Supplementary material

Content list:

1. Search string:

(cirrhosis OR cirrhotic) AND (ascites OR refractory ascites) AND (natriuretic peptide OR ANP OR atrial natriuretic peptide OR atrial natriuretic factor OR ANF OR atriopeptin OR carperitide OR BNP OR brain natriuretic peptide OR ventricular natriuretic peptide OR Type B natriuretic peptide OR nesiritide OR urodilatin OR ularitide).

2. Assumptions regarding units and unit conversions:

For the parameters natriuresis and diuresis, data were easily extracted in units of µmol/min and mL/min, respectively. Renin was predominantly presented as plasma renin activity (conversion of angiotensinogen to angiotensin I) with only one study providing the exact renin concentration. We transformed the latter to renin activity by dividing with 11.2 [1]. Plasma aldosterone concentration was extracted as pmol/L. Original data on aldosterone presented as ng/dL was converted by multiplying with the conversion factor 27.74 (generated by a molar mass of 360.4g/mol [2]).

3. Adjusted Newcastle-Ottawa-Scale for quality assessment of non-randomised studies [3]:

NEWCASTLE - OTTAWA QUALITY ASSESSMENT SCALE
COHORT STUDIES

Note: A study can be awarded a maximum of one star for each numbered item within the Selection and Outcome categories. A maximum of two stars can be given for Comparability

Selection

1) Representativeness of the exposed cohort:

a) truly representative of the average *Cirrhosis patient with ascites* (describe) in the community

- *Cirrhosis diagnosed by clinical and laboratory findings, or by a liver biopsy.*
- *Ascites diagnosed by physical examination, ultrasonography or explorative paracentesis.*

b) somewhat representative of the average *Cirrhosis patient with ascites* in the community

c) selected group of users eg nurses, volunteers

d) no description of the derivation of the cohort

2) Selection of the non exposed cohort:

a) drawn from the same community as the exposed cohort

b) drawn from a different source

c) no description of the derivation of the non exposed cohort

3) Ascertainment of exposure:

a) secure record (eg surgical records)

b) structured interview

c) written self report

d) no description

4) Demonstration that outcome of interest was not present at start of study – *That included patients were naïve to natriuretic peptide treatment, thus the natriuretic effect of natriuretic peptides were unknown before start of study:*

a) yes

b) no

Comparability

1) Comparability of cohorts on the basis of the design or analysis:

a) study controls for *Effects of natriuretic peptides on natriuresis* (select the most important factor)

- *Natriuresis must be measured at baseline AND during infusion of a natriuretic peptide*

b) study controls for additional factors

- *Effects on diuresis at baseline AND during infusion of a natriuretic peptide*
- *Reporting of adverse events*
- *Withdrawal of diuretic treatments AT LEAST one week before study start*

Outcome

1) Assessment of outcome

a) independent blind assessment

b) record linkage

c) self report

d) no description

2) Was follow-up long enough for outcomes to occur

a) yes (select an adequate follow up period for outcome of interest)

- *For the endpoints diuresis and natriuresis, the adequate follow-up is 30 minutes or more*
- *For adverse events and hypotension adequate follow-up is 30 minutes or more*

b) no

3) Adequacy of follow up of cohorts

a) complete follow up - all subjects accounted for

b) subjects lost to follow up unlikely to introduce bias - small number lost

- *≥90% follow up, or description provided of those lost*

c) follow up rate

- *<90% and no description of those lost*

d) no statement

4. Assumptions regarding treatment dose and ascites severity at study level:

4.1. Treatment dose:

In one study [4] participants were randomised to receive two different doses of ANP and a vehicle, while another study [5] doubled the intervention dose halfway. In these particular cases we only collected data on the first dose received. In [6] a fixed bolus injection of 33,000 ng ANP was administered to all participants. To make this comparable to other included studies applying bolus injections, we transformed the dose to 500 ng/kg, assuming an average bodyweight of 66 kg for their participants (original bodyweight was not provided). In [7] four repeated doses of 1000 ng/kg were administered with three hour intervals to all

participants. We assumed that the effects on our outcomes were identical after each bolus injection and thus the dose was extracted as 1000 ng/kg.

4.2. Ascites severity:

In [4,8] the presence of ascites were not confirmed in all participants, and study authors stated, that the majority of the participants had diuretic responsive ascites and mild ascites, respectively. In [9] all participants had ascites but without classifying the severity, although it was stated that none had undergone paracentesis for at least 14 days. In [10] ascites was confirmed by ultrasound, but without mentioning the exact severity. Therefore, we categorised all participants in these four studies as having mild ascites. In [5,11,12] all participants had persistent ascites detected by physical examination, ultrasound, and confirmed by explorative paracentesis, and thus we assumed an overall classification of moderate ascites was suitable since mild ascites is undetectable by physical examination [13]. In a few trials, gender and cirrhosis aetiology data were only presented for the whole study population and not for the relevant subgroups.

5. Data extraction and language:

20 publications were in English, one was in German [14], and one was in Japanese [15]. RHG and MBK are fluent in English and German, thus data extraction from studies published in English and German was unproblematic. Figure and table legends of the Japanese study were in English while the remaining text was translated to English with Google Translate. Hence, this procedure was performed independently by the two reviewers.

6. Cirrhosis aetiologies:

The cause of cirrhosis was provided for 185 patients. 131 (71%) had alcohol-related cirrhosis, 23 (12%) had cirrhosis due to chronic infection with hepatitis B or C virus, 18 (10%) were characterised as having cryptogenic cirrhosis, and 13 (7%) had cirrhosis from other aetiologies. If cirrhosis due to metabolic associated liver disease was misrecognized as cryptogenic cirrhosis, the distribution of aetiologies in these 185 patients largely resemble the present distribution of cirrhosis aetiologies.

7. Figure 1

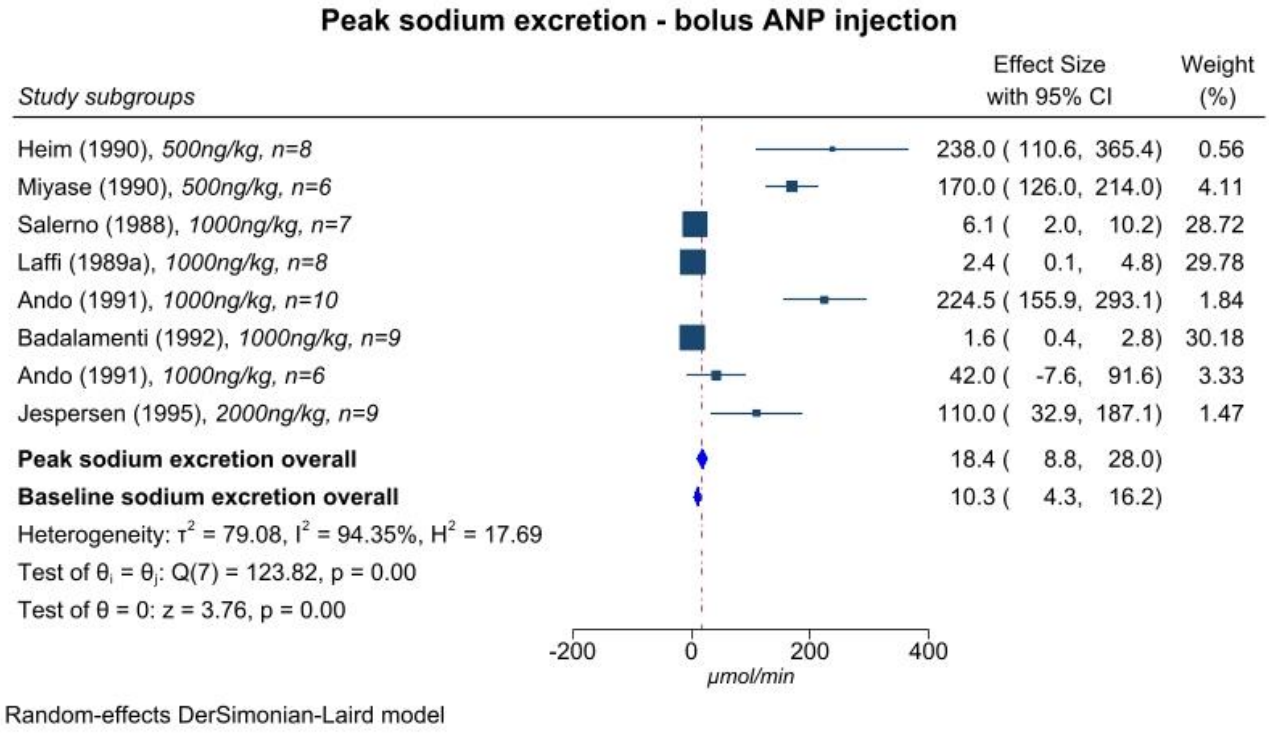

Figure 1 Effect of intravenous ANP bolus injection on sodium excretion (µmol/min). Heim et al did not withdraw diuretics prior to the treatment. When we perform the analysis without this study, the baseline natriuresis is 9.4 µmol/min (95% CI: 3.6 – 15.1) and peak natriuresis is 16.0 (95% CI: 6.9 – 25.2).

8. Figure 2:

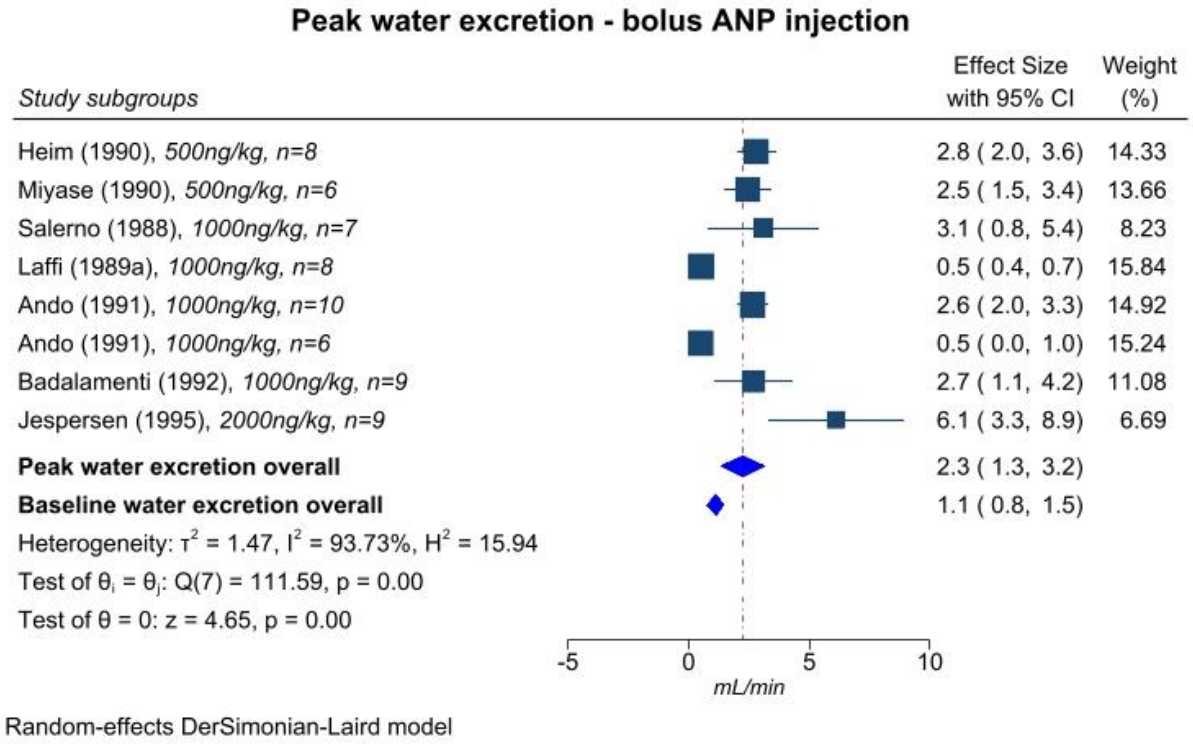

Figure 2 Effect of intravenous ANP bolus injection on water excretion (mL/min).

9. Figure 3:

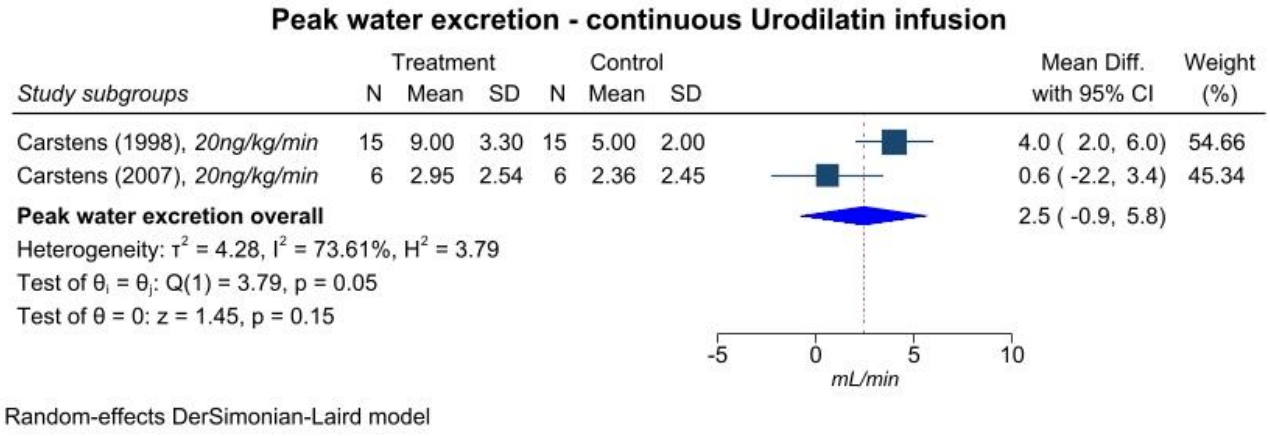

Figure 3 Effect of intravenous Urodilatin and placebo infusion on water excretion (mL/min). Since both studies were cross-over RCTs we used peak diuretic response with Urodilatin and placebo infusion to generate the forest plot.

10. Figure 4:

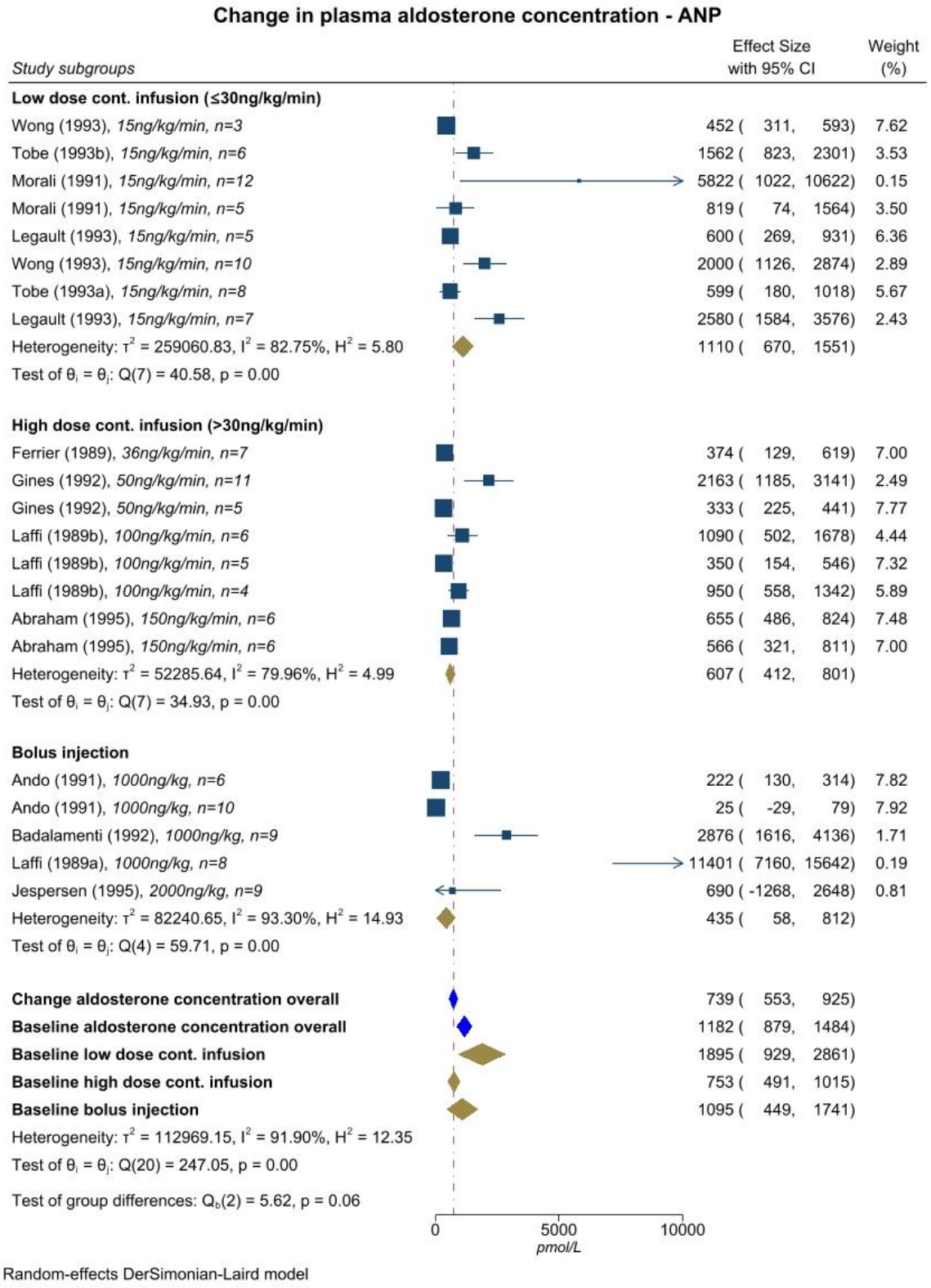
Change in plasma aldosterone concentration - ANP
Study subgroups
Effect Size with 95% CI
Weight (%)
Low dose cont. infusion (≤30ng/kg/min)
Wong (1993), 15ng/kg/min, n=3 452 (311, 593) 7.62
Tobe (1993b), 15ng/kg/min, n=6 1562 (823, 2301) 3.53
Morali (1991), 15ng/kg/min, n=12 5822 (1022, 10622) 0.15
Morali (1991), 15ng/kg/min, n=5 819 (74, 1564) 3.50
Legault (1993), 15ng/kg/min, n=5 600 (269, 931) 6.36
Wong (1993), 15ng/kg/min, n=10 2000 (1126, 2874) 2.89
Tobe (1993a), 15ng/kg/min, n=8 599 (180, 1018) 5.67
Legault (1993), 15ng/kg/min, n=7 2580 (1584, 3576) 2.43
Heterogeneity: τ² = 259060.83, I² = 82.75%, H² = 5.80 1110 (670, 1551)
Test of θi = θj: Q(7) = 40.58, p = 0.00
High dose cont. infusion (>30ng/kg/min)
Ferrier (1989), 36ng/kg/min, n=7 374 (129, 619) 7.00
Gines (1992), 50ng/kg/min, n=11 2163 (1185, 3141) 2.49
Gines (1992), 50ng/kg/min, n=5 333 (225, 441) 7.77
Laffi (1989b), 100ng/kg/min, n=6 1090 (502, 1678) 4.44
Laffi (1989b), 100ng/kg/min, n=5 350 (154, 546) 7.32
Laffi (1989b), 100ng/kg/min, n=4 950 (558, 1342) 5.89
Abraham (1995), 150ng/kg/min, n=6 655 (486, 824) 7.48
Abraham (1995), 150ng/kg/min, n=6 566 (321, 811) 7.00
Heterogeneity: τ² = 52285.64, I² = 79.96%, H² = 4.99 607 (412, 801)
Test of θi = θj: Q(7) = 34.93, p = 0.00
Bolus injection
Ando (1991), 1000ng/kg, n=6 222 (130, 314) 7.82
Ando (1991), 1000ng/kg, n=10 25 (-29, 79) 7.92
Badalamenti (1992), 1000ng/kg, n=9 2876 (1616, 4136) 1.71
Laffi (1989a), 1000ng/kg, n=8 11401 (7160, 15642) 0.19
Jespersen (1995), 2000ng/kg, n=9 690 (-1268, 2648) 0.81
Heterogeneity: τ² = 82240.65, I² = 93.30%, H² = 14.93 435 (58, 812)
Test of θi = θj: Q(4) = 59.71, p = 0.00
Change aldosterone concentration overall 739 (553, 925)
Baseline aldosterone concentration overall 1182 (879, 1484)
Baseline low dose cont. infusion 1895 (929, 2861)
Baseline high dose cont. infusion 753 (491, 1015)
Baseline bolus injection 1095 (449, 1741)
Heterogeneity: τ² = 112969.15, I² = 91.90%, H² = 12.35
Test of θi = θj: Q(20) = 247.05, p = 0.00
Test of group differences: Qb(2) = 5.62, p = 0.06
0
5000
10000
pmol/L
Random-effects DerSimonian-Laird model

Figure 4 Effect of intravenous ANP on plasma aldosterone concentration (pmol/L) in study subgroups receiving continuous infusions and bolus injections. Analysis were performed on overall data and separately for study subgroups receiving low-dose continuous infusion (≤ 30 ng/kg/min), high-dose continuous infusion (> 30 ng/kg/min), and bolus injection.

11. Figure 5:

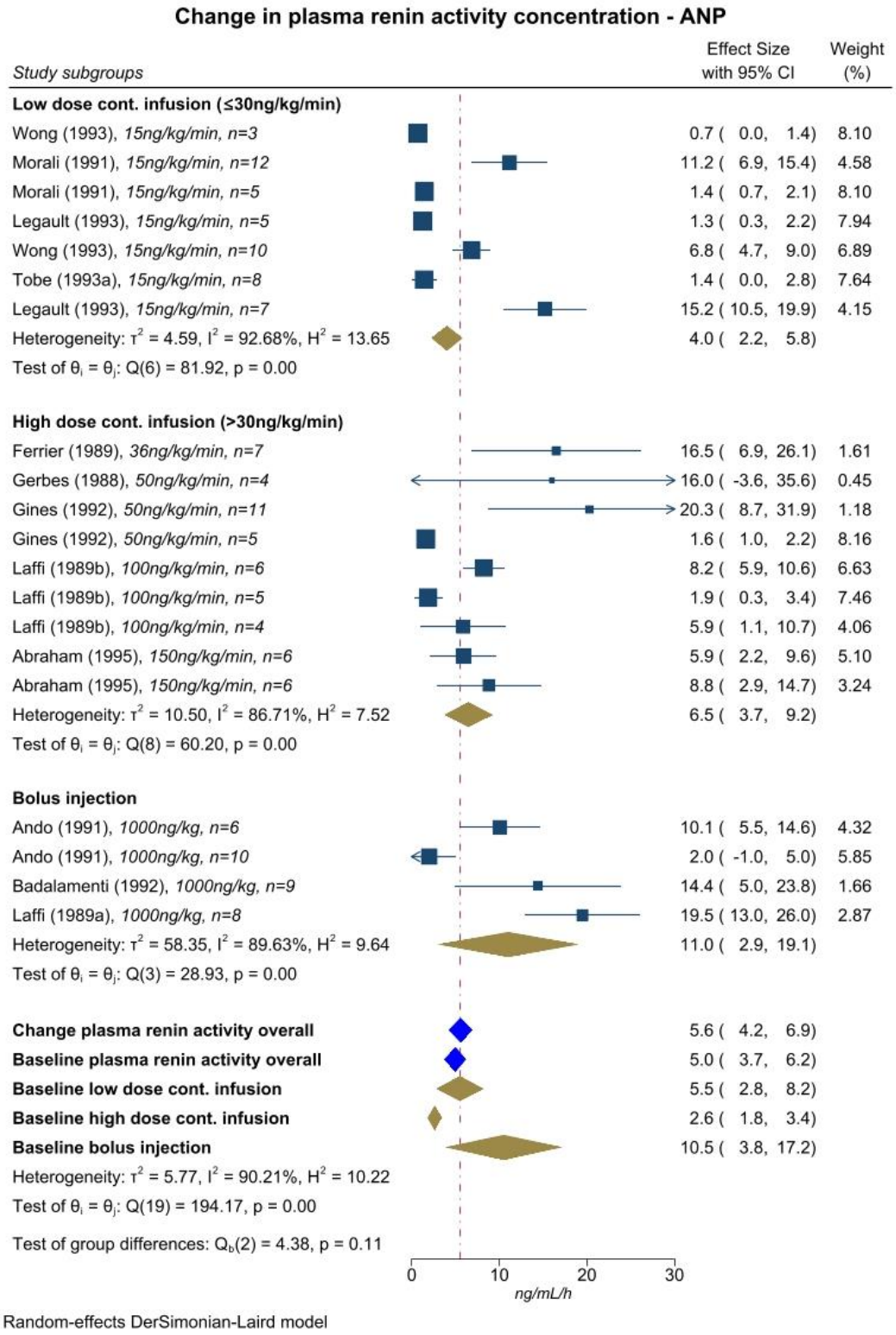

Figure 5 Effect of intravenous ANP on plasma renin activity (ng//mL/h) in study subgroups receiving continuous infusions and bolus injections. Analysis were performed on overall data and separately for study subgroups receiving low-dose

continuous infusion (≤ 30 ng/kg/min), high-dose continuous infusion (> 30 ng/kg/min), and bolus injection.

12. Table 1:

Adverse events (no. of observations)
Facial flushing (5)
Hypotensive episode (5)†
Feeling cold and sweaty (3)
Premature ventricular contractions (2)‡
Dizziness (2)
Light-headedness (2)
Sensation of heat in the face (1)
Increased salivation (1)
Dryness in mouth (1)
Abdominal cramps (1)
Anxiety (1)
Chest pain (1)
Vomiting (1)
Orthostasis (1)

Summary of reported adverse events.

† Reported at individual level in three studies that did not observe hypotension when data were pooled.

‡ From the only study that monitored patients with electrocardiography (ECG) during intervention.

13. Table 2:

Adm.	Drug	Dose	No. of study subgroups (no. of patients) Reporting post-infusion blood pressure drops			No. of study subgroups (no. of patients) Reporting recovery of blood pressure			
			Yes	**No**	**NR**	**Yes**	**Partial recovery**	**No**	**NR**
BOLUS	**ANP**	500 ng/kg	2 (14)	-	-	2 (14)	-	-	-
		1000 ng/kg	5 (40)	-	-	4 (33)	-	-	1 (7)
		2000 ng/kg	1 (9)	-	-	-	1 (9)	-	-
CONTINUOUS		15 ng/kg/min	-	7 (50)	4 (27)	**NA**			
		20 ng/kg/min	1 (4)	-	-	-	-	-	1 (4)
		30 ng/kg/min	-	1 (8)	-	**NA**			
		36 ng/kg/min	1 (7)	-	-	-	1 (7)	-	-
		50 ng/kg/min	2 (16)	1 (4)	-	-	-	-	2 (16)

	60 ng/kg/min	1 (9)	-	-	-	-	1 (9)	-
	100 ng/kg/min	3 (15)	-	-	-	3 (15)	-	-
	150 ng/kg/min	2 (12)	-	-	-	-	-	2 (12)
BNP	4 pmol/kg/min	-	1 (7)	-	**NA**			
URO	20 ng/kg/min	-	2 (21)	-	**NA**			

Occurrence of blood pressure drops and post-infusion follow-up recovery for the 34 study subgroups originating from the 22 included studies. ANP, atrial natriuretic peptide; BNP, B-type natriuretic peptide; URO, Urodilatin; adm., mode of administration; NA, not applicable; NR, not reported.

14. Figure 6:

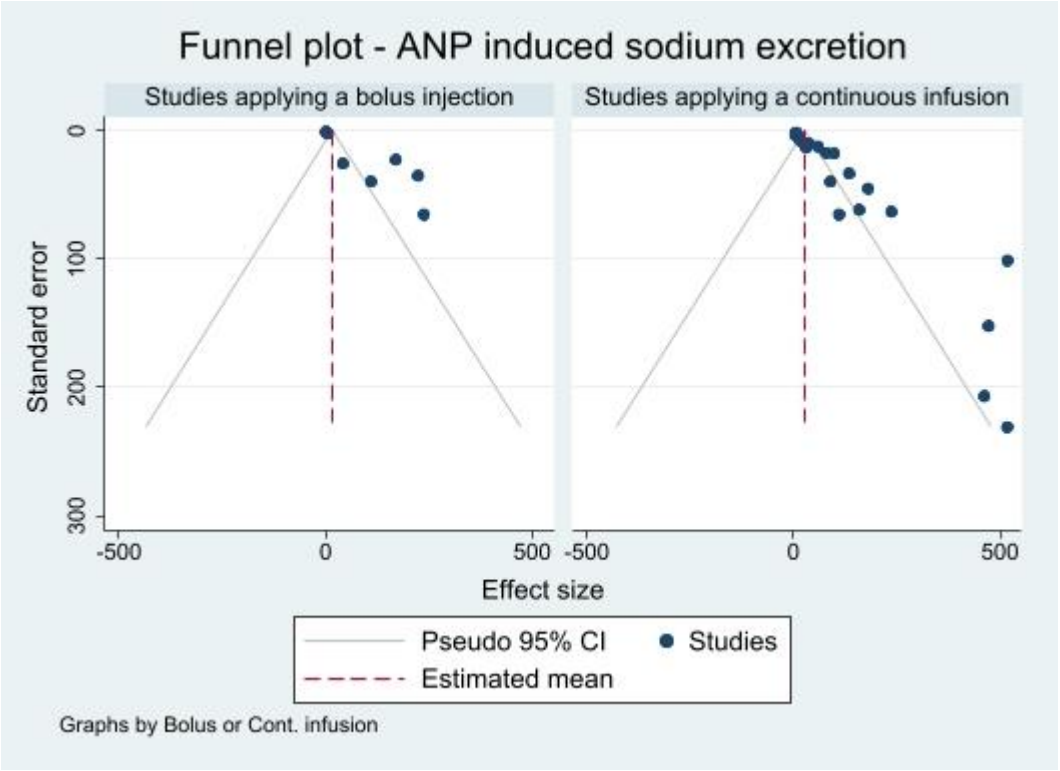

Figure 6 Funnel plots of peak sodium excretion induced by ANP administration, separately for bolus injections and continuous infusions.

15. Search protocol:

15.1. MEDLINE

Searched August 13, 2020.

Search number	Query	Results
22	((((((((((("natriuretic peptide*") OR (ANP)) OR ("atrial natriuretic factor*")) OR (ANF)) OR (Atriopeptin*)) OR ("Carperitide")) OR (BNP)) OR ("Nesiritide")) OR (Urodilatin*)) OR ("ularitide")) OR ("Natriuretic Peptides"[Mesh])) AND (((ascit*) OR ("Ascites"[Mesh])) OR ("Ascitic Fluid"[Mesh]))) AND ((((cirrhotic*) OR ("cirrhosis")) OR ("Liver Cirrhosis"[Mesh])) OR ("liver fibrosis"))	233
21	((((((((("natriuretic peptide*") OR (ANP)) OR ("atrial natriuretic factor*")) OR (ANF)) OR (Atriopeptin*)) OR ("Carperitide")) OR (BNP)) OR ("Nesiritide")) OR (Urodilatin*)) OR ("ularitide")) OR ("Natriuretic Peptides"[Mesh])	44,618
20	"Natriuretic Peptides"[Mesh]	29,204
19	"ularitide"	234
18	Urodilatin*	239
17	"Nesiritide"	541
16	BNP	10,598
15	"Carperitide"	125
14	Atriopeptin*	573
13	ANF	4,052
12	"atrial natriuretic factor*"	16,724
11	ANP	9,715
10	"natriuretic peptide*"	33,989
9	((ascit*) OR ("Ascites"[Mesh])) OR ("Ascitic Fluid"[Mesh])	60,214
8	"Ascitic Fluid"[Mesh]	13,281
7	"Ascites"[Mesh]	16,561
6	ascit*	60,214
5	(((cirrhotic*) OR ("cirrhosis")) OR ("Liver Cirrhosis"[Mesh])) OR ("liver fibrosis")	139,062

4	"liver fibrosis"	16,178
3	"Liver Cirrhosis"[Mesh]	89,362
2	"cirrhosis"	130,416
1	cirrhotic*	23,287

15.2. Cochrane Library

Searched August 13, 2020.

ID	Search	Hits
#1	(cirrhotic*):ti,ab,kw (Word variations have been searched)	3153
#2	(cirrhosis):ti,ab,kw (Word variations have been searched)	9270
#3	MeSH descriptor: [Liver Cirrhosis] explode all trees	2894
#4	("liver fibrosis"):ti,ab,kw (Word variations have been searched)	1193
#5	{OR #1-#4}	10898
#6	(ascit*):ti,ab,kw (Word variations have been searched)	2703
#7	MeSH descriptor: [Ascites] explode all trees	417
#8	MeSH descriptor: [Ascitic Fluid] explode all trees	111
#9	{OR #6-#8}	2703
#10	(natriuretic NEXT peptide*):ti,ab,kw (Word variations have been searched)	4685
#11	(anp):ti,ab,kw (Word variations have been searched)	916
#12	("atrial natriuretic" NEXT factor*):ti,ab,kw (Word variations have been searched)	1102
#13	(anf):ti,ab,kw (Word variations have been searched)	243
#14	(Atriopeptin*):ti,ab,kw (Word variations have been searched)	4
#15	(Carperitide):ti,ab,kw (Word variations have been searched)	57
#16	(bnp):ti,ab,kw (Word variations have been searched)	4269
#17	(Nesiritide):ti,ab,kw (Word variations have been searched)	199
#18	(Urodilatin*):ti,ab,kw (Word variations have been searched)	59
#19	(ularitide):ti,ab,kw (Word variations have been searched)	31

#20	MeSH descriptor: [Natriuretic Peptides] explode all trees	2045
#21	{OR #10-#20}	7364
#22	#5 AND #9 AND #21	35

15.3. Embase (embase.com)

Searched August 13, 2020.

No.	Query	Results
#23	#6 AND #10 AND #22	395
#22	#11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21	91044
#21	'natriuretic factor'/exp	69571
#20	ularitide	75
#19	urodilatin*	548
#18	nesiritide	1771
#17	bnp	24285
#16	carperitide	261
#15	atriopeptin*	758
#14	anf	4966
#13	'atrial natriuretic factor*'	23248
#12	anp	17370
#11	'natriuretic peptide*'	61905
#10	#7 OR #8 OR #9	94418
#9	'ascites fluid'/exp	9255
#8	'ascites'/exp	53536
#7	ascit*	94354
#6	#1 OR #2 OR #3 OR #4 OR #5	241712
#5	'liver fibrosis'/exp	48307
#4	'liver cirrhosis'/exp	173093
#3	'liver fibrosis'	53540

#2	cirrhotic*	40937
#1	cirrhosis	202305

15.4. Scopus

Searched August 13, 2020.

Search history — Combine queries... e.g.

17	((TITLE-ABS-KEY (cirrhosis)) OR (TITLE-ABS-KEY (cirrhotic*)) OR (TITLE-ABS-KEY ("liver fibrosis"))) AND (TITLE-ABS-KEY (ascit*)) AND ((TITLE-ABS-KEY ("natriuretic peptide*")) OR (TITLE-ABS-KEY (anp)) OR (TITLE-ABS-KEY ("atrial natriuretic factor*")) OR (TITLE-ABS-KEY (anf)) OR (TITLE-ABS-KEY (atriopeptin*)) OR (TITLE-ABS-KEY (carperitide)) OR (TITLE-ABS-KEY (bnp)) OR (TITLE-ABS-KEY (nesiritide)) OR (TITLE-ABS-KEY (urodilatin*)) OR (TITLE-ABS-KEY (ularitide))) View Less	327 document results
16	(TITLE-ABS-KEY ("natriuretic peptide*")) OR (TITLE-ABS-KEY (anp)) OR (TITLE-ABS-KEY ("atrial natriuretic factor*")) OR (TITLE-ABS-KEY (anf)) OR (TITLE-ABS-KEY (atriopeptin*)) OR (TITLE-ABS-KEY (carperitide)) OR (TITLE-ABS-KEY (bnp)) OR (TITLE-ABS-KEY (nesiritide)) OR (TITLE-ABS-KEY (urodilatin*)) OR (TITLE-ABS-KEY (ularitide))	69,112 document results
15	TITLE-ABS-KEY (ularitide)	82 document results
14	TITLE-ABS-KEY (urodilatin*)	542 document results
13	TITLE-ABS-KEY (nesiritide)	1,673 document results
12	TITLE-ABS-KEY (bnp)	12,765 document results
11	TITLE-ABS-KEY (carperitide)	183 document results
10	TITLE-ABS-KEY (atriopeptin*)	793 document results
9	TITLE-ABS-KEY (anf)	5,527 document results
8	TITLE-ABS-KEY ("atrial natriuretic factor*")	23,406 document results
7	TITLE-ABS-KEY (anp)	14,515 document results
6	TITLE-ABS-KEY ("natriuretic peptide*")	49,434 document results
5	TITLE-ABS-KEY (ascit*)	89,173 document results
4	(TITLE-ABS-KEY (cirrhosis)) OR (TITLE-ABS-KEY (cirrhotic*)) OR (TITLE-ABS-KEY ("liver fibrosis"))	193,780 document results
3	TITLE-ABS-KEY ("liver fibrosis")	40,093 document results
2	TITLE-ABS-KEY (cirrhotic*)	26,769 document results
1	TITLE-ABS-KEY (cirrhosis)	173,313 document results

15.5. Web of science

Searched August 13, 2020.

#17	326	#16 AND #5 AND #4 Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=All years
#16	60,572	#15 OR #14 OR #13 OR #12 OR #11 OR #10 OR #9 OR #8 OR #7 OR #6 Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=All years
#15	61	**TOPIC:** (ularitide) Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=All years
#14	341	**TOPIC:** (Urodilatin*) Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=All years
#13	981	**TOPIC:** (Nesiritide) Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=All years
#12	12,343	**TOPIC:** (BNP) Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=All years
#11	167	**TOPIC:** (Carperitide) Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=All years
#10	900	**TOPIC:** (Atriopeptin*) Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=All years
#9	4,213	**TOPIC:** (ANF) Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=All years

#8	6,297	**TOPIC:** ("atrial natriuretic factor*") Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=All years
#7	11,827	**TOPIC:** (ANP) Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=All years
#6	44,524	**TOPIC:** ("natriuretic peptide*") Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=All years
#5	42,575	**TOPIC:** (Ascit*) Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=All years
#4	135,009	#3 OR #2 OR #1 Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=All years
#3	22,406	**TOPIC:** ("Liver Fibrosis") Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=All years
#2	27,732	**TOPIC:** (Cirrhotic*) Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=All years
#1	107,044	**TOPIC:** (Cirrhosis) Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=All years

16. PRISMA ckecklist [16]:

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	3-4
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4-5
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	5
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	5
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	5-6
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors	6

		to identify additional studies) in the search and date last searched.	
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Sup. 12-16
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	7, fig. 1
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	7-8
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	6-7, sup. 1-2
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	8
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	8
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	8
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	8
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	8
RESULTS			

Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	9, fig. 1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	9-10, tab. 1
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	Tab. 1
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	10-14
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	10-13
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	14-15, tab. 1
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	10-14
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	Tab. 2, 15-18
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	17-18
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for	16-18

		future research.	
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	19

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