

## **Appendix: Influence of sodium intake and change in sodium intake on plasma-renin in man.**

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### **Methods**

#### Search string for identification of studies

- 1 sodium chloride, dietary/
- 2 sodium, dietary/
- 3 sodium/
- 4 (sodium or salt?).tw,kf.
- 5 or/1-4
- 6 diet, sodium-restricted/
- 7 ((salt? or sodium) adj5 (chang\$ or curb\$ or diet\$ or free or intake or limit\$ or load\$ or low\$ or minimi\$ or reduc\$ or restrict\$ or supplement\$)).tw,kf.
- 8 dash diet?.tw,kf.
- 9 or/6-8
- 10 hypertension/
- 11 essential hypertension/
- 12 (antihypertens\$ or hypertens\$ or normotens\$ or prehypertens\$).tw,kf.
- 13 exp blood pressure/
- 14 (blood pressure or bloodpressure or bp or dbp or hbp or mbp or sbp).tw,kf.
- 15 or/10-14
- 16 renin/
- 17 renin.tw,kf.
- 18 aldosterone/

- 19 aldosterone.tw,kf.
- 20 exp catecholamines/
- 21 (catecholamine\$ or sympathin\$ or dopamine\$ or hydroxytyramine\$ or dihydroxyphenethylamine or intropin or epinephrine or adrenaline or epitrate or vaponefrin or medihaler-epi or micronefrin or micronephrine or racepinephrine or epifrin or lyophrin or norepinephrin\$ or noradrenaline or levarterenol or levonorepinephrine or levophed or arterenol or levonor or orciprenaline or metaproterenol or alupent or metaprel or alotec or astmopent).tw,kf.
- 22 exp cholesterol/
- 23 (cholesterol\$ or epicholesterol\$ or azacosterol\$ or diazacholesterol\$ or hydroxycholesterol\$ or 19-iodocholesterol\$ or iodocholesterol\$ or ketocholesterol\$ or oxocholesterol\$ or lipid\$ or glyceride\$ or triglyceride\$ or glycolipid\$ or lipoprotein\$ or ldl or hdl).tw,kf.
- 24 or/16-23
- 25 randomized controlled trial.pt.
- 26 controlled clinical trial.pt.
- 27 randomized.ab.
- 28 placebo.ab.
- 29 clinical trials as topic/
- 30 randomly.ab.
- 31 trial.ti.
- 32 or/25-31
- 33 animals/ not (humans/ and animals/)
- 34 32 not 33
- 35 5 and 9 and (15 or 24) and 34

## Results

*Study selection:* The primary search was performed March 10, 2016. This search revealed 6831 articles and after de-duplication 3269 remained. After a screening based on reading of abstracts 2983 were eliminated. Thus 291 full-text articles were reviewed and of these 204 were included and 87 excluded. In addition, we included 3 studies from our 1998 version<sup>1</sup>, one from our 2011 version<sup>2</sup>, and one from another meta-analysis<sup>3</sup>. Thus, a total of 209 references were included based on the March 2016 search. The secondary search was performed April 11, 2018. This search revealed 8335 articles and after de-duplication 4014 remained. Of these, 877 were new compared with the primary search. After a primary screening 561 were eliminated. Based on a screening of abstracts 277 of the remaining 316 articles were excluded. Thus 39 full-text articles were reviewed and of these 10 were included. Thus, by April 11 2018, 219 articles were included. The last search was performed on March 18, 2020. This search covered the period from March 2016 to March 18 2020 and revealed 2222 references and after de-duplication 1448 remained. Compared with the April 11, 2018 search 843 were new. After a primary screening 271 were eliminated. Based on a screening of abstracts, 537 of the remaining 572 articles were excluded. Thus 35 full-text articles were reviewed and of these 12 fulfilled criteria for inclusion. Thus, by March 18 2020, 231 articles were included. From this pool we selected 105 studies, which measured renin as outcome.

*Reasons for exclusion of studies:* Four studies<sup>4-7</sup> were excluded due to use of anti-hypertensive medications. Four parallel trials were excluded<sup>8-11</sup>. As the large majority of cross-over studies reported separate data for each intervention period instead of overall estimates of effect, the continuous data type was used in the separate analyses of the cross-over studies. We transformed the outcomes of 14 studies which reported renin as concentrations (mU/L) to renin as activities (ng/ml/h) by division with 8.2, which is the

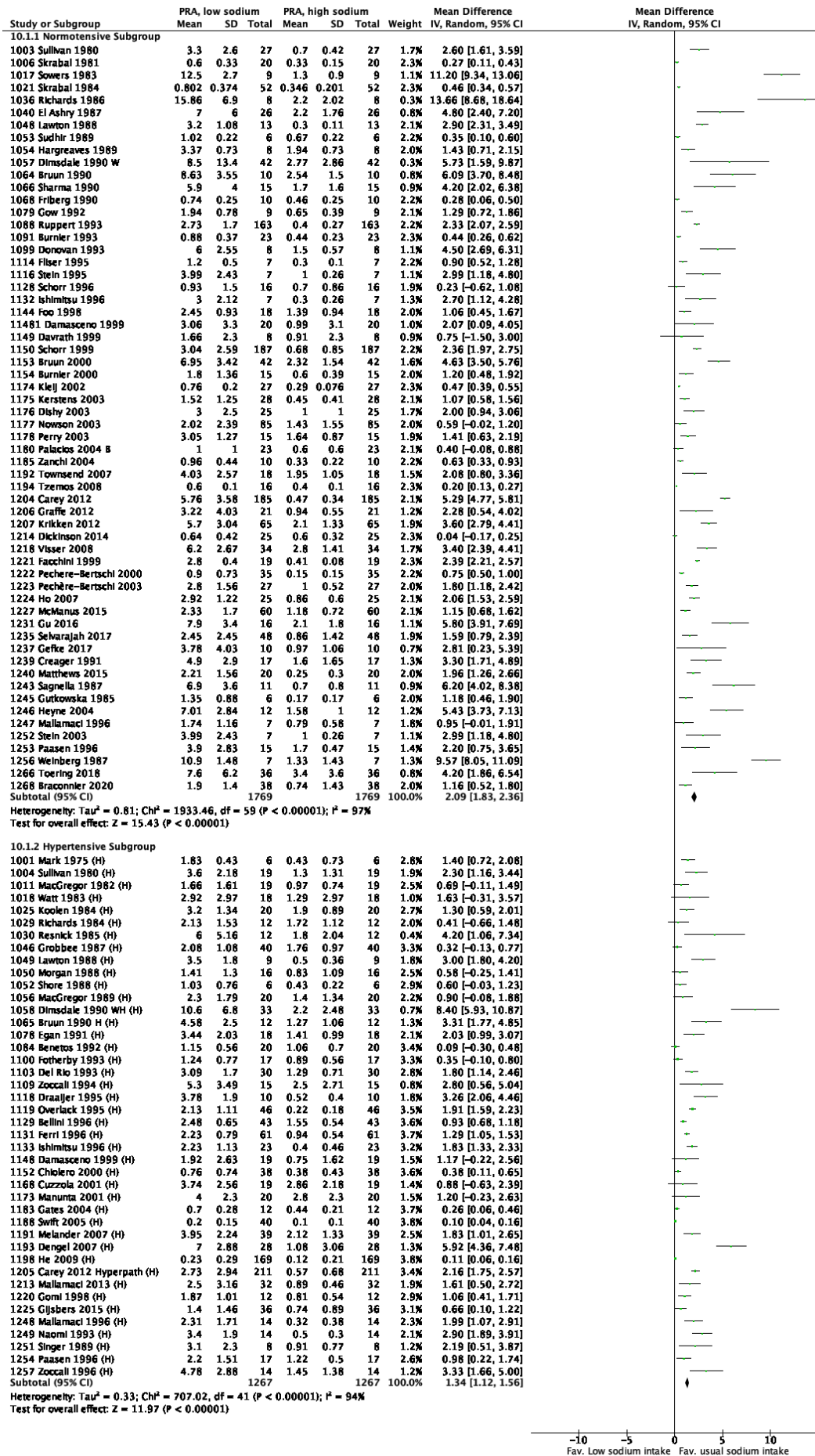
regression coefficient assessed from the regression line associating renin concentration (mU/L) with renin activity (ng/ml/h) in figure 2 in the study by De Bruin et al.<sup>12</sup>. Three studies with no information to decide the unit of the outcome<sup>13-15</sup> were excluded from the statistical analysis. One outlier study did not reduce sodium intake from a high level to a low level but from a very high level (357 mmol) to another very high level (310 mmol) and was therefore also excluded from the analysis<sup>16</sup>. Thus 93 references<sup>17-109</sup> were integrated in the statistical analyses.

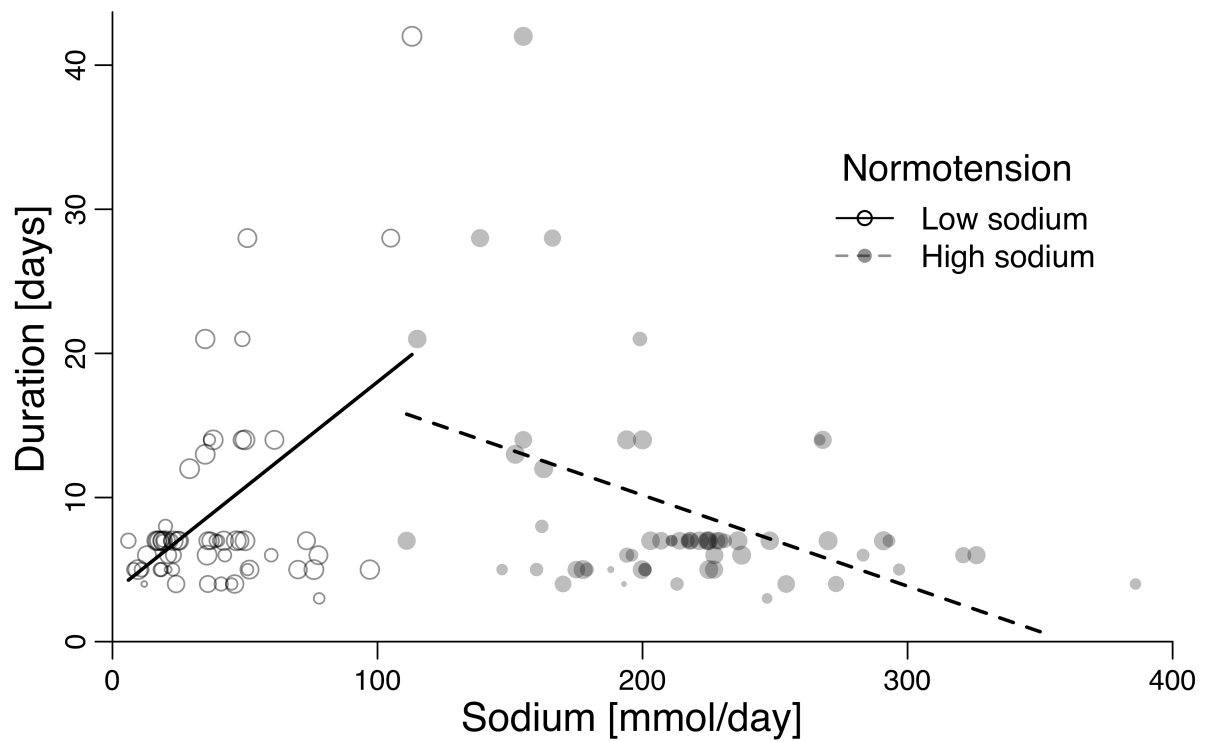
Final search: On January 21<sup>st</sup>, 2021, we performed a last additional search to record potentially eligible studies, which might have been published during the preparation of our manuscript and therefore not included in the present analysis.

We used a broad search term in PubMed (Medline and additional databases), “sodium and renin” giving 13484 results, then using publication date 1 year (overlapping our official search date, March 18 2020) as a filter to cover the period January 21<sup>st</sup> 2020 - January 21<sup>st</sup> 2021, giving 231 results. We identified four RCTs from this pool, of which two were in patients with chronic kidney disease<sup>110-111</sup> and one was in patients with diabetes<sup>112</sup>. In the last study, the strategy to reduce sodium intake did not succeed in one treatment arm and the other treatment arm included an unbalanced concomitant intervention<sup>113</sup>. As none of these 4 studies were eligible, we believe that the present analysis is up-to-date per January 21<sup>st</sup> 2021.

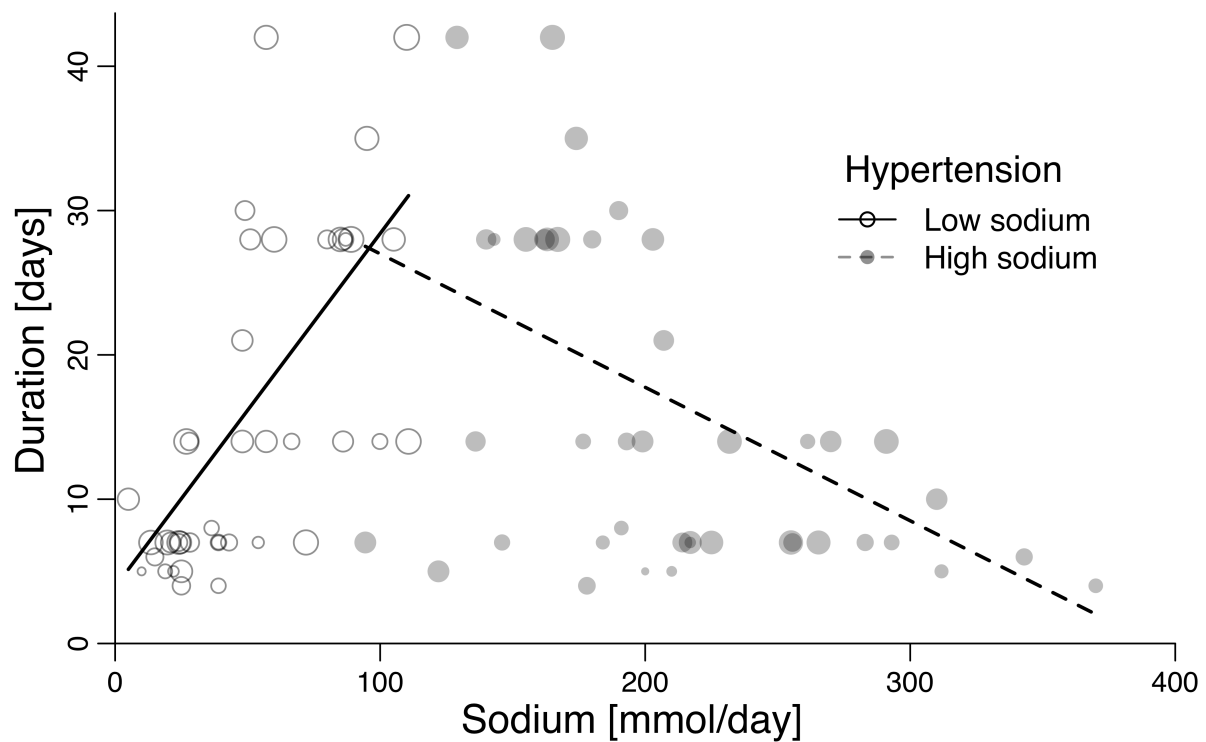
*Risk of bias across studies:* In populations with usual/high sodium intake there was significant inverse collinearity and in populations with low sodium intake there was a significant direct collinearity between sodium intake and duration of sodium intake (appendix figures 2-3). In populations with usual/high sodium intake there was an inverse collinearity between sodium reduction and duration of sodium intake in normotensive and hypertensive studies (appendix figure 4).

In study populations with a usual/high sodium intake the level of pl-renin and sodium intake did not differ between studies with low and high/unclear risks of bias or between studies with sodium tablet intervention and diet intervention (appendix table 3 A, lines 1-2, and 3B, lines 1-2). In study populations with a low sodium intake the level of pl-renin was lower in studies with low risk of bias and studies with sodium tablet intervention, but associated with correspondingly higher sodium intakes (Appendix Table 3 A, lines 3-4 and 3B, lines 3-4). The difference in pl-renin between usual/high sodium intake and low sodium intake was smaller in studies with low risk of bias and studies with sodium tablet intervention, but concurrently associated with a smaller change in sodium intake (Appendix Table 3 A, lines 5-6 and 3B, lines 5-6)).

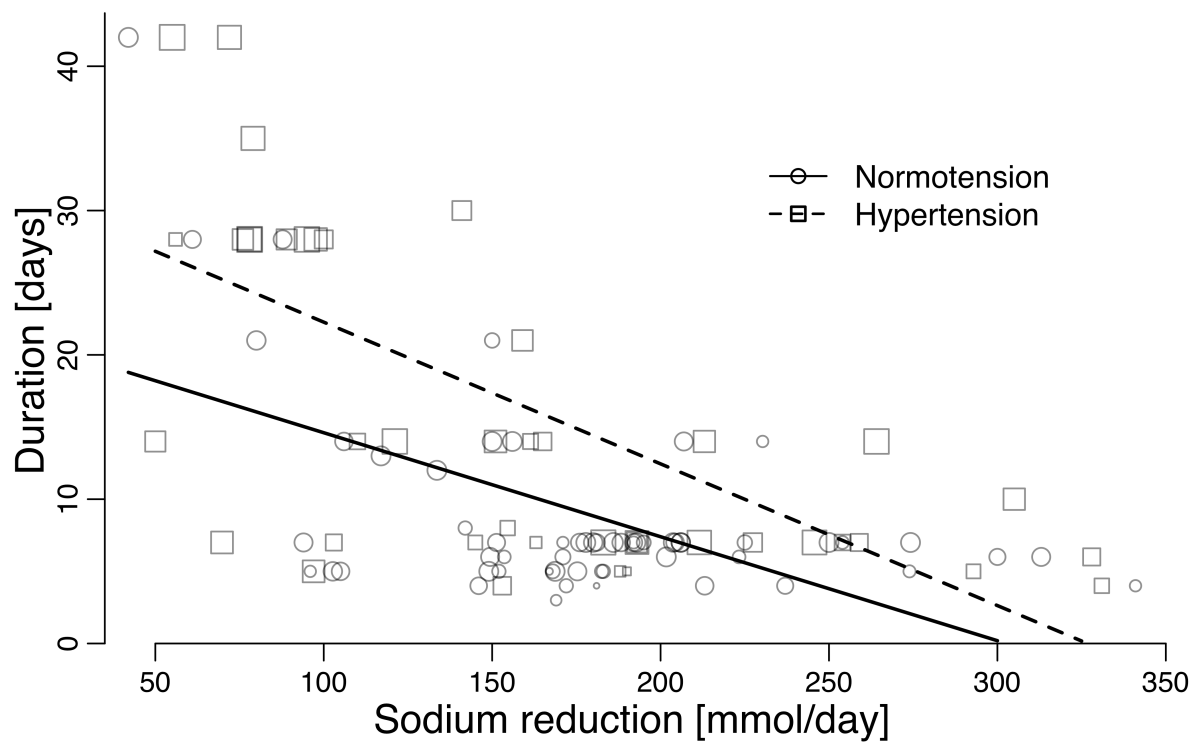




**Appendix Figure 2:** Association between sodium intake and study duration in normotensive studies at low sodium intake (solid line) and high sodium intake (dotted line)



**Appendix Figure 3:** Association between sodium intake and study duration in hypertensive studies at low sodium intake (solid line) and high sodium intake (dotted line)



**Appendix Figure 4:** Association between change in sodium intake (sodium reduction) and study duration in normotensive studies (solid line) and hypertensive studies (dotted line)



**Appendix Table 1: Characteristics of included studies**

Ref no	Study ID	First Author	Dur. (Days)	Restriction	BP	No	Age	Weight kg	S (Hi)	S (L)	SR	SBP (Hi)	DBP (Hi)	SBP (L)	DBP (L)
17	1001	Mark	10	diet	H	6	28	80,3	310	5	305	132,8	79,8	119,7	72,8
18	1003	Sullivan	4	diet	N	27	28,8	68,1	170	24	146	107,0	59,6	113,9	60,7
19	1004	Sullivan H	4	diet	H	19	27	76,8	178	25	153	120,3	74,7	121,5	73,5
20	1006	Skrabal	14	diet	N	20	23	75,8	200	50	150	125,0	73,1	122,3	70,1
20	1011	Mcgregor	28	SS	H	19	49	80,1	162	86	76	156,0	98,0	146,0	93,0
21	1017	Sowers	6	diet	N	9	39		196	42	154				
22	1018	Watt	28	SS	H	18	52	77,4	143	87	56	149,9	91,3	149,4	91,0
23	1021	Skrabal	14	diet	N	52	23	76,5	194	38	156	121,1	63,6	118,0	61,8
24	1025	Koolen	14	SS	H	20	40,8	76,9	270	57	213	147,7	95,4	141,5	90,5
25	1029	Richards	28	SS	H	12	36	74,3	180	80	100	149,9	92,4	145,9	89,4
26	1030	Resnick	5	SS	H	12	51,9		200	10	190	159,0	105,0	156,0	104,0
27	1036	Richards	4	diet	N	8	36		193	12	181	110,0	56,0	108,0	63,0
28	1040	El Ashry	14	SS	N	26	25,5	70,0	267	37	230	128,1	67,1	128,1	64,5
29	1046	Grobee	42	SS	H	40	24	74,7	129	57	72	143,0	78,0	142,2	77,2
30	1048	Lawton	6	diet	N	13	24,3		326	13	313	109,0	70,0	107,0	72,0
31	1049	Lawton H	6	diet	H	9	24,8		343	15	328	125,0	82,0	124,0	86,0
32	1050	Morgan	14	SS	H	16	63	81,0	136	86	50	173,0	102,0	170,0	98,0
32	1052	Shore	5	SS	H	6	51,9	77,3	122	25	97	157,0	101,0	148,0	95,4
33	1053	Sudhir	12	SS	N	6	34,7		163	29	134	128,9	80,7	121,0	75,7
34	1054	Hargreaves	14	SS	N	8	23,4	71,4	155	49	106	129,0	66,0	123,0	63,0
35	1056	McGregor	30	SS	H	20	57	73,6	190	49	141	163,0	100,0	147,0	91,0
36	1057	Dimsdale	5	SS	N	42	32		188	21	167	122,0	76,0	123,2	80,2
37	1058	Dimsdale H	5	SS	H	33	34		210	22	188	149,0	96,5	146,0	97,9
38	1064	Eske Brun	4	SS	N	10	46	72,2	386	45	341	116,0	69,0	111,0	68,0
38	1065	Eske Brun H	4	SS	H	12	47	77,2	370	39	331	150,0	96,0	142,0	92,0
39	1066	Sharma	7	SS	N	15	24	74,4	211	19	192	106,5	68,3	105,6	64,6
39	1068	Friberg	13	SS	N	10	33,3	76,3	152	35	117	114,0	69,0	114,0	68,0
40	1078	Egan H	7	SS	H	18	35	79,5	214	21	193	124,4	77,8	121,7	76,1
41	1079	Gow	7	diet	N	9	30,3		111	17	94	120,0	68,0	112,0	65,0
42	1084	Benetos	28	SS	H	20	41,5	71,6	163	85	78	149,1	93,2	142,6	89,5
43	1088	Ruppert	7	SS	N	163	38	70,7	291	17	274	113,2	71,5	111,0	72,5
44	1091	Burnier	6	diet	N	23	29		237	36	202	111,7	72,2	110,7	73,0
45	1099	Donovan	5	diet	N	8	36	67,0	160	8	152	116,0	63,0	114,0	64,0
46	1100	Fotherby	35	SS	H	17	73	67,4	174	95	79	176,0	96,0	168,0	97,0
47	1103	Del Rio	14	SS	H	30	49,2	72,4	199	48	151	156,1	95,5	154,7	95,0
48	1109	Zoccali	7	SS	H	15	45	79,6	217	54	163	144,0	92,0	130,0	84,0
49	1114	Fliser	7	diet	N	7	25,5	71,4	203	23	180	114,2	71,3	113,1	70,6
50	1116	Stein	5	diet	N	7	33,7		201	18	183	122,9	70,9	124,3	69,7
51	1118	Draaijer	7	SS	H	10	41	90,3	283	24	259	159,0	92,0	153,6	92,8
52	1119	Overlack	7	SS	H	46	45,3	80,5	265	20	246	138,0	90,2	134,1	87,7
53	1128	Schorr	28	SS	N	16	64,1	73,9	166	105	61	140,0	84,0	139,0	84,0
54	1129	Bellini	14	SS	H	43	45,4	78,0	232	111	121	159,8	103,6	155,9	98,7
55	1131	Ferri	14	SS	H	61	47,1	78,2	291	27	264	168,7	107,7	161,3	104,2
56	1132	Ishimitsu A	7	Diet	N	7	53	56,8	217	22	195	116,0	77,0	114,0	75,0
57	1133	Ishimitsu AH	7	Diet	H	23	55	59,7	217	24	193	157,2	94,5	141,5	89,0
58	1144	Foo	6	SS	N	18	51,1	71,9	227	78	149	122,8	76,9	115,1	79,3
58	1148	Damasceno	7	SS	N	20	37,5	73,0	293	39	254	108,5	67,7	109,0	68,0
59	1148	Damasceno H	7	SS	H	19	42,5	75,0	293	39	254	144,7	90,8	136,2	85,4
60	1149	Davrath	5	diet	N	8	25,1	74,5	147	51	96	124,0	70,0	132,0	75,0
60	1150	Schorr	7	SS	N	187	25	73,0	225	19	206	110,7	58,0	110,5	58,3
61	1152	Chiolero H	7	SS	H	38	43	75,4	255	72	183	143,1	89,8	136,6	85,6
62	1153	Bruun	4	diet	N	42	26	72,6	273	36	237	117,0	70,0	117,0	71,0
63	1154	Burnier	7	SS	N	15	22,7	72,3	207	19	188	126,0	75,0	125,0	80,0
64	1168	Cuzzola	14	SS	H	19	47	77,1	261	100	161	153,8	97,8	148,7	97,9
65	1173	Manunta	14	SS	H	20	48,3	79,6	177	67	110	152,4	99,2	147,2	95,9
66	1174	Kleij	7	Diet	N	27	23,7	74,1	236	50	186	118,5	74,1	118,7	74,2
67	1175	Kerstens	7	Diet	N	28	23,3	73,6	248	42	206	114,5	71,5	117,6	73,5

68	1176	Dishy	6	diet	N	25	34	78,9	321	21	300	112,0	59,0	114,0	60,0
69	1177	Nowson	28	SS	N	92	45	69,6	139	51	88	123,0	75,4	122,3	75,4
70	1178	Perry	5	SS	N	15	26	74,0	175	70	105	115,0	60,0	115,0	58,0
71	1180	Palacios B	21	diet	N	23	12,8	56,0	115	35	80	112,7	56,5	115,1	57,9
72	1183	Gates	28	SS	H	12	63,5	72,0	155	60	95	140,0	84,0	137,0	82,8
73	1185	Zanchi	7	diet	N	9	25	70,6	270	20	250	117,0	72,0	114,0	72,0
74	1188	Swift	28	SS	H	40	50	79,0	167	89	78	156,0	100,0	148,0	97,0
75	1191	Melander	28	SS	H	39	53	77,4	140	51	89	144,0	90,6	138,0	88,3
76	1192	Townsend	6	SS	N	18	30	69,6	194	23	171	117,0	69,0	111,0	65,0
77	1193	Dengel	8	diet	H	28	63	81,3	191	36	155	152,0	79,0	142,0	75,0
78	1194	Tzemos	5	SS	N	16	27	76,8	225	76	149	121,0	71,0	117,0	70,0
79	1198	He W	42	SS	H	169	50	85,3	165	110	55	146,0	90,0	141,2	87,8
80	1204	Carey	7	Diet	N	185	47	70,3	221	18	204	124,0	74,2	119,9	73,3
80	1205	Hyperpath	7	Diet	H	211	49,2	76,2	225	14	212	147,5	88,8	131,5	79,5
81	1206	Graffe	4	Diet	N	21	26	77,8	213	41	172	124,0	76,0	126,0	77,0
82	1207	Krikken	7	Diet	N	65	23	81,0	228	36	192	114,5	71,5	113,2	70,7
83	1213	Mallamaci	14	SS	H	32	48	74,0	193	28	165	143,1	91,0	135,1	88,0
84	1214	Dickinson	42	Diet	N	25	35,1	91,0	155	113	42	123,0	72,0	121,0	70,0
85	1218	Visser	7	diet	N	34	26,5	80,7	218	37	181	122,0	70,0	117,0	69,0
86	1220	Gomi A	7	Diet	H	12	51,8	59,3	94	25	70	145,7	93,3	144,6	93,6
87	1221	Facchini	5	SS	N	19	43	79,4	178	10	169	109,2	68,1	108,9	67,9
88	1222	Pechere-Bertchi	7	Diet	N	35	28,9	60,0	225	47	178	109,2	75,2	106,8	74,5
89	1223	Pechere-Bertchi	7	diet	N	27	26	59,7	218	25	193	108,0	71,0	107,0	73,0
90	1224	Ho	14	SS	N	25	48,8	85,7	268	61	207	127,0	77,0	122,0	75,2
91	1225	Gijsbers	28	SS	H	36	65,8	82,5	203	105	98	145,3	80,6	137,8	77,9
92	1227	McManus	5	SS	N	60	50,1	NA	200	97	103	126,7	76,0		
93	1231	Gu	6	Diet	N	16	28,8	69,3	283	60	223	117,7	70,8	118,1	73,9
94	1235	Selvarajah	7	SS	N	48	30	68,9	225	73	151	120,0	73,0	116,9	71,4
95	1237	Gefke	3	Diet	N	10	25	69	247	78	169	114,0	68,0	113,0	68,0
96	1257	Zoccali	7	Diet	H	14	47	NA	184	39	145	156,0	101,0	141,0	94,0
97	1243	Sagnella	5	SS	N	11	22	69	297	23	274	118,4	73,0	117,8	74,2
98	1256	Weinberg	7	Diet	N	7		NA	231	6	225	116,0	72,0	116,0	76,0
99	1253	Paasen	21	Diet	N	15	39	72,6	199	49	150	115,8	72,3	118,4	74,0
99	1254	Paasen H	21	Diet	H	17	51	82,5	207	48	159	149,6	94,1	143,0	91,5
100	1252	Stein	5	Diet	N	7	33,7	NA	201	18	183	122,9	70,9	124,3	69,7
101	1251	Singer	5	SS	H	8	52,4	NA	312	19	293	164,0	106,0	163,0	106,0
102	1249	Naomi	7	SS	H	9	46,9	60,2	256	28	227	145,1	86,9	130,3	80,2
103	1247	Mallamci	7	Diet	N	7	34	81,3	214	48	176	121,0		118,0	
103	1248	Mallamaci H	7	Diet	H	14	47	76,4	146	43	103	138,0		127,0	
104	1246	Heyne	8	Diet	N	12	25,5	NA	162	20	142	127,5	79,8	126,2	79,0
105	1245	Gutkowska	4	Diet	N	6	29,3	68,2	254	46	213				
106	1239	Creager	5	Diet	N	17	30	74	179	11	168	122,0	60,0	124,0	62,0
107	1240	Matthews	7	Diet	N	20	40,5	79,5	229	25	204	120,0	74,5	115,0	71,6
108	1268	Braconnier	5	SS	N	38	33,5	66,2	227	52	175	113,6	69,6	112,9	69,4
109	1266	Toering	7	Diet	N	36	33,5	NA	211	40	171	119,5	72,0	116,0	69,5

Dur: Study duration; SS: Slow sodium tablet; BP: Blood pressure; H: Hypertension; N: Normotension; No: Number; S: Sodium; Hi: High; L: Low; SR: Sodium reduction

**Appendix Table 2: Bias Assessment (L: Low risk of bias; H: High risk of bias, U: Unclear risk of bias)**

Ref no	1 <sup>st</sup> Author	Selection	Performance	Attrition	Over-all Bias *
17	Mark	U	H	L	U
18	Sullivan	H	H	L	H
19	Sullivan H	H	H	L	H
20	Skrabal	U	H	L	U
20	Mcgregor	U	L	L	L
21	Sowers	U	H	L	U
22	Watt	U	L	U	U
23	Skrabal	U	H	L	U
24	Koolen	U	H	L	U
25	Richards	U	H	H	H
26	Resnick	U	H	L	U
27	Richards	U	H	L	U
28	El Ashry	U	H	L	U
29	Grobee	U	L	L	L
30	Lawton	U	H	L	U
31	Lawton H	U	H	L	U
32	Morgan	U	H	L	U
32	Shore	U	H	L	U
33	Sudhir	U	H	L	U
34	Hargreaves	U	L	L	L
35	McGregor	U	L	L	L
36	Dimsdale	U	H	L	U
37	Dimsdale H	U	H	L	U
38	Eske Brun	U	H	L	U
38	Eske Brun H	U	H	L	U
39	Sharma	U	H	U	U
39	Friberg	U	H	H	H
40	Egan	L	L	L	L
41	Gow	U	H	L	U
42	Benetos	U	L	L	L
43	Ruppert/Overlack	U	H	L	U
44	Burnier	U	H	L	U
45	Donovan	U	H	L	U
46	Fotherby	U	L	L	L
47	Del Rio	U	L	H	U
48	Zoccali	U	H	L	U
49	Fliser	U	H	L	U
50	Stein	U	H	L	U
51	Draaijer	U	H	L	U
52	Overlack	U	L	L	L
53	Schorr	U	L	H	U
54	Bellini	U	L	H	U
55	Ferri	U	L	L	L
56	Ishimitsu	U	H	L	U
57	Ishimitsu H	U	H	L	U
58	Foo	U	L	L	L
58	Damasceno	U	L	L	L
59	Damasceno H	U	L	L	L
60	Davrath	U	H	L	U
60	Schorr	U	H	L	U
61	Chiolero	U	H	L	U
62	Bruun	U	H	L	U
63	Burnier	U	H	L	U
64	Cuzzola	U	L	H	U
65	Manunta	U	H	L	U
66	Kleij	U	H	L	U
67	Kerstens	U	H	L	U
68	Dishy	U	H	L	U
69	Nowson	U	H	U	U
70	Perry	U	H	L	U
71	Palacios	U	H	H	H
72	Gates	U	L	L	L
73	Zanchi	U	L	L	L
74	Swift	U	L	U	U
75	Melander	U	L	U	U
76	Townsend	U	H	L	U

77	Dengel	U	L	L	L
78	Tzemos	U	L	L	L
79	He	L	L	L	L
80	Carey	U	H	U	U
81	Carey H	U	H	U	U
82	Graffe	L	L	L	L
82	Krikken	U	H	U	U
83	Mallamaci	U	H	L	U
84	Dickinson	U	U	L	U
85	Visser	U	H	U	U
86	Gomi	U	H	L	U
87	Facchini	U	H	L	U
88	Pechere-Bertchi	U	H	L	U
89	Pechere-Bertchi	U	H	L	U
90	Ho	U	H	L	U
91	Gijsbers	L	L	L	L
92	McManus	U	H	L	U
93	Gu	U	H	H	H
94	Selvarajah	U	L	U	U
95	Gefke	U	H	U	U
96	Zoccali	U	H	U	U
97	Sagnella	U	H	U	U
98	Weinberg	U	H	U	U
99	Paasen	U	H	U	U
100	Paasen H	U	H	U	U
101	Stein	U	H	U	U
101	Singer	U	H	U	U
102	Naomi	U	H	U	U
103	Mallamaci	L	H	U	U
104	Mallamaci H	L	H	U	U
105	Heyne	U	H	U	U
105	Gutkowska	U	H	U	U
106	Creager	U	H	U	U
107	Matthews	U	H	U	U
108	Braconnier	U	H	U	U
109	Toering	U	H	U	U

Over-all bias was defined by two or three identical assessments of L (low risk of bias), H (high risk of bias) or U (unclear risk of bias). Three different assessments (1L,1H, 1U) were assessed as U. As renin was measured blindly, detection bias was assumed to be low in all studies

**Appendix Table 3:** Impact of bias (low versus high/unclear) and type of sodium intake (diet or tablet) on plasma renin.

A: Bias	Low (n = 19)	High/Unclear (n =83)	p
1) Renin (high sodium)	0.94	1.14	0.28
2) High sodium intake	209	214	0.72
3) Renin (low sodium)	2.17	3.89	0.02
4) Low sodium intake	57	40	0.013
5) Renin Change	1.23	2.57	0.023
6) Change sodium intake	152	174	0.22
B: Type of sodium intake	Diet (n = 47)	Sodium Tablet (n = 55)	p
1) Renin (high sodium)	0.99	1.2	0.14
2) High sodium intake	213	214	0.9
3) Renin (low sodium)	3.87	3	0.11
4) Low sodium intake	33	52,5	0.0002
5) Renin Change	2.88	1.84	0.023
6) Change sodium intake	180	162	0.17

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