Original Investigation | HEALTH CARE REFORM

Effectiveness of Multicomponent Nonpharmacological Delirium Interventions
A Meta-analysis

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Invited Commentary page 521

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IMPORTANCE Delirium, an acute disorder with high morbidity and mortality, is often preventable through multicomponent nonpharmacological strategies. The efficacy of these strategies for preventing subsequent adverse outcomes has been limited to small studies to date.

OBJECTIVE To evaluate available evidence on multicomponent nonpharmacological delirium interventions in reducing incident delirium and preventing poor outcomes associated with delirium.

DATA SOURCES PubMed, Google Scholar, ScienceDirect, and the Cochrane Database of Systematic Reviews from January 1, 1999, to December 31, 2013.

STUDY SELECTION Studies examining the following outcomes were included: delirium incidence, falls, length of stay, rate of discharge to a long-term care institution (institutionalization), and change in functional or cognitive status.

DATA EXTRACTION AND SYNTHESIS Two experienced physician reviewers independently and blindly abstracted data on outcome measures using a standardized approach. The reviewers conducted quality ratings based on the Cochrane risk-of-bias criteria for each study.

MAIN OUTCOMES AND MEASURES We identified 14 interventional studies. The results for outcomes of delirium incidence, falls, length of stay, and institutionalization were pooled for the meta-analysis, but heterogeneity limited our meta-analysis of the results for change in functional or cognitive status. Overall, 11 studies demonstrated significant reductions in delirium incidence (odds ratio [OR], 0.47; 95% CI, 0.38-0.58). Four randomized or matched trials reduced delirium incidence by 44% (OR, 0.56; 95% CI, 0.42-0.76). The rate of falls decreased significantly among intervention patients in 4 studies (OR, 0.38; 95% CI, 0.25-0.60); in 2 randomized or matched trials, the rate of falls was reduced by 64% (OR, 0.36; 95% CI, 0.22-0.61). Length of stay and institutionalization also trended toward decreases in the intervention groups, with a mean difference of −0.16 (95% CI, −0.97 to 0.64) day shorter and the odds of institutionalization 5% lower (OR, 0.95; 95% CI, 0.71-1.26). Among higher-quality randomized or matched trials, length of stay trended −0.33 (95% CI, −1.38 to 0.72) day shorter, and the odds of institutionalization trended 6% lower (OR, 0.94; 95% CI, 0.69-1.30).

CONCLUSIONS AND RELEVANCE Multicomponent nonpharmacological delirium prevention interventions are effective in reducing delirium incidence and preventing falls, with a trend toward decreasing length of stay and avoiding institutionalization. Given the current focus on prevention of hospital-based complications and improved cost-effectiveness of care, this meta-analysis supports the use of these interventions to advance acute care for older persons.

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Delirium is an acute confusional state marked by inattention and global cognitive dysfunction. It is multifactorial and develops owing to interactions between risk factors and noxious insults.[1] Common yet underdiagnosed, delirium is particularly prevalent among the hospitalized elderly, occurring in 29% to 64%, and contributes to more than $164 billion in health care costs in the United States annually.[1,2] Delirium significantly increases risk of falls, functional decline, dementia, prolonged hospital length of stay, and institutionalization.[3] The strong correlation between delirium and hospital-related falls has led to calls for delirium prevention quality metrics to improve hospital care and prevent falls in older persons.[4] Most important, at least 30% to 40% of delirium cases are preventable.[1,5,6] Surprisingly, most hospitals do not have delirium prevention programs or their protocols are inconsistently implemented, with variable adherence.[1,7]

Systematic reviews and clinical guidelines have recommended targeted multicomponent nonpharmacological intervention strategies for prevention of delirium (eTable in the Supplement).[8,9] The Hospital Elder Life Program (HELP) is the original evidence-based approach targeted to delirium risk factors, which is widely known and disseminated.[5,10,11] The HELP uses an interdisciplinary team and trained volunteers to implement practical interventions, including reorientation, early mobilization, therapeutic activities, hydration, nutrition, sleep strategies, and hearing and vision adaptations. The HELP has been cost-effective and successful in preventing delirium and functional decline.[2,12,13] Studies[12,14,15] have evaluated modified HELP models. New multicomponent nonpharmacological delirium interventions have been developed, targeting perioperative patients[16-18] or using volunteers, family members, and nurses in the delivery of interventions.[19,20] However, differing outcomes were examined across studies, and a systematic examination of their effectiveness has not been conducted to our knowledge. Most recently, there have been systematic reviews and guidelines,[7,8] but these statements underscored the limitations of small samples, heterogeneous outcomes, and variable adherence. A need exists for more definitive review to expedite dissemination in practice and spur further research into areas of uncertain outcomes.

Therefore, the primary aims of our study were (1) to perform a systematic review of all studies related to multicomponent nonpharmacological delirium interventions and (2) to conduct a quantitative meta-analysis evaluating the effect of these interventions on important clinical outcomes. Secondary aims were to evaluate whether the quality of studies with respect to risk of bias influenced effectiveness.

Methods

Literature Search

We conducted a comprehensive systematic literature review to identify all studies related to delirium prevention from January 1, 1999, to December 31, 2013. Databases searched included PubMed, Google Scholar, ScienceDirect, and the Cochrane Database of Systematic Reviews. For search terms, we used a combination of keyword terms and specific phrases representing *delirium prevention*, *targeted multicomponent intervention*, *multicomponent intervention*, *nonpharmacological intervention*, and *Hospital Elder Life Program*. Review articles were examined for secondary references, and all bibliographies from retrieved articles were screened for other relevant studies. Studies were included in the review if they met the following inclusion criteria: they were original articles, the median or mean age of participants was 65 years or older, they discussed relevant topics given the search terms, they were published in English, and they included human participants. Studies were excluded after full review for the following reasons: they contained no relevant outcome measures, they were study protocols, they used no control groups, they were a cost-effective analysis, or they were qualitative studies, case series, commentaries, reviews, guidelines, or recommendations. Studies involving patients with terminal illness or insufficient data were also excluded. The remaining articles were evaluated and excluded if they failed the following second-level inclusion criteria: (1) they studied multicomponent nonpharmacological delirium interventions, (2) they assessed delirium incidence and not prevalence, and (3) they used a validated delirium instrument for ascertainment (**Figure 1**).

Study Selection

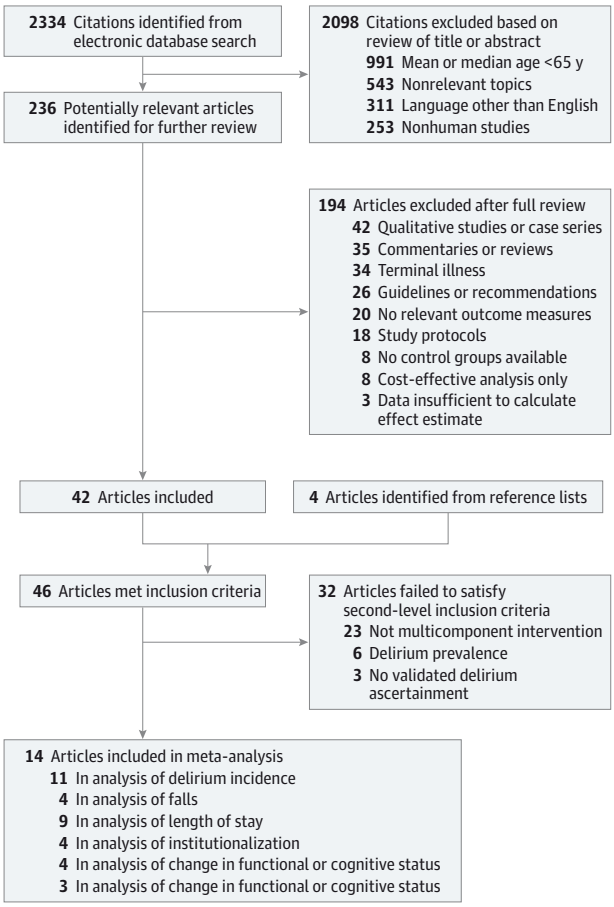
The study followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram and checklist.[21,22] The initial search yielded 2334 articles published between January 1, 1999, and December 31, 2013 (Figure 1). After exclusion based on screening criteria (relevance, language, age range, and nonhuman study), the number of articles was narrowed to 236. More than half of these articles (n = 119) were not interventional studies. Based on this initial screen and augmented by article reference lists, 46 articles were selected for full review by 2 independent clinical reviewers (T.T.H. and J.Y.). Thirty-two articles did not meet second-level inclusion criteria, which required delirium prevention (not treatment), validated delirium assessment methods, and multicomponent nonpharmacological delirium interventions. Therefore, 14 original articles were selected for inclusion in the meta-analysis, encompassing 12 unique intervention trials. The 2 additional studies included addressed different outcomes in other study subgroups. Bogardus et al[23] examined function and cognition after discharge in a subgroup from a study by Inouye et al.[5] Stenvall et al[18] focused on falls among the participants from a study by Lundström et al.[17]

Outcome Measures

Primary outcomes examined in this study were delirium incidence and falls. Incident delirium, defined as new-onset delirium during hospitalization, was measured with validated delirium instruments. Of 14 articles, 12 used the Confusion Assessment Method,[24] and 2 used the Delirium Observation Screening Scale.[17,18,25] Falls were defined as the total number per 1000 patient-days, and presented values were recalculated to adhere to these units.

The secondary outcomes examined in this study included length of stay, rate of discharge to a long-term care institution (institutionalization), and change in functional or cog-

Figure 1. Literature Identification, Review, and Selection for Inclusion in the Meta-analysis



The study followed the approaches outlined by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram and checklist, the Meta-analysis of Observational Studies in Epidemiology (MOOSE) consensus statement, and the *Cochrane Handbook for Systematic Reviews of Interventions*. In total, 2334 articles were found. Of these, 2098 were excluded based on our screening criteria. A further 189 were excluded after full review, yielding 46 articles that met our initial screening criteria. On further review, 32 of these did not meet our second-level inclusion criteria.

nitive status. According to standard use, length of stay was defined as the total number of calendar days the patient was in the hospital from the date of arrival in the emergency department to the date of discharge. Institutionalization was defined as new placement in a senior residential or nursing home facility on discharge for long-term care. Cognitive status was evaluated by the mean difference in Mini-Mental State Examination scores between admission and discharge. Alterations in functional status were measured by changes on the Activities of Daily Living Scale (Lawton Scale) in 2 studies[5,26] and Barthel Index in 2 studies.[16,20] For one study,[23] admission and 6-month postdischarge functional scores were used. Functional change was evaluated using standardized mean differences to compare the results across studies using different scoring systems. Standardized mean differences take the difference between functional scores and divide it by the standard deviation of scores.

Quality Assessment

We examined the quality of studies included in the meta-analysis using the 6 domains of the Cochrane Collaboration's tool for assessing risk of bias.[21] These domains included a random or balanced allocation method, allocation concealment, completeness of outcome data, lack of selective outcome reporting, and absence of other sources of bias, as well as blinding of participants, personnel, and outcome assessors.

Data Collection

A standardized data extraction protocol was developed with input from experts in delirium (J.Y. and S.K.I.), multicomponent interventions (J.Y. and S.K.I.), geriatrics (T.T.H., J.Y., E.O., and S.K.I.), and systematic reviews and meta-analysis (J.Y., E.O., and T.T.). Two reviewers (T.T.H. and J.Y.) independently extracted and cross-checked data from all articles, assessing study quality using standard criteria. Two additional reviewers (E.O. and S.K.I.) conducted spot checks to confirm the accuracy of extracted data and resolve any discrepancies.

The 14 articles were abstracted for the reference (primary author and publication year), study characteristics (design, duration, setting, country of study, and number of patients), and patient characteristics (mean age, sex, and type). For each outcome (delirium incidence, falls, length of stay, institutionalization, and change in functional or cognitive status), the reviewers extracted the means (SDs), number of occurrences or total number in the sample, and odds ratios (ORs) or relative risks (95% CIs), as applicable. Finally, quality ratings were conducted as described above. When essential data were not reported, corresponding authors were contacted up to 3 times.

Statistical Analysis

Following standard procedures,[21,22] we performed a meta-analysis on 14 articles. Intervention trials that used formal methods for balanced allocation between treatment and control arms through randomization or prospective individual matching designs were combined into the group we refer to as randomized or matched trials (RMTs). We considered these trials separately from other interventional studies (non-RMTs) that did not use such rigorous designs. We made the decision to include randomized clinical trials (RCTs) with matched blinded trials because the few RCTs precluded a meta-analysis separately. We also judged that the robust methods and balanced allocation with prospective matching and blinded outcome assessment made some studies of comparable quality to RCTs and combinable without excessive heterogeneity.

For proportions and rates (eg, delirium incidence, falls, and institutionalization), ORs (95% CIs) were estimated according to intent-to-treat principles. For statistically significant effects, we calculated the number needed to treat (NNT) from the risk difference using the inverse of the pooled absolute risk. For continuous data (eg, length of stay and change in functional or cognitive status), the means (SDs) and mean differences were used for outcomes pooled on the same scale (eg, length of stay and Mini-Mental State Examination score), and standardized mean differences were used for outcomes pooled on different scales (eg, various functional status measures).

Table 1. Characteristics of Studies

Source	Study Design	Study Duration, mo	Patient Type or Setting	Mean Patient Age, y	Quality Measures[a]	Interventions[b]
Andro et al,[27] 2012 (France)	Historically controlled (non-RMT)	18	Medical (n = 256)	84.7	1/6 (O)	5/6 (C, E, H, V, W)
Babine et al,[14] 2013 (United States)	Historically controlled (non-RMT)	3	Medical (n = 516)	≥70.0	1/6 (O)	6/6 (C, E, H, P, V, W)
Bo et al,[28] 2009 (Italy)	Nonrandomized clinical trial (non-RMT)	4	Medical (n = 252)	82.4	3/6 (I, O, X)	4/6 (C, E, P, W)
Bogardus et al,[23] 2003 (United States)	Nonrandomized clinical trial, matched/blinded (RMT)	36	Medical/geriatric (n = 705)	80.0	5/6 (B, I, O, S, X)	6/6 (C, E, H, P, V, W)
Caplan and Harper,[20] 2007 (Australia)	Historically controlled (non-RMT)	5	Medical/geriatric (n = 37)	84.7	3/6 (I, O, S)	4/6 (C, H, V, W)
Chen et al,[16] 2011 (Taiwan)	Historically controlled (non-RMT)	20	Surgical (n = 179)	73.0	3/6 (B, I, O)	2/6 (E, C)
Holt et al, [29] 2013 (England)	Historically controlled (non-RMT)	12	Medical/geriatric (n = 362)	85.4	4/6 (B, I, O, X)	5/6 (C, E, H, V, W)
Inouye et al,[5] 1999 (United States)	Nonrandomized clinical trial, matched/blinded (RMT)	36	Medical (n = 852)	79.7	5/6 (B, I, O, S, X)	6/6 (C, E, H, P, V, W)
Jeffs et al,[30] 2013 (Australia)	Randomized clinical trial (RMT)	30	Medical (n = 648)	79.3	6/6 (A, B, I, O, S, X)	2/6 (C,E)
Kratz,[31] 2008 (United States)	Nonrandomized clinical trial (non-RMT)	36	Medical/surgical (n = 137)	≥70.0	1/6 (O)	6/6 (C, E, H, P, V, W)
Lundström et al,[17] 2007 (Sweden)	Randomized clinical trial (RMT)	32	Surgical (n = 199)	82.2	5/6 (A, I, O, S, X)	1/6 (E)
Martinez et al,[32] 2012 (Chile)	Randomized clinical trial (RMT)	9	Medical (n = 287)	78.2	6/6 (A, B, I, O, S, X)	3/6 (C, H, V)
Stenvall et al,[18] 2007 (United States)	Randomized clinical trial, single-blind (RMT)	32	Surgical (n = 199)	82.2	5/6 (A, B, I, S, X)	3/6 (E, H, P)
Vidán et al,[26] 2009 (Spain)	Nonrandomized clinical (non-RMT)	18	Medical/geriatric (n = 542)	84.0	1/6 (O)	6/6 (C, E, H, P, V, W)

Abbreviation: RMT, randomized or matched trial.

[a] Quality measures include the following: allocation concealment (A); blinding of participants, personnel, and outcome assessors (B); completeness of outcome data (I); selective outcome reporting (O); random-sequence generation or balanced allocation (S); and other sources of bias (X).

[b] Evidence-based nonpharmacological interventions include the following: cognition or orientation (C), early mobility (E), hearing (H), sleep-wake cycle preservation (P), vision (V), and hydration (W).

The study results considered for inclusion in the meta-analysis were assessed for heterogeneity using χ^2 statistic Q, with $P < .10$ as the threshold indicator for heterogeneity of effects. In addition, I^2 was used to estimate the proportion of total variation due to heterogeneity across studies. I^2 values of less than 25% were regarded as low heterogeneity, and fixed-effects models for the meta-analysis were used. I^2 values of 25% to 75% represented moderate heterogeneity, and a random-effects model was applied. I^2 values exceeding 75% represented high heterogeneity, and a meta-analysis was not considered appropriate for the interpretation. All statistical analyses for the meta-analysis were performed using Review Manager software (RevMan, version 5.2; The Cochrane Collaboration).

To assess associations between study quality and effectiveness of interventions, we used linear regression analysis to determine at the study level whether there was an association between the continuous Cochrane Collaboration's risk of bias score (range, 0-6) and the multiplicative increase in odds (ie, OR) of incident delirium with intervention vs control. In addition, we divided studies into lower-quality and higher-quality subgroups based on a Cochrane Collaboration risk of bias score of less than 3 vs 4 or higher and performed an independent meta-analysis of studies falling into each of these 2 categories.

All statistical tests performed were 2-sided. Statistical significance was indicated by $P < .05$ or a 95% CI that excluded the null.

Results

Study Characteristics

The analytic sample for the present study included 14 articles. Six studies involved RMTs, and 8 studies involved non-RMTs (**Table 1**). Two nonrandomized trials had high-quality study designs, with prospective individual matching and rigorously blinded outcome assessment.[5,23] Among 8 non-RMTs, 3 used nonmatched concurrent controls, and 5 used historical controls. Overall, approximately 4267 patients at 12 sites (acute medical and surgical wards in academic and community hospitals) were involved; their mean age was 79.7 years. All studies involving non-acute care settings were excluded based on our criteria. Of 14 studies, 9 involved HELP adapta-

Table 2. Meta-analysis of the Effect of Multicomponent Nonpharmacological Delirium Interventions

Variable	Intervention		Control		Odds Ratio or Mean Difference (95% CI)	I^2 Value, %
	Outcome Events	Total Patients	Outcome Events	Total Patients		
Delirium Incidence						
RMTs[5,17,30,32]	83	977	137	1009	0.56 (0.42 to 0.76)	0
Non-RMTs[16,20,26-29,31]	46	752	164	1013	0.37 (0.27 to 0.53)	20
Combined	**129**	**1729**	**301**	**2022**	0.47 (0.38 to 0.58)	18
Falls						
RMTs[18,32]	18	245	64	240	0.36 (0.22 to 0.61)	0
Non-RMTs[14,20]	6	274	31	279	0.46 (0.19 to 1.10)	0
Combined	**24**	**519**	**95**	**519**	0.38 (0.25 to 0.60)	0
Institutionalization						
RMTs[17,23]	101	389	105	388	0.94 (0.69 to 1.30)	0
Non-RMTs[20,29]	19	168	27	231	0.79 (0.25 to 2.51)	56
Combined	**120**	**557**	**132**	**619**	0.95 (0.71 to 1.26)	0
Length of Stay						
RMTs[5,17,18,30,32]	NA	977	NA	1009	−0.33 (−1.38 to 0.72)	65
Non-RMTs[16,20,26,28,29]	NA	561	NA	811	0.01 (−1.72 to 1.73)	69
Combined	NA	**1538**	NA	**1820**	−0.16 (−0.97 to 0.64)	63
Change in Functional Status						
RMTs[5]	NA	426	NA	426	0.00 (−0.13 to 0.13)	0
Non-RMTs[16,20,26]	NA	118	NA	98	0.79 (−0.26 to 1.84)	96
Combined	NA	**544**	NA	**524**	0.57 (−0.03 to 1.18)	96
Change in Cognitive Status						
RMTs[5]	NA	426	NA	426	−0.20 (−0.83 to 0.43)	0
Non-RMTs[16,20]	NA	188	NA	470	2.23 (−0.78 to 5.24)	75
Combined	NA	**714**	NA	**896**	0.97 (−0.46 to 2.41)	83

Abbreviations: NA, not applicable; RMT, randomized or matched trials.

tions or included at least 4 of 6 evidence-based interventions from HELP (Table 1).

Delirium Incidence

Eleven studies measured delirium incidence (**Table 2**). Overall, the meta-analysis involving 4267 patients showed that the odds of delirium were 53% lower in the intervention group compared with controls (OR, 0.47; 95% CI, 0.38-0.58) (**Figure 2**). The NNT in the combined sample was 14.3 (95% CI, 11.1-20.0).

Stratified by study type, multicomponent nonpharmacological delirium interventions lowered the odds of delirium by 44% (relative risk, 0.56; 95% CI, 0.42-0.76) among 977 intervention patients included in 4 RMTs and by 63% (OR, 0.37; 95% CI, 0.27-0.53) among 752 intervention patients included in 7 non-RMTs (Table 2 and eFigure 1 in the Supplement). The NNTs were 20.0 (95% CI, 12.5-33.3) among RMTs and 11.1 (95% CI, 8.3-16.7) among non-RMTs. Delirium incidence was also stratified by patient type (eFigure 2 in the Supplement).

Falls

Four studies examined the number of falls per patient-days (Table 2). Combined, the meta-analysis involving 1038 patients showed that the odds of falling were 62% lower among intervention patients (OR, 0.38; 95% CI, 0.25-0.60) (Table 2 and Figure 2). This outcome represents the equivalent of 4.26 falls prevented per 1000 patient-days or 2.79 falls per 1000 patient-days among intervention patients compared with 7.05 falls per 1000 patient-days among controls.

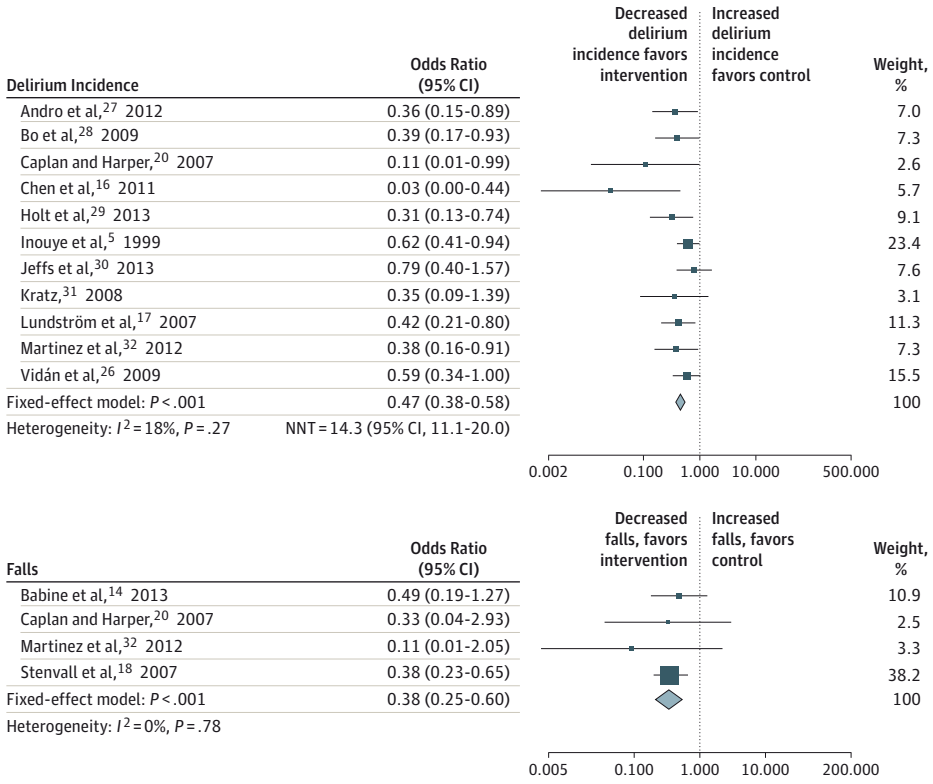
Stratified by study type, multicomponent nonpharmacological delirium interventions lowered the odds of falling significantly among 245 intervention patients included in 2 RMT studies (OR, 0.36; 95% CI, 0.22-0.61) (Table 2 and eFigure 3 in the Supplement). This outcome represents 8.53 falls prevented per 1000 patient-days or 4.34 falls per 1000 patient-days among intervention patients compared with 12.87 falls per 1000 patient-days among controls. The odds of falling trended lower among 274 intervention patients included in 2 non-RMT studies (OR, 0.46; 95% CI, 0.19-1.10).This outcome represents the equivalent of 2.34 falls prevented per 1000 patient-days or 1.35 falls per 1000 patient-days among intervention patients compared with 3.69 falls per 1000 patient-days among controls.

Length of Stay

Nine studies measured length of stay (Table 2). Overall, the meta-analysis involving 3358 patients showed that the mean difference was −0.16 (95% CI, −0.97 to 0.64) day shorter in the intervention group, with a trend toward significance (Table 2 and **Figure 3**).

Stratified by study type, multicomponent nonpharmacological delirium interventions decreased length of stay by −0.33 (95% CI, −1.38 to 0.72) day among 977 intervention patients in-

Figure 2. Meta-analysis of Delirium Incidence and Falls



Eleven studies measured delirium incidence. Three randomized or matched trials and 5 non–randomized or matched trials demonstrated significant reductions in delirium incidence. $P < .001$, and heterogeneity was low at $I^2 = 18\%$. Weighting was assigned according to the inverse of the variance. Odds ratios less than 1 indicate decreased delirium incidence. Four studies examined the number of falls per patient-days. Individually, only Stenvall et al[18] (a randomized or matched trial) demonstrated significant reduction in the number of falls. $P < .001$, and heterogeneity was low at $I^2 = 0\%$. Weighting was assigned according to the inverse of the variance. Odds ratios less than 1 indicate decreased rate of falls. NNT indicates the number needed to treat.

cluded in 4 RMTs (Table 2 and eFigure 4 in the Supplement). Length of stay was increased by 0.01 (95% CI, −1.72 to 1.73) day among 561 intervention patients included in 5 non-RMTs. Neither of these stratified analyses achieved statistical significance. Length of stay was also stratified by patient type (eFigure 5 in the Supplement).

Institutionalization

Four studies examined institutionalization after hospital discharge (Table 2). Overall, the meta-analysis involving 1176 patients showed that the odds of discharge to long-term care were 5% lower (OR, 0.95; 95% CI, 0.71-1.26) in the intervention group, but the results did not achieve statistical significance (Table 2 and Figure 3).

Stratified by study type, the trends are consistent, with an OR for institutionalization among 389 intervention patients in 2 RMTs of 0.94 (95% CI, 0.69-1.30) in favor of multicomponent nonpharmacological delirium interventions, but the results were not statistically significant (Table 2 and eFigure 6 in the Supplement). The OR for institutionalization among 168 patients involved in 2 non-RMTs was 0.79 (95% CI, 0.25-2.51) in favor of targeted interventions, but the results did not achieve statistical significance.

Change in Functional Status

Four studies measured change in functional status, including 1 high-quality RMT and 3 non-RMTs (Table 2). Random-effects models were used owing to high heterogeneity of these studies. Combined, the standard mean difference for functional improvement among 1068 patients was 0.57 (95% CI, −0.03 to 1.18) in favor of multicomponent nonpharmacological delirium interventions, but this result was not statistically significant. Heterogeneity was high at $I^2 = 96\%$, with $P < .001$. Therefore, the pooled results must be interpreted with caution (eFigure 7 in the Supplement).

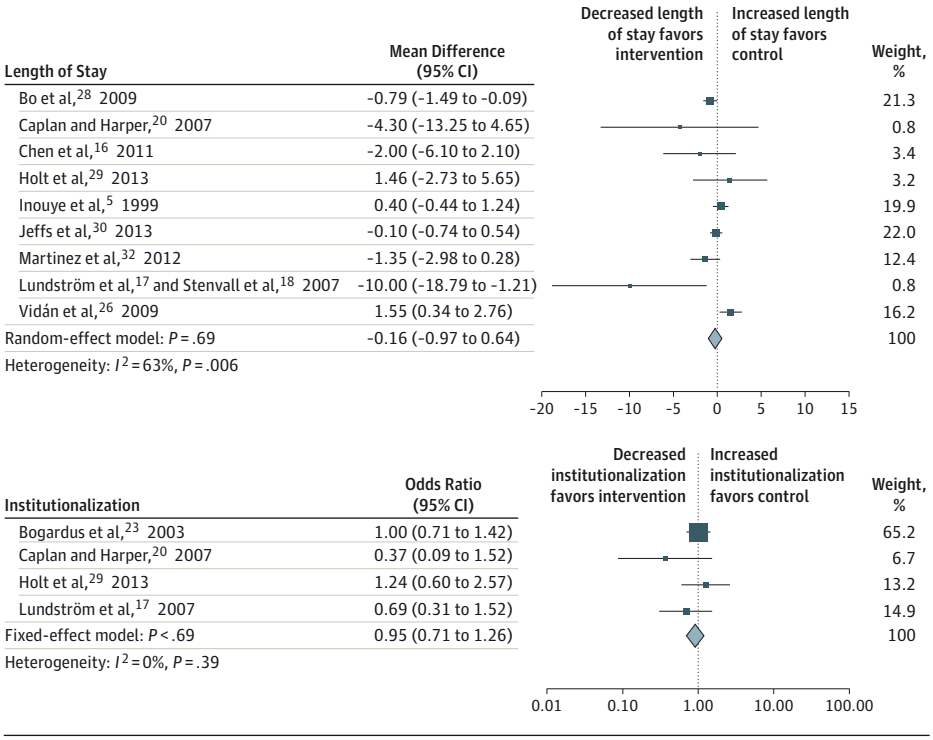
Change in Cognitive Status

Three studies measured change in cognition, including 1 high-quality RMT and 2 non-RMTs (Table 2). Random-effects models were used owing to high heterogeneity of these studies. Combined, the mean difference for cognitive improvement among 1610 patients was 0.97 (95% CI, −0.46 to 2.41) in favor of multicomponent nonpharmacological delirium interventions, but this outcome did not achieve statistical significance. In addition, heterogeneity was high at $I^2 = 83\%$, with $P = .002$, again indicating that the pooled results must be interpreted with caution (eFigure 7 in the Supplement).

Association Between Quality Ratings and Effectiveness

We observed limited, statistically nonsignificant evidence of any association between study quality and effectiveness of interventions in preventing incident delirium. Per unit increase on the Cochrane Collaboration's measure, the decreases attributable to the intervention in the odds of delirium incidence and falls were 4% ($R^2 = 0.025$) and 10% ($R^2 = 0.438$), respectively. The results did not change when lower-quality and higher-quality studies were compared. The OR for delirium incidence was 0.53 (95% CI, 0.39-0.71) among higher-

Figure 3. Meta-analysis of Length of Stay and Institutionalization



Nine studies measured length of stay. Individually, Bo et al[28] (a non–randomized or matched trial) and Lundström et al[17] (a randomized or matched trial) demonstrated significant reductions in length of stay. $P = .006$, and heterogeneity was moderate at $I^2 = 64\%$. Weighting was assigned according to the inverse of the variance. Mean differences less than 0 indicate decreased length of stay in days. Four studies examined the rate of institutionalization. Heterogeneity was low at $I^2 = 0\%$, with $P = .69$ among intervention patients, but there was little to no significant effect. Weighting was assigned according to the inverse of the variance. Odds ratios less than 1 indicate decreased rate of institutionalization.

quality studies compared with 0.38 (95% CI, 0.23-0.64) among lower-quality studies ($P = .28$). When examining whether higher quality yielded better outcomes for falls, length of stay, and institutionalization, the subgroup differences were also not statistically significant ($P = .65$, $P > .99$, and $P = .18$, respectively). Therefore, study quality ratings were not highly correlated with effectiveness.

Discussion

This systematic review and meta-analysis of 14 studies involving 12 unique interventions demonstrate that multicomponent nonpharmacological interventions for delirium prevention are highly effective in decreasing the occurrence of both delirium and falls during hospitalization in older persons. The effect of intervention strategies on delirium prevention across 11 studies is striking, with a greater than 50% odds reduction that was highly significant (OR, 0.47; 95% CI, 0.38-0.58). In 2008, there were 13.2 million hospital discharges of older patients in the United States, with a mean hospital stay of 5.5 days.[33] Based on our results, approximately 1 million cases of delirium in the hospital could have been prevented by multicomponent nonpharmacological interventions each year, resulting in Medicare cost savings of approximately $10 000 per case prevented or $10 billion per year.[1,2]

The effect on fall prevention is a novel and important finding, with greater than 60% odds reduction (OR, 0.38; 95% CI, 0.25-0.60). Because delirium is the leading contributor to hospital falls,[1,8] prevention of falls with these interventions is a consistent and compelling result. Furthermore, given their status as Medicare no-pay conditions, fall prevention has become a top priority among US hospitals.[34] If 4.26 falls can be avoided with multicomponent nonpharmacological delirium interventions per 1000 patient-days, 326 996 falls can be prevented annually with these interventions. This finding translates into an additional $4.5 billion to $6.7 billion Medicare savings annually from preventable falls.[35,36]

Few intervention strategies have proved effective for fall prevention in the hospital. Most fall interventions have focused on identifying fall risk and implementing various alarms that limit patient mobility. Although minimally effective for preventing falls, these approaches result in unintended consequences of decreased physical and cognitive functioning.[34] Notably, 12 of 14 studies examined in this meta-analysis included exercise interventions designed to enhance mobility. The well-documented effectiveness of these strategies for fall prevention is worthy of special emphasis.

While a trend toward benefit existed, the lack of significant association between delirium interventions and length of stay and institutionalization is not surprising given multiple complex influences on these outcomes, including multimorbidity and psychosocial factors (supports, finances, and caregiver preferences), all of which make the ultimate disposition unpredictable. Furthermore, because sample sizes were small, our meta-analysis may have been underpowered to detect true differences.

The few studies examining functional and cognitive decline, as well as their substantial heterogeneity, limited our ability to examine these outcomes. In addition, the preferred outcome with delirium prevention should be functional and

cognitive stability (ie, maintenance) and not improvement or decline. Only 1 study[23] examined function and cognition at admission and 6 months after discharge. Performing cognitive and functional reassessments at the time of discharge when patients may still be delirious and acutely deconditioned is suboptimal, and waiting until they have returned to a stable condition should be the preferred approach.

Our study has several noteworthy strengths. The meta-analysis allowed us to extend conclusions beyond populations contained in a single study, particularly given the variable and limited number of studies and the small study sizes available for review. We used a comprehensive search strategy and systematic review method.[21,22] With more than 4200 study participants in the pooled analyses, there was improved power for a meta-analysis of the study results. We limited heterogeneity and rigorously controlled for potential sources of bias by adhering to clear, predetermined selection criteria and evaluating the quality of our selected studies based on the Cochrane risk-of-bias guidelines.[21] Our stratified models for delirium incidence, falls, and institutionalization confirmed that observed outcome associations were robust across study designs. Heterogeneity analysis allowed us to account for study factors that could be influencing our outcomes of interest across multiple trials. The use of quality ratings facilitated our evaluation of the studies; however, quality scores did not correlate significantly with effectiveness.

Several limitations of our study are worthy of comment. The final number of included studies is small, and many of them had limited sample sizes. Less than one-third of the interventions evaluated were RCTs (29% [4 of 14]), the criterion standard for evidence-based practice. Blinding was difficult to achieve in nonpharmacological intervention studies by the unitwide nature of many interventions. Therefore, data available for synthesis may have been limited, restricting the strength of our conclusions. In particular, there were only 4 studies examining the outcome of falls, 2 of which were historically controlled studies with smaller sample sizes. Most important, selective reporting bias in the literature would have resulted in our meta-analysis reflecting an overestimation of the effect on falls. Despite similarities in research questions and interventions across studies, there remained a moderate degree of heterogeneity for all studies examining length of stay and change in functional or cognitive status and for non-RMTs examining institutionalization. This heterogeneity, which likely stems from variations in study designs, sample characteristics, sample sizes, and outcome measures used, limits the interpretation of our pooled estimates. Despite these limitations, the findings of this meta-analysis are highly clinically relevant for the hospitalized geriatric population.

A few studies were not included in our meta-analysis despite their being well designed and influential in the field of delirium prevention. These articles were excluded based on our predetermined inclusion criteria. Studies by Marcantonio et al[6] and Milisen et al[19] were excluded because they primarily involved consultation for preventive management of delirium and not multicomponent nonpharmacological delirium interventions. Cole et al,[37] Naughton et al,[38] and Zaubler et al[39] published work on effective multicomponent nonpharmacological interventions but included patients with delirium in their studies. Therefore, these were not considered primary prevention studies because incident delirium rates could not be calculated.

Conclusions

In conclusion, this meta-analysis suggests that multicomponent nonpharmacological interventions are effective in decreasing delirium incidence and preventing falls, potentially saving more than $16 billion annually in the United States alone. Therefore, these strategies hold great promise to influence 2 of the most important and prevalent conditions affecting seniors during hospitalization. Our systematic review and meta-analysis demonstrate that these interventions decrease the substantial health care and societal burden of delirium incidence and falls, improving quality of life for these patients and their families.

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REFERENCES

1. Inouye SK, Westendorp RG, Saczynski JS. Delirium in elderly people. *Lancet*. 2014;383(9920):911-922.

2. Leslie DL, Marcantonio ER, Zhang Y, Leo-Summers L, Inouye SK. One-year health care costs associated with delirium in the elderly population. *Arch Intern Med*. 2008;168(1):27-32.

3. Witlox J, Eurelings LS, de Jonghe JF, Kalisvaart KJ, Eikelenboom P, van Gool WA. Delirium in elderly patients and the risk of postdischarge mortality, institutionalization, and dementia: a meta-analysis. *JAMA*. 2010;304(4):443-451.

4. Lee EA, Gibbs NE, Fahey L, Whiffen TL. Making hospitals safer for older adults: updating quality metrics by understanding hospital-acquired delirium and its link to falls. *Perm J*. 2013;17(4):32-36.

5. Inouye SK, Bogardus ST Jr, Charpentier PA, et al. A multicomponent intervention to prevent delirium in hospitalized older patients. *N Engl J Med*. 1999;340(9):669-676.

6. Marcantonio ER, Flacker JM, Wright RJ, Resnick NM. Reducing delirium after hip fracture: a randomized trial. *J Am Geriatr Soc*. 2001;49(5):516-522.

7. Reston JT, Schoelles KM. In-facility delirium prevention programs as a patient safety strategy: a systematic review. *Ann Intern Med*. 2013;158(5, pt 2):375-380.

8. O'Mahony R, Murthy L, Akunne A, Young J; Guideline Development Group. Synopsis of the National Institute for Health and Clinical Excellence guideline for prevention of delirium. *Ann Intern Med*. 2011;154(11):746-751.

9. Greer N, Rossom R, Anderson P, et al. *Delirium: Screening, Prevention, and Diagnosis: A Systematic Review of the Evidence*. Washington, DC: Dept of Veterans Affairs; 2011.

10. Inouye SK. Prevention of delirium in hospitalized older patients: risk factors and targeted intervention strategies. *Ann Med*. 2000;32(4):257-263.

11. Inouye SK, Bogardus ST Jr, Baker DI, Leo-Summers L, Cooney LM Jr; Hospital Elder Life Program. The Hospital Elder Life Program: a model of care to prevent cognitive and functional decline in older hospitalized patients. *J Am Geriatr Soc*. 2000;48(12):1697-1706.

12. Rubin FH, Neal K, Fenlon K, Hassan S, Inouye SK. Sustainability and scalability of the Hospital Elder Life Program at a community hospital. *J Am Geriatr Soc*. 2011;59(2):359-365.

13. Rizzo JA, Bogardus ST Jr, Leo-Summers L, Williams CS, Acampora D, Inouye SK. Multicomponent targeted intervention to prevent delirium in hospitalized older patients: what is the economic value? *Med Care*. 2001;39(7):740-752.

14. Babine RL, Farrington S, Wierman HR. HELP prevent falls by preventing delirium. *Nursing*. 2013;43(5):18-21.

15. Inouye SK, Baker DI, Fugal P, Bradley EH; HELP Dissemination Project. Dissemination of the Hospital Elder Life Program: implementation, adaptation, and successes. *J Am Geriatr Soc*. 2006;54(10):1492-1499.

16. Chen CC, Lin MT, Tien YW, Yen CJ, Huang GH, Inouye SK. Modified Hospital Elder Life Program: effects on abdominal surgery patients. *J Am Coll Surg*. 2011;213(2):245-252.

17. Lundström M, Olofsson B, Stenvall M, et al. Postoperative delirium in old patients with femoral neck fracture: a randomized intervention study. *Aging Clin Exp Res*. 2007;19(3):178-186.

18. Stenvall M, Olofsson B, Lundström M, et al. A multidisciplinary, multifactorial intervention program reduces postoperative falls and injuries after femoral neck fracture. *Osteoporos Int*. 2007;18(2):167-175.

19. Milisen K, Foreman MD, Abraham IL, et al. A nurse-led interdisciplinary intervention program for delirium in elderly hip-fracture patients. *J Am Geriatr Soc*. 2001;49(5):523-532.

20. Caplan GA, Harper EL. Recruitment of Volunteers to Improve Vitality in the Elderly: the REVIVE study. *Intern Med J*. 2007;37(2):95-100.

21. Higgins JPT, Green S; Cochrane Collaboration. *Cochrane Handbook for Systematic Reviews of Interventions*. Version 5.1.0. Updated March 2011. http://www.cochrane-handbook.org. Accessed December 16, 2014.

22. Stroup DF, Berlin JA, Morton SC, et al; Meta-analysis of Observational Studies in Epidemiology (MOOSE) Group. Meta-analysis of Observational Studies in Epidemiology: a proposal for reporting. *JAMA*. 2000;283(15):2008-2012.

23. Bogardus ST Jr, Desai MM, Williams CS, Leo-Summers L, Acampora D, Inouye SK. The effects of a targeted multicomponent delirium intervention on postdischarge outcomes for hospitalized older adults. *Am J Med*. 2003;114(5):383-390.

24. Inouye SK, van Dyck CH, Alessi CA, Balkin S, Siegal AP, Horwitz RI. Clarifying confusion: the Confusion Assessment Method: a new method for detection of delirium. *Ann Intern Med*. 1990;113(12):941-948.

25. Schuurmans MJ, Shortridge-Baggett LM, Duursma SA. The Delirium Observation Screening Scale: a screening instrument for delirium. *Res Theory Nurs Pract*. 2003;17(1):31-50.

26. Vidán MT, Sánchez E, Alonso M, Montero B, Ortiz J, Serra JA. An intervention integrated into daily clinical practice reduces the incidence of delirium during hospitalization in elderly patients. *J Am Geriatr Soc*. 2009;57(11):2029-2036.

27. Andro M, Comps E, Estivin S, Gentric A. Prevention of delirium in demented hospitalized patients. *Eur J Intern Med*. 2012;23(2):124-125.

28. Bo M, Martini B, Ruatta C, et al. Geriatric ward hospitalization reduced incidence delirium among older medical inpatients. *Am J Geriatr Psychiatry*. 2009;17(9):760-768.

29. Holt R, Young J, Heseltine D. Effectiveness of a multi-component intervention to reduce delirium incidence in elderly care wards. *Age Ageing*. 2013;42(6):721-727.

30. Jeffs KJ, Berlowitz DJ, Grant S, et al. An enhanced exercise and cognitive programme does not appear to reduce incident delirium in hospitalised patients: a randomised controlled trial. *BMJ Open*. 2013;3(6):pii: e002569. doi: 10.1136/bmjopen-2013-002569.

31. Kratz A. Use of the acute confusion protocol: a research utilization project. *J Nurs Care Qual*. 2008;23(4):331-337.

32. Martinez FT, Tobar C, Beddings CI, Vallejo G, Fuentes P. Preventing delirium in an acute hospital using a non-pharmacological intervention. *Age Ageing*. 2012;41(5):629-634.

33. Wier L, Pfuntner A, Steiner C. Hospital utilization among oldest adults, 2008. Rockville, MD: Agency for Health Care Policy and Research; December 2010. Healthcare Cost and Utilization Project (HCUP) Statistical Briefs. Statistical Brief 103.

34. Inouye SK, Brown CJ, Tinetti ME. Medicare nonpayment, hospital falls, and unintended consequences. *N Engl J Med*. 2009;360(23):2390-2393.

35. Rizzo JA, Friedkin R, Williams CS, Nabors J, Acampora D, Tinetti ME. Health care utilization and costs in a Medicare population by fall status. *Med Care*. 1998;36(8):1174-1188.

36. Shumway-Cook A, Ciol MA, Hoffman J, Dudgeon BJ, Yorkston K, Chan L. Falls in the Medicare population: incidence, associated factors, and impact on health care. *Phys Ther*. 2009;89(4):324-332.

37. Cole MG, McCusker J, Bellavance F, et al. Systematic detection and multidisciplinary care of delirium in older medical inpatients: a randomized trial. *CMAJ*. 2002;167(7):753-759.

38. Naughton BJ, Saltzman S, Ramadan F, Chadha N, Priore R, Mylotte JM. A multifactorial intervention to reduce prevalence of delirium and shorten hospital length of stay. *J Am Geriatr Soc*. 2005;53(1):18-23.

39. Zaubler TS, Murphy K, Rizzuto L, et al. Quality improvement and cost savings with multicomponent delirium interventions: replication of the Hospital Elder Life Program in a community hospital. *Psychosomatics*. 2013;54(3):219-226.