Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Meta-analysis

Effects of fluid and drinking on pneumonia mortality in older adults: A systematic review and meta-analysis

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SUMMARY

Background and aims: Advice to drink plenty of fluid is common in respiratory infections. We assessed whether low fluid intake (dehydration) altered outcomes in adults with pneumonia.

Methods: We systematically reviewed trials increasing fluid intake and well-adjusted, well-powered observational studies assessing associations between markers of low-intake dehydration (fluid intake, serum osmolality, urea or blood urea nitrogen, urinary output, signs of dehydration) and mortality in adult pneumonia patients (with any type of pneumonia, including community acquired, health-care acquired, aspiration, COVID-19 and mixed types). Medline, Embase, CENTRAL, references of reviews and included studies were searched to 30/10/2020. Studies were assessed for inclusion, risk of bias and data extracted independently in duplicate. We employed random-effects meta-analysis, sensitivity analyses, subgrouping and GRADE assessment. Prospero registration: CRD42020182599.

Results: We identified one trial, 20 well-adjusted cohort studies and one case–control study. None suggested that more fluid (hydration) was associated with harm. Ten of 13 well-powered observational studies found statistically significant positive associations in adjusted analyses between dehydration and medium-term mortality. The other three studies found no significant effect. Meta-analysis suggested doubled odds of medium-term mortality in dehydrated (compared to hydrated) pneumonia patients (GRADE moderate-quality evidence, OR 2.3, 95% CI 1.8 to 2.8, 8619 deaths in 128,319 participants). Heterogeneity was explained by a dose effect (greater dehydration increased risk of mortality further), and the effect was consistent across types of pneumonia (including community-acquired, hospital-acquired, aspiration, nursing and health-care associated, and mixed pneumonia), age and setting (community or hospital). The single trial found that educating pneumonia patients to drink ≥1.5 L fluid/d alongside lifestyle advice increased fluid intake and reduced subsequent healthcare use.

No studies in COVID-19 pneumonia met the inclusion criteria, but 70% of those hospitalised with COVID-19 have pneumonia. Smaller COVID-19 studies suggested that hydration is as important in COVID-19 pneumonia mortality as in other pneumonias.

Conclusions: We found consistent moderate-quality evidence mainly from observational studies that improving hydration reduces the risk of medium-term mortality in all types of pneumonia. It is remarkable that while many studies included dehydration as a potential confounder, and major

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pneumonia risk scores include measures of hydration, optimal fluid volume and the effect of supporting hydration have not been assessed in randomised controlled trials of people with pneumonia. Such trials, are needed as potential benefits may be large, rapid and implemented at low cost. Supporting hydration and reversing dehydration has the potential to have rapid positive impacts on pneumonia outcomes, and perhaps also COVID-19 pneumonia outcomes, in older adults.

1. Introduction

Pneumonia is responsible for one in six deaths in the United States [1]. In Europe pneumonia mortality had fallen over the past 20 years [2,3] until the COVID-19 pandemic [4,5]. A systematic review of clinical characteristics of Chinese COVID-19 patients suggests 73% of COVID-19 patients had bilateral pneumonia (91% of those with critical and 40% with non-critical illness) on computed tomography [6]. Similarly, data from 3948 adults hospitalised with COVID-19 within the US Veterans Health Administration healthcare system suggests 70% (compared to 35% of influenza patients) developed pneumonia [7].

The basic mechanism of *Pneumonia*, regardless of type, is an acute infection of the lungs causing inflammatory tissue damage. There are many similarities across pneumonia types although SARS-CoV-2 may have some distinctive pathogeneses [8–10]. Many persons with initially mild SARS-CoV-2 infection progress to pneumonia caused by other opportunistic pathogens [11,12] a tendency noted for other viral respiratory diseases [13]. Some pneumonia treatments are consistent across all types of pneumonia (for example, oxygen therapy may be used in all types of pneumonia), while others are more specific (specific antibiotics are prescribed, or not, according to specific causal microorganisms [14]). Our approach to assessing the utility of a wide range of modifiable nutrition factors was to systematically review the evidence for any and all types of pneumonia – helping to provide power to see small effects – but also to carry out subgrouping by type of pneumonia to check whether effects and associations are generic for pneumonia, or specific to particular types of pneumonia.

ESPEN guidance for nutritional management of people with COVID-19 infection does not mention fluid, drinking or dehydration except in the context of treating shock [15]. Adequate hydration ("drink plenty of fluids") is commonly advised in pneumonia and other respiratory illnesses but for many older adults, who are at highest risk of both developing pneumonia and experiencing poor outcomes from pneumonia, fluid intake is chronically insufficient, resulting in low-intake dehydration [16–19]. Malaise and loss of chemosensation associated with COVID-19 infection [20–22] may reduce fluid intake further. Sufficient fluid could reduce mucous viscosity, replace losses due to fever, support immune function and help to counteract blood thickening resulting in inappropriate clotting. However, as water excretion may be impaired in people with pneumonia, additional fluids could cause fluid overload [23,24]. For this reason, early management of COVID-19 in Intensive Care Units (ICU) aimed for negative fluid balance, but resultant kidney injury has led to more liberal fluid strategies [25,26].

Simple, cost-effective ways to improve outcomes in adults with pneumonia would be valuable, particularly since the COVID-19 epidemic has increased rates of pneumonia hospitalisation. Our primary aim was to systematically review trial evidence on effects of increasing fluid intake in adults with any type of pneumonia on mortality and other key outcomes. Where trials were lacking, we aimed to assess associations between hydration status and pneumonia outcomes in well-adjusted observational studies. To assess the strength and generalisability of our findings we aimed to assess whether associations differed by pneumonia type, age, setting and methodological strength.

2. Materials and methods

Methods were based on Cochrane and Grading of Recommendations, Assessment, Development and Evaluations (GRADE), using Covidence (www.covidence.org), RevMan (version 5.4) and GradePRO software, reported according to Meta-Analysis of Observational Studies in Epidemiology (MOOSE) guidelines [27–32]. The protocol was registered on PROSPERO in April 2020 [33]. As this was entirely secondary research we did not require or seek ethical approval.

We included controlled trials, cohort and case–control studies, published, unpublished (including theses and pre-prints) or abstracts. We restricted inclusion of observational studies to those that adjusted for key potential confounders. Eligible observational studies had to include $\geq$1000 participants or $\geq$100 participants who experienced an eligible primary or secondary outcome and had to have adjusted for (or matched on or limited by) age, sex and $\geq$1 comorbidity by including them in univariate analysis (and multivariate analysis where appropriate). We did not restrict the size of eligible RCTs because randomised trials should have roughly equal numbers in intervention and control participants, potential confounding factors are likely to be balanced between arms and most trials are explicitly powered to assess effects. While we originally did not restrict inclusion of observational studies by cohort size we pre-specified that we would explore cohort size in sensitivity analyses as large cohorts are less likely to be underpowered [33]. When we carried out these sensitivity analyses it was clear that smaller studies were (as suspected) underpowered, so we decided to exclude smaller studies from further analyses. This exclusion of poorly adjusted and smaller studies increased the likelihood that the included observational studies would have the power and discrimination to identify relationships where they do exist and not identify spurious relationships due to confounding. Such eligibility restrictions are a common and useful strategy in systematic reviews of good quality observational evidence, and restricting to 1000 participants is common for dietary studies [34–38]. Participants were adults with a diagnosis of pneumonia (any type, including COVID-19 associated) and mean age $\geq$50 years. The intervention (in trials) was increased or decreased oral or supplemental fluid intake, compared to usual care or a control intervention. The exposure (in observational studies) was a measure of hydration or fluid intake, such as serum or salivary osmolality or osmolarity, blood urea nitrogen (BUN), serum urea, fluid or drinks intake, urinary output or signs of dehydration [39], comparing higher with lower status of the exposure. Exposures had to have been assessed in univariate analysis, but did not need to be statistically significant in that analysis (to prevent the bias of excluding studies that did not find a statistically significant relationship).

Primary outcomes included:

- Medium-term mortality (all-cause or pneumonia-specific mortality occurring within 7–31 days of pneumonia diagnosis, including in-hospital mortality).
- Long-term mortality (>31 days).
- Duration of hospital, institutional or intensive care stay.
- Hospital admission for those treated as outpatients.
- Measures of functional status, disability and quality of life.

Secondary outcomes included relevant composite outcomes, cardiovascular events, need for ICU admission, or ventilator support as reported by otherwise relevant studies.

Some observational studies assessing risk factors for poor outcome in pneumonia incorporated established community-acquired pneumonia (CAP) risk assessment tools that include a measure of dehydration as exposures in their univariate and multivariate analyses. These tests included CURB-65 (named for the elements assessed: confusion, urea, respiratory rate, blood pressure and older age), pneumonia severity index (PSI) and A-DROP (again named for the elements assessed: age, dehydration, respiratory failure, confusion and blood pressure), see Supplemental Table A. As hydration was included in the risk assessment tool, hydration was often not added into the multivariate analysis, even when it was found significant in univariate analysis. When risk scores were used alone it was not possible to disentangle associations with dehydration and other measures included in the risk scores. Analyses including both a measure of hydration and a risk assessment tool including hydration in multivariate analysis were inappropriate, and unlikely to provide useful information on the relationship between the hydration marker and outcome. For this reason we excluded observational studies that included established community-acquired pneumonia (CAP) risk assessment tools that incorporated some measure of dehydration in multivariate analysis.

Complex and comprehensive searches were developed and run in Medline (Ovid), Embase (Ovid) and Cochrane CENTRAL to 30th October 2020 without language or date restrictions. The full texts of the search strategies (including indexing/MeSH terms) are shown in Supplemental Text 1. Reference lists of relevant reviews and included studies were assessed, authors were not contacted.

Assessment of titles, abstracts and full text papers (in Covidence), data extraction and assessment of risk of bias (onto forms developed and piloted for this review) were carried out by two reviewers independently (all authors took part in these steps), disagreements were resolved by discussion. Data extraction included information on the population, intervention/exposure and comparator type, dose, duration and baseline status, outcome data, study design and duration of assessment period. Association of hydration or fluid intake with an outcome measure in observational studies was taken from multivariate analysis. Where hydration data were assessed in univariate analyses and not used in multivariate analysis, we assumed no statistically significant association. Risk of bias was assessed in intervention studies using the Cochrane tool (version 1.0) [40], and in cohort studies using a modified Newcastle Ottawa scale (scored out of 8) [41].

2.1. Analysis

Characteristics and findings of included studies were tabulated (Supplemental Table B). We planned that effects of hydration on each outcome (in trials) would be combined in random-effects meta-analysis. We combined adjusted odds ratios (ORs) or hazard ratios (HRs, separately) from observational studies using generic inverse variance methods, assessing heterogeneity using the I^2 statistic, and small study bias by comparing fixed and random effects meta-analysis [42,43].

Sensitivity analyses for primary outcomes removed observational studies at higher risk of bias (scoring <6 in quality assessment). We originally planned to include observational studies of any size [33], but after running a pre-specified sensitivity analysis removing studies with ≤1000 participants and ≤100 people experiencing outcomes (see Supplemental Tables D and E) we realised that these smaller studies were comprehensively underpowered, so removed these smaller studies from all analyses. We used subgrouping to assess associations by:

- Type of pneumonia: CAP, hospital-acquired pneumonia (HAP), nursing and health care-acquired pneumonia (NHCAP, including healthcare-acquired pneumonia, HCAP, and psychiatric hospital-acquired pneumonia, PHAP), aspiration pneumonia (AP), COVID-19-related pneumonia, mixed pneumonias, and other (more specific) pneumonias
- Age (mean age 50 to <65, 65 to <80, 80+)
- Setting: community, hospital or mixed
- Measure of hydration: Post-hoc, because of the diversity of dehydration measures, we subgrouped by measure of hydration, including BUN or urea, BUN/albumin ratio and fluid intake.

While we excluded observational studies with fewer than 1000 participants as potentially underpowered we systematically tabulated all these studies (in Supplemental Table D), assessed results by study size (our planned sensitivity analysis, Supplemental Table E) and have discussed the smaller COVID-19 studies to gain an idea of whether and how COVID-19 pneumonia may differ from other types of pneumonia in respect of hydration.

GRADE assessment was used to assess quality of evidence [44].

3. Results

Searching identified 12,243 titles and abstracts, deduplicated to 9063 (Fig. 1). Of these 8190 were not relevant; we assessed 873 full texts and included 138 studies, presented in 217 papers (13 RCTs, 123 cohort and 2 case–control studies). We combined individual observational analyses into cohorts (to avoid over-representation of well-studied groups). Inclusion of 51 full texts was unclear (usually because it was not possible to assess whether age, sex and at least one comorbidity, or the exposure, had been included in univariate analysis). Of the 138 potentially included studies, 60 related to dehydration and the other 78 considered other nutritional factors (published separately) [45]. Of the 60 studies providing data on dehydration, 20 included a risk score including dehydration in multivariate analysis so were excluded (Supplemental Table C). Eighteen observational studies were judged to be underpowered as they included fewer than 1000 participants and fewer than 100 participants experienced any outcome (Supplemental Table D). Twenty two studies were included in this review (1 RCT, 20 cohorts, 1 case–control study).

3.1. RCT data

We found a single trial, EDUCAP, that randomised Spanish adults hospitalised with CAP to an individualised education programme before discharge, or conventional information [46]. The educational intervention included support and encouragement to increase fluid intake, decrease alcohol, cease smoking, adhere to medications, update vaccines and manage pneumonia. Of the 207 CAP patients enrolled 24% of intervention and 43% of control participants experienced the primary outcome (a composite of additional healthcare visits and re-hospitalisations within 30 days of hospital

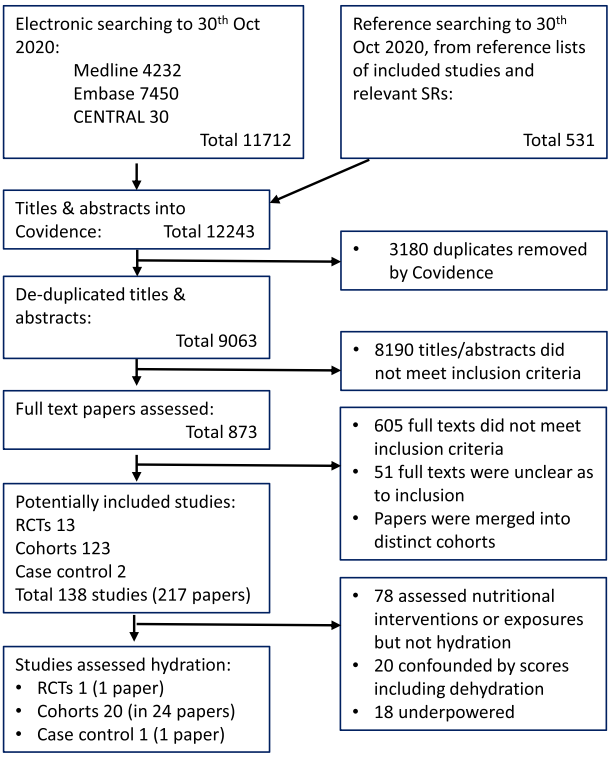


Fig. 1. Flow chart for process of the systematic review.

discharge, RR 0.55, 95% CI 0.36 to 0.83). Secondary outcomes suggested that the intervention improved fluid intake (RR 1.88, 95% CI 1.55 to 2.29 for an intake of at least 1.5 L fluid/day), knowledge, physical activity and smoking but not drug therapy, pneumococcal or influenza vaccinations or alcohol cessation. While this improvement in health and resource use cannot be assumed due to hydration (as the intervention was multifactorial) it is encouraging.

3.2. Characteristics of included cohort and case–control studies

One case–control study [47] and 20 cohort studies were included (Fig. 1, Supplemental Table B). Six were conducted in Asia, seven each in Europe and North America, and one included people from multiple continents [48]. Twelve cohorts included people with CAP [48–59], one with HAP [60], none with COVID-19 pneumonia, one with AP [61–63], three with HCAP or NHCAP [64–66], five described "pneumonia" only, or included mixed types of pneumonias [47,67–70]. One of these cohorts published data on two sub-cohorts, one of people with CAP, the other with pneumonia and chronic kidney disease [70].

Thirteen studies reported medium-term mortality, four longer term mortality, and one each cardiovascular events, readmission, bacteraemia, eating orally, and a composite outcome, poor prognosis. The proportion of participants experiencing medium-term mortality varied from 3% (Japanese adults mean age just over 50 years hospitalised with any type of pneumonia except AP) [69] to 83% (Dutch nursing home residents with pneumonia not given antibiotics) [65].

Most studies aimed to develop risk scores for poor outcome in pneumonia patients, and none appeared to have set out specifically to assess associations between hydration and pneumonia outcome, so we sometimes gleaned information on hydration factors only by their presence in univariate analyses and subsequent presence or absence in the results of multivariate analysis. Fifteen studies assessed hydration status using serum BUN, two serum urea, one fluid intake, one both fluid intake and signs of dehydration (skin turgor and dry mucous membranes), and two BUN/albumin ratio. BUN and urea are interconvertible measures used routinely in different parts of the world so data in this paper have been converted to mmol/L of urea to facilitate comparison.

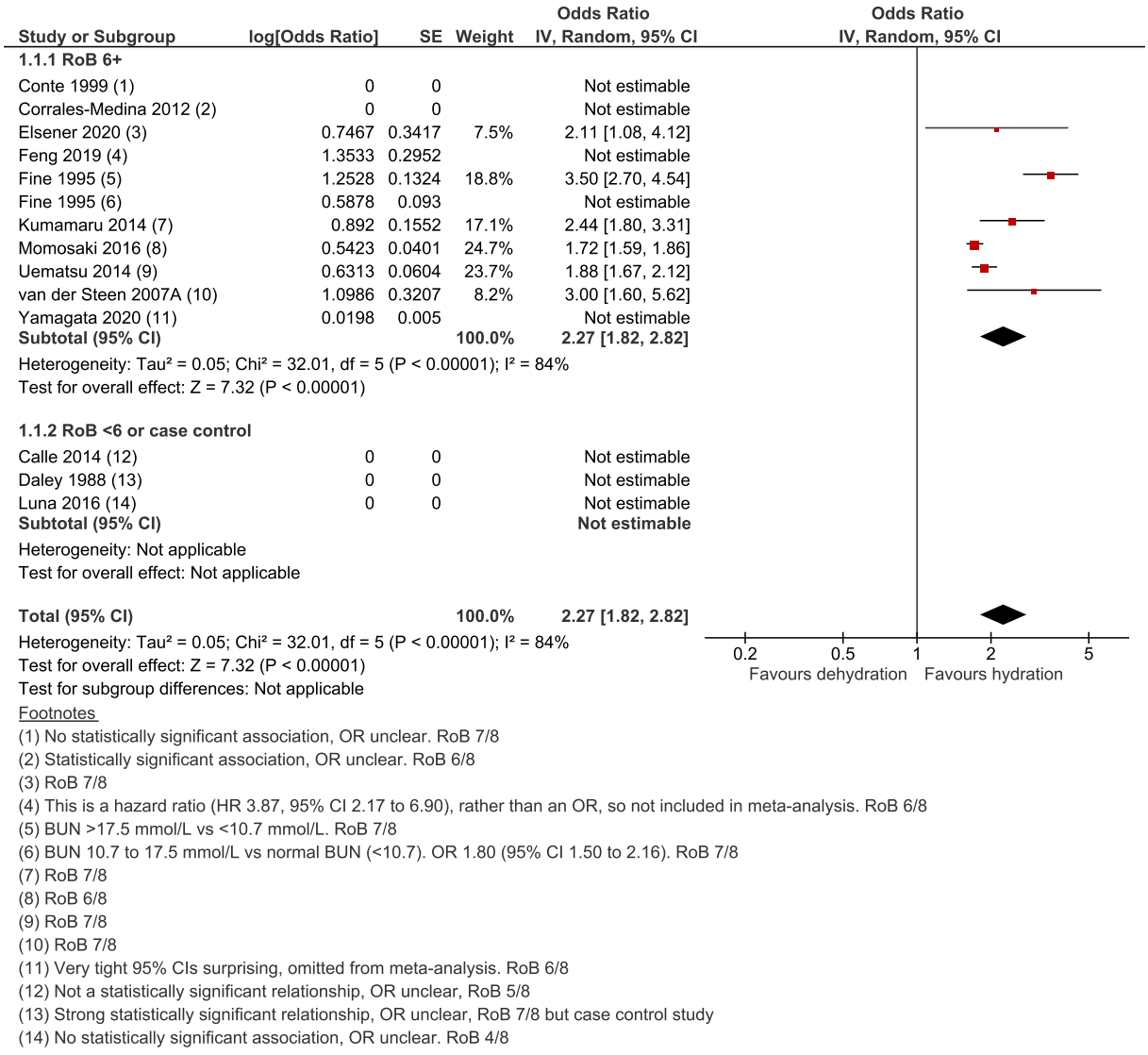
3.3. Association of dehydration with medium-term mortality

No studies suggested that dehydration was associated with better outcome. Of the thirteen studies reporting medium term mortality, ten found a statistically significant relationship suggesting dehydration increases mortality, of which two did not provide a summary statistic [47,71], one provided a hazard ratio (HR 3.9, 95% CI 2.2 to 6.9) [60], and one assessed the odds ratio for each 1 mg/dL of BUN rather than high vs low [66], so could not be included in meta-analysis. The three studies that suggested no statistically significant relationship in multivariate analysis did not provide summary statistics (Fig. 2) [48–50]. Overall, seven studies, four suggesting statistically significant positive associations between dehydration and mortality in multivariate analysis [47,60,66,71] and three non-significant relationships [48–50], could not be included in meta-analysis. The six studies that could be combined [54,57,61,64,67,69] suggested that dehydration was associated with doubled odds of medium-term mortality (OR 2.3, 95% CI 1.8 to 2.8, I^2 84%).

All of the studies providing summary statistics (including the one providing a hazard ratio) suggest that dehydration increases risk of medium-term mortality. The high heterogeneity (I^2 84%) relates to the size of the association, rather than the presence of the association. Heterogeneity is partially explained by degree of dehydration: analysis of the US MedisGroup Comparative database separated out two degrees of dehydration, higher BUN was associated with higher odds of medium-term mortality (BUN of 10.7–17.5 mmol/L vs < 10.7 mmol/L gives an adjusted OR of 1.8 of (95% CI 1.5 to 2.9) for in-hospital mortality, comparing BUN of >17.5 mmol/L vs < 10.7 mmol/L gives an adjusted OR of 3.5 (95% CI 2.7 to 4.5), see Fine 1995 [54] in Fig. 2). The main meta-analysis excludes the less extreme comparison (comparing BUN of 10.7–17.5 mmol/L vs lower BUN) of Fine 1995 [54] as the control group is shared between the two analyses.

Sensitivity analysis including the less extreme arm of Fine 1995 (comparing BUN of 10.7–17.5 mmol/L vs lower BUN) in place of the more extreme Fine 1995 comparison, suggests an OR of 1.9 (95% CI 1.7 to 2.1, I^2 40%). Sensitivity analysis, limiting to cohort studies with quality scores of ≥6, shows 9 of 10 cohorts found an association between hydration and mortality, and meta-analysis again suggested doubled odds of death with dehydration (OR 2.3, 95% CI 1.8 to 2.8, I^2 84%). Dehydration was also associated with doubled odds of medium-term mortality when we combined using fixed effects meta-analysis (OR 1.9, 95% CI 1.8 to 2.0). Similarity of effects between fixed and random-effects meta-analysis suggests that small study bias was not problematic [43].

We checked that our cut-off, excluding studies with <1000 participants and <100 events, was appropriate by tabulating all the included observational studies alongside the smaller ones (detailed in Supplemental Table D). Supplemental Table E shows that while 4/15 studies with <1000 participants showed a significant relationship between hydration and medium-term mortality, 7/9 studies with ≥1000 participants showed a significant relationship in adjusted analyses. This rose to 7/8 in studies at lower risk of bias with ≥1000 participants (Supplemental Table E.i). The set of studies with <100 participants reaching the outcome overlapped with the studies of <1000 participants. Results were similar: 7/7 studies at lower risk of bias and with ≥100 participants experiencing



Footnotes

(1) No statistically significant association, OR unclear. RoB 7/8
(2) Statistically significant association, OR unclear. RoB 6/8
(3) RoB 7/8
(4) This is a hazard ratio (HR 3.87, 95% CI 2.17 to 6.90), rather than an OR, so not included in meta-analysis. RoB 6/8
(5) BUN >17.5 mmol/L vs <10.7 mmol/L. RoB 7/8
(6) BUN 10.7 to 17.5 mmol/L vs normal BUN (<10.7). OR 1.80 (95% CI 1.50 to 2.16). RoB 7/8
(7) RoB 7/8
(8) RoB 6/8
(9) RoB 7/8
(10) RoB 7/8
(11) Very tight 95% CIs surprising, omitted from meta-analysis. RoB 6/8
(12) Not a statistically significant relationship, OR unclear, RoB 5/8
(13) Strong statistically significant relationship, OR unclear, RoB 7/8 but case control study
(14) No statistically significant association, OR unclear. RoB 4/8

Fig. 2. Forest plot of included observational studies assessing the association between dehydration and medium-term mortality, subgrouped by risk of bias. The studies with data included in meta-analysis incorporated 8619 deaths in 128,319 participants. RoB: risk of bias score. "Favours hydration" suggests that dehydration is associated with higher odds of medium-term mortality.

medium-term mortality showed a statistically significant relationship between hydration status and the outcome (Supplemental Table E.ii). This confirmed that there was a problem with underpowering in the smaller studies, and that relying solely on the better powered studies was appropriate.

The relationship between hydration status and all-cause mortality appears consistent (consistent in the association between dehydration and mortality, though not necessarily in the size of that effect) across different types of pneumonia (Supplemental Fig A), different age groups (Supplemental Fig B), across community and hospital settings (Supplemental Figure C) and across different measures of hydration (Supplemental Figure D). GRADE assessment suggested moderate-quality evidence that dehydration probably increases the odds of medium-term mortality (Table 1).

3.4. Association of hydration with other primary outcomes

The other primary outcome assessed in four cohorts was long-term mortality. As all four cohorts provided hazard ratios (HRs) we carried out meta-analysis, which suggested dehydration in early pneumonia is associated with greater risk of longer-term death (HR 1.4, 95% CI 1.1 to 1.8, I^2 90%, Fig. 3). There was a suggestion that effects were smaller in the studies at lower risk of bias, but there was no statistically significant difference between the subgroups ($p = 0.06$, Fig. 3). There were too few studies to formally assess causes of the high heterogeneity (I [2] 90%) but heterogeneity may relate to study duration, effects appear to diminish with longer follow-up. GRADE assessment provides low-quality evidence that dehydration may increase the odds of long-term mortality.

No studies reported other primary outcomes: duration of hospital, institutional or intensive care stay, hospital admission, measures of functional status, disability or quality of life.

3.5. Secondary outcomes

One cohort study reported each of the following secondary outcomes: 30-day readmission; cardiac complications; bacteraemia; returning to eating normally; and poor prognosis (a composite outcome).

Table 1
GRADE table for the relationship between hydration status and health outcomes in older adults with pneumonia.

Quality assessment							No. studies suggesting statistically significant relationship	No. of events/participants (% with events)	Relative effect (95% CI)	Certainty	Meaning
No. of studies in meta-analysis	Study design	Risk of bias	Incon-sistency	Indirectness	Imprecision	Other considerations					
Dehydration and medium-term mortality (mortality from 7 to 31 days, including in-hospital mortality)											
6	Obser-vational studies	not serious[a]	not serious[b]	not serious[c]	not serious[d]	publication bias strongly suspected strong association dose response gradient[e]	10/13 studies found a statistically significant relationship suggesting that dehydration increased risk of death, the others non-significant relationships	8619/128,319 (6.7%)	**OR 2.3** (1.8−2.8)	⊕⊕⊕ MODERATE	Moderate-quality evidence suggests that dehydration probably increases the odds of medium-term mortality
Dehydration and long-term mortality											
4	Obser-vational studies	not serious[f]	not serious[g]	not serious[h]	not serious[i]	none[j]	4/4 cohorts found a statistically significant relationship suggesting dehydration increased risk of death	905/3539 (26%)	**HR 1.4** (1.1−1.8)	⊕⊕ LOW	Low-quality evidence suggests that dehydration may increase the hazard of long-term mortality
Dehydration and length of stay, quality of life, functional status, hospital admissions											
0	Obser-vational studies								not estimable	–	We found little or no evidence on effects of dehydration on hospital admission, length of stay, quality of life, functional status or disability

CI: Confidence interval; **OR:** Odds ratio.

Explanations

[a] Risk of bias. When limiting to studies with lower risk of bias the effect size did not alter and 9/10 studies suggested a statistically significant effect.The observational data were partially supported by the single small trial. Not downgraded.

[b] Inconsistency. Although heterogeneity was high this was partly explained by different cut-offs in different analyses (suggesting a dose effect). Omitting the analysis with the highest cut-off reduced heterogeneity to below 50%. Not downgraded.

[c] Indirectness. The studies include populations from Asia, Europe and North America, middle-aged to very elderly participants, any type of pneumonia, CAP and AP, people with pneumonia in hospital and in the community. Not downgraded.

[d] Imprecision. The OR was 2.3 (95% CI 1.8 to 2.8) so all potential values within the 95% CI suggested a strong relationship between dehydration and medium-term mortality. Not downgraded.

[e] Other considerations: Publication bias: detected. Unlikely as few of our studies were particularly interested in hydration, but simply used it as a potential confounder, however the degree of association appears not to be reported when a non-statistically significant relationship is found. Not downgraded. Large effect: yes. When limited to studies at lower risk of bias the OR was 2.3 (95% CI 1.8 to 2.8) suggesting a large effect. Upgraded once for large effect and dose response together. Plausible confounding: no. Plausible confounding could move the effect size in either direction. Not upgraded. Dose response: yes. While most studies did not assess a dose response, Fine 1995 assessed two bands of BUN concentration, finding that for patients with BUN of 10.7−17.5 mmol/L that the OR if in-hospital mortality was 1.8 (95% CI 1.5 to 2.9) compared to those with BUN of <10.7 mmol/L. For those with BUN >17.5 mmol/L (compared to BUN <10.7 mmol/L) the OR of in-hospital mortality was 3.5 (95% CI 2.7 to 4.5).

[f] Risk of bias. The effect is present (and smaller, but not statistically significantly smaller) in the two studies with RoB score of 6, as well as in the two with RoB of 5/8. Not downgraded.

[g] Inconsistency. I [2] 90%. The heterogeneity is potentially partially explained by risk of bias and duration of follow up (the effect appears to be smaller over a longer follow up). Not downgraded.

[h] Indirectness. The studies include populations from Europe (the Netherlands, Spain and Turkey), elderly and very elderly participants, any type of pneumonia and CAP, people with pneumonia in hospital and in the community. Not downgraded.

[i] Imprecision. The HR was 1.4 (95% CI 1.1 to 1.8) so all potential values within the 95% CI suggested a positive relationship between dehydration and medium-term mortality. Not downgraded.

[j] Other considerations: Publication bias: undetected. Unlikely as few of our studies were particularly interested in hydration, but simply used it as a potential confounder. Not downgraded. Large effect: no. The HR was 1.4 (95% CI 1.1 to 1.8). Not upgraded. Plausible confounding: no. Plausible confounding could move the effect size in either direction. Not upgraded. Dose response: no. Not upgraded.

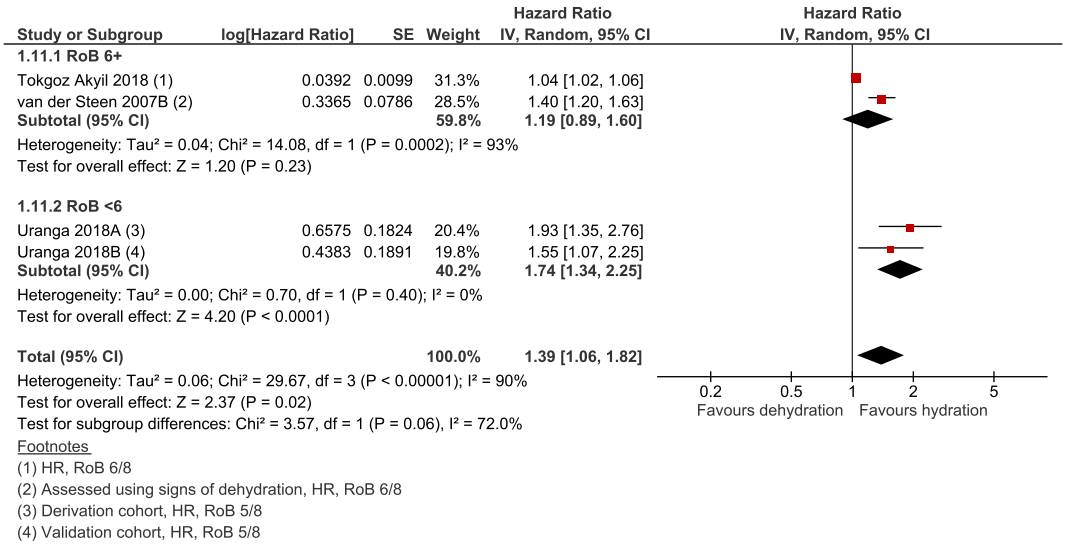


Fig. 3. Forest plot of observational studies assessing the association between dehydration and long-term mortality, subgrouped by risk of bias. RoB: risk of bias score. "Favours hydration" suggests that dehydration is associated with higher odds of long-term mortality.

In 2287 North Americans with CAP, of whom some were hospitalised and others treated in the community, BUN ≥30 mg/dL (≥10.7 mmol/L urea) was associated with higher risk of cardiac complications (OR 1.5, 95% CI 1.1 to 2.2) [51–53].

In 66,611 Japanese patients hospitalised with AP those who had raised BUN (≥21 mg/dL BUN or 7.5 mmol/L urea) were significantly less likely to achieve normal oral intake by 30 days after admission (HR 0.83, 95% CI 0.82 to 0.85) [61–63]. The same researchers ran a similar analysis with an overlapping and slightly larger dataset also finding a statistically significant relationship between BUN and total oral intake (OR 0.77, 95% CI 0.74 to 0.80) [62].

In 1191 US adults hospitalised with pneumonia it was unclear whether those who had raised BUN on admission were at higher risk of 30-day readmission for any cause, as the model entered final BUN assessment rather than the correlated initial BUN measure into the multivariate model (maximum BUN within the final 24 h of their hospital stay was significantly associated with increased risk of readmission) [68].

In 13,043 US Medicare recipients with CAP in the derivation cohort, and 2771 in the validation cohort, raised BUN (BUN ≥30 mg/dL or ≥10.7 mmol/L urea) was associated with increased odds of bacteraemia (OR 2.0, 95% CI 1.8 to 2.3 and OR 2.2, 95% CI 1.9 to 2.5 respectively) [55].

In 346 older people (mean age 78 years) hospitalised with NHCAP in China, the odds of poor prognosis (death in hospital or automatic discharge due to adverse prognosis) were greater in those with higher BUN (OR 1.06, 95% CI 1.02 to 1.09) in univariate analysis, but not significant in multivariate analysis [59].

3.6. Relevance to COVID-19 pneumonia

The evidence suggests dehydration is associated with poor outcome across a diverse range of pneumonia types, so it is likely that dehydration is associated with poor outcome in COVID-19 pneumonia. But it would be useful to understand the direct evidence for COVID-19 pneumonia. We note here what evidence exists on hydration and COVID-19 pneumonia, while suggesting caution in interpretation as these studies are likely to be underpowered. We excluded two cohorts using multivariate analysis in people with COVID-19 pneumonia as they included too few participants experiencing too few outcomes, so are likely to be underpowered. One, including 194 adults (mean 64 years, 59% male), assessed predictors of poor outcome in COVID-19 pneumonia. BUN was higher in those who died (mean 10.5 mmol/L) than those who survived (8.2 mmol/L) but was not statistically significant in multivariate analysis (OR 1.05, 95% CI 0.98 to 1.12, 46 deaths) [72]. The other (114 participants, mean 64 years, 62% male) assessed the relationship between BUN (≥8.2 mmol/L) and a composite of death or mechanical ventilation by 28 days. Raised BUN was associated with higher risk of poor outcome (HR 5.6, 95% CI 2.2 to 14.5) [73].

Another six COVID-19 studies were not included as they recruited small cohorts with COVID-19 but not necessarily pneumonia (although ~70% hospitalised with COVID-19 have pneumonia) [6,7] and did not conduct multivariate analyses. These univariate analyses suggest that dehydration maybe important in COVID-19 outcome. Data from Wuhan, China showed that BUN was higher in 28 severe covid patients (4.7 mmol/L) than 161 non-severe cases (3.9 mmol/L, $p = 0.08$) [74]. Of 20 COVID-19 patients in a Hubei Province ICU mean BUN was higher in the 10 who died (8.7 mmol/L) than those who survived (5.8 mmol/L, $p = 0.09$) [75]. Twenty one patients with severe COVID-19 from Wuhan had mean serum urea of 7.8 mmol/L compared with 3.8 mmol/L in 32 with mild disease ($p < 0.001$) [76].

In 162 COVID-19 patients from Israel urea was highest in severe COVID-19 and lowest in mild COVID-19 (3 categories, 38.0, 31.5 and 26.0 mg/dL, $p = 0.005$) [77]. This was also seen in 260 Egyptian COVID-19 patients (mean urea 39.2 mg/dL in 60 severe/critical patients, 28.5 mg/dL in moderate patients and 25.5 mg/dL in mild patients, $p = 0.0014$ for mild vs severe, $p = 0.0045$ for moderate vs severe) [78]. In 184 New Yorkers hospitalised with COVID-19 mean BUN was higher in 30 who were intubated (68.4 mg/dL) than 154 not intubated (40.8 mg/dL, $p = 0.001$), and higher in 19 not intubated who died (62.3 mg/dL) than 135 not intubated and lived (37.8 mg/dL, $p = 0.04$) [79].

Finally, pneumonia risk scores including hydration assessment appear more useful in predicting COVID-19 outcome. Area under the curve (AUC) assessing the accuracy of pneumonia risk scores in predicting in-hospital death in 654 COVID-19 cases [80] were 0.87, 0.85 and 0.85 for scores including dehydration (A-DROP, CURB-65, PSI respectively), compared to 0.84, 0.81, 0.80 and 0.73 for scores ignoring dehydration (SMART-COP, NEWS2, CRB-65, qSOFA). CURB-65 (AUC 0.85) and CRB-65 (AUC 0.80) are identical risk scores

except CRB-65 omits dehydration. Omitting dehydration reduces prediction accuracy. See Supplemental Table A for further details of risk scores.

4. Discussion

The single small trial found that educating pneumonia patients to drink ≥1.5 L fluid/d alongside lifestyle advice increased fluid intake and reduced later healthcare visits and hospitalisations. Observational data suggest that dehydration probably doubles the odds of medium-term mortality (GRADE medium-quality evidence) and increases long-term mortality (GRADE low-quality evidence) in people with pneumonia. The presence of this relationship was consistent across different types of pneumonia, settings and age groups. Heterogeneity in the size of the relationships appears to relate to the degree of dehydration in medium-term mortality (a type of dose effect), and to duration for long-term mortality (with smaller associations over longer periods). There was a suggestion in secondary outcomes that dehydration was associated with higher risk of cardiac complications and increased odds of bacteraemia.

This is the first systematic assessment of hydration on pneumonia outcomes to include trials and observational studies. There are no perfect measures for assessment of low-intake dehydration [39], although the closest is probably serum osmolality. Other specific measures of low-intake dehydration (which relates to limited fluid intake) are calculated serum osmolarity, fluid intake and fluid output. Other measures used in assessment of hydration status in clinical practice, but which are less specific to low-intake dehydration include blood urea nitrogen (BUN), serum urea, BUN/creatinine ratio, and clinical signs and symptoms individually or as a panel [18,39,81]. BUN and serum urea are commonly measured, but may indicate renal problems or heart failure as well as low-intake dehydration [81], and for this reason we have not included data from the cohort study of people with both pneumonia and chronic kidney disease within the meta-analyses in this review [70]. We decided to accept research using any of these dehydration markers on the basis that although not perfect they all tend to indicate low-intake dehydration. That we found consistent existence (if not size) of relationships across these markers strengthens the evidence of a relationship between dehydration and poor outcome, although the majority of evidence comes from assessment of BUN or urea, a poor marker in its own right. The existence of a relationship between dehydration and medium-term mortality (although the effect size was heterogeneous all studies suggested a large effect) was regardless of whether dehydration was assessed using BUN [54,57,63,69], BUN/albumin ratio [60] or fluid drunk [65] (Fig. 2). The existence of this relationship was also regardless of pneumonia type, age and setting.

By including only studies that adjusted for sex, age and comorbidities we aimed to reduce the risk of confounding. By including only larger cohorts we minimise the risk of missing a relationship due to lack of power. To understand the relationship between dehydration and outcomes, despite lack of trials and observational studies aiming to assess this relationship, we included studies using hydration markers as potential confounders. This reduces the risk of publication bias, but led to a lack of numerical data on this association in studies where dehydration did not appear as a significant factor in multivariate analysis. As we included studies assessing measures of hydration as confounders we may have missed some reports assessing hydration within univariate analyses but not reporting it.

Previous research on hydration in pneumonia is limited and inconclusive. Almirall [82] systematically reviewed observational studies finding malnutrition was associated with increased risk of developing pneumonia, but did not report on dehydration or fluid intake, or assess associations in people with existing pneumonia [82]. Guppy [24] found no trials of fluid intake in adults or children with pneumonia when attempting a systematic review in 2004 [24].

The importance of dehydration in pneumonia is recognised by its regular inclusion in pneumonia risk scores (these are defined and referenced in Supplemental Table A), and in studies comparing the utility of different severity risk scores. When assessing risk of severe pneumonia in 767 older adults with nursing home-acquired pneumonia, the scores including dehydration assessment (PSI, CURB-65, revised-ATS and España, with Areas Under the Curve (AUCs) of 0.69, 0.70, 0.71 and 0.65 respectively) were more accurate than the score not including dehydration (M-ATS, AUC 0.63) [83]. This relationship was duplicated in prediction of in-hospital death in COVID-19 patients [80]. CRB-65 is the same score as CURB-65 but without dehydration assessment. Directly comparing CURB-65 (AUC 0.85) and CRB-65 (AUC 0.80) showed the reduction in predictive value when dehydration is ignored.

We found consistent moderate-quality evidence that improving hydration reduces the risk of medium-term mortality in all types of pneumonia. Evidence is weaker for COVID-19 pneumonia, but suggests that dehydration is associated with increased mortality in COVID19 too. It is remarkable that while many studies included dehydration as a potential confounder of outcome in people with pneumonia, and all major pneumonia risk scores include measures of hydration, optimal fluid volume and the effect of supporting hydration have not been assessed in randomised controlled trials of people with pneumonia, including COVID-19. Such trials, are needed as potential benefits may be large, rapid and implemented at low cost. Supporting hydration and reversing dehydration has the potential to have an immediate positive impact on pneumonia outcomes, and perhaps also COVID-19 outcomes, in older adults.

Statement of authorship

LH developed the idea for the review, wrote the first draft of the protocol, organised the research and wrote the first draft of the paper. All authors contributed to the protocol and the full paper, assessment of inclusion, data extraction and risk of bias. All authors were involved in revising the manuscript for key intellectual content and agreed the final text of the submitted paper. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

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All authors have completed the Unified Competing Interest form (available on request from the corresponding author) and declare: Covidence allowed us to use their software free of charge; CP declares personal fees from Sanofi-Genzyme and GSK, and a programme grant from NIHR outside the submitted work. Otherwise we declare no financial relationships with any organisations that

might have an interest in the submitted work in the previous three years, no other relationships or activities that could appear to have influenced the submitted work.

Contributor and guarantor information

The lead author, Lee Hooper, affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned and registered have been explained. LH is the guarantor for this research.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clnesp.2021.11.021.

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