

## Review

# Electrolyte disturbances after bowel preparation for colonoscopy: Systematic review and meta-analysis

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**Background and study aims:** We conducted a systematic review and meta-analysis of population-based studies to explore pooled prevalence and magnitude of electrolyte changes after bowel preparation for colonoscopy based on the most recent guidelines.

**Patients and methods:** PubMed and Cochrane were queried for population-based studies examining changes in electrolyte values after bowel preparation, published by July 1, 2021. We report prevalences of serum hypokalemia, hyponatremia, hyperphosphatemia, and hypocalcemia after bowel preparation and changes in mean electrolyte values after vs. before bowel preparation using sodium phosphate (NaP) and polyethylene glycol (PEG).

**Results:** Thirteen studies met the inclusion criteria; 2386 unique patients were included. Overall, hypokalemia was found

in 17.2% (95% CI 6.7, 30.9) in the NaP group vs. 4.8% (95% CI 0.27, 13.02) in the PEG group. The magnitude of potassium decrease after NaP bowel preparation was significantly increased compared to PEG (mean difference  $-0.38$ ; 95% CI  $-0.49$  to  $-0.27$ ,  $P < 0.001$ ). No study reported on major complications.

**Conclusions:** Hypokalemia was found in 17.2% of patients after bowel preparation with NaP and in 4.8% of patients with PEG, a finding that is clinically relevant with respect to choosing the type of bowel preparation. The magnitude of the potassium decrease after NaP was significantly higher compared to PEG. These data provide the evidence that supports the recommendation of the European Society of Gastrointestinal Endoscopy against routine use of NaP for bowel preparation.

**Key words:** bowel preparation, colonoscopy, electrolyte disorder, hypokalemia, low potassium

## INTRODUCTION

COLONOSCOPY IS CONSIDERED as a safe procedure. An optimally cleansed bowel is a prerequisite for diagnosis and treatment of colorectal disorders. However, bowel preparation should not cause clinically important shifts in systemic electrolytes, in fluids, or in patient comfort.

Two main groups of bowel preparation solutions are available: the high-volume and low-volume solutions. High-volume polyethylene glycol (PEG) is included in the high-volume bowel preparation solutions, while sodium

phosphate (NaP), low-volume PEG, and sodium picosulfate with magnesium citrate (SPMC) are included in the low-volume bowel preparation solutions.

High-volume PEG solutions may cause discomfort, due to unpleasant smell or taste or occurrence of gastrointestinal symptoms, i.e., cramping and bloating. Due to lower prevalences of these side-effects with low-volume solutions, these solutions are increasingly used in endoscopy units. SPMC and low-volume PEG solutions provide efficient bowel preparation with only minimal adverse effects. Among the low-volume PEG solutions, a commonly used solution is 2 L polyethylene glycol with ascorbic acid (PEG-asc) as additive<sup>1,2</sup> for its more pleasant taste and low risk for side-effects.

Bowel preparations may cause electrolyte disturbances which remain asymptomatic and unrecognized in the majority of cases. A recent publication reported on two patients who died because of cardiac arrhythmias that occurred after low-volume PEG resulting in severe

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postcolonoscopy hypokalemia.<sup>3</sup> This publication was the first to report on patients with fatal consequences of electrolyte disturbances after bowel preparation for colonoscopy.

Up to now, the extent, magnitude, and risk factors for electrolyte disturbances remain unclear. In a meta-analysis, Tan and colleagues have studied the mean differences in serum potassium levels occurring in patients before vs. after bowel preparation with NaP or PEG. Based on 16 studies, the authors concluded that decreases in serum potassium levels were significantly more often associated with use of NaP than with use of PEG solutions.<sup>4</sup> However, the pooled prevalence of electrolyte disturbances was not evaluated in their study. Apart from this meta-analysis, only a few small sample size population-based studies have examined the frequency of electrolyte disturbances and mean differences in serum electrolyte levels after vs. before bowel preparation.<sup>5</sup> Current clinical guidelines do not include recommendations on electrolyte measurement before or after bowel preparation for colonoscopy. The European Society of Gastrointestinal Endoscopy (ESGE) guideline strongly recommends against the routine use of NaP, while the evidence level for this recommendation is low.<sup>6</sup> To provide an upgrade for the level of evidence on which clinical recommendations are given, we conducted a systematic review and meta-analysis of population-based studies, up to July 1, 2021, examining the pooled prevalence rate of electrolyte disturbances and mean differences after bowel preparation. In addition, pooled changes in mean electrolyte levels after vs. before bowel preparation were analyzed.

## MATERIAL AND METHODS

THE PREFERRED REPORTING items for systematic reviews and meta-analyses (PRISMA) methodology was employed for reporting systematic reviews.<sup>7</sup> A local protocol for conducting a meta-analysis was applied, which is available on request.<sup>8,9</sup>

### Selection criteria

The studies included in this systematic review are population-based studies of plasma electrolyte disorders or serum electrolyte measurement after bowel preparation. Randomized, retrospective, and prospective studies were included. We report on: (i) studies that evaluated serum electrolyte measurements after bowel preparation vs. before bowel preparation; and (ii) studies that examine prevalences of serum electrolyte disorders after bowel preparation. We defined serum electrolyte measurements as measurement of one or more of the following: potassium, sodium,

magnesium, phosphorus, and/or calcium. Electrolyte concentrations had to be checked both before and after bowel preparation. Prevalences of serum electrolyte disorders were defined as the prevalence of hypokalemia (serum potassium <3.5 mmol/L or mEq/L), hyponatremia (serum sodium <135 mmol/L or mEq/L), or hypernatremia (serum sodium >150 mmol/L or mEq/L) after bowel preparation. Definitions of electrolyte disorders were equal among the included studies.

### Search strategy

A systematic search was conducted in PubMed and the Cochrane Library using search terms ‘colonoscopy’ and ‘hypokalemia’ or ‘potassium’. We retrieved key original population-based studies, whenever available up to July 1, 2021. The following key words were used: *Colonoscopy* AND (*bowel cleansing* OR *bowel preparation*) AND (*potassium* OR *hypokalemia*) AND (*sodium* OR *hyponatremia*) including corresponding Mesh terms. Studies in English language were included. We reviewed all reference lists of eligible studies identifying additional population-based studies.

Case reports, review articles, studies reporting bowel preparation quality, studies investigating bowel preparation effects on electrolytes for other purposes than colonoscopy, and studies only reporting mean serum electrolyte values after bowel preparation were excluded. Studies investigating only prevalences of electrolyte disorders after bowel preparation were included.

Two reviewers (A.R. and Q.Z.) screened all studies independently. Study characteristics (first author, year of publication, country), study design (randomized controlled trial, prospective cohort study, retrospective cohort study), study outcomes (mean electrolyte values with standard deviations [SD], when available, prevalence of electrolyte disorders), and mean age with ranges were retrieved. In case of discrepancy between the two reviewers, a senior investigator (S.S.) reviewed the data to achieve consensus.

We used published criteria<sup>7,10–12</sup> to evaluate the quality of clinical prevalence studies. The most suitable subsets of questions of the quality assessment tool for diagnostic accuracy studies-2 (QUADAS-2) tool<sup>13</sup> and the Loney scale<sup>10</sup> were used, as summarized in Table S1.

### Endpoints

The primary end-point was to estimate pooled prevalences of hypokalemia after bowel preparation and to calculate pooled changes in mean potassium values after vs. before bowel preparation.

The secondary end-point was to estimate pooled prevalences after bowel preparation and pooled changes in mean electrolyte values after vs. before bowel preparation for sodium, magnesium, phosphorus, and calcium.

## Statistical analysis

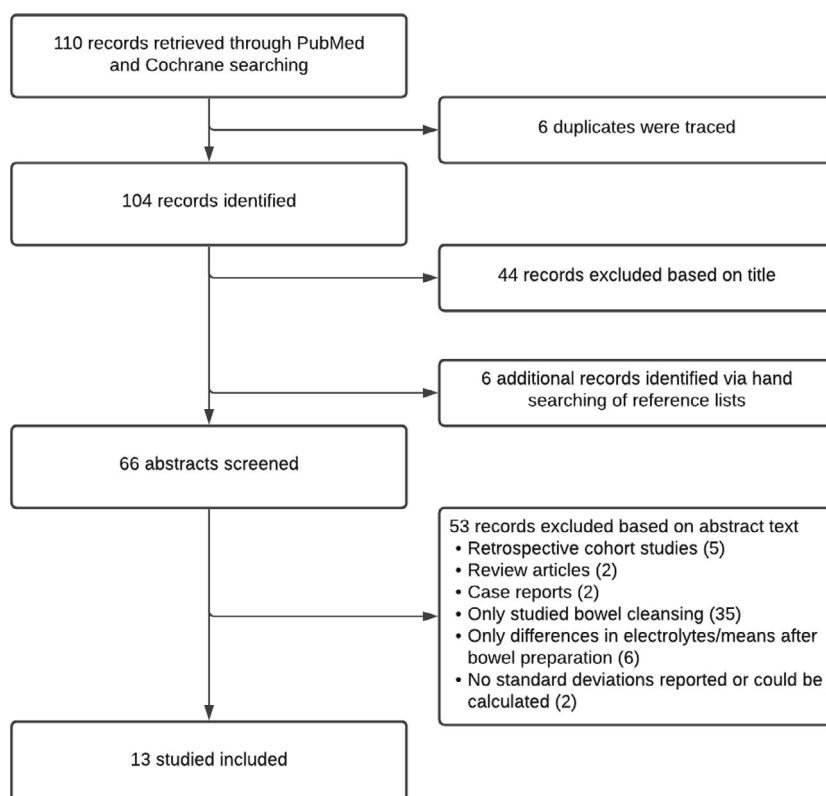
Random effects model was used to calculate pooled prevalences of electrolyte disorders and corresponding 95% confidence intervals (CI) from meta-analysis. Double arcsine transformations for these prevalences were applied because of the low expected prevalences and possibly negative lower limits of the confidence intervals. Using double arcsine back-conversion, prevalences were translated to the original scale.<sup>14,15</sup> Heterogeneity among the studies was measured using  $I^2$  statistics.<sup>16</sup> Pooled overall prevalences of hypokalemia, hyponatremia, hyperphosphatemia, and hypocalcemia were calculated. From the studies that included both groups (NaP and PEG) pooled odds ratios (ORs), corresponding 95% CIs and  $P$ -values were computed using a random effects model. Pooled changes in mean

electrolyte values after vs. before bowel preparation were calculated for potassium, sodium, magnesium, phosphorus, and calcium. In case standard deviations were not reported, standard deviations were estimated using information such as standard errors, 95% CI, or test results, where possible. Pooled mean difference in change scores between NaP and PEG were obtained using a random effects model. We followed the Cochrane Handbook (section 16.1.3.2) in imputing standard deviations for change scores using a correlation coefficient from another study.<sup>17</sup> Statistical analyses were performed using the metafor package<sup>18</sup> in R statistics 3.1.2.<sup>19</sup> Pooled meta-analysis data were presented in forest plots and tables.

## RESULTS

### Included studies

THE STUDY SELECTION flowchart is shown in Figure 1. The PubMed search resulted in 103 studies and Cochrane search in seven studies. Six duplicates were traced and deleted. A total of 104 studies were identified, of



**Figure 1** Study selection flowchart of studies who examined pooled prevalence and magnitude of electrolyte changes after bowel preparation for colonoscopy.

**Table 1** Characteristics of included studies

Study	Country	Study design	Bowel preparation	Mean age $\pm$ SD (range), in years <sup>†</sup>	Participants undergoing colonoscopy	Electrolyte prevalences or means (SD)/ range	Blood samples	Exclusion criteria
Ainley <i>et al.</i> <sup>22</sup>	United Kingdom	Prospective cohort study	NaP 90 mL	61.6 (19–89)	100 outpatients	Prevalences	After bowel preparation	No exclusion criteria
Bae <i>et al.</i> <sup>23</sup>	Korea	Randomized	PEG 4 L PEG 2 L plus NaP <sup>‡</sup>	53.7 $\pm$ 14 53.4 $\pm$ 14	271 outpatients	Means plus SD	Before and after bowel preparation	Renal insufficiency Congestive heart failure Bowel obstruction/surgery
Beloosesky <i>et al.</i> <sup>24</sup>	Israel	Prospective cohort study	NaP 90 mL or barium enema <sup>‡</sup>	80.5 $\pm$ 6 (65–90)	36 inpatients	Means plus SD, prevalence of hypokalemia	Before and after bowel preparation	Renal or liver insufficiency Congestive heart failure Myocardial infarction $\leq$ 6 months CVA <3 months Active IBD or diverticulitis Bowel obstruction Age >75 years Renal insufficiency Congestive heart failure IBD
Bitoun <i>et al.</i> <sup>33</sup>	France	Prospective cohort study	PEG-asc 2L NaP 90 mL	53.0	340 outpatients	Prevalences	Before and after bowel preparation	Bowel obstruction/surgery Age >65 years Renal insufficiency Congestive heart failure
Clarkston <i>et al.</i> <sup>25</sup>	United States of America	Randomized	PEG 4L NaP 90 mL	57.0 $\pm$ 2 (27–85)	98 outpatients	Means plus SD, prevalences	Before and after bowel preparation	Bowel obstruction/surgery Age >65 years Renal insufficiency Congestive heart failure Bowel surgery
Huppertz-Haus <i>et al.</i> <sup>26</sup>	Norway	Randomized	PEG 4L PEG 2 L + bisacodyl NaP	58.0	231 outpatients	Means	Before and after bowel preparation	Renal or liver insufficiency Congestive heart failure Serum electrolyte abnormalities
Johanson <i>et al.</i> <sup>34</sup>	United States of America	Randomized	PEG 2L + bisacodyl NaP tablets 90 mL	56.1 (20–83)	411 outpatients	Means plus SD	Before and after bowel preparation	Renal insufficiency Congestive heart failure Serum electrolyte abnormalities Use of digitalis preparations Myocardial infarction IBD Bowel obstruction/surgery

**Table 1** (Continued)

Study	Country	Study design	Bowel preparation	Mean age ± SD (range), in years <sup>†</sup>	Participants undergoing colonoscopy	Electrolyte prevalences or means (SD)/ range	Blood samples	Exclusion criteria
Klare <i>et al.</i> <sup>27</sup>	Germany	Randomized	PEG 4L SPMC 300 mL	56.4 ± 16	200 out/inpatients	Means plus SD, prevalences	Before and after bowel preparation	Renal insufficiency Congestive heart failure ASA V or VI Urgent procedures Non-veterans Renal insufficiency
Lieberman <i>et al.</i> <sup>28</sup>	United States of America	Prospective cohort study	NaP 90 mL	62.3 (29–77)	32 outpatients	Means plus range	Before and after bowel preparation	Renal or liver insufficiency Congestive heart failure Bowel obstruction/surgery Urgent procedures Renal or liver insufficiency (NaP) Congestive heart failure Severe gastrointestinal ulcers (PEG)
Marin Gabriel <i>et al.</i> <sup>29</sup>	Spain	Randomized	PEG 4L NaP 90 mL	57.9 ± 16 46.9 ± 18	42 outpatients	Means plus SD, prevalences	Before, immediately after and 1 h after the end of colonoscopy	Renal or liver insufficiency Congestive heart failure Bowel obstruction/surgery Urgent procedures
Mathus-Vliegen <i>et al.</i> <sup>30</sup>	The Netherlands	Randomized	PEG 4L NaP 90 mL	48.8 ± 17 55.0 ± 17	94 outpatients	Means plus SD, prevalences	Before and after bowel preparation	Renal or liver insufficiency (NaP) Congestive heart failure Severe gastrointestinal ulcers (PEG)
Rex <i>et al.</i> <sup>31</sup>	United States of America	Randomized	NaP 90 mL SPMC 10 mg	58 (21–83)	338 outpatients	Means plus SD	Before and after bowel preparation	Renal or liver insufficiency Congestive heart failure Serum electrolyte abnormalities Bowel obstruction/surgery IBD
Rostom <i>et al.</i> <sup>32</sup>	Canada	Randomized	PEG 4L NaP 90 mL	55 52	193 outpatients	Prevalences	Before and after bowel preparation	Renal or liver insufficiency Congestive heart failure Bowel obstruction/surgery

<sup>†</sup>Not in all studies available.

<sup>‡</sup>Not implemented in the analysis.

ASA, American Association of Anesthesiologists; Asc, ascorbic acid; CVA, cerebrovascular accident; IBD, inflammatory bowel disease; NaP, sodium phosphate; OSS, oral sulfate solution; PEG, polyethylene glycol; SD, standard deviation; SPMC, sodium picosulfate plus magnesium citrate.

**Table 2** Pooled prevalences of electrolyte disorders after bowel preparation with NaP or PEG

Bowel preparation	Electrolyte disorder	Number of studies included in the analysis	Number of patients included in the analysis	Pooled prevalence	95% CI	$I^2$
NaP	Hypokalemia <sup>22,24,25,29,30,32,33</sup>	7	564	17.19%	6.69, 30.95	92.37%
	Hyponatremia <sup>22,29,30,32</sup>	4	308	0.86%	0.00, 4.07	54.8%
	Hyperphosphatemia <sup>22,25,28–30,32,33</sup>	7	560	37.26%	12.24, 66.45	97.8%
	Hypocalcemia <sup>22,24,25,28–30,32,33</sup>	8	596	15.59%	3.67, 32.94	95.6%
High-volume PEG	Hypokalemia <sup>25,27,29,30,32</sup>	5	271	4.83%	0.27, 13.02	80.19%
	Hyponatremia <sup>27,29,30,32</sup>	5	222	3.30%	0.00, 12.41	82.3%
	Hyperphosphatemia <sup>30,32</sup>	2	96	0.65%	0.00, 4.06	5.12%
	Hypocalcemia <sup>25,27,29,30,32</sup>	5	271	8.07%	1.39, 18.63	83.43%

CI, confidence interval; NaP, sodium phosphate; PEG, polyethylene glycol.

those 44 studies could be excluded based on title. Six additional records were identified via hand searching of reference lists. Of the 66 screened abstracts, 53 were excluded (i.e., two reviews, five retrospective cohort studies, two case reports, 38 studies that contained only information on bowel preparation, seven studies reported only differences in electrolytes [no means] or only means after bowel preparation, and two studies did not report standard deviations or provided no information to estimate standard deviations<sup>20,21</sup>).

Summary data of the 13 included studies are described in Table 1. All studies were published between January 1, 1995 and July 1, 2021.<sup>22–34</sup> Nine studies were randomized controlled trials,<sup>23,25–27,29–32,34</sup> four were prospective cohort studies.<sup>22,24,28,33</sup> Six studies originated from Europe,<sup>22,26,27,29,30,33</sup> four from the United States,<sup>25,28,31,34</sup> one from Asia,<sup>23</sup> one from Canada,<sup>32</sup> and one from the Middle East.<sup>24</sup> Overall, 2386 (range 32–147,832) unique patients were included in the studies<sup>22–34</sup> (Table 1). In the included studies, mean age of subjects varied from 46.9 to 80.5 years<sup>22–34</sup> (Table 1). Ten studies reported means of serum electrolytes, mostly with changes after vs. before bowel preparation,<sup>23–31,34</sup> 11 studies reported prevalences of electrolyte disorders after bowel preparation.<sup>22,24,25,27–30,32,33</sup>

Since there were only two studies on means in SPMC,<sup>27,31</sup> two prevalence studies on SPMC,<sup>27</sup> and one on PEG-asc,<sup>33</sup> a meta-analysis based on these studies was not performed. In the study focusing on PEG-asc, no electrolyte disorders were reported.

### Pooled prevalences

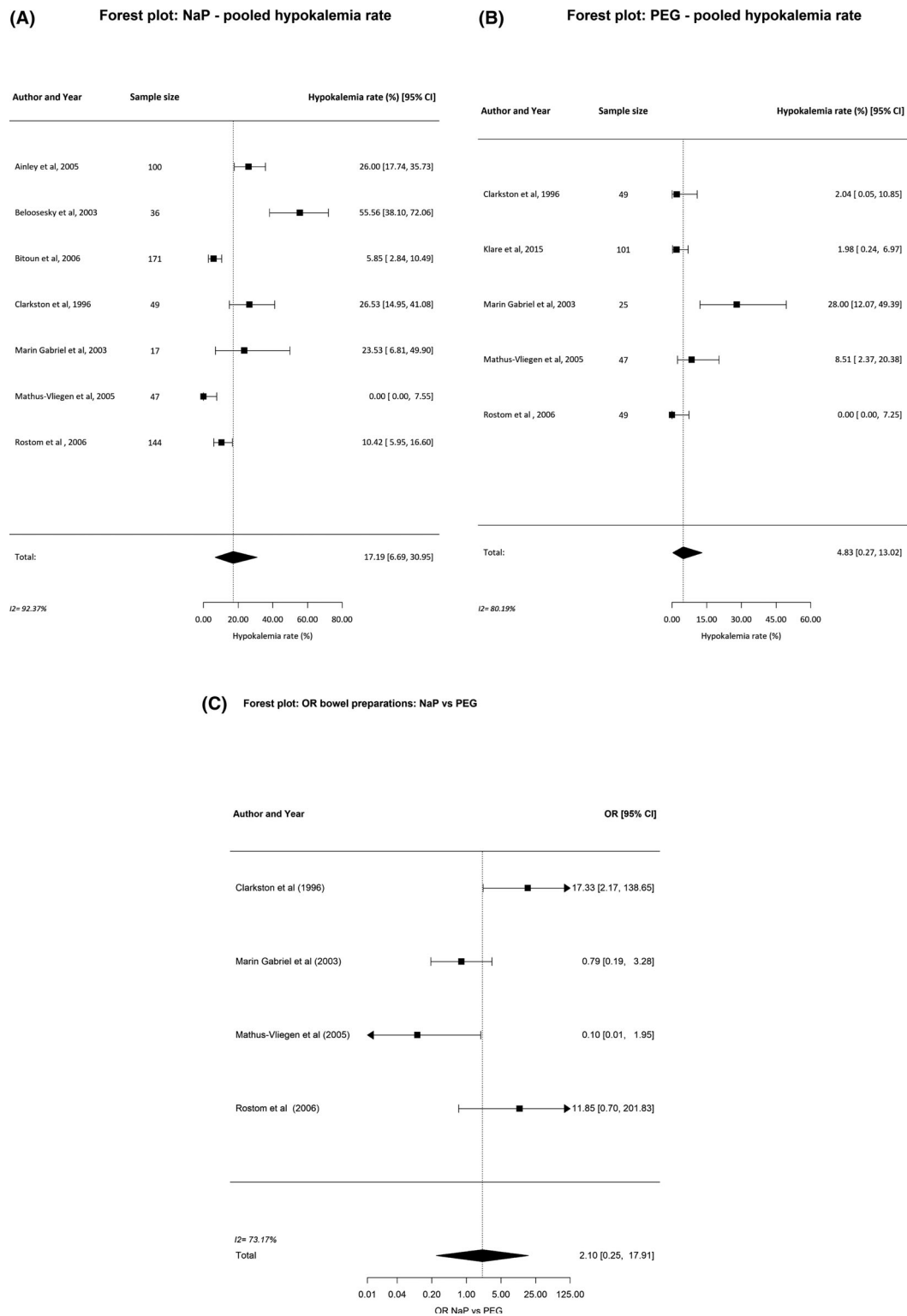
Overall, the prevalence of hypokalemia was 17.2% (95% CI 6.7, 30.9) in patients after NaP bowel preparation for

colonoscopy. After PEG bowel preparation hypokalemia was present in 4.8% (95% CI 0.3, 13.0; Table 2 and Fig. 2). The risk of hypokalemia after NaP was not significantly different from PEG (OR 2.10; 95% CI 0.2, 17.9,  $P = 0.49$ ). Hyponatremia was found in 0.9% (95% CI 0.0, 4.1) in the NaP group vs. 3.3% (95% CI 0.0, 12.4) in the PEG group, hyperphosphatemia in 37.3% (95% CI 12.2, 66.5) vs. 0.65% (95% CI 0.0, 4.1), and hypocalcemia in 15.6% (95% CI 3.7, 32.9) vs. 8.1% (95% CI 1.4, 18.6; Table 2).

### Mean differences in serum electrolyte concentrations

Table 3 (based on Tables 4–6) and Figure 3 show a pooled mean difference in serum potassium values of  $-0.58$  mmol/L (95% CI  $-0.70$ ,  $-0.45$ ) in NaP patients and  $-0.25$  mmol/L (95% CI  $-0.32$ ,  $-0.17$ ) in the PEG group. A pooled change in mean sodium of  $+2.4$  mmol/L (95% CI 1.3, 3.5) was found in the NaP vs.  $+0.4$  mmol/L (95% CI  $-0.1$ , 0.9) in the PEG group. For magnesium, phosphorus, and calcium minor alterations were shown (Table 3). The magnitude of potassium decrease after NaP bowel preparation was significantly increased compared to PEG (mean difference  $-0.38$ ; 95% CI  $-0.49$ ,  $-0.27$ ,  $P < 0.001$ ).

In all of the included studies, heterogeneity was high for the mean changes in electrolytes ( $I^2 = 74.6$ – $99.1\%$ , Table 3), except for magnesium (0.0%) in the NaP group. Heterogeneity was also high for all electrolyte prevalences ( $I^2 = 73.6$ – $97.5\%$ , Table 2). In none of the included studies major complications (e.g., cardiac arrhythmias, epileptic seizures, paralysis, coma, or death) related to electrolyte disturbances after bowel preparation were reported or specified.



**Figure 2** Pooled prevalences (%) of hypokalemia after bowel preparation with (A) sodium phosphate (NaP), (B) polyethylene glycol (PEG), and (C) odds ratio (OR) for NaP vs. PEG.



**Table 3** Pooled changes in mean serum electrolyte values after vs. before bowel preparation for NaP and PEG

Bowel preparation	Serum electrolytes	Number of studies included in the analysis	Number of patients included in the analysis	Pooled change in means (after minus before) [mmol/L]	95% CI	$I^2$
NaP	Potassium <sup>24–26,28–30,34</sup>	7	470	–0.58	–0.70, –0.45	87.9%
	Sodium <sup>24–26,28–30,34</sup>	7	470	+2.39	1.25, 3.53	94.5%
	Magnesium <sup>24,30,34</sup>	3	288	–0.03	–0.04, –0.02	0.0%
	Phosphorus <sup>24–26,28,30,34</sup>	6	453	+0.91	0.57, 1.25	99.1%
	Calcium <sup>24–26,28,30,34</sup>	6	453	–0.13	–0.17, –0.09	92.0%
High-volume	Potassium <sup>23,25–27,29,30,34</sup>	7	645	–0.25	–0.32, –0.17	74.6%
	Sodium <sup>23,25–27,29,30,34</sup>	7	645	+0.41	–0.05, 0.87	95.7%
PEG	Magnesium <sup>27,30,34</sup>	3	354	–0.03	–0.05, –0.01	76.8%
	Phosphorus <sup>23,25–27,30,34</sup>	6	620	–0.02	–0.08, 0.05	89.9%
	Calcium <sup>23,25–27,30,34</sup>	6	620	–0.06	–0.12, –0.01	93.1%

CI, confidence interval; NaP, sodium phosphate; PEG, polyethylene glycol.

## DISCUSSION

THIS SYSTEMATIC REVIEW and meta-analysis examined the safety of bowel preparation for colonoscopy with respect to electrolyte disturbances. A significant proportion of patients developed serum electrolyte disturbances after bowel preparation: 35–360/1000 patients after NaP vs. 9–92/1000 patients after PEG. We found a pooled prevalence of hypokalemia of 17.2% (95% CI 6.7, 30.9) in patients after NaP vs. 4.8% (95% CI 0.27, 13.02) after PEG bowel preparation.

The difference in prevalence of hypokalemia after NaP vs. high-volume PEG is in line with larger retrospective studies (1.2% vs. 0.1%),<sup>35</sup> although the amounts are smaller, probably due to higher study numbers. Practical clinical guidelines recommend to continuously monitor the quality and safety standards in colonoscopy.<sup>36,37</sup> Since bowel preparation is an essential part of the colonoscopy procedure, quality and safety requirements should be clearly defined and monitored. There should be a balance between the benefits (optimal luminal clearance, patient compliance) and harms (complications, i.e., electrolyte disturbances) in bowel cleansing. In general PEG is preferred over other bowel cleansing preparations in individuals of older age, in patients with renal impairment, heart failure, and inflammatory bowel disease.<sup>38</sup> The bowel cleansing agents NaP and SPMC have higher patient tolerance and compliance compared to PEG.<sup>39</sup> Routine use of NaP should be avoided in patients with impaired renal function.<sup>38</sup> In previous studies no significant differences in mean total cleansing scores were found between various preparation solutions,<sup>39,40</sup> while in one study<sup>39</sup> the mean total cleansing score was significantly worse in the NaP group vs. the PEG group.

Serum electrolyte values outside the normal range may increase patient and procedure risks. Electrolyte disturbances may vary from asymptomatic via mild and moderate symptoms (i.e., muscle weakness, constipation, nausea, and vomiting), to severe symptoms (i.e., paralysis, seizures, cardiac arrhythmias, coma, and death).<sup>4</sup> It should be noted that the degree of electrolyte disturbances is not directly related to the severity of the adverse event.

Bowel preparation solutions are supposed to effectively clean the colon with minimal or no side-effects. NaP and PEG are among the most commonly used and studied preparations worldwide.<sup>36,37</sup> PEG is a nondigestible and nonabsorbable lavage solution. PEG is iso-osmotic with plasma, causing no net absorption or excretion of water or ions. Therefore, PEG does not result in significant changes in systemic fluid and electrolyte balance.<sup>41</sup> NaP is a saline laxative, containing monobasic and dibasic sodium phosphate. NaP is highly osmotic and therefore results in fluid shifts from the systemic compartment to the gastrointestinal tract.<sup>41</sup> From a pharmacokinetic point of view, this may explain why NaP results more often in disturbances in the electrolytes balance compared to PEG.

As shown, the use of NaP results in higher prevalences of electrolyte disturbances after bowel preparation compared to use of PEG<sup>22,24,25,27–30,32,33</sup> (Table 2). Nowadays low-volume preparations, such as SPMC and PEG-asc, are more frequently used and these preparations may also result in electrolyte disturbances.<sup>42–44</sup> Up to now, SPMC or PEG-asc induced electrolyte disturbances have not been extensively studied and reported in the literature.<sup>5,27,33</sup> To date, Di Nardo *et al.*<sup>5</sup> found no significant changes in serum potassium values after PEG-asc bowel preparation in children. Bitoun *et al.*<sup>33</sup> reported that the hypokalemia



**Table 4** Mean (±SD) electrolytes before and after bowel preparation with NaP and change in mean values (after minus before) in mmol/L

Study	Number of patients	Electrolytes before and after bowel preparation														
		Potassium			Sodium			Magnesium			Phosphorus			Calcium		
		Before	After	Δ	Before	After	Δ	Before	After	Δ	Before	After	Δ	Before	After	Δ
Belooesky et al. <sup>24</sup>	36	4.5 ± 0.3	3.5 ± 0.5	-1.0	137.8 ± 4.5	142.2 ± 4.2	+4.4	1.07 ± 0.17	1.02 ± 0.17	-0.05	1.15 ± 0.16	2.25 ± 0.48	+1.10	2.29 ± 0.12	2.06 ± 0.15	-0.23
Clarkston et al. <sup>25</sup>	49	4.1 ± 0.4	3.7 ± 0.4	-0.4	139.7 ± 3.2	143.8 ± 2.5	+4.1	-	-	-	1.13 ± 0.16	2.23 ± 0.58	+1.10	2.38 ± 0.10	2.25 ± 0.13	-0.13
Huppertz-Haus et al. <sup>26</sup>	84	4.4 ± 0.1	3.8 ± 0.1	-0.6	142.1 ± 0.3	143.2 ± 0.5	+1.1	-	-	-	1.06 ± 0.02	1.62 ± 0.05	+0.56	2.37 ± 0.02	2.29 ± 0.02	-0.08
Johanson et al. <sup>34</sup>	205	4.3 ± 0.4	3.7 ± 0.5	-0.6	140.8 ± 2.5	142.7 ± 2.9	-1.9	0.85 ± 0.07	0.82 ± 0.06	-0.03	1.17 ± 0.17	2.38 ± 0.46	+0.11	2.47 ± 0.09	2.33 ± 0.11	-0.14
Lieberman et al. <sup>28</sup>	32	4.3 ± 0.3	3.8 ± 0.2	-0.5	139.9 ± 1.8	144.6 ± 2.0	+4.7	-	-	-	1.00 ± 0.12	2.20 ± 0.32	+1.20	2.30 ± 0.13	2.15 ± 0.08	-0.15
Marin Gabriel et al. <sup>29</sup>	17	3.7 ± 0.4	3.7 ± 0.4	-0.1	139.4 ± 2.1	138.2 ± 2.1	-1.2	-	-	-	-	-	-	-	-	-
Mathus-Vliegen et al. <sup>30</sup>	47	4.1 ± 0.5	3.3 ± 0.4	-0.8	138.0 ± 3.2	140.0 ± 2.6	+2.0	0.84 ± 0.06	0.81 ± 0.06	-0.05	1.10 ± 0.20	1.40 ± 0.48	+0.30	2.40 ± 0.11	2.30 ± 0.09	-0.10

NaP, sodium phosphate; SD, standard deviation; Δ, delta.

**Table 5** Mean (±SD) electrolytes before and after bowel preparation with PEG and change in mean values (after minus before) in mmol/L

Study	Number of patients	Electrolytes before and after bowel preparation														
		Potassium			Sodium			Magnesium			Phosphorus			Calcium		
		Before	After	Δ	Before	After	Δ	Before	After	Δ	Before	After	Δ	Before	After	Δ
High-volume PEG																
Bae et al. <sup>23</sup>	141	4.1 ± 0.4	3.9 ± 0.4	-0.2	141.1 ± 0.2	142.6 ± 0.2	+1.5	-	-	-	1.23 ± 0.16	1.35 ± 0.19	+0.12	2.25 ± 0.10	2.20 ± 0.09	-0.05
Bae et al. <sup>23</sup>	49	4.2 ± 0.4	4.1 ± 0.4	-0.1	140.4 ± 3.2	141.4 ± 2.6	+1.0	-	-	-	1.20 ± 0.13	1.16 ± 0.16	-0.04	2.40 ± 0.13	2.35 ± 0.18	-0.05
Bae et al. <sup>23</sup>	76	4.4	4.1	-0.3	141.7	141.5	-0.2	-	-	-	1.10	1.07	-0.03	2.40	2.37	-0.08
Bae et al. <sup>23</sup>	101	4.5 ± 0.5	4.2 ± 0.4	-0.4	140.7 ± 2.9	139.9 ± 2.5	-0.8	0.84 ± 0.07	0.80 ± 0.06	-0.04	1.16 ± 0.19	1.09 ± 0.19	-0.07	2.37 ± 0.12	2.32 ± 0.13	-0.05
Marrin Gabriel et al. <sup>29</sup>	25	4.0 ± 0.5	3.9 ± 0.4	-0.1	138.2 ± 2.3	136.9 ± 2.2	-1.5	-	-	-	-	-	-	-	-	-
Mathus-Vliegen et al. <sup>30</sup>	47	4.2 ± 0.4	3.8 ± 0.4	-0.4	139.4 ± 2.8	140.0 ± 2.1	+0.6	0.84 ± 0.06	0.80 ± 0.07	-0.04	1.10 ± 0.23	0.97 ± 0.23	-0.13	2.50 ± 0.13	2.40 ± 0.15	-0.10
Low-volume PEG																
Johanson et al. <sup>34</sup>	206	4.3 ± 0.4	4.2 ± 0.5	-0.1	140.7 ± 2.7	140.2 ± 3.3	-0.5	0.85 ± 0.07	0.84 ± 0.06	-0.01	1.14 ± 0.18	1.13 ± 0.16	-0.01	2.46 ± 0.08	2.46 ± 0.10	0.00
Huppertz-Haus et al. <sup>26</sup>	71	4.4	4.1	-0.3	141.8	141.2	-0.6	-	-	-	1.05	1.05	0.00	2.38	2.37	-0.01

PEG, polyethylene glycol; SD, standard deviation; Δ, delta.

**Table 6** Mean ( $\pm$ SD) electrolytes before and after bowel preparation with SPMC and change in mean values (after minus before) in mmol/L

Study	Number of patients	Electrolytes before and after bowel preparation														
		Potassium			Sodium			Magnesium			Phosphorus			Calcium		
		Before	After	$\Delta$	Before	After	$\Delta$	Before	After	$\Delta$	Before	After	$\Delta$	Before	After	$\Delta$
Klare <i>et al.</i> <sup>27</sup>	99	4.5 $\pm$ 0.5	4.3 $\pm$ 0.5	-0.20	140.7 $\pm$ 3.3	137.2 $\pm$ 4.2	-2.8	0.84 $\pm$ 0.07	0.88 $\pm$ 0.08	+0.04	1.09 $\pm$ 0.17	1.14 $\pm$ 0.18	+0.05	2.39 $\pm$ 0.11	2.36 $\pm$ 0.11	-0.03
Rex <i>et al.</i> <sup>31</sup>	169	4.3 $\pm$ 0.4	4.3 $\pm$ 0.4	0.0	140.0 $\pm$ 2.0	139.0 $\pm$ 3.0	+1.0	1.29 $\pm$ 0.04	0.82 $\pm$ 0.08	-0.47	1.16 $\pm$ 0.16	1.09 $\pm$ 0.16	-0.07	2.40 $\pm$ 0.1	2.38 $\pm$ 0.1	-0.02

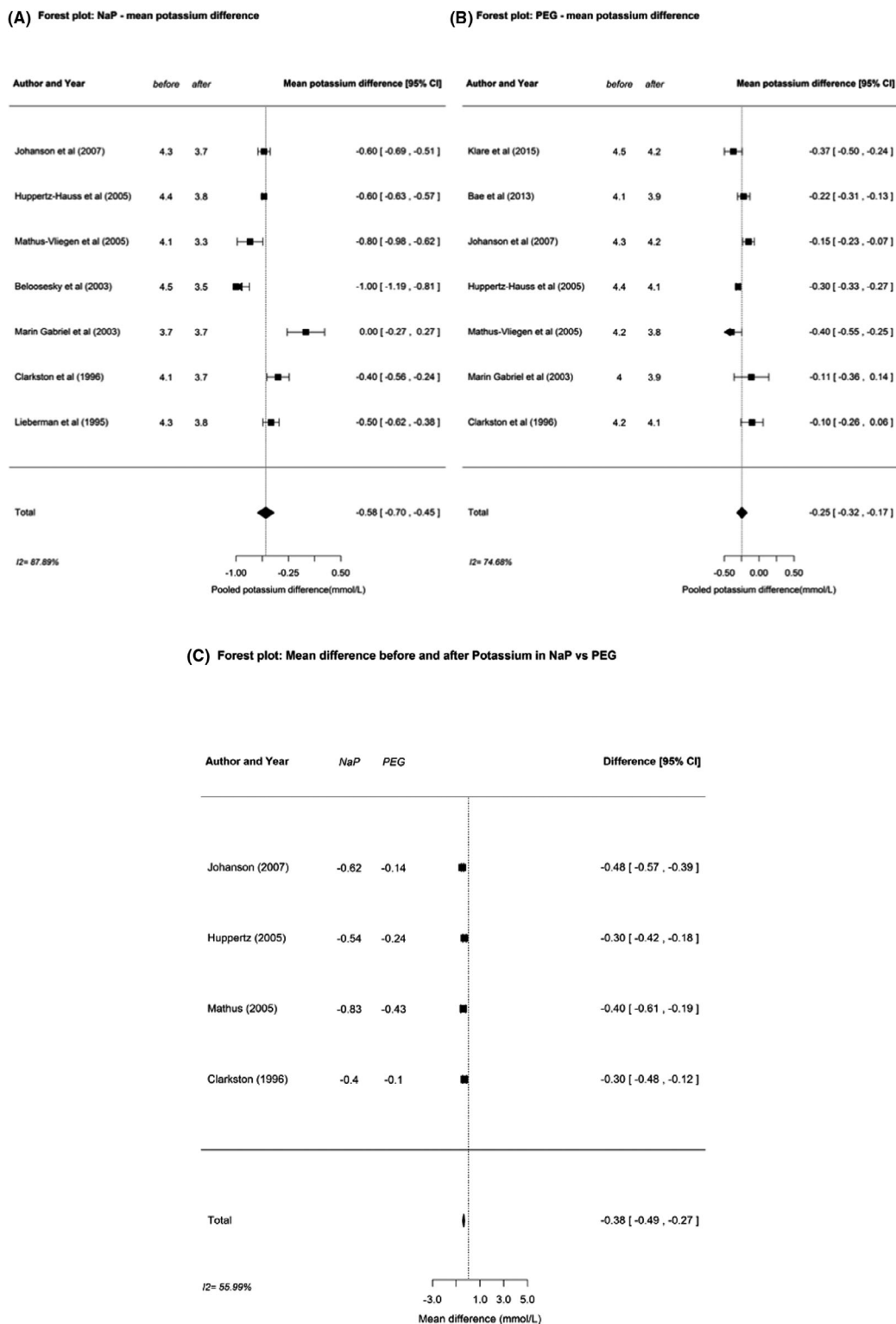
SD, standard deviation; SPMC, sodium picosulfate plus magnesium citrate;  $\Delta$ , delta.

risk was not increased after PEG-asc (Table 7). In a retrospective study, Lee *et al.*<sup>45</sup> showed that hypokalemia was significantly more frequently seen in 2 L PEG-asc compared to 4 L PEG. Considering the small number of (prospective) studies and the small sample sizes, the observed low risk of potassium disturbances after PEG-asc should be interpreted with caution and cannot be considered to reliably represent the real-life population-based risk. Notably, severe hypokalemia and cardiac death in two patients following bowel preparation with low-volume PEG-asc has recently been reported.<sup>3</sup> Based on these cases, a study was undertaken to explore the magnitude of hypokalemia associated with bowel preparation in high risk patients. It was shown that 4.2% of patients had hypokalemia before bowel preparation and 23.6% developed hypokalemia after bowel preparation with low-volume PEG-asc.<sup>46</sup>

In general, postcolonoscopy mortality is very low.<sup>9</sup> All doctors and medical workers ordering colonoscopies, especially (nurse) endoscopists, should be aware that colonoscopy related morbidity and mortality risks also include effects related to the use of bowel preparation regimens. Current gastroenterology- or endoscopy-based professional guidelines do not recommend to routinely measure serum electrolyte levels prior to colonoscopy.<sup>36,37</sup> Unfortunately, risk profiles of patients developing hypokalemia after bowel preparation, especially with the low-volume preparations, are lacking. To our knowledge, our manuscript is the first systematic review and meta-analysis reporting on prevalences of electrolyte disturbances after use of NaP and PEG bowel preparations. We provided actual prevalences of electrolyte disturbances and changes in mean electrolytes levels after vs. before bowel preparation.

The most recently published guideline of the ESGE recommends the use of both PEG-based (high-volume PEG or low-volume PEG with ascorbate, citrate, or bisacodyl) and non-PEG-based (SPMC, oral sulfate sodium) agents taking into account the precisely defined contraindications.<sup>6</sup> The ESGE recommends against the routine use of NaP, but this recommendation is based on low quality evidence. Given the high prevalences of electrolyte disturbances reported in this systematic review and meta-analysis, we now provide additional and high quality evidence to support the ESGE recommendation against the routine use of NaP based bowel preparation solutions.

At present, SPMC and PEG-asc low-volume bowel preparation regimens are increasingly used instead of NaP and high-volume PEG.<sup>36,37</sup> More data on prevalences of electrolyte disturbances after low-volume bowel preparations using SPMC and PEG-asc should become available in order to examine pooled risks. Furthermore, 1 L PEG



**Figure 3** Pooled changes in mean potassium values (in mmol/L) after vs. before bowel preparation for (A) sodium phosphate (NaP), (B) polyethylene glycol (PEG), and (C) difference in mean change for NaP vs. PEG.

**Table 7** Prevalence of electrolyte disorder after bowel preparation

Bowel preparation	Study	Number of patients	Hypokalemia	Hyponatremia	Hypernatremia	Hyperphosphatemia	Hypocalcemia
High-volume PEG 4 L	Clarkston et al. <sup>25</sup>	49	2.0%	–	–	–	4.1%
	Klare et al. <sup>27</sup>	101	2.0%	4.0%	–	–	11.9%
	Marin Gabriel et al. <sup>29</sup>	25	28.0%	24.0%	–	–	8.0%
	Mathus-Vliegen et al. <sup>30</sup>	47	8.3%	0.0%	0.0%	2.9%	0.0%
	Rostom et al. <sup>32</sup>	49	0.0%	0.0%	–	0.0%	26.0%
Low-volume NaP	Ainley et al. <sup>22</sup>	100	26.0%	2.0%	0.0%	45.0%	16.0%
	Beloosesky et al. <sup>24</sup>	36	56.0%	14.0%	–	–	58.0%
	Bitoun et al. <sup>33</sup>	171	5.8%	–	–	5.8%	0.6%
	Clarkston et al. <sup>25</sup>	49	26.5%	–	–	98.0%	12.2%
	Lieberman et al. <sup>28</sup>	32	–	–	–	28.1%	6.3%
	Marin Gabriel et al. <sup>29</sup>	17	23.5%	5.9%	–	47.1%	12.9%
	Mathus-Vliegen et al. <sup>30</sup>	47	0.0%	2.4%	2.4%	39.0%	5.0%
	Rostom et al. <sup>32</sup>	144	10.4%	0.0%	0.7%	6.3%	41.7%
	Bitoun et al. <sup>33</sup>	169	0.0%	–	–	0.0%	0.0%
	SPMC	Klare et al. <sup>27</sup>	99	1.0%	21.2%	–	–

NaP, sodium phosphate; PEG, polyethylene glycol; PEG-asc, polyethylene glycol ascorbic acid; SPMC, sodium picosulfate plus magnesium citrate.

appears to be also promising in safety and efficacy, but electrolyte alterations were not studied.<sup>47</sup> Because of rapidly increasing numbers of colonoscopies for population-based screening, surveillance, and regular care, the number of elderly patients and patients with comorbidity at risk for electrolyte disturbances will also increase in the near future. Therefore, population-based data on patient-specific risk factors for electrolyte disturbances and disorders after bowel preparation should become available. Only thereafter, evidence based recommendations on monitoring serum electrolyte levels, especially in high risk patients with specific regimens, can be made. Such recommendations are critical to ensure high quality and safety standards in colonoscopy.

Several limitations should be addressed with respect to our study. First, prevalences of electrolyte disturbances may have been underreported in the separate studies because not all cases could be identified (treatment in other hospital, gastroenterologist did not notify the electrolyte disturbance). Second, as shown in Table 1, patients who suffer from renal insufficiency, heart failure, and/or bowel problems have been excluded in almost all studies. These patients run a higher risk for electrolyte disturbances associated with bowel preparation. For example, diuretics are frequently prescribed in heart failure, renal disease, and hypertension. Hypokalemia is a common consequence of specific types of diuretics.<sup>48</sup> Unfortunately, diuretic use was not specifically reported in the included studies. In real life, patients with renal insufficiency, heart failure, or bowel problems regularly undergo colonoscopy for diagnostic, screening, or surveillance indications. To be informed about the real-life prevalences of electrolyte disorders, these patient groups should be identified and examined in more detail in future studies. Third, not all studies provided bowel cleansing scores or reported every adverse event (Table S2). Furthermore, because of the limited amount of data available on SPMC and PEG-asc, we could not present pooled prevalences or mean changes for these bowel preparation regimens. It should be taken into account that heterogeneity was high in most studies. No significant funnel plot asymmetry was seen (Fig. S1) for hypokalemia prevalences. In conclusion, electrolyte disturbances in response to bowel preparation have regularly been observed. Hypokalemia was found in 17.2% of patients after bowel preparation with NaP and in 4.8% of patients with PEG, a finding that is clinically relevant with respect to choosing the type of bowel preparation. The magnitude of the potassium decrease after NaP was significantly higher compared to PEG. These data provide the evidence that supports the recommendation of the ESGE against routine use of NaP for bowel preparation.

## CONFLICT OF INTEREST

**A**UTHORS DECLARE NO conflict of interest for this article.

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**N**ONE.

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## SUPPORTING INFORMATION

ADDITIONAL SUPPORTING INFORMATION may be found in the online version of this article at the publisher's web site.

**Figure S1** Funnel plots pooled hypokalemia rate NaP (A) and PEG (B).

**Table S1** The quality assessment of prevalence studies using a modified version of the QUADAS-2 and the Loney scale.

**Table S2** The bowel cleansing efficacy and serious adverse events per study.