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REVIEW ARTICLE

Non-Pharmacologic Multicomponent Interventions Preventing Delirium in Hospitalized People

Paul Ludolph MD, Jutta Stoffers-Winterling MSc,*† Angela M. Kunzler MSc,† Romina Rösch MD,‡ Katharina Geschke MD,* Christian Friedrich Vahl MD,‡ and Klaus Lieb MD*†*

BACKGROUND/OBJECTIVES: Delirium is a common neurobehavioral complication in hospitalized patients with a high prevalence in various clinical settings. Prevention of delirium is critical due to its common occurrence and associated poor outcomes. Our objective was to evaluate the efficacy of multicomponent interventions in preventing incident delirium in hospitalized patients at risk.

DESIGN: Systematic review and meta-analysis.

SETTING: Hospital.

PARTICIPANTS: We included a study if it was a randomized controlled trial and was evaluating effects of coordinated non-pharmacologic multicomponent interventions in the prevention of delirium.

MEASUREMENTS: We performed a systematic literature search in PubMed and CENTRAL (PROSPERO: CRD42019138981; last update May 24, 2019). We assessed the quality of included studies by using the criteria established by the Cochrane Collaboration. We extracted the measured outcomes for delirium incidence, duration of delirium, length of hospital stay, falls during hospital stay, discharge to institutional care, and inpatient mortality.

RESULTS: In total, we screened 1,027 eligible records and included eight studies with 2,105 patients in the review. We found evidence of an effect (ie, reduction) of multicomponent interventions on the incidence of delirium (risk ratio = .53; 95% confidence interval = .41-.69; I^2 = 0). We detected no clear evidence of an effect for delirium duration, length of hospital stay, accidental falls, and mortality. Subgroup analyses did not result in findings of substantial effect modifiers, which can be explained by the high homogeneity within studies.

CONCLUSION: Our findings confirm the current guidelines that multicomponent interventions are effective in preventing delirium. Data are still lacking to reach evidence-based conclusions concerning potential benefits for hard outcomes such as length of hospital stay, return to independent living, and mortality. **J Am Geriatr Soc 68:1864-1871, 2020.**

Keywords: delirium; prevention; multicomponent interventions; non-pharmacologic interventions

RATIONALE FOR THE STUDY

Delirium is a common neurobehavioral complication in hospitalized patients. The occurrence of delirium varies across different hospital settings. Following major surgery, delirium is particularly common with incidence rates up to 51% and a prevalence of 17%. In intensive care units (ICUs), up to 82% of older patients develop delirium.[1] Patients with delirium experience prolonged hospitalizations, functional and cognitive decline, higher mortality, and a higher risk for institutionalization.[2-5]

Strategies differ about how to prevent delirium. In the most recent guideline of the Scottish Intercollegiate Guidelines Network, no recommendation for the use of a specific medication, except a critical medication review, was given.[6] However, suggestions for the use of multicomponent interventions were made. Components of multicomponent interventions vary but usually consist of physiotherapy, reorientation training, early mobilization, identification and treatment of underlying causes or postoperative complications, pain control, regulation of bowel and bladder function, hydration and nutrition, and oxygen delivery.[7]

From the *Department of Psychiatry and Psychotherapy, University Medical Center Mainz, Mainz, Germany; †Leibniz Institute for Resilience Research (LIR), Mainz, Germany; and the ‡Department of Cardiothoracic and Vascular Surgery, University Medical Center Mainz, Mainz, Germany.

Address correspondence to Paul Ludolph, MD, Department of Psychiatry and Psychotherapy, University Medical Center Mainz, Untere Zahlbacher Straße 8, 55131 Mainz, Germany. E-mail: paul.ludolph@unimedizin-mainz.de

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An example of a well-structured non-pharmacologic multicomponent intervention is the Hospital Elder Life Program (HELP) whose goal is to maintain cognitive and physical functioning of older adults at high risk throughout hospitalization and to maximize independence at discharge.[8] In a 2018 meta-analysis, the effectiveness of HELP in reducing the incidence of delirium and the rate of falls was shown, with a trend toward a decreasing length of stay and the prevention of institutionalization, while operating cost efficiently.[9]

OBJECTIVES

The two most recent systematic reviews on randomized controlled trials (RCTs) regarding delirium prevention that included non-ICU populations were published in 2015[10] and 2016.[11] A Cochrane review for ICU patients only identified one study using a multicomponent intervention.[12] However, both reviews in non-ICU patients included studies investigating patients with and without delirium at baseline, resulting in highly heterogeneous data and imprecise findings. In the meantime, a considerable number of new RCTs evaluating multicomponent interventions have been published. Furthermore, a comparison between the effect of interventions based on HELP and interventions using other protocols is not available. Also, the effects of specific elements of multicomponent interventions, such as early mobilization or sleep enhancement, are unclear.

In this review, we integrate the latest evidence on the effectiveness of multicomponent interventions preventing delirium to compare the effectiveness of HELP with other multicomponent interventions and to investigate the impact of distinct single components of multicomponent strategies.

METHODS

Systematic Review

We published the protocol on PROSPERO (CRD42019138981) and conducted the systematic review in accordance with the Preferred Reporting Items for Systematic Review and Meta-analyses guidelines[13] (Supplementary Table S1). RCTs and cluster RCTs that assessed the effects of coordinated non-pharmacologic multicomponent interventions preventing delirium compared with usual care were eligible. If usual care also consisted of a multicomponent intervention, we included the study if the intervention arm introduced at least two additional new elements. Participants had to be aged 18 years and older, admitted to acute hospitals, and at least one validated risk factor for developing delirium.[1] We excluded other settings, such as participants with prevalent delirium or alcohol withdrawal delirium, as well as studies assessing pharmacologic interventions (beyond regular medication reviews). The full eligibility criteria are detailed in Supplementary Table S2.

We searched the Cochrane Library (CENTRAL) and PubMed for all years (last update May 24, 2019) and traced reference lists of reviews in the field for additional relevant publications. Search strategies are detailed in Supplementary Table S3. We only considered English-language publications.

Data Collection

Two review authors (P.L. and J.S.W.) independently examined all titles/abstracts for eligibility and subsequently assessed the full texts of potentially eligible studies. We used a pre-piloted standardized form for data extraction and risk of bias assessment, which these two review authors did independently for each study. We resolved any disagreements by discussion or by calling in a third reviewer (K.L.) if necessary. We inquired about missing information from study authors.

The primary outcome was the incidence of delirium during the hospital stay or the longest available observation period. Delirium had to be assured by using a validated delirium screening tool (eg, Confusion Assessment Method[14]) or application of *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (DSM-IV) criteria by a trained professional (eg, a psychiatrist). Secondary outcomes were the duration of delirium (days), length of hospital stay (days), falls during hospital stay, discharge to institutional care, and inpatient mortality.

We assessed risk of bias according to the *Cochrane Handbook for Systematic Reviews of Interventions*[15] and used prespecified criteria to assess selection bias, detection bias, attrition bias, and reporting bias. We did not rate the risk of performance bias (ie, blinding of participants and study personnel) due to the nature of the intervention. We evaluated publication bias using a funnel plot for the primary outcome.

Statistical Analysis

We undertook all analyses in Review Manager (RevMan, v.5.3) and summarized intervention effects for all studies by calculating risk ratios (RRs) for dichotomous outcomes and mean differences (MDs) for continuous outcomes. We pooled dichotomous outcomes with 95% confidence intervals (CIs) using random effects methods and continuous outcomes with 95% CIs using random effects inverse variance methods. We assessed heterogeneity using Cochrane's Q and I^2 statistics. We categorized the I^2 heterogeneity as follows: below 25% = low, 25% to 50% = moderate, and above 50% = high. We intended to investigate high heterogeneity by doing subgroup analyses, data permitting.

We performed subgroup analyses for the primary outcome of the different clinical scenarios (ie, medical, surgical, or intensive care ward). In another analysis, we compared HELP-based interventions with non–HELP-based interventions. We analyzed different components of the interventions by comparing trials using a specific part of multicomponent interventions with trials not including them. We compared effects from studies including dementia patients with studies excluding dementia. We intended to conduct further subgroup analyses focusing on specific patient characteristics, such as a prior history of delirium, older age, and delirium subtypes. However, we were unable to perform these analyses due to missing information in several studies (history of delirium and delirium subtypes) and high homogeneity across studies (eg, all studies in older adults), respectively.

RESULTS

Study Selection

The search yielded 1,029 articles. We screened 69 publications in full text, leaving eight eligible studies comprising 2,105 participants (Figure 1).

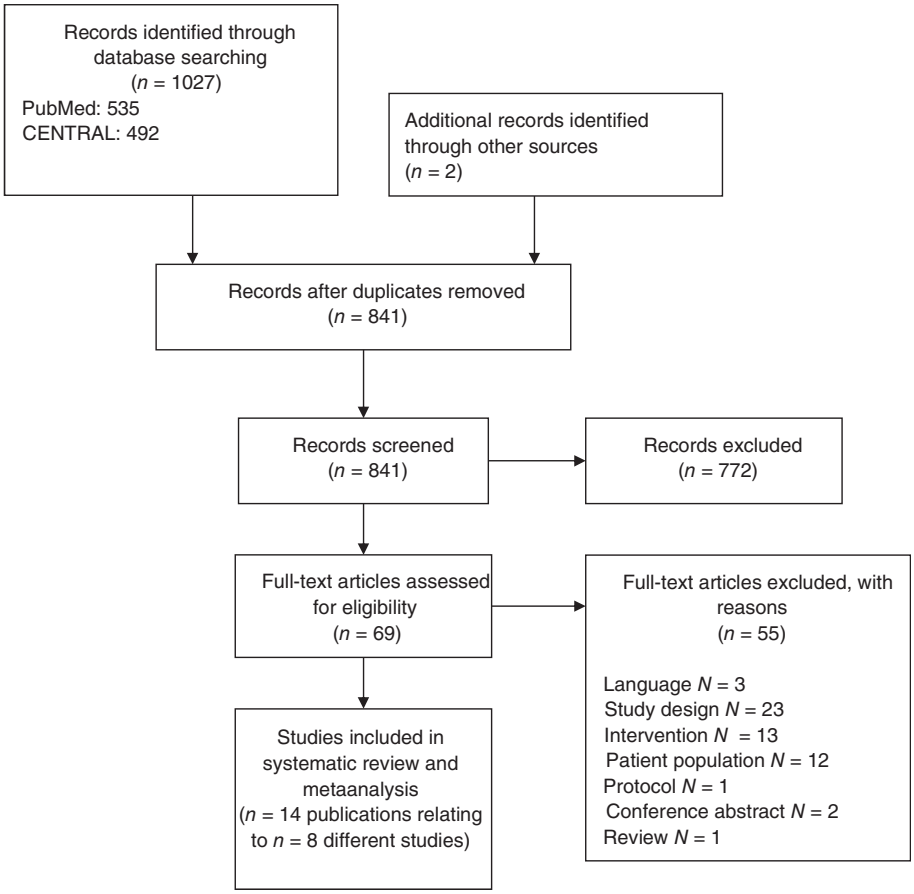

Figure 1 Preferred Reporting Items for Systematic Review and Meta-analyses flow diagram of study selection.

Study Characteristics

The main study characteristics are listed in Table 1 and Supplementary Table S4. Three trials were conducted on surgical wards,[16-18] two trials in acute medical wards,[19,20] two trials in ICUs,[21,22] and one trial in the intensive care and stroke unit.[23] Three trials excluded patients with dementia.[17,21,22] A further overview of sample characteristics is available in Supplementary Table S5.

The newly introduced intervention components were heterogeneous, but specific components were shared (Table 2). Six of the eight trials included therapeutic activities for cognitive stimulation. Other interventions included daily orientation

Table 1 Summary of Key Characteristics of Included Studies

Study	Population	Sample size, I/C	Age, y, mean ± SD	Control group[a]	Delirium diagnostic instrument
Álvarez et al[21]	ICU	70/70	I: Md = 68 (IQR = 63-75.5); C: Md = 71 (IQR = 63-78.5)	Usual care	CAM
Chen et al[16]	Abdominal surgery	196/179	I: 74.3 ± 5.8; C: 74.8 ± 6.0	Usual care	CAM
Guo et al[17]	Tumor surgery	67/80	I: 73.3 ± 6.1; C: 73.7 ± 5.2	Usual care	CAM-ICU
Hempenius et al[18]	Tumor surgery	127/133	I: 77.5 ± 6.7; C: 77.6 ± 7.7	Usual care	DOSS, if >3 assessments using DSM-IV
Jeffs et al[19]	Acute medical ward	305/343	I: 79.6 ± 7.5; C: 79.1 ± 7.9	Usual care	CAM
Martinez et al[20]	Internal medicine ward	144/143	I: 78.1 ± 6.3; C: 78.3 ± 6.1	Usual care	CAM
Moon and Lee[22]	ICU	60/63	I: 70.4 ± 13.8; C: 69.0 ± 12.4	Usual care	CAM-ICU
Rice et al[23]	Neurologic ICU and stroke unit	59/66	I: 65.6 ± 10.6; C: 66.5 ± 9.4	Usual care	CAM

[a]Further details are provided in the supplement.

Abbreviations: C, control; CAM, Confusion Assessment Method; CAM-ICU, Confusion Assessment Method for the ICU; DOSS, Delirium Observation Screening Scale; DSM-IV, *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition;* I, intervention; ICU, intensive care unit; IQR, interquartile range; Md, median; SD, standard deviation.

Table 2 Summary of Primary and Secondary Outcomes

	N	Effect size	95% CI	*P*	No. of studies with reference cites
Delirium incidence	2,105	RR = .53	.41 to .69	<.0001	8[16-23]
Delirium duration, d	124	MD = −.65	−1.45 to .16	.11	5[18-21,23]
Length of hospital stay, d	1,819	MD = −.71	−1.47 to .05	.07	6[16,18-20,21,23]
Return to independent living	871	RR = .92	.82 to 1.04	.17	2[18,19]
Falls	547	RR = .61	.03 to 11.62	.74	2[18,20]
Mortality	891	RR = .83	.26 to 2.66	.75	4[16,18,21,22]

Abbreviations: CI, confidence interval; MD, mean difference; RR, risk ratio.

training (5/8), early mobilization (4/8), vision protocol (3/8), hearing protocol (3/8), fluid repletion/constipation (3/8), feeding assistance (3/8), sleep enhancement (2/8), and family involvement (2/8). One study used a checklist and not a protocol.[18] Three of eight studies were based on the HELP intervention or mentioned it as their theoretical basis.

Healthcare professionals delivered the interventions in most studies. One intervention was performed by family members[20] and one by trained nonmedical volunteers.[23]

The Confusion Assessment Method (CAM[14]) was used for the diagnosis of delirium by five of eight studies, two of eight studies measured delirium incidence with the CAM-ICU,[17,22,24]and in one of eight, a trained specialist applied the DSM-IV criteria.[18] Delirium assessment was conducted three times daily in one study,[18] twice daily in four studies,[17,21-23] daily in two studies,[16,20] and every 2 days in one study.[19]

Risk of Bias

Risk of bias ratings for each study are summarized in Supplementary Table S6. We assessed two studies to be at low risk of bias in all domains.[16,21] One study showed an unclear risk of selection bias because it did not describe the random sequence generation.[19] All included studies described allocation concealment well. We assessed two studies to be at high risk of detection bias because they did not blind the outcome assessors.[20,22] Two studies were at high risk of attrition bias because they excluded patients due to a not prespecified reason or they showed some inconsistencies in the reported data.[17,23] One study had an unclear risk of attrition bias because it did not provide the reasons for missing data.[18] We assessed three studies to be at unclear risk of reporting bias because a study protocol or preregistration was not available.[17,22,23] A funnel plot for the primary outcome was inconclusive because of the small number of included studies but did not clearly suggest systematic bias in reporting (Supplementary Table S7).

Synthesis of Results

For the primary outcome *delirium incidence*, the pooled data indicated strong evidence of a difference between multicomponent intervention and control (ie, reduction) (RR = .53; 95% confidence interval [CI] = .41-.69; $P < .001$; eight studies; 2,105 participants; Figure 2), with no heterogeneity across studies ($I^2 = 0\%$).

For the secondary outcomes, we found little or no evidence of an effect of interventions, respectively (Figure 3).

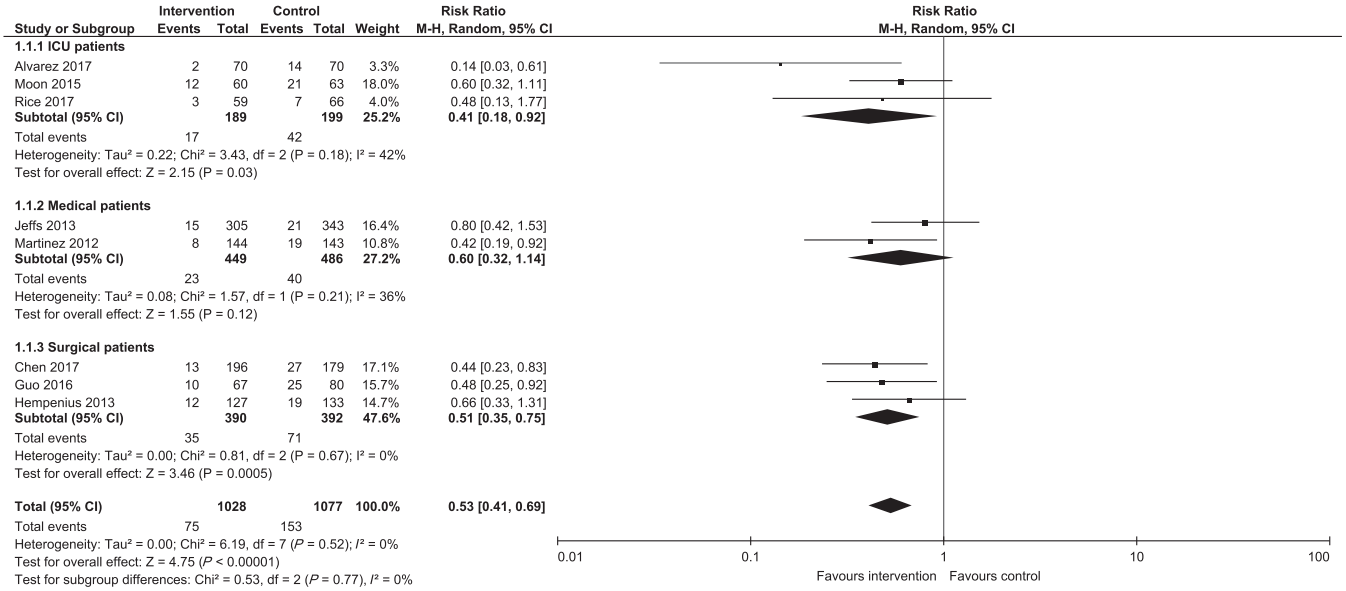

Figure 2 Forest plot for the primary outcome of delirium incidence.

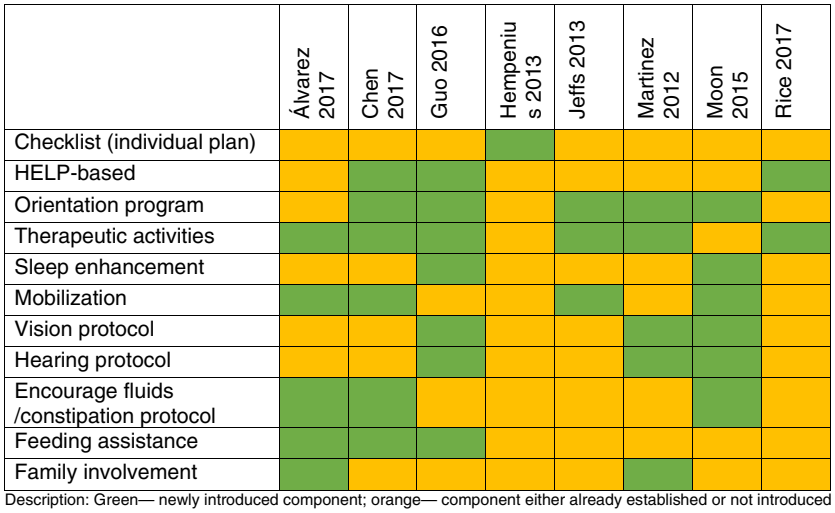

Figure 3 Newly introduced intervention components. Green cells show newly introduced component; orange cells show component either already established or not introduced. HELP, Hospital Elder Life Program.

The forest plots for the secondary outcomes are available in Supplementary Table S8.

Five trials measured *delirium duration*.[17,19-21,23] By pooling data of 124 cases of delirium with a mean duration of 2.89 days, we found a trend toward reduced duration of delirium in the intervention group that was not statistically significant (MD = −.65 days; 95% CI = −1.45 to .16; P = .11) with high heterogeneity observed (I^2 = 58%).

Six trials reported hospital *length of stay*.[16,18-21,23] Meta-analysis of 1,819 stays with a mean length of 10.16 days indicated a trend toward reduced length of stay that was not statistically significant through multicomponent interventions compared with usual care (MD = −.71 days; 95% CI = −1.47 to .05; P = .07) with low heterogeneity (I^2 = 4%).

Two studies reported data regarding *return to independent living*.[18,19] There was no evidence of an effect of multicomponent intervention on this outcome (RR = .92; 95% CI = .82-1.04; P = .17) with moderate heterogeneity between studies (I^2 = 43%).

We pooled data on the incidence of *falls* during the hospital stay from two trials with 547 patients.[18,20] There was no evidence of an effect of multicomponent interventions (RR = .61; 95% CI = .03-11.62; P = .74). High heterogeneity (I^2 = 68%) detected.

Four studies with 891 patients reported results of *mortality* during hospitalization.[16,18,21,22] Pooled analysis provided no evidence of an effect of interventions with high heterogeneity (RR = .83; 95% CI = .26-2.66; P = .75; I^2 = 59%).

Additional Analyses

We performed the subgroup analyses for the primary outcome as described in the Methods section. However, the I^2 score indicated maximum homogeneity throughout all included studies (I^2 = 0; n = 8 studies). As a result, none of the subgroup analyses yielded evidence of any difference concerning the characteristics considered in this review (eg, HELP-based, orientation included) (Supplementary Table S9).

Sensitivity analyses for the primary outcome showed a trend of larger effect sizes in more recent studies. A sensitivity analysis regarding the risk of bias showed no difference in pooled results compared with the primary analysis but one on the level of individual studies. We only considered Jeffs et al[19] as having an unclear risk of selection bias, although it was the study with the lowest risk reduction (.80; 95% CI = .42-1.53).

For three studies,[17,19,20] we found inconsistent or implausible data for some outcomes in primary publications or reviews including these studies[10,11] (Supplementary Table S10). To test our decision for what we deemed the most probable or convincing version of data, we conducted sensitivity analyses including any other potential data versions. We found no substantially different findings when comparing the results on the primary outcomes for the different data.

For the continuous outcomes of delirium duration and length of stay, one[19] and two studies,[18,19] respectively, fulfilled the criteria for skewness.[15] We performed sensitivity analyses for both outcomes by excluding asymmetrical data. Both analyses did not provide different results compared with the primary analysis.

DISCUSSION

Summary of Evidence

This systematic review and meta-analysis of eight RCTs strengthens the hypothesis that multicomponent interventions may effectively prevent delirium in at-risk populations. The strength of this meta-analysis of RCTs on multicomponent interventions for delirium prevention in at-risk populations is the first including only studies where prevalent delirium was excluded at baseline. It also is the first systematic review and meta-analysis of RCTs on this topic that included non-ICU populations since 2016.[11]

The risk of developing delirium during hospitalization for patients receiving multicomponent interventions was 53% of the risk of patients receiving usual care, resulting in a number needed to treat (NNT) of 12.5. This result is highly significant and consistent with other meta-analyses on this outcome, even though prior reviews did not analyze four of eight of our included studies.[10,11,25] Four of eight studies provided evidence

of an effect of interventions.[16,17,20,21] The two large studies failing to show evidence of an effect of multicomponent interventions were possibly influenced by a very low-frequent outcome assessment of every 48 hours and had an unclear risk of selection bias[19] or rather used a checklist and not a protocol to deliver the intervention.[18]

Based on five studies measuring the duration of delirium whenever it occurred, we found no clear evidence of an effect of multicomponent intervention, although the delirium was on average .65 days shorter in the intervention arm compared with the control. This might be clinically relevant, regardless of the nonsignificance of the effect, considering the mean length of delirium of 2.89 days in this analysis. Other systematic reviews pooling data for the duration of delirium showed similar findings of a nonsignificant positive effect,[10,11] which does not rule out an undetected true effect due to insufficient power.

Pooled meta-analysis in this review showed a clear and consistent trend toward shorter hospital stays in patients receiving multicomponent interventions. Although not exceeding the boundaries of statistical significance, this positive effect is closer to significance than in other reviews on this topic. Potential reasons might be the limited power of analyses in previous reviews or imprecision due to the heterogeneity of included studies in previous reviews.[10,11,25] Although length of stay may be influenced by many factors like further complications or hospital standards, an association between delirium incidence and length of hospital stay most likely exists.[4,26,27] The possible reduction of length of stay by multicomponent interventions might be counterintuitive because extra efforts to plan and conduct interventions need to be made in the first place. However, our findings indicate a trend of such treated patients being discharged earlier because they seem to develop fewer complications that can be prevented (eg, delirium, falls). A possible conclusion might be that preventive interventions pay off in the medium and long term.

Two of eight studies reported "return to independent living" and "falls." For the outcome "return to independent living," we found no evidence of an effect of the intervention. These results are consistent with recent reviews that also did not show a clear effect of the interventions on the prevention of institutionalization.[10,11,25] Regarding "falls," we detected no evidence of an effect of the intervention. Our analysis included fewer patients than previous reviews, which found evidence for the reduction of falls.[10,25] The amount of high-quality data is not yet enough for these two outcomes, implicating the necessity of high-quality RCTs to measure them.

Four of eight studies measured mortality during hospitalization. Pooled analysis showed no clear evidence of an effect of the intervention on the reduction of deaths caused by inconsistencies in results between studies. Other reviews reported similar results and also failed to show evidence of an effect of multicomponent interventions for delirium prevention on mortality.[10,11] A meta-analysis by Witlox et al in 2010 provided evidence that delirium in older patients is associated with poor outcomes including mortality independent of important confounders.[3] Therefore, it has to be considered that the results in our analysis might be caused by insufficient statistical power, as stated earlier.[10]

The conducted subgroup analyses did not result in relevant findings, which can be explained by the high homogeneity within studies. Therefore, subgroup analyses regarding HELP-based compared with non–HELP-based interventions also did not find clear differences in the effects between the two groups with slightly better results in the three studies that were HELP based. The results are consistent with prior reviews of multicomponent interventions not being HELP based[10,11] and a review only including HELP-based interventions.[9] Notable is that prior reviews only included four of eight studies of this review.

Even if there is not sufficient evidence for HELP being more effective than other multicomponent interventions, HELP is a structured way to introduce multicomponent interventions with proven benefits and has already been implemented by hundreds of hospitals worldwide.[9] However, there is no evidence that other intervention programs focusing on similar improvements in patient care are inferior. Less comprehensive programs should be considered, especially if resources for implementing a more complex multicomponent intervention are not available. An example is the existing evidence that even very simple interventions like the use of earplugs at night can reduce delirium incidence in ICU settings.[28]

Limitations

One limitation of this review occurred during data extraction because some results of included studies from earlier meta-analyses were inconsistent with data from the original publication or data in a publication itself were contradictory. First, we requested information regarding missing or inconsistent data from the study authors. If we were not successful after contacting the authors twice and the issue could not be solved otherwise, we chose a pragmatic approach by discussing these data in a team, using the most convincing data for the review (Supplementary Table S10). However, based on a sensitivity analysis, these decisions did not have a relevant impact on the outcomes. In terms of open science, these problems were summarized in a table in the supplement to facilitate data extraction for future reviewers.

Missing information regarding the exclusion of delirium in two studies was another limitation.[16,18] Although we only included studies if delirium at baseline was clearly excluded, we decided to consider these two studies because delirium at baseline was deemed very unlikely (eg, elective surgery, able to give informed consent, severe cognitive impairment excluded). Sensitivity analyses on the primary outcome did not show a considerable difference after excluding the two studies at risk, supporting our decision to include them.

Overall, due to the small number of respective studies, there was a lack of power for secondary outcomes, rendering definitive conclusions difficult. We cannot rule out a true effect that we were unable to detect. Therefore, future research still may challenge the current findings substantially.

In addition, some of the prespecified subgroup analyses were not feasible due to a lack of sufficient information for the subgroup (history of delirium, delirium subtype) or highly homogeneous patient characteristics (mean age >65 years in all studies). For some outcomes, data pooling was complicated by different forms of outcome assessment

and reporting (eg, delirium duration: different frequencies of outcome assessment, duration reported in hours or days) leading to higher heterogeneity. Furthermore, subgroup analyses did not provide evidence of any effect modifiers due to the high homogeneity across studies.

In conclusion, the findings of this systematic review and meta-analysis support current guidelines recommending multicomponent interventions for delirium prevention in populations at risk.[6,29] Our results were consistent and indicated an NNT of 12.5 for multicomponent interventions for delirium prevention in comparison with standard care. Our findings show a trend that delirium duration and length of hospital stay may be reduced by multicomponent interventions. Although there were no statistically significant effects, the consistency of findings throughout the studies allows us to conclude that an effect could be detected if more observations were available. Our findings strongly support existing guidelines that recommend implementing non-pharmacologic multicomponent interventions in hospitalized patients at risk for delirium because delirium leads to functional and cognitive decline, higher mortality, and higher risk for institutionalization. This recommendation is all the more important considering evidence for the economic efficiency of multicomponent interventions.[9] Further research should not only focus on the incidence of delirium but also hard outcomes, such as return to independent living and mortality. Future studies should also investigate comparative efficacy and cost effectiveness of distinct components.

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Author Contributions: Obtained funding for the study: Lieb. Designed the study: Ludolph, Stoffers-Winterling, Rösch, Vahl, and Geschke. Screened the literature search, acquired reports of relevant trials, selected included studies, and extracted data: Ludolph and Stoffers-Winterling. Contacted trial investigators for additional information: Ludolph and Stoffers-Winterling. Performed all statistical analyses: Ludolph and Stoffers-Winterling. Analyzed and interpreted the data: Ludolph, Stoffers-Winterling, Geschke, and Lieb. Drafted the report: Ludolph, Stoffers-Winterling, and Lieb. All authors critically reviewed the report for important intellectual content and approved the final submitted version.

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article.

Supplementary Appendix S1: Supporting Information.