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Choice of creep or maintenance fluid type and their impact on total daily ICU sodium burden in critically ill patients: A systematic review and meta-analysis

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ABSTRACT

Purpose: Maintenance and hidden/creep fluids are a major source of fluid and sodium intake in intensive care unit (ICU) patients. Recent research indicates that low versus high sodium content maintenance fluids could decrease fluid and sodium burden. We conducted a systematic review (SR) with meta-analysis to summarize the impact of maintenance fluid choice on total daily sodium in ICU patients.
Materials and methods: Systematic literature search in Pubmed, Embase, the Cochrane Library and the.
Clinical Trials registry. Only controlled clinical trials were included. Exclusion criteria: trials on resuscitation fluids, performed in the emergency department only and in pediatric patients. Primary objective was the reduction in mean total sodium intake with low versus high sodium content maintenance/creep fluids.
Results: Five studies (1105 patients) were included. Heterogeneity was high.Risk of bias was moderate. Mean daily sodium reduction was 117 mmol (95%Confidence Interval [CI] -174; −59; $p < 0.001$) with low versus high sodium content maintenance/creep fluids. Incidence of hyperchloremia was lower (OR 0.26; 95%CI 0.1; 0.64) with low sodium. There were no differences in the incidences of hyper−/hyponatremia and fluid balances.
Conclusion: Using low sodium content maintenance/creep fluids substantially reduces daily sodium burden in adult ICU patients. Significant knowledge/research gaps exist regarding relevance and safety.
Trial Registration: PROSPERO 2022 CRD42022300577 (February 2022).

1. Introduction

Intravenous fluid therapy is one of the most commonly administrated treatments in critical care [1-3]. While most attention is usually paid to resuscitation fluids, other sources of fluid intake are less obvious [4]. In reality, patients are exposed to a large variety of non-resuscitation fluids namely maintenance fluids and "hidden" or creep fluids (fluids for drug administration, to keep lines open and as "flush" fluids) [2,5]. Physician's awareness concerning resuscitation fluids has risen considerably over the past decade [6,7]. However, these fluids only account for a relatively small proportion (i.e. 6–20%) of a typical intensive care unit (ICU) patient's fluid intake [2], especially with ongoing duration of ICU stay. In contrast, non-resuscitation fluids account for 65% and more of total fluid intake in critically ill patients and thus impose a substantial fluid and sodium burden [2,8,9]. It has been shown that maintenance/creep fluids are associated with considerable sodium and fluid load leading to hypernatremia and fluid overload (FO) in critical illness [2,10]. Hypernatremia and FO in critical care patients are both independent risk factors for mortality [11,12]. Thus, recent investigations have suggested, that the use of solutions containing a reduced sodium

Abbreviations: CI, Confidence intervals; ED, Emergency department; G5%, Glucose 5%; ICU, Intensive care unit; NaCl, Sodium chloride; OR, Odds ratio; PRISMA, Preferred Reporting Items for Systematic Reviews; RCT, Randomized controlled trial; SD, Standard deviation.

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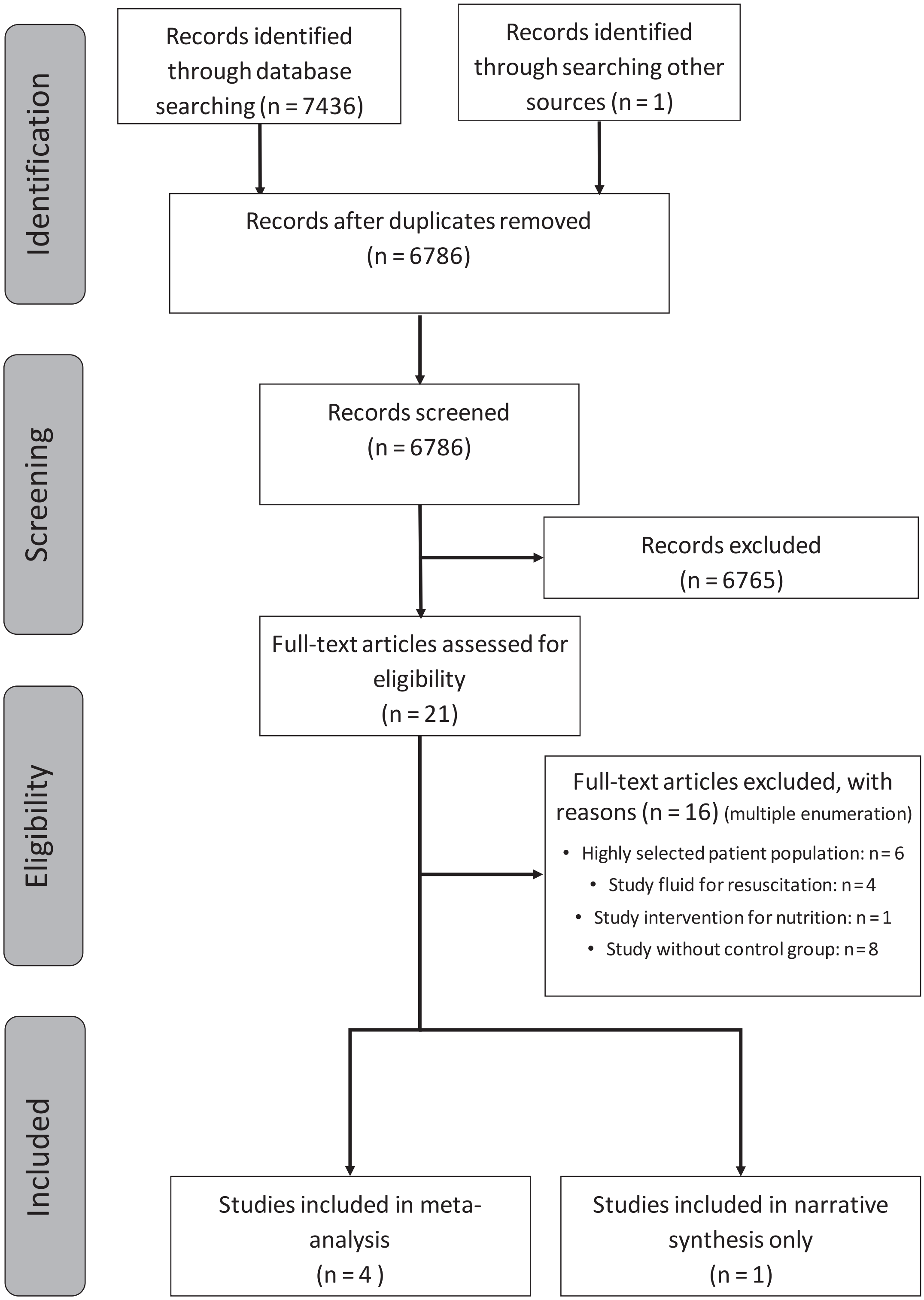

Fig. 1. PRISMA-Flowchart.

concentration (e.g. 54 mmol/l sodium chloride [NaCl]) or no sodium (e.g. Glucose 5% [G5%]) as maintenance or creep fluid may lead to a decrease in daily fluid load and ICU acquired hypernatremia [10,13]. In contrast, others have shown no influence on the incidence of hypernatremia but an increased risk of hyponatremia and an association with more delirium with the use of hypotonic vs isotonic maintenance solutions [14,15]. Thus, it is currently not clear, whether the choice of maintenance fluid and creep fluid might influence sodium and fluid load in the critically ill.

Therefore, we aim to conduct a systematic review and meta-analysis to evaluate the impact of maintenance and hidden/creep fluid choice on sodium and fluid load in adult ICU patients.

2. Methods

For this systematic review and meta-analysis, we adhered to the

Table 1
Quality assessment of studies included in the meta-analysis.

Study	Year	ROBIN-I							RoB2						Risk of bias judgement
		Bias due to confounding	Bias in selection of participants into the study	Bias in classification of interventions	Bias due to deviations from intended interventions	Bias due to missing data	Bias in measurement of outcomes	Bias in selection of the reported result	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (detection bias)	Selective reporting (reporting bias)	
Okada et al. [14]	2017	M	L	L	M	L	L	M							Moderate
Bihari et al. [10]	2018	M	L	L	M	L	L	M							Moderate
Magee CA et al. [28]	2018	M	L	L	M	M	L	M							Moderate
van Regenmortel N. et al. [13]	2019								L	L	L	L	L	L	Low

ICU: Intensive care unit; I: Intervention; C: Control; APACHE II: Acute Physiology and Chronic Health Evaluation II score; SD: Standard deviation; G5%: Glucose 5% solution; NS: Normal saline solution; IQR: Interquartile range.

Cochrane Collaboration Guidelines for the conduct of systematic reviews [16], the guidelines for Preferred Reporting Items for Systematic Reviews (PRISMA) [17] and the MOOSE Reporting Guidelines for Meta-analyses of Observational Studies [18]. We registered our protocol on PROSPERO in February 2022 (CRD42022300577).

2.1. In- and exclusion criteria

We included all studies investigating the influence of the type of maintenance or "creep" fluids on electrolyte and/or fluid status in critically ill patients. The following types of studies were eligible: randomized controlled trials (RCTs) and non-randomized controlled studies (i.e. cohort and observational studies with retrospective or prospective design). Non-controlled trials were excluded. In addition, the following exclusion criteria were applied: studies not available in English, studies evaluating resuscitation fluids, studies performed in the emergency department (ED) only, investigations in children and studies targeting only highly selected patient populations (e.g. patients with chronic kidney or heart disease, burn patients). Further, we excluded all review articles (narrative, systematic, meta-analysis), and case reports. However, we screened the bibliographies of respective publications for potential further studies.

2.2. Information sources and search strategy

The search strategy was developed in collaboration with an information specialist of the University Library of Bern. Two authors (SMS, JW) independently performed a systematic search in PubMed, Embase, and the Cochrane Library databases for articles until the 01st of May 2023. Furthermore, we systematically searched the bibliographies of all eligible publications, as well as references of reviews, editorials, and case reports for further potentially eligible trials. Entry terms for the database search are described in Supplementary Fig. 1. For all trials we extracted for full text analysis, full texts and data were accessible.

2.3. Study selection, data collection, data extraction and Assessment of risk of bias

Details on study selection, data collection and extraction and risk of bias assessment can be found in the online supplement.

2.4. Objectives

The primary objective of this systematic review and meta-analysis was to evaluate whether maintenance fluid/creep fluid with a low sodium content results in a reduction in total daily sodium load in adult ICU patients compared to the use of solutions with a standard high sodium content. Secondary objectives can be found in the online supplement.

Secondary objectives were whether the choice of sodium content (high vs low sodium content) for maintenance fluid/creep fluid on the ICU results in different incidences of hypernatremia, hyponatremia or delirium/new neurological symptoms, difference in fluid balances and impacts patient-centred clinical outcomes (mortality, need of renal replacement therapy (RRT), time on mechanical ventilation (MV), ICU length of stay (LOS)). The incidences of hypo-, respectively hyperchloremia were added as a post-hoc outcome.

2.5. Definitions

Maintenance fluids

Fluids given iv to cover the daily needs of a patient unable to provide them orally or enterally [4,21]. The administration should be adapted to the patient's context and should include ongoing losses [4].

Hidden or creep fluids

Fluids administered as a carrier for oral or enteral medication, for

Table 2
Characteristics of studies included in the meta-analysis.

Study	Study type	Study population	Sample Size	Intervention	Control	APACHE II
Okada et al. [14]	Single-center retrospective before-and-after study	ICU patients, after elective surgery for oesophageal cancer or for head and neck cancer.	I: $n = 87$ C: $n = 92$	Sodium-poor solution (35 mmol/L of sodium) as postoperative maintenance fluid	Isotonic solution (140 mmol/L of sodium) as postoperative maintenance fluid	Mean (SD) I: 11 (4) C: 12 (4)
Bihari et al. [10]	Single-center prospective before-and-after study	Mixed ICU patients	I: $n = 133$ C: $n = 146$	G5% as drug diluent and maintenance fluid	NS as drug diluent and maintenance fluid	Median (IQR) I: 17 (13;21) C: 18 (14;23)
Magee CA et al. [28]	Single-center prospective before-and-after study	Medical ICU patients	I: $n = 210$ C: $n = 216$	G5% as the primary medication diluent	NS as the primary medication diluent	Median (IQR) I: 24 (19;30) C: 23 (18;30)
van Regenmortel N. et al. [13]	Single-center randomized controlled double-blind trial	Surgical ICU patients undergoing major thoracic surgery	I: $n = 33$ C: $n = 34$	Na54 (54 mmol/L of sodium) as perioperative maintenance fluid	Na154 (154 mmol/L of sodium) as perioperative maintenance fluid	n/a

ROBIN-I: The Risk Of Bias In Non-randomized Studies – of Interventions assessment tool; RoB2: Revised Cochrane risk-of-bias tool for randomized trials.
L Low Risk of Bias; M Moderate Risk of Bias.

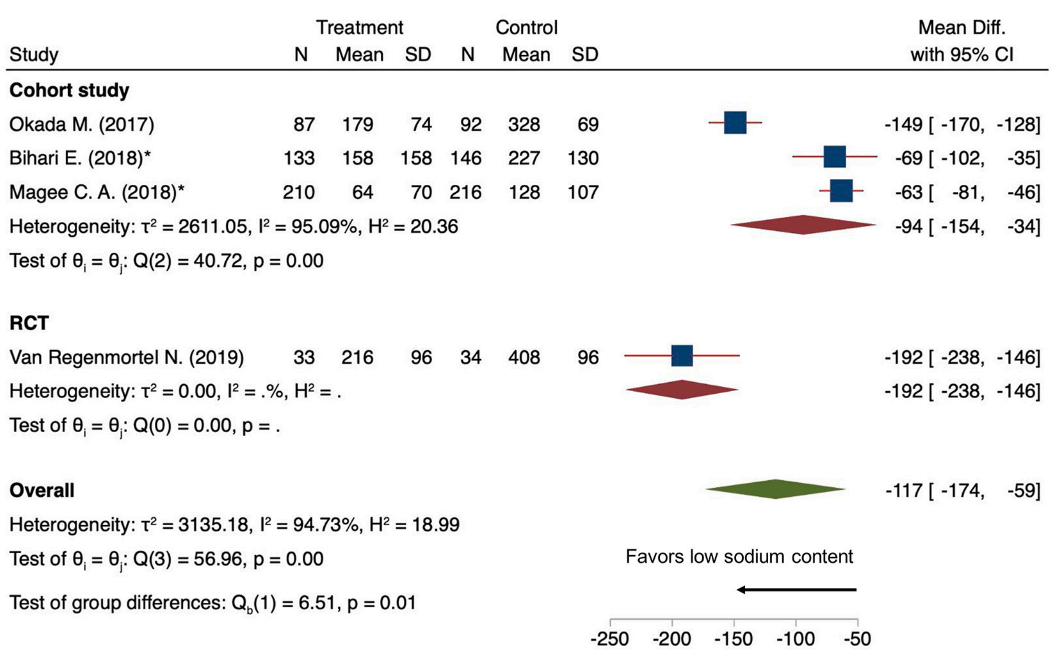

Fig. 2. Primary outcome Impact of choice of low vs high sodium content maintenance and/or creep fluids on mean daily sodium administration. Sodium-values are given in mmol. Mean Diff.: Mean Difference. *Mean and standard deviation were calculated by Wan's method out of n, median and IQR.

flushing of intravenous lines or to keep (arterial or venous) lines open [2,22].

Hypernatremia: Serum sodium >145 mmol/l [23].
Hyponatremia: Serum sodium <135 mmol/l [10].
Hyperchloremia: Serum chloride >106 mmol/l [10,13,24,25].
Hypochloremia: Serum chloride <96 mmol/l [10,13,24].

2.6. Data synthesis and statistical analysis

We extracted the data separately using a pre-defined spreadsheet, following the recommendation by the Cochrane Collaboration handbook [16]. We extracted data to calculate effect sizes (odds ratios for binary outcomes, mean differences for continuous outcomes). The mean and standard deviation (SD) in the treatment groups were calculated by Wan's method out of n, median and interquartile range for continuous outcomes if the mean and SD was not presented [26]. For the primary outcome (mean difference of sodium per day) respectively for the secondary binary outcomes with more than two identified trials (i.e. risk of hypernatremia, hyponatremia, hyperchloremia, and ICU mortality), pooled unstandardized mean difference respectively odds ratios (OR) with 95% confidence intervals (CI) were obtained using a random-effect model as proposed by DerSimonian and Laird [27]. We assessed heterogeneity among trials using I2-statistics. Funnel plots and Egger's regression asymmetry test were used to assess publication bias and small study effects. Stratification according to the study design (RCT vs cohort trial) was performed and Stata's test of group differences (significance $p < 0.05$) was used to assess difference of the pooled effect sizes of RCTs vs. cohort trials. We used Stata, version 16.1 (StataCorp, The College Station, TX, USA) to perform the statistical analysis.

Table 3
Secondary Outcomes of studies included in the systematic review.

Study	I	C	Hyper-Na	Hypo-Na	Hypo-Cl	Hyper-Cl	Delirium	FB
Okada et al. [14]	Sodium-poor solution (35 mmol/L of sodium): postop. Maintenance fluid	Isotonic solution (140 mmol/L of sodium): Postop. Maintenance fluid	No	**Yes**	n/a	n/a	n/a	n/a
Bihari et al. [10]	G5%: drug diluent and Maintenance fluid	NS: drug diluent and Maintenance fluid	No	No	No	**Yes**	n/a	**Yes**
Magee CA et al. [28]	G5%:primary medication diluent	NS:primary medication diluent	No	No	n/a	**Yes**	n/a	n/a
van Regenmortel N. et al. [13]	Na54 (54 mmol/L of sodium): periop. Maintenance fluid	Na154 (154 mmol/L of sodium): periop. Maintenance fluid	No	No	No	**Yes**	n/a	**Yes**
Nagae et al. [15]	Sodium-poor solution (35 mmol/L of sodium): postop Maintenance fluid	Isotonic solution (140 mmol/L of sodium): postop Maintenance fluid	n/a	**Yes**	n/a	n/a	**Yes**	n/a

I: Intervention; C: Control; Hyper-Na: Hypernatremia; Hypo-Na: Hyponatremia; Hypo-Cl: Hypochloremia; Hyper-Cl: Hyperchloremia; FB: fluid balance; Yes: statistically significant difference between groups; No: no statistically significant difference between groups. N/A: outcome not reported.

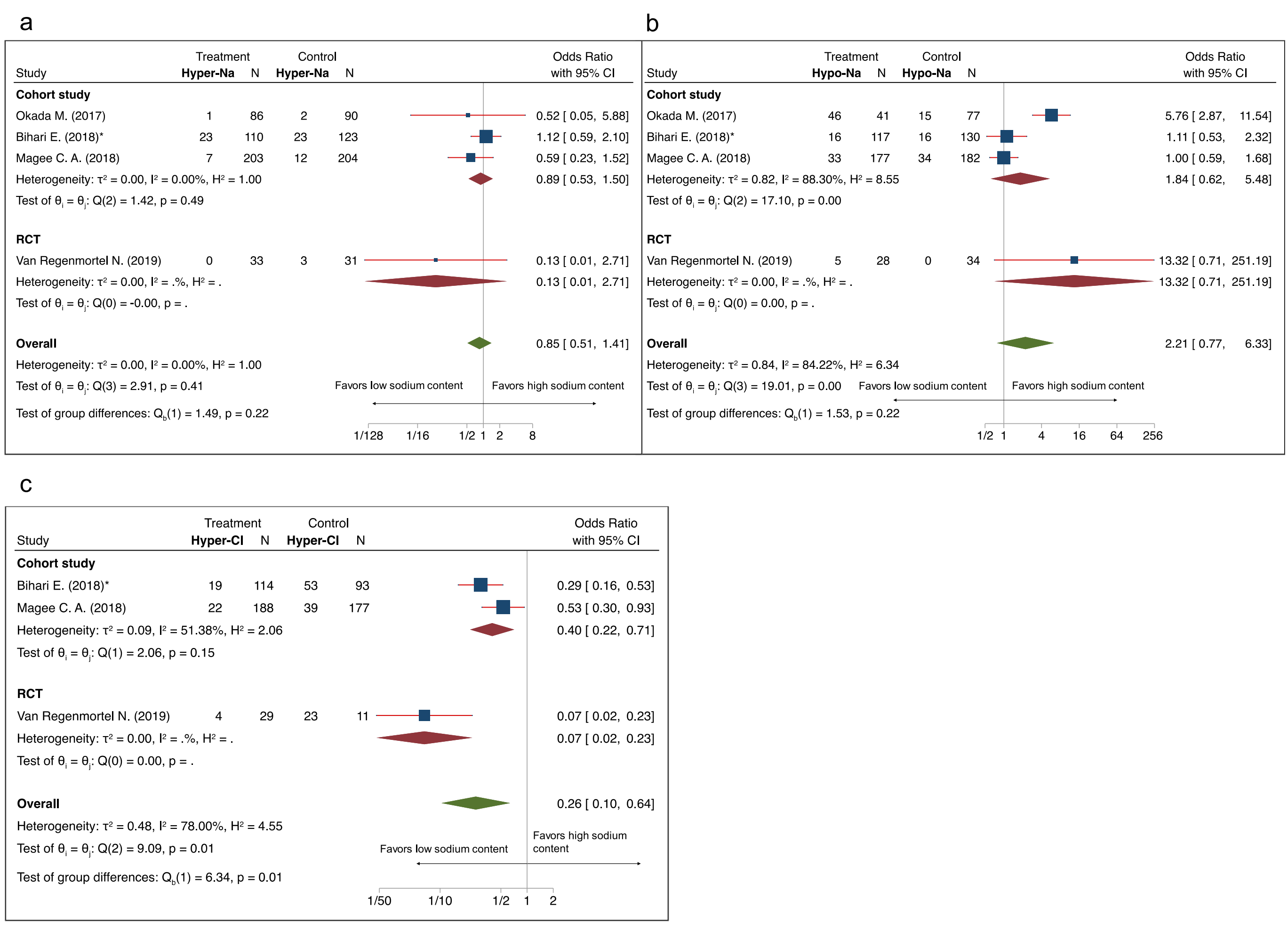

Fig. 3. Secondary outcomes Impact of choice of low vs high sodium content maintenance and/or creep fluids on a) Hypernatremia; b) Hyponatremia; c) Hyperchloremia *The numbers and incidences were calculated out of the given rates.

3. Results

Out of 7436 identified articles, 21 were retrieved for full-text analysis (Fig. 1). We excluded 16 studies with reasons (Suppl. Table 1). A total of 5 trials including 1105 patients were included in our systematic review (Suppl. Table 2). Two of these studies had significant data overlap, thus all data from the first trial [14] were included in this meta-analysis, while only outcomes not reported in the primary trial were included in this review for the secondary trial [15]. Of the four studies [10,13,14,28] eligible for meta-analysis, one was a randomized controlled trial [13], two were prospective studies [10,28] and one was retrospective cohort study [14] (Table 2). Risk of bias was moderate across studies (Table 1).

3.1. Primary endpoint

All studies included in the meta-analysis showed a reduction of total daily sodium load on the ICU with the use of maintenance fluids/creep fluids with a low versus high sodium content in adult ICU patients. Meta-analysis revealed a mean difference (low-high) of -117 mmol/d (95%CI

-174; −59; $p < 0.001$) (Fig. 2). This equals a reduction of total daily sodium load of 2.7 g (95%CI -4.0; −1.8 g) in patients undergoing a low sodium content strategy for maintenance and creep fluid choice. Heterogeneity ($I^2 = 95\%$) was considerable (Fig. 2). Egger-test showed no evidence of small-study effects ($p = 0.34$) (Suppl. Fig. 2).

3.2. Secondary endpoints

Table 3 shows the results for our secondary objectives.

3.2.1. Hypernatremia

In the four studies assessing the risk of hypernatremia [10,13,14,28] the OR for hypernatremia was 0.85 (95%CI 0.51; 1.41) with a low-sodium content strategy (Fig. 3). Heterogeneity between studies was low ($I^2 = 0\%$) (Fig. 3).

3.2.2. Hyponatremia

The OR for hyponatremia was 2.21 (95% CI 0.77; 6.33) in patients with a low sodium content strategy (Fig. 3). Heterogeneity between the studies was considerable ($I^2 = 84\%$) (Fig. 3).

3.2.3. Hyperchloremia

Three out of four studies assessed the incidence of hyperchloremia [10,13,28]. The overall OR was 0.26 (95%CI 0.1; 0.64) in patients with a low sodium content strategy. Heterogeneity between the studies was considerable ($I^2 = 78\%$) (Fig. 3).

3.2.4. Hypochloremia

Two out of four studies reported the incidence of hypochloremia [10,13]. Van Regenmortel and colleagues found a higher incidence of hypochloremia in their postsurgical ICU-patients receiving a low sodium-content maintenance fluid (Na 54 mmol/l) compared to the group receiving high sodium content (Na 154 mmol/l) maintenance fluids (17.6% vs 0%; $p = 0.01$) [13]. In contrast, Bihari and group could not find a difference in incidence of hypochloremia between mixed ICU patients receiving either low-sodium content maintenance and creep fluids (G5%) vs high sodium content maintenance and creep fluids (NaCl 0.9%) (11% vs 8%; $p = 0.07$) [10].

3.2.5. Fluid balance

Only two out of five studies reported data on fluid balance [10,13] (Table 3). Van Regenmortel and colleagues observed a higher estimated fluid balance at 72 h in the high sodium arm compared to the low-sodium arm (Na154-group: 4490 ml, 95%CI 3925; 5054 ml vs Na54-group 3120 ml, 95%CI 2580; 3661 ml; $p < 0.001$) [13]. In the study of Bihari S. et al., patients in the high sodium group had a higher daily fluid balance compared to those in the study group with low sodium group (median 393 ml, IQR −560;1217 ml vs 201 ml, IQR −588; 956 ml; $p = 0.04$) [10]. Median LOS ICU was 90 h (IQR 55; 187) in the high and 92 h (IQR 43; 207) in the low sodium group (10).

3.2.6. Delirium and new neurological symptoms

Delirium or neurological symptoms arising from hyponatremia were assessed in two studies [13,15]. In their propensity-score-matched cohort, Nagae and co-workers observed a significantly higher incidence of delirium in the group with maintenance fluids with low sodium content compared to maintenance fluids with high sodium content (26% vs 11.7%, OR 2.65% (95%CI 1.12; 6.28), $p = 0.02$) [15]. Van Regenmortel and colleagues did not observe a difference in new neurological symptoms between the study groups (zero patients in both groups) [13].

Further outcomes (mortality, incidence of renal replacement therapy, length of mechanical ventilation and ICU length-of-stay) are reported in the supplementary results section (online supplement and supplementary Fig. 3 and supplementary Table 3).

4. Discussion

This systematic review and meta-analysis summarizes recent evidence for the use of low-sodium maintenance and/or creep fluids compared to solutions with a high sodium content in adult ICU patients. Our data indicate that the use of low-sodium solutions as maintenance and/or creep fluid substantially reduces daily ICU sodium load compared to sodium solutions with a standard content used. Hyperchloremia was substantially reduced, fluid balances are hinted to be higher in the high sodium group. However caution needs to be applied, because of the substantial heterogeneity, considerable bias and the lack of high quality trials. There is a considerable research and knowledge gap regarding relevance and safety with the use of low-sodium content maintenance/creep fluids in critical illness.

The importance of sodium input in critical illness has recently gained attention with the main source of sodium load (>50%) being maintenance and creep fluids [2,8]. In our meta-analysis, patients in the high sodium arm received a sodium load of 5.2 to up to 9.4 g sodium per day (average 6.2 g) with high sodium content maintenance fluids/creep fluids, namely NaCl 0.9%. While patients receiving the study intervention, namely low-sodium content maintenance and/or creep fluids, had a substantially reduced mean daily sodium intake by minus 2.7 g on average. Nonetheless, the average sodium intake the patients in the intervention group received still remained substantial with 3.7 g daily sodium intake on average. In comparison, the mean nutritional daily sodium intake for U.S.-adults aged 19 years and older in 2015–2016 was approximately 3.5 g (152 mmol) [29], for the Australian population approximately 3.5 g (152 mmol/l) [30], and in Japan approximately 4 g (175 mmol/l) [31]. In contrast, the WHO recommends to lower the daily sodium intake in healthy adults to <2 g (86 mmol) [32] and the US National Academies of Sciences, Engineering, and Medicine defines a daily adequate intake level of 1.5 g (63 mmol) [33]. In ICU patients, there is a recent recommendation to provide approximately 1–1.5 mmol/kg/day of sodium with maintenance fluids, this extrapolates to 1.5 - 2 g for a 60 kg adult [3]. Thus, the daily sodium load of ICU patients with maintenance and/or creep fluids included in our meta-analysis still exceeds the recommended goal many times over, independent of the group. However, the examined intervention in our meta-analysis (low sodium content maintenance and creep fluids) was able to reduce the intake relevantly by almost 50%, to values much closer to the recommended sodium intake. Thus, while low-sodium maintenance/creep fluids may not entirely solve the problem of excess sodium burden in critically ill patients, their use maybe a substantial contributor to reduce total daily sodium burden in critically illness.

Is it relevant to reduce sodium input in critically ill patients? Our meta-analysis indicates that there is currently insufficient data and mostly low quality data on the effect of a low sodium content maintenance/creep fluid strategy compared to a high-sodium content strategy on important patient-centered outcomes. However, data hints towards two major advantages of a low-sodium content strategy potentially being less fluid load and less hyperchloremia. It was shown that sodium-rich fluids, especially maintenance and creep fluids, may facilitate fluid retention in the critically ill [2,10,13,34,35]. Recently, an extended summary of the MIHMoSA (healthy volunteers) [34] and the TOPMAST (patients undergoing thoracic surgery) [13] clinical trials compared maintenance solutions containing 54 mmol/l versus 154 mmol/l sodium, and showed that large sodium loads administrated in form of sodium-rich maintenance fluids lead to sustained fluid accumulation (when compared to low-sodium maintenance fluids) [35]. In these studies, fluid accumulation within 48 h was >0.5 L increased in healthy volunteers, while it was about 1 L in peri-operative patients receiving sodium-rich fluids [35]. In contrast, the HERACLES trial, a randomized controlled trial on the use of hypertonic saline in patients after cardiac surgery, revealed no influence on peri-operative fluid accumulation measured by bio-impendance analysis [36] and a substantially lower cumulative fluid balance in the intervention group receiving hypertonic saline [37]. It however has to be acknowledged that in patients after cardiac surgery, the situation may be different from patients receiving high-sodium content maintenance/creep fluids. The vast and sudden administration of sodium as in the HERACLES trial, may have a pronounced osmotic effect and lead to recruitment of excess water already accumulated in the intracellular space intraoperatively. This may be reflected by the sudden temporary increase in urinary output in the HERACLES trial [37] and tendency towards a non-statistically significant increased renal perfusion index in the intervention group observed [36] in the initial phase. It also supports the hypothesis of the recent extended analysis of the MIHMoSA and TOPMAST trials that fluid accumulation due to a large sodium burden may eventually be limited [35] due to a presumed process of non-osmotic storage. In addition, a recently published pre-defined post-hoc trial of the HERACLES trial in patients a statistically non-significant trend towards higher total body water was seen [36]. Thus, this taken together with the also non-statistically significant trend towards a higher increase in body weight in the HERALCES intervention group, might imply a biphasic reaction of the body to a large sudden sodium burden, with an osmotically driven increased diuresis (by recruitment of intravascular fluid) in the initial phase and re-distribution with fluid accumulation in the later phase [36,37].

The tendency towards fluid accumulation with high-sodium maintenance/creep fluids may be related to the fact that under controlled circumstances (no additional fluid intake), some data indicate that the kidneys may reabsorb free water in excess of what is necessary as a reaction to a continuous sodium burden over a longer time period [34]. Additionally, while the ability of the kidneys to concentrate urine is limited [38], a continuous "source" of free water is necessary to ensure timely sodium excretion. Isotonic maintenance fluids/creep fluids are despite common perception not a source of free water [39]. Removal of accumulated water and sodium may prove difficult, as conventional diuretics remove water in excess of sodium (diuresis) rather than sodium with water (natriuresis) typically resulting in hypernatremia, thus triggering a vicious cycle [40,41]. Thus, in combination the factors outlined above may explain why sodium-rich maintenance/creep fluids aggravate fluid retention and why the reduction of sodium input by lowering the sodium-content of maintenance/creep fluids may substantially reduce sodium and fluid retention in critically ill patients. However, if this translates into improvement of clinically important patient outcomes still remains unclear. Further high quality studies are warranted.

Is it safe to choose a solution with a low-sodium content? Our systematic review with meta-analysis underlines that data on safety endpoints for the use of low sodium content solutions as maintenance and creep fluids in general adult ICU patients is scarce. Our data suggest that the risk for hyponatremia ($\leq$ 135 mmol/l) is non-significantly different in both groups. However, the low number of included patients limits generalizability. Additionally, the development of in-hospital hyponatremia at least partially depends on the presence of non-osmotic stimulation of vasopressin release and the patients in the current studies might have had a low disease severity. On the other hand, it has to be acknowledged also that the clinical impact of hyponatremia depends on the level of the decrease, the time of development, its cause and whether chronic hyponatremia is present [42]. Additionally, there is currently no data available in specific subgroups of patients especially at risk for hyponatremia, such as i.e. patients with traumatic brain injury. Recent evidence comparing normal saline to balanced solutions (both containing at least 140 mmol/L of sodium) in a general critically ill population in >10,000 patients hints towards a survival benefit in neuro-critically ill patients, when NaCl 0.9% is used for fluid resuscitation [43]. Thus, the use of a high-sodium maintenance/creep fluid strategy in neuro-critically ill patients could affect patient outcomes. As shown in this work, there is currently insufficient data investigating said strategy in neuro-critically patients and it should thus be applied with caution.

A further issue that warrants discussion is the potential of low-sodium content maintenance and creep fluid to cause delirium/new neurological derangement. Hyponatraemia, whether or not caused by low-sodium content maintenance and/or creep fluid, might be a substantial contributor to new onset delirium or neurological derangement [44,45]. A retrospective before and after study in propensity score-matched postsurgical ICU-patients indicated an association between a higher incidence of hyponatremia and more delirium in the study group receiving low sodium content (Na 35 mmol/) compared to high sodium content (Na 140 mmol/l) maintenance fluid [15]. In contrast, a small RCT in postsurgical ICU-patients that compared a low sodium-content (Na 54 mmol/l) to a high sodium content (Na 154 mmol/l) maintenance fluid choice did not observe any new onset neurological symptoms [13]. Different explanations for this difference exist, but the difference between the selected fluids and the patient's usual dietary sodium intake is one of them. Asian populations are known to consume more sodium through their diets [46] and as such a solution containing only 35 mmol/l of sodium could have increased the problem. It has further to be mentioned, that most likely the incidence of new onset neurological symptoms/delirium substantially depend on the actual degree of hyponatraemia. Recent research on implementing the National Institute for Health and Care Excellence (NICE) guidelines on intravenous fluids for adult non-ICU patients [47] suggested a stricter threshold defining hyponatremia as sodium concentrations <126 mmol/l as clinically significant complications from sodium concentrations between 126 and 135 mmol/l are judged to be mostly insignificant [48]. This recommendation is based on a study that did not observe a higher incidence of hyponatremia <126 mmol/l with the prescription of less NaCl 0.9% and more balanced solutions and sodium chloride 0.18% plus glucose 4% as maintenance solution in 15,639 patients admitted before and 17,033 patients admitted after guideline implementation [48]. However, we would like to emphasize that generally, delirium/new neurological impairment might be caused by a wide range of diseases, medications and constellations, hyponatremia being only one potential factor [45,49].Further, we would like to mention that the relationship between blood sodium content delirium/new onset neurological symptoms might be U-shaped [45,49,50]. Not only low sodium levels, but also hypernatremia and the speed in change of sodium concentration, which may be associated with a high sodium-content fluid choice, might cause new onset neurological symptoms/delirium [50]. Our systematic review and meta-analysis shows a non-significant tendency towards a lower hypernatremia rate in patients undergoing a low-sodium content maintenance and/or creep fluid strategy.

Lastly, as this meta-analysis and systematic review shows, the odds ratio for hyperchloremia was substantially reduced in the group with a low-sodium content maintenance and/or creep fluid choice. Sodium rich infusions for fluid resuscitation (and associated hyperchloremia) were found to be associated with MAKE 30 in two large trials [51,52], while observational investigations point towards a substantially increased risk of mortality in patients suffering from hyperchloremia on the ICU [53,54].

In summary, there exists a substantial knowledge and research gap concerning the safety of maintenance and/or creep fluid strategy applied. Thus, potential advantages and disadvantages should be weighed carefully before applying a maintenance and/or creep fluid strategy to the individual patient.

4.1. Limitations

This systematic review with meta-analysis has several important limitations that warrant discussion. First, the number of studies and the number of included patients are small. Second, most of the eligible studies were of observational nature and only one study was a randomized controlled trial. Third, the heterogeneity of the included studies was considerable and risk of bias moderate. It is currently not known whether creep or maintenance fluids are intrinsically different drivers of the problem. Fourth, another important limitation lies in the heterogeneity of fluid types in the intervention arm of our meta-analysis, e.g. no sodium up to 54 mmol/l sodium. This may be a source of considerable bias. Fifth, exposure times to the study intervention differed between studies. Sixth, most studies were not powered to detect differences in patient-centered outcome variables. Therefore, we could not specifically investigate these. Seventh, we excluded patients in highly selected patient populations as burn patients limiting the transferability of our results to those patient groups. Eighth, incidences given for hyper- and hypochloremia are based on different reference values of the included papers. Using a single, dedicated reference value for hypo- and hypernatremia could lead to different incidences. Lastly, the clinically relevance of sodium intake through hidden or maintenance fluids may be different in other patient cohorts (outpatients, non-critically ill patients) than in critically ill patients. This was not investigated here.

5. Conclusion

Our systematic review and meta-analysis demonstrates that reducing the mean daily sodium intake using low sodium content maintenance and/or creep fluids reduces sodium burden by a relevant amount compared to the use of standard high sodium content fluids. However and importantly, heterogeneity of included trials was substantial and risk of bias moderate across studies. Additionally, evidence is limited by the lack of sufficient high-quality RCTs and the small sample sizes. There is a considerable research and knowledge gap regarding relevance and safety with the use of low-sodium content maintenance/creep fluids in critical illness. Further adequately powered studies are required to determine if the reduction in mean daily sodium intake affects patient-centred outcomes.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data and material

The datasets used and/or analyzed during the current study can be made available from the corresponding author on reasonable non-commercial request.

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Authors contributions

JW and SMS performed the literature search and selected eligible trials. JW, SMS, CAP did the data extraction on all trials selected for the quantitative analysis. JW, CAP and SMS performed the risk of bias assessment. JW and CAP drafted the manuscript, with all other authors co-drafting and revising the manuscript for important intellectual content. MM performed all statistical analyses. All authors approved the final version of the manuscript and agreed to submission.

Declaration of Competing Interest

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jcrc.2023.154403.

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