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Improvement of cardiovascular risk factors after adrenalectomy in patients with adrenal tumors and subclinical Cushing's syndrome: A systematic review and meta-Analysis

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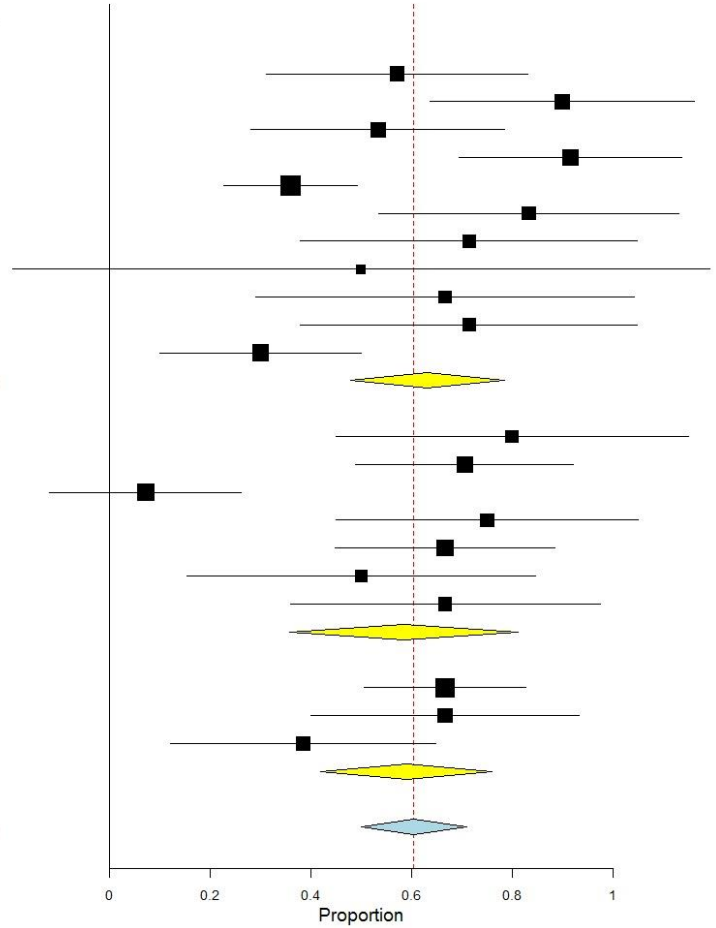
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(Article begins on next page)

Supplemental figure 1. Effect of adrenalectomy on hypertension in patients with SCS (Subgroup analysis)

Studies	Estimate (95% C.I.)	Ev/Trt
Chiodini	0.571 (0.312, 0.831)	8/14
Rossi	0.900 (0.637, 1.163)	4/4
Iacobone	0.533 (0.281, 0.786)	8/15
Akaza	0.917 (0.696, 1.138)	5/5
Alesina	0.360 (0.227, 0.493)	18/50
Tsiuki	0.833 (0.535, 1.132)	5/6
Erbil	0.714 (0.380, 1.049)	5/7
Morioka	0.500 (-0.193, 1.193)	1/2
Reincke	0.667 (0.289, 1.044)	4/6
Maehana	0.714 (0.380, 1.049)	5/7
Papierska	0.300 (0.099, 0.501)	6/20
Subgroup 1 (I²=73% , P=0.000)	0.632 (0.479, 0.784)	69/136
Bernini	0.800 (0.449, 1.151)	4/5
Persynakis	0.706 (0.489, 0.922)	12/17
Giordano	0.071 (-0.119, 0.262)	0/6
Mauclere-Denost	0.750 (0.450, 1.050)	6/8
Toniato	0.667 (0.449, 0.884)	12/18
Mitchell	0.500 (0.154, 0.846)	4/8
Kawate	0.667 (0.359, 0.975)	6/9
Subgroup 2 (I²=81% , P=0.000)	0.584 (0.357, 0.811)	44/71
Miyazato	0.667 (0.506, 0.828)	22/33
Guerrieri	0.667 (0.400, 0.933)	8/12
Kang	0.385 (0.120, 0.649)	5/13
Subgroup 3 (I²=42% , P=0.179)	0.590 (0.420, 0.761)	35/58
Overall (I²=72% , P=0.000)	0.605 (0.500, 0.711)	148/265



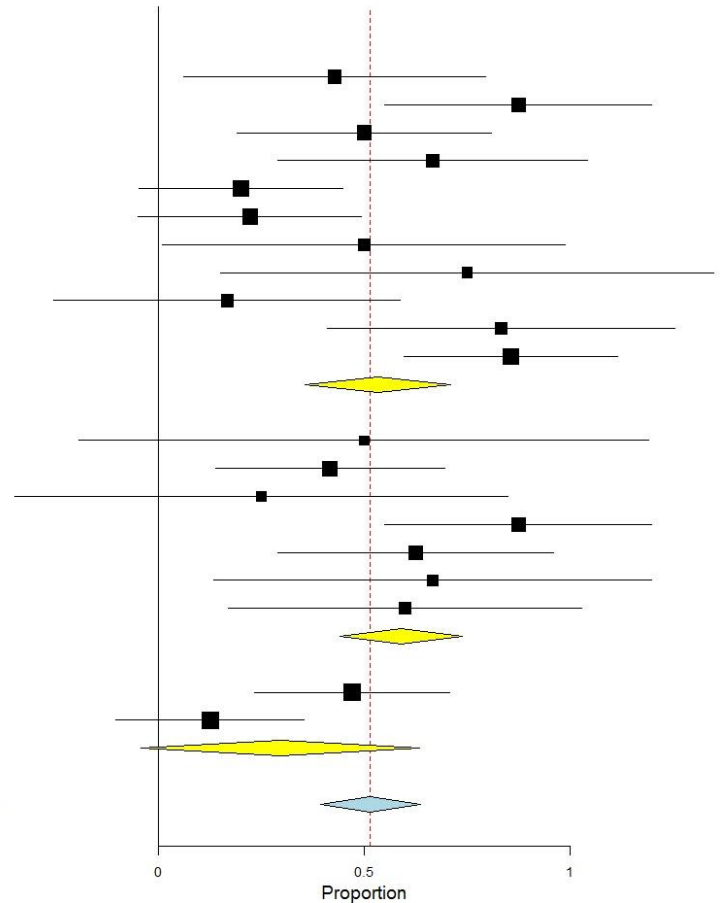
Subgroup 1: DST cortisol of 1-2.5 mcg/dl

Subgroup 2: DST cortisol of 3-5 mcg/dl

Subgroup 3 – DST cortisol cutoff not reported

Supplemental figure 2. Effect of adrenalectomy on diabetes mellitus type 2 in patients with SCS (Subgroup analysis)

Studies	Estimate (95% C.I.)	Ev/Trt
Chiodini	0.429 (0.062, 0.795)	3/7
Rossi	0.875 (0.551, 1.199)	3/3
Iacobone	0.500 (0.190, 0.810)	5/10
Akaza	0.667 (0.289, 1.044)	4/6
Alesina	0.200 (-0.048, 0.448)	2/10
Tsiuki	0.222 (-0.049, 0.494)	2/9
Erbil	0.500 (0.010, 0.990)	2/4
Morioka	0.750 (0.150, 1.350)	1/1
Reincke	0.167 (-0.255, 0.588)	0/2
Maehana	0.833 (0.412, 1.255)	2/2
Papierska	0.857 (0.598, 1.116)	6/7
Subgroup 1 (I²=65% , P=0.002)	0.534 (0.357, 0.711)	30/61
Bernini	0.500 (-0.193, 1.193)	1/2
Persynakis	0.417 (0.138, 0.696)	5/12
Giordano	0.250 (-0.350, 0.850)	0/1
Mauclere-Denost	0.875 (0.551, 1.199)	3/3
Toniato	0.625 (0.290, 0.960)	5/8
Mitchell	0.667 (0.133, 1.200)	2/3
Kawate	0.600 (0.171, 1.029)	3/5
Subgroup 2 (I²=0% , P=0.437)	0.590 (0.441, 0.739)	19/34
Miyazato	0.471 (0.233, 0.708)	8/17
Kang	0.125 (-0.104, 0.354)	1/8
Subgroup 3 (I²=76% , P=0.040)	0.296 (-0.042, 0.635)	9/25
Overall (I²=59% , P=0.001)	0.515 (0.394, 0.637)	58/120



Subgroup 1: DST cortisol of 1-2.5 mcg/dl

Subgroup 2: DST cortisol of 3-5 mcg/dl

Subgroup 3 – DST cortisol cutoff not reported

Supplemental figure 3. Effect of adrenalectomy on hypertension, diabetes mellitus and dyslipidemia in patients with NF adrenal tumors

Studies	Proportion (95% C.I.)	Events/Total
Improvement in Hypertension		
Chiodini	0.312 (0.085, 0.540)	5/16
Bernini	0.800 (0.449, 1.000)	4/5
Maehana	0.200 (0.000, 0.551)	1/5
Izaki	0.636 (0.352, 0.921)	7/11
Kang	0.235 (0.034, 0.437)	4/17

Overall (I²=67% , P=0.018) 0.421 (0.209, 0.632) 21/54

Improvement in Diabetes Mellitus

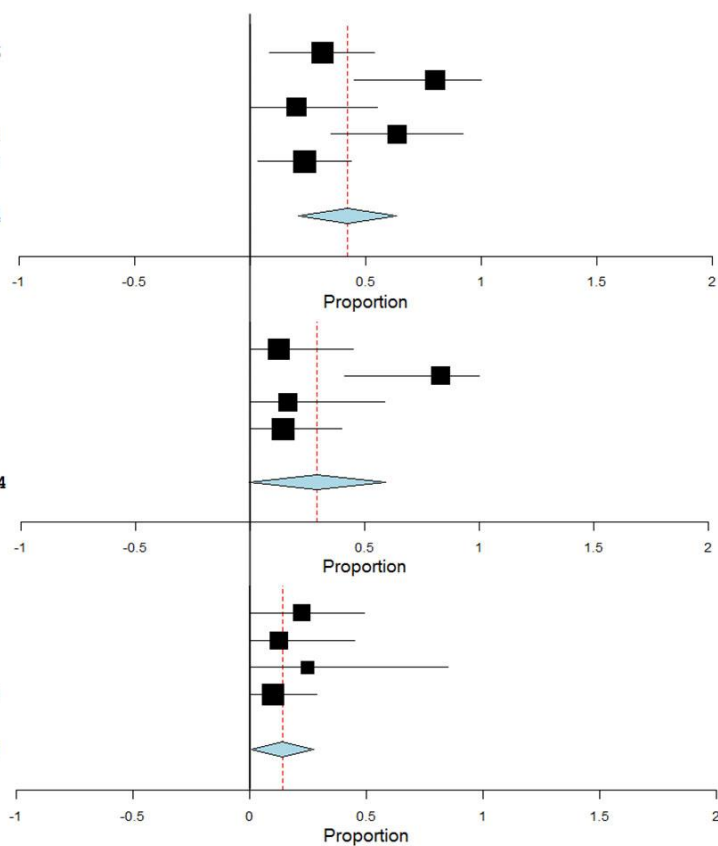
Chiodini	0.125 (0.000, 0.449)	0/3
Bernini	0.833 (0.412, 1.000)	2/2
Maehana	0.167 (0.000, 0.588)	0/2
Kang	0.143 (0.000, 0.402)	1/7

Overall (I²=66% , P=0.033) 0.294 (-0.004, 0.591) 3/14

Improvement in Dyslipidemia

Chiodini	0.222 (0.000, 0.494)	2/9
Bernini	0.125 (0.000, 0.449)	0/3
Maehana	0.250 (0.000, 0.850)	0/1
Kang	0.100 (0.000, 0.286)	1/10

Overall (I²=0% , P=0.881) 0.142 (0.007, 0.277) 3/23



Supplemental Table 1: Search strategyOvid

Database(s): Embase 1988 to 2015 Week 46, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) 1946 to Present, EBM Reviews - Cochrane Central Register of Controlled Trials October 2015, EBM Reviews - Cochrane Database of Systematic Reviews 2005 to October 2015

Search Strategy:

#	Searches	Results
1	exp Adrenal Gland Neoplasms/su [Surgery]	14159
2	exp Cushing syndrome/su [Surgery]	2656
3	((adrenal or adrenocort*) adj3 (cancer* or neoplasm* or tumor* or tumour* or incidentaloma* or adenoma* or carcinoma* or metastas* or metastatic* or hyperplasia*)).mp.	63592
4	(adrenocorticohyperplasia* or "arenocortical hyperplasia*" or "Cushings syndrome" or "cushing syndrome" or hypercortisolism).mp.	26760
5	surg*.mp. or su.fs.	5378995
6	(Adrenalectom* or ((adrenal* or adrenocort*) adj enucleation) or hemiadenectomy*).mp.	37975
7	exp Adrenalectomy/	30589
8	(3 or 4) and (5 or 6 or 7)	29292
9	1 or 2 or 8	31524
10	(subclinical* or mild or "non-function*" or nonfunction*).mp.	742997
11	9 and 10	2709
12	exp evidence based medicine/	840748
13	exp meta analysis/	163958
14	exp Meta-Analysis as Topic/	38705
15	exp "systematic review"/	98160
16	exp Guideline/ or exp Practice Guideline/	380341
17	exp controlled study/	4933524
18	exp Randomized Controlled Trial/	791095
19	exp triple blind procedure/	113
20	exp Double-Blind Method/	360426
21	exp Single-Blind Method/	55720
22	exp latin square design/	307
23	exp comparative study/	2585594
24	exp intervention studies/	36779
25	exp Cross-Sectional Studies/	371755
26	exp Cross-Over Studies/	109052
27	exp Cohort Studies/	1844075

28 exp longitudinal study/	281527
29 exp retrospective study/	998272
30 exp prospective study/	786223
31 exp clinical trial/	1868163
32 clinical study/	65466
33 exp case-control studies/	880083
34 exp confidence interval/	135831
35 exp multivariate analysis/	399518
36 odds ratio/	427385
37 "limit odds ratio above to embase. medline maps to risk".ti. ((evidence adj based) or (meta adj analys*) or (systematic* adj3 review*) or guideline* or (control* adj2 study) or (control* adj2 trial) or (randomized adj2 study) or (randomized adj2 trial) or (randomised adj2 study) or (randomised adj2 trial) or (doubl* adj blind*) or (doubl* adj mask*) or (singl* adj blind*) or (singl* adj mask*) or (tripl* adj blind*) or (tripl* adj mask*) or (trebl* adj blind*) or (trebl* adj mask*) or "latin square" or placebo* or multivariate or "comparative study" or "comparative survey" or "comparative analysis" or (intervention* adj2 study) or (intervention* adj2 trial) or "cross-sectional study" or "cross-sectional analys*" or "cross- sectional survey*" or "cross-sectional design*" or "prevalence study" or "prevalence analys*" or "prevalence survey*" or "disease frequency study" or "disease frequency analys*" or "disease frequency survey*" or crossover or "cross-over" or "cohort study" or "cohort survey" or "cohort analysis" or "longitudinal study" or "longitudinal survey" or "longitudinal analysis" or "retrospective study" or "retrospective survey" or "retrospective analysis" or "prospective study" or "prospective survey" or "prospective analysis" or "concurrent study" or "concurrent survey" or "concurrent analysis" or "clinical study" or "clinical trial" or "case control study" or "case base study" or "case referent study" or "case referent study" or "case compeer study" or "case comparison study" or "odds ratio" or "confidence interval" or cohort* or "multivariate analysis" or "change analysis" or study or "control group" or ((study or trial or random* or control*) and compar*).mp.	0
38	19853410
39 from 36 keep 1-356409	356409
40 or/12-35	11338392
41 38 or 39 or 40	20485396
42 11 and 41	1239
43 from 11 keep 1570-2685 limit 43 to (clinical trial, all or clinical trial, phase i or clinical trial, phase ii or clinical trial, phase iii or clinical trial, phase iv or clinical trial or comparative study or controlled clinical trial or evaluation studies or guideline or meta analysis or multicenter study or observational study or practice guideline or pragmatic clinical trial or randomized controlled trial or systematic reviews or validation studies) [Limit not valid in Embase,CCTR,CDSR; records were retained]	1116
44	144
45 42 or 44	1245
46 limit 45 to (book or book series or editorial or erratum or letter or note or addresses or	13

autobiography or bibliography or biography or comment or dictionary or directory or interactive tutorial or interview or lectures or legal cases or legislation or news or newspaper article or overall or patient education handout or periodical index or portraits or published erratum or video-audio media or webcasts) [Limit not valid in Embase,Ovid MEDLINE(R),Ovid MEDLINE(R) In-Process,CCTR,CDSR; records were retained]

47 45 not 46 1232

48 from 11 keep 2686-2709 24

49 47 or 48 1243

50 limit 49 to ("all infant (birth to 23 months)" or "all child (0 to 18 years)" or "newborn infant (birth to 1 month)" or "infant (1 to 23 months)" or "preschool child (2 to 5 years)" or "child (6 to 12 years)" or "adolescent (13 to 18 years)") [Limit not valid in Embase,CCTR,CDSR; records were retained] 871

51 limit 50 to (embryo or infant or child or preschool child <1 to 6 years> or school child <7 to 12 years> or adolescent <13 to 17 years>) [Limit not valid in Ovid MEDLINE(R),Ovid MEDLINE(R) In-Process,CCTR,CDSR; records were retained] 212

52 limit 51 to ("all adult (19 plus years)" or "young adult (19 to 24 years)" or "adult (19 to 44 years)" or "young adult and adult (19-24 and 19-44)" or "middle age (45 to 64 years)" or "middle aged (45 plus years)" or "all aged (65 and over)" or "aged (80 and over)") [Limit not valid in Embase,CCTR,CDSR; records were retained] 192

53 limit 52 to (adult <18 to 64 years> or aged <65+ years>) [Limit not valid in Ovid MEDLINE(R),Ovid MEDLINE(R) In-Process,CCTR,CDSR; records were retained] 176

54 51 not 53 36

55 49 not 54 1207

56 remove duplicates from 55 818

Scopus

- 1 TITLE-ABS-KEY((adrenal or adrenocort*) W/3 (cancer* or neoplasm* or tumor* or tumour* or incidentaloma* or adenoma* or carcinoma* or metastas* or metastatic* or hyperplasia*))
- 2 TITLE-ABS-KEY(adrenocorticohyperplasia* or "arenocortical hyperplasia*" or "Cushings syndrome" or "cushing syndrome" or hypercortisolism)
- 3 1 or 2
- 4 TITLE-ABS-KEY(subclinical* or mild or "non-function*" or nonfunction*)
- 5 TITLE-ABS-KEY(surg* or (Adrenalectom* or ((adrenal* or adrenocort*) W/1 enucleation) or hemiadenectomy*))
- 6 TITLE-ABS-KEY((evidence W/1 based) or (meta W/1 analys*) or (systematic* W/3 review*) or guideline* or (control* W/2 study) or (control* W/2 trial) or (randomized W/2 study) or (randomized W/2 trial) or (randomised W/2 study) or (randomised W/2 trial) or (doubl* W/1 blind*) or (doubl* W/1 mask*) or (singl* W/1 blind*) or (singl* W/1 mask*) or (tripl* W/1 blind*) or (tripl* W/1 mask*) or (trebl* W/1 blind*) or (trebl* W/1 mask*) or "latin square" or placebo* or multivariate or "comparative study" or "comparative survey" or "comparative analysis" or (intervention* W/2 study) OR (intervention* W/2 trial) OR "cross-sectional study" or "cross-sectional analys*" or "cross-sectional survey*" or "cross-sectional design*" or "prevalence study" or "prevalence analys*" or "prevalence survey*" or "disease frequency study" or "disease frequency analys*" or "disease frequency survey*" or crossover or "cross-over" or "cohort study" or "cohort survey" or "cohort analysis" or "longitudinal study" or "longitudinal survey" or "longitudinal analysis" or "retrospective study" or "retrospective survey" or "retrospective analysis" or "prospective study" or "prospective survey" or "prospective analysis" or "concurrent study" or "concurrent survey" or "concurrent analysis" or "clinical study" or "clinical trial" or "case control study" or "case base study" or "case referent study" or "case referent study" or "case compeer study" or "case comparison study" or "odds ratio" or "confidence interval" or cohort* or "multivariate analysis" or "change analysis" or study or "control group" or ((study or trial or random* or control*) and compar*))
- 7 3 and 4 and 5 and 6
- 8 TITLE(newborn* or neonat* or infant* or child* or adolescent* or paediatric* or pediatric*)
- 9 TITLE(adult or adults)
- 10 8 and not 9
- 11 7 and not 10
- 12 DOCTYPE(le) OR DOCTYPE(ed) OR DOCTYPE(bk) OR DOCTYPE(er) OR DOCTYPE(no) OR DOCTYPE(sh)
- 13 11 and not 12
- 14 PMID(0*) OR PMID(1*) OR PMID(2*) OR PMID(3*) OR PMID(4*) OR PMID(5*) OR PMID(6*) OR PMID(7*) OR PMID(8*) OR PMID(9*)
- 15 13 and not 14

