	Italy 1992-2009	Retrospective	270 PA compared with 810 matched non-PA hypertensive patients; 270 PA before and after treatment	No	4.1/4.1 matching criterion
Murase K., 2013	Japan 2009-2012	Retrospective	14 PA compared with 110 non-PA hypertensive patients	No	100/100
Murata M., 2017	Japan 2004-2015	Retrospective Multicenter	292 PA compared with 498 non-PA hypertensive patients	No	25.7/31.7
Park K.S., 2017	Korea 2000-2015	Retrospective Multicenter	48 BAH and 221 APA before and after treatment	n.a.	n.a.
Pilz S., 2014	Austria 2009-2011	Prospective	9 PA compared with 151 non-PA hypertensive patients	No	n.a.
Pimenta E., 2011 (1)	Australia n.a.	Prospective (?)	21 PA compared with 21 matched non-PA hypertensive patients	No	n.a.
Pimenta E., 2011 (2)	Australia n.a.	n.a.	24 APA before and after treatment	No	0 (excluded)
Reincke M., 2009	Germany	Multicenter Retrospective	408 PA compared with 408 matched non-PA hypertensive patients	No	20/15
Ribstein J., 2005	France n.a.	Prospective	25 PA compared with 25 matched non-PA hypertensive patients	Yes; if serum creatinine >115 mol/L (1.3 mg/dl) and/or estimated creatinine clearance < 90 mL/min	0/0 (excluded)
Rosa J., 2012	Czech Republic n.a.	n.a.	49 PA compared with 49 non-PA hypertensive patients	No	n.a.
Rossi G.P., 2006	n.a.-2004	Prospective Multicenter	31 APA and 33 BAH compared with	Yes; if serum creatinine >115 µmol/L (1.3 mg/d)	0/0 (excluded)

			426 non-PA hypertensive patients	and estimated creatinine clearance < 61 mL/min	
Savard S., 2013	France 2001-2006	Retrospective	459 PA compared 1290 matched non-PA hypertensive patients	No	17.1/14.3
Sechi L.A., JAMA 2006	Italy		50 PA compared with 100 non-PA hypertensive patients	Yes; if creatinine clearance <30 mL/min/1.73m <sup>2</sup> and/or proteinuria > 1 g/24h	0/0 (excluded)
Sechi L.A., JCEM 2009	Italy n.a.	Prospective	54 PA (24 APA, 30 BAH) compared with 100 matched non-PA hypertensive patients	Yes; if creatinine clearance <30 mL/min/1.73m <sup>2</sup> and/or proteinuria > 1 g/24h	0/0 (excluded)
Somloova Z., 2010	Czech Republic 2002-2009	Retrospective	100 PA compared with 90 matched non-PA hypertensive patients	Yes; patients with renal failure were excluded	20/22.2
Takeda R., 1995	Japan 1984-1987	Prospective	224 PA compared with 224 matched non-PA hypertensive patients	No	0.4/0
Tanase-Nakao K., 2014	Japan 2006-2013	n.a.	45 PA compared with 31 non-PA hypertensive patients	Yes; if pre-operative eGFR < 60 ml/min/1.73 m <sup>2</sup>	11.1/n.a.
Turchi F., 2014	Italy 2003-2011	Prospective	66 PA compared with 132 matched non-PA hypertensive patients	No	15/15
Utsumi T., 2017	Japan 1995-2014	Retrospective	130 APA before and after treatment	Yes; patients with primary renal disease were excluded	15.4
Wu V.C., 2011 Clin Chim Acta	Taiwan 2003-2007	Prospective Multicenter	330 PA compared with 246 non-PA hypertensive patients	No	12.1/7.3

1 PA = patients with primary aldosteronism; APA = patients with aldosterone producing adenoma;

2 RHT = patients with resistant hypertension; uACR = urinary albumin creatinine ratio; eGFR =

3 estimated glomerular filtration rate; n.app. = not applicable; n.a. = not available; see Supplemental

4 file for complete reference list.

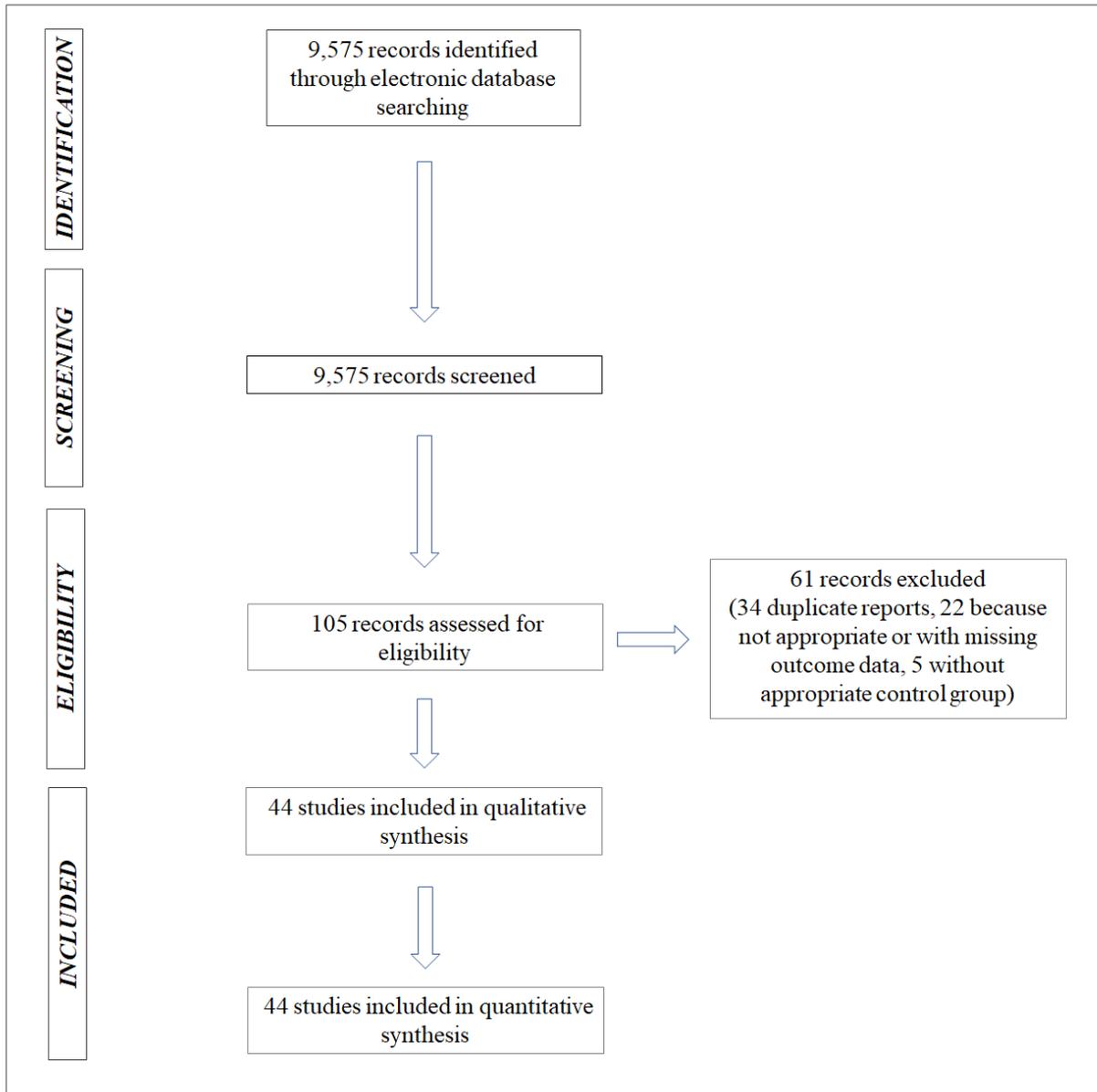
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1 **Figure Legends**

2 **Figure 1.** Flow-chart of literature search and study selection.

3 **Figure 2.** Forest plot of GFR (ml/min) in patients affected by PA and patients affected by non-PA  
4 arterial hypertension. Central squares of each horizontal line represent the mean difference for each  
5 study. Horizontal lines indicate the range of the 95% confidence interval and the vertical line at zero  
6 indicates no difference between groups.

7 **Figure 3.** Forest plot of GFR (ml/min) in patients affected by PA before and after treatment,  
8 distinguishing between unilateral adrenalectomy and medical treatment. Central squares of each  
9 horizontal line represent the mean difference for each study. Horizontal lines indicate the range of  
10 the 95% confidence interval and the vertical line at zero indicates no difference between groups.



**Figure 1**

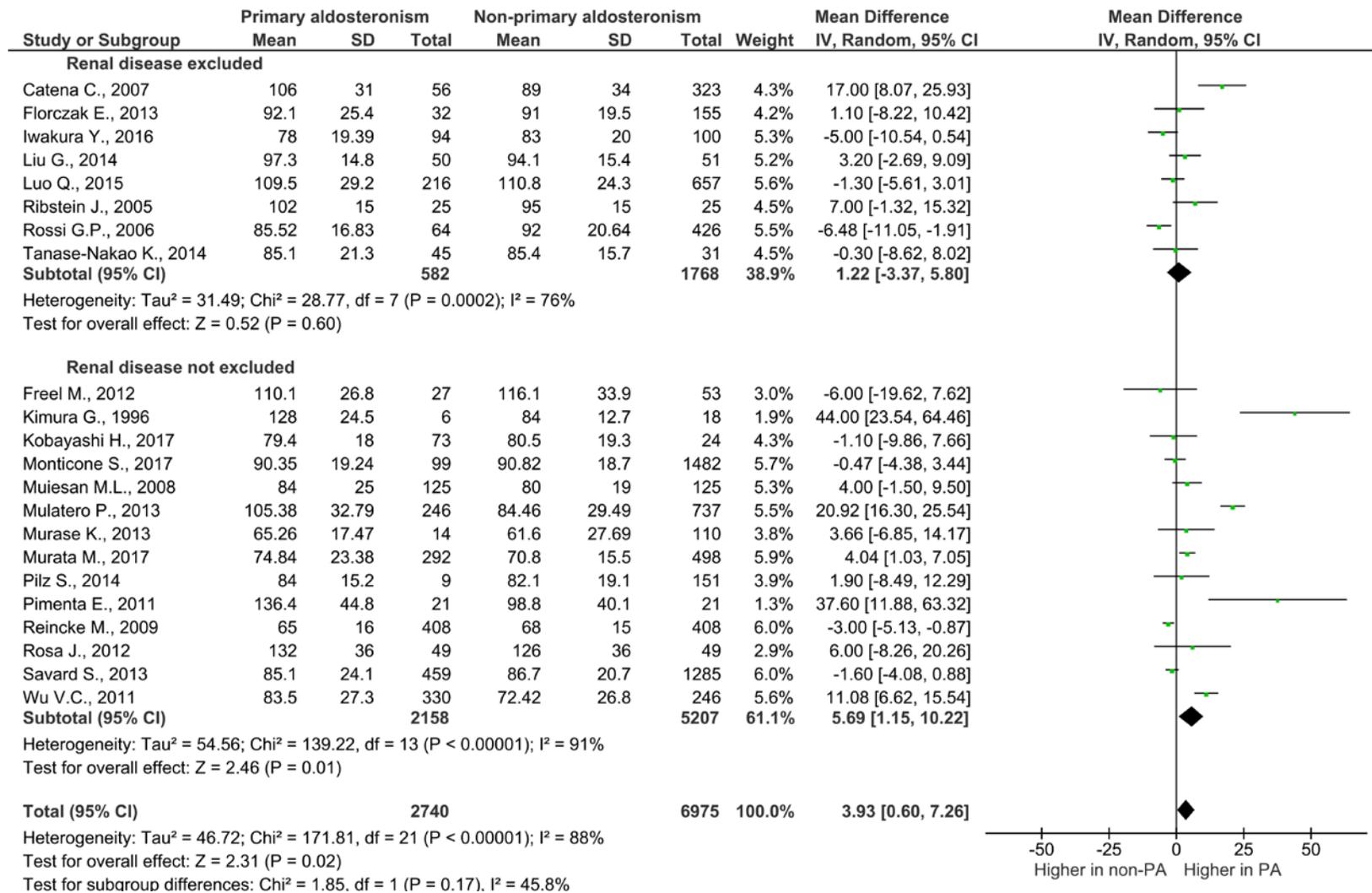


Figure 2

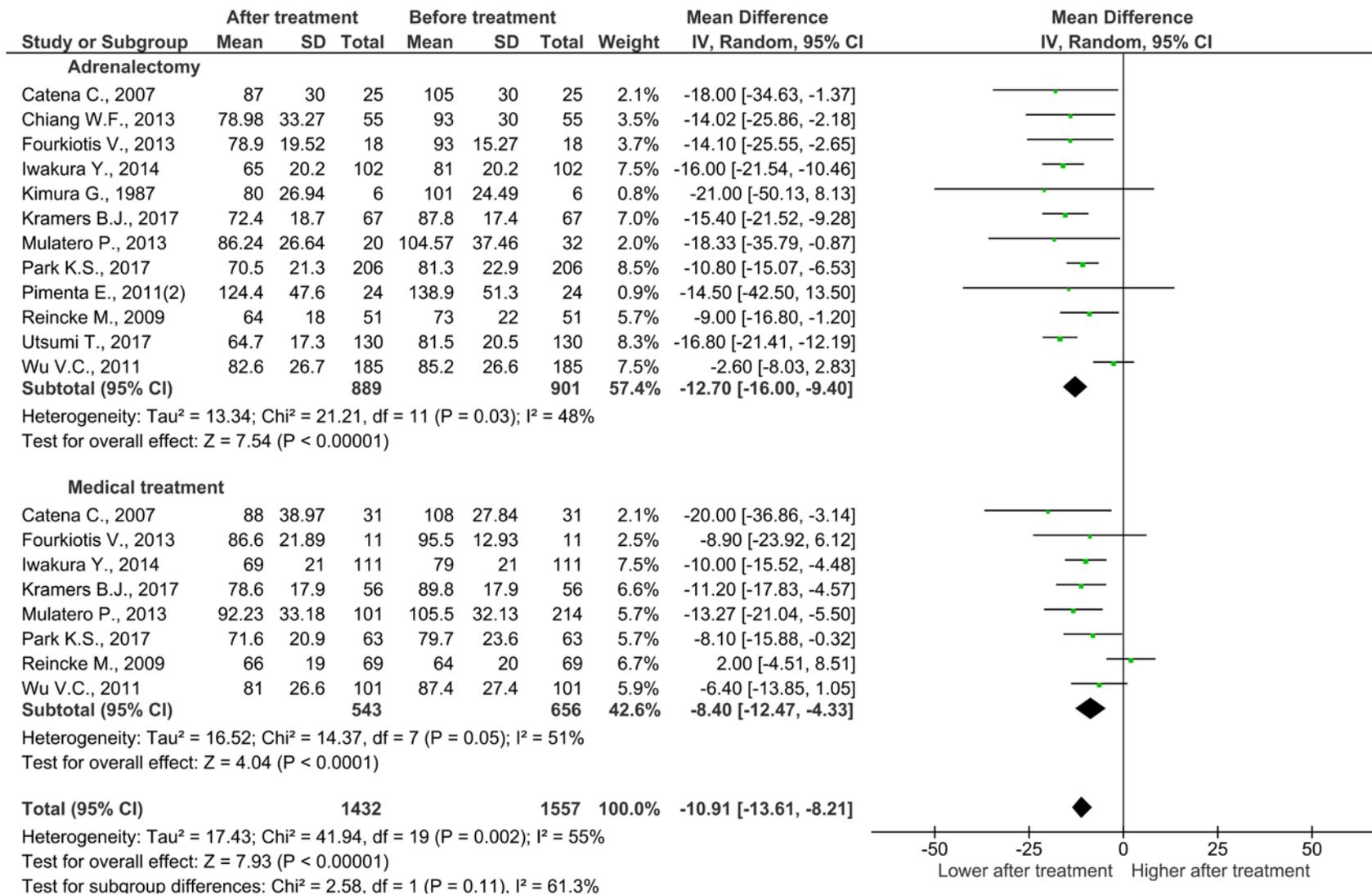


Figure 3