Delirium in Elderly Patients and the Risk of Postdischarge Mortality, Institutionalization, and Dementia

A Meta-analysis

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Context Delirium is a common and serious complication in elderly patients. Evidence suggests that delirium is associated with long-term poor outcome but delirium often occurs in individuals with more severe underlying disease.

Objective To assess the association between delirium in elderly patients and long-term poor outcome, defined as mortality, institutionalization, or dementia, while controlling for important confounders.

Data Sources A systematic search of studies published between January 1981 and April 2010 was conducted using the databases of MEDLINE, EMBASE, PsycINFO, and CINAHL.

Study Selection Observational studies of elderly patients with delirium as a study variable and data on mortality, institutionalization, or dementia after a minimum follow-up of 3 months, and published in the English or Dutch language. Titles, abstracts, and articles were reviewed independently by 2 of the authors. Of 2939 references in the original search, 51 relevant articles were identified.

Data Extraction Information on study design, characteristics of the study population, and outcome were extracted. Quality of studies was assessed based on elements of the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) checklist for cohort studies.

Data Synthesis The primary analyses included only high-quality studies with statistical control for age, sex, comorbid illness or illness severity, and baseline dementia. Pooled-effect estimates were calculated with random-effects models. The primary analysis with adjusted hazard ratios (HRs) showed that delirium is associated with an increased risk of death compared with controls after an average follow-up of 22.7 months (7 studies; 271/714 patients [38.0%] with delirium, 616/2243 controls [27.5%]; HR, 1.95 [95% confidence interval {CI}, 1.51-2.52]; I^2, 44.0%). Moreover, patients who had experienced delirium were also at increased risk of institutionalization (7 studies; average follow-up, 14.6 months; 176/527 patients [33.4%] with delirium and 219/2052 controls [10.7%]; odds ratio [OR], 2.41 [95% CI, 1.77-3.29]; I^2, 0%) and dementia (2 studies; average follow-up, 4.1 years; 35/56 patients [62.5%] with delirium and 15/185 controls [8.1%]; OR, 12.52 [95% CI, 1.86-84.21]; I^2, 52.4%). The sensitivity, trim-and-fill, and secondary analyses with unadjusted high-quality risk estimates stratified according to the study characteristics confirmed the robustness of these results.

Conclusion This meta-analysis provides evidence that delirium in elderly patients is associated with poor outcome independent of important confounders, such as age, sex, comorbid illness or illness severity, and baseline dementia.

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Delirium is a syndrome of acutely altered mental status characterized by inattention and a fluctuating course.[1] With occurrence rates of up to half of older patients postoperatively, and even higher in elderly patients admitted to intensive care units, delirium is the most common complication in hospitalized older people.[2-4] Delirium causes distress to patients and caregivers, has been associated with increased morbidity and mortality, and is a major burden to health care services in terms of expenditures.[5]

Numerous studies have addressed the long-term prognosis of older individuals who experienced delirium during hospitalization. The evidence that these studies provide is not entirely consistent (eg, older patients with delirium experienced increased long-term mortality in one study,[6] but not in another[7]). Elements of study design, such as delirium and outcome ascertainment and time to follow-up, may affect conclusions. Whether delirium independently contributes to poor outcome or merely represents a marker of underlying disease is especially relevant. The long-term detrimental se-

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quelae of delirium are difficult to disentangle from the effects of specific characteristics of the study population, such as the extent of medical illness and the presence or absence of dementia.

These issues preclude drawing reliable conclusions regarding the long-term prognosis after delirium, which could be instrumental in assessing the value of prevention and treatment[8] and in counseling patients and caregivers. Therefore, we systematically reviewed and summarized data regarding the risk of long-term poor outcome (defined as mortality, institutionalization, or dementia) after delirium. Our main objective was to assess the association between delirium and long-term poor outcomes in elderly patients while controlling for important confounders.

METHODS

We followed the Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines.[9] We conducted a comprehensive literature search of MEDLINE, EMBASE, PsycINFO, and CINAHL databases for studies published between January 1981 and April 2010. We started our search in January 1981 because a formal nomenclature that differentiates delirium from dementia was first established with the *Diagnostic and Statistical Manual of Mental Disorders* (Third Edition) in 1980.[10] Search key words for delirium (ie, delirium, confusion, acute confusional state, acute confusional syndrome) were cross-referenced to citations pertinent to outcome (ie, mortality, prognos*, predict*, course). Studies that met each of the following criteria were considered eligible: (1) mean or median age of the study population of 65 years or older; (2) delirium as a study variable; (3) presentation of quantitative data (ie, event rates, odds ratios [ORs] or hazard ratios [HRs]) reflecting the association between delirium and outcome (ie, mortality, institutionalization, or dementia); (4) hospital or postacute care setting; and (5) follow-up assessment at 3 months or later. Searches were restricted to articles published in the English or Dutch language. Articles were excluded if they recruited (1) delirium patients only and no controls; (2) homogeneous populations of terminally ill patients (eg, patients with end-stage cancer); and (3) homogeneous populations of patients with central nervous system disease (eg, only patients with stroke or Parkinson disease). After exclusion of case studies and case series, the database searches identified 2939 articles. Reviews were hand searched for additional references but yielded no additional articles. Title and abstract review of all articles was completed by 3 of the authors (J.W., L.S.M.E., W.A.vG.). Full reports of 162 potentially relevant articles were independently reviewed by at least 2 investigators (J.W., L.S.M.E., W.A.vG.) to establish eligibility according to the inclusion criteria.

A standardized, piloted data extraction form was used for recording information. Data extraction was completed by 3 of the authors (J.W., L.S.M.E., W.A.vG.) using the following approach. For the primary analyses, we obtained statistically adjusted ORs and HRs with corresponding 95% confidence intervals (CIs) and noted the type of statistical adjustment (ie, the variables that were examined as possible covariates in relation with the outcomes of interest). For the secondary analyses, we extracted the number of events relative to the total number of participants in the delirium and control groups (ie, event rates). Because of our interest in the long-term outcomes after delirium, we preferentially extracted event rates that considered only postdischarge mortality and incident cases of institutionalization (or dementia). Therefore, if specified, event rates for mortality were corrected for death during the index hospitalization and event rates for institutionalization (and dementia) were corrected for baseline rates of institutionalization (or dementia).

Study populations were characterized as surgical, medical, or mixed and the following information was recorded: primary author, publication year, country of origin, study design, criteria for delirium and dementia ascertainment, duration of follow-up, average or median age, and (if applicable) the proportion of in-hospital mortality, baseline institutionalization, and dementia. Additional information such as separate event rates for patients with and without dementia were requested from 33 authors and 26 authors responded. Disagreement between reviewers during the selection and extraction process was resolved through consensus.

To limit heterogeneity resulting from differences in study design, we only included high-quality articles in the primary and secondary analyses. Lesser-quality articles were not included in any of our analyses. The quality of the studies was assessed based on elements from the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) checklist for cohort studies.[11] High-quality articles were defined as studies that diagnosed delirium prospectively, as opposed to, for example, retrospective chart review, and used a validated method for delirium ascertainment.

Studies were included in the primary analyses only if adequate statistical control was provided to account for the effect of important covariates on the association between delirium and poor outcome. Adequate adjustment was defined as statistical control for the covariables of age, sex, comorbid illness or illness severity, and baseline dementia. We selected these variables because they are risk factors for delirium in elderly patients that can themselves be associated independently with poor outcome.[2,5]

Secondary analyses were performed on a much larger sample of studies to examine the robustness of results from our primary analyses. In these secondary analyses, the studies' unadjusted ORs were stratified according to source of the study population, age (<80 years vs ≥80 years), country of origin (United States vs Europe), length of follow-up, and whether individuals who were

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institutionalized or had dementia were included in the study population.

Finally, an exploratory secondary analysis was conducted to specifically examine the association of baseline dementia with the long-term prognosis after delirium. This analysis was performed using studies that allowed separate calculation of effect estimates among homogeneous populations of individuals with and without dementia.

Mortality, institutionalization, and dementia were examined as separate outcomes. In primary analyses, we pooled adjusted ORs and HRs across all studies based on the extracted risk estimates and corresponding 95% CIs. In secondary analyses, we combined ORs and 95% CIs that we recalculated based on event rates in the delirium and control groups.[12] If recalculation was not possible, the reported unadjusted ORs and 95% CIs were used.

Each study contributed only 1 effect size per analysis. If data were duplicated between studies, the largest study was used. If studies reported data on several follow-up assessments, we included only data from the latest follow-up. If necessary, different subgroups (eg, based on age) were combined to create 1 estimate per study.

The pooled ORs and HRs were calculated as the weighted average and weighting was assigned according to the inverse of the variance. An OR or HR greater than 1 indicates an increased risk of an outcome among delirium patients compared with controls. The I^2 statistic was used to examine the heterogeneity of effect sizes in the overall aggregations. The I^2 values of 25% or less indicate low heterogeneity, values near 50% indicate moderate heterogeneity, and values near 75% or greater indicate high heterogeneity.[13] Unless otherwise specified, random-effects models were used in all analyses.[14] Fixed-effects models were only used in sensitivity analyses that examined if these models yielded similar results.

Publication bias was evaluated with a combination of 2 funnel plot–based methods: the Egger regression asymmetry test[15] to investigate funnel plot asymmetry and the trim-and-fill method[16] to estimate the number of missing studies and to calculate a corrected OR as if these studies were present. Because 5 studies are usually too few to detect an asymmetrical funnel, only aggregated analyses with more than 5 studies were subjected to trim-and-fill analysis.[17] The effect of potential outliers was examined by comparing the pooled estimate with estimates obtained after iterations using $k-1$ findings. Studies were treated as statistical outliers when the $k-1$ estimate produced a 95% CI that did not overlap with the 95% CI of the aggregated estimate.

Sensitivity analyses were performed on our primary and secondary data sets to examine if risk estimates using postdischarge mortality only (excluding in-hospital or postacute care deaths) provided a more conservative estimate of the association between delirium and mortality and if the strength of the relationship between delirium and institutionalization was affected by including only risk estimates that were based on incident cases of institutionalization. Furthermore, we performed a sensitivity analysis to examine if studies that used different methods to diagnose baseline dementia (eg, chart review) and incident dementia at follow-up (eg, cognitive testing) overestimated the association between delirium and dementia. Studies with the same method to diagnose dementia at baseline and follow-up and that thus included only incident cases of dementia were pooled in these analyses.

Statistical analyses were performed using Comprehensive Meta-Analysis software (Englewood, New Jersey) version 2.2.048. *P* values of less than .05 were considered statistically significant.

RESULTS

Our literature search yielded 2939 articles, of which we identified 162 for further review. Fifty-one studies met our inclusion criteria (see eTable 1, eTable 2, and eTable 3 at http://www.jama.com). Most excluded studies lacked either follow-up assessment, sufficient data to extract a risk estimate, a control group, or original data. Of the 51 studies that met our inclusion criteria, 9 studies[18-26] did not satisfy our quality criteria and were not included in the primary or secondary analyses (FIGURE 1).

Of the remaining 42 high-quality studies,[6,7,27-66] 23 studies* reported statistically adjusted effect estimates for the outcome of mortality and 16 studies† fulfilled criteria for adequate adjustment. Four studies[27,29,30,48] did not report sufficient information to extract an adjusted risk estimate for the latest follow-up assessment. The remaining 12 studies‡ provided 7 HRs and 7 ORs for the primary analysis of the association between delirium and mortality. Eight studies[6,7,30,32,40,43,61,63] reported adjusted ORs for the association between delirium and institutionalization, of which 7 studies[6,7,30,32,40,43,63] were adequately adjusted and provided 9 ORs for the primary analysis. Three studies presented adjusted ORs for the dementia outcome, of which 2 studies[32,54] were adequately adjusted and their ORs are included in our primary analysis.

For the secondary analyses with unadjusted ORs, 38 studies§ provided 40 ORs on mortality, 18 studies‖ provided 20 ORs on institutionalization, and 6 studies[32,41,47,49,54,65] provided 6 ORs on dementia. In 2 instances, ORs were recalculated based on the data supplied by the authors because nursing home residents had been excluded[6,63] and data had been provided on a substantially larger sample.[48] Four sets of studies[28-30,38,52,54,57] reported data on the same group of patients; the studies that reported postdischarge mortality[54] or presented data of the largest sample[29,30,52] were included.

*References 6, 7, 27-30, 32, 34, 35, 40, 41, 44, 45, 48, 51, 52, 55, 56, 60, 61, 63-65.
†References 6, 7, 27, 29, 30, 32, 35, 40, 41, 45, 48, 51, 52, 60, 63, 65.
‡References 6, 7, 32, 35, 40, 41, 45, 51, 52, 60, 63, 65.
§References 6, 7, 27, 29, 31-37, 39-56, 58-66.
‖References 6, 7, 30, 32, 33, 37, 40, 42, 43, 46, 47, 49, 55, 57, 61-63, 66.

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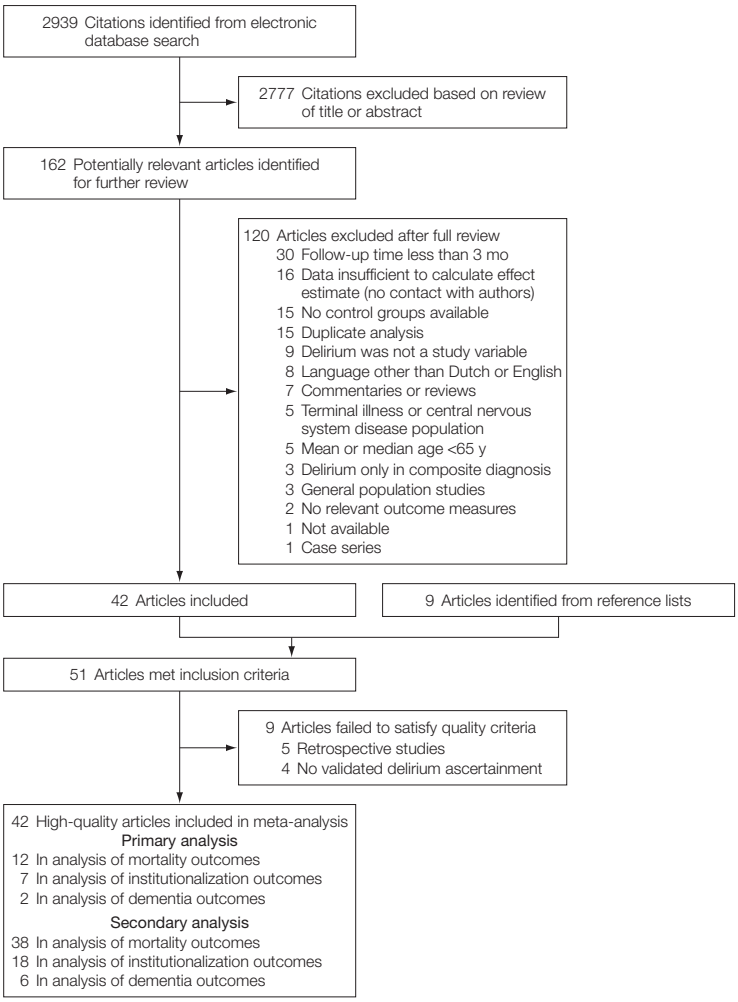
Figure 1. Identification, Review, and Selection of Articles Included in the Meta-analysis



In our exploratory secondary analyses, we examined to what extent baseline dementia affected the association between delirium and poor outcome. A total of 18 studies¶ provided 18 ORs on mortality and 5 ORs on institutionalization in a homogeneous population of individuals with dementia, and 17 ORs on mortality and 6 ORs on institutionalization in a homogeneous population of individuals without dementia. Descriptive information regarding the studies that were included from each analysis is listed in eTables 1-3 and information on excluded studies is listed in eTable 4 at http://www.jama.com.

¶References 6, 27, 28, 35, 37-39, 41, 43, 45, 47-49, 59, 62, 63, 65, 66.

Mortality

The primary analysis of adequately adjusted HRs included a total of 2957 participants. After a mean (SD) follow-up of 22.7 (15.5) months (range, 3-48 months) in 7 studies, 271 of 714 patients with delirium (38%) had an increased risk of death compared with 616 of 2243 controls (27.5%) (HR, 1.95 [95% CI, 1.51-2.52]; I^2, 44.0%; FIGURE 2). There was no evidence of publication bias according to the Egger regression asymmetry test ($\beta = 0.16$; $P = .94$) or the trim-and-fill method and outliers were not identified. The aggregated analysis of adequately adjusted ORs included a total of 2066 participants and also showed a significant association between delirium and mortality after a mean (SD) follow-up of 11.4 (14.0) months (range, 3-38 months) in 183 of 483 participants with delirium (37.9%) vs 316 of 1583 controls (20.0%) (OR, 1.71 [95% CI, 1.27-2.30]; I^2, 0%). No evidence of publication bias (Egger $\beta = -0.37$; $P = .43$) or outliers was found.

A sensitivity analysis with adjusted HRs showed that the association between delirium and death remained significant when only studies for which postdischarge mortality could be determined were included (TABLE 1). Secondary analyses with unadjusted ORs (see the eFigure at http://www.jama.com) were consistent with the results of the primary analyses. Additional stratified analyses with these unadjusted data revealed that excess mortality was present among patients who had experienced delirium regardless of the source of the study population, inclusion of nursing home residents or individuals with dementia, age, country of origin, and follow-up time (see eTable 5).

Our exploratory secondary analysis showed that the association of delirium with mortality persisted independent of preexisting dementia. Delirium remained significantly associated with mortality when 222 of 643 patients with delirium superimposed on dementia (34.5%) were compared with 135 of 564 patients with dementia only (23.9%) (OR, 1.75 [95% CI, 1.30-2.36]; I^2, 0.7%), and when 168 of 575 patients with delirium only (29.2%) were compared with 266 of 1620 patients with neither delirium nor dementia (16.4%) (OR, 2.36 [95% CI, 1.82-3.05]; I^2, 2.1%; TABLE 2).

Institutionalization

The primary analysis of adjusted ORs included 2579 participants in 7 studies. Delirium was associated with an increased risk of institutionalization after a mean (SD) follow-up of 14.6 (12.0) months (range, 3-38 months) in 176 of

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527 participants with delirium (33.4%) vs 219 of 2052 controls (10.7%) (OR, 2.41 [95% CI, 1.77-3.29]; I^2, 0%; (Figure 2). No evidence of publication bias was identified using the Egger regression asymmetry test ($\beta = 0.45$; $P = .65$) but the trim-and-filled method simulated 1 missing study (OR, 2.32 [95% CI, 1.69-3.21]). No evidence of outliers was found. A sensitivity analysis showed that the association between delirium and institutionalization remained when only cases who had not resided in an institution at baseline were considered (Table 1).

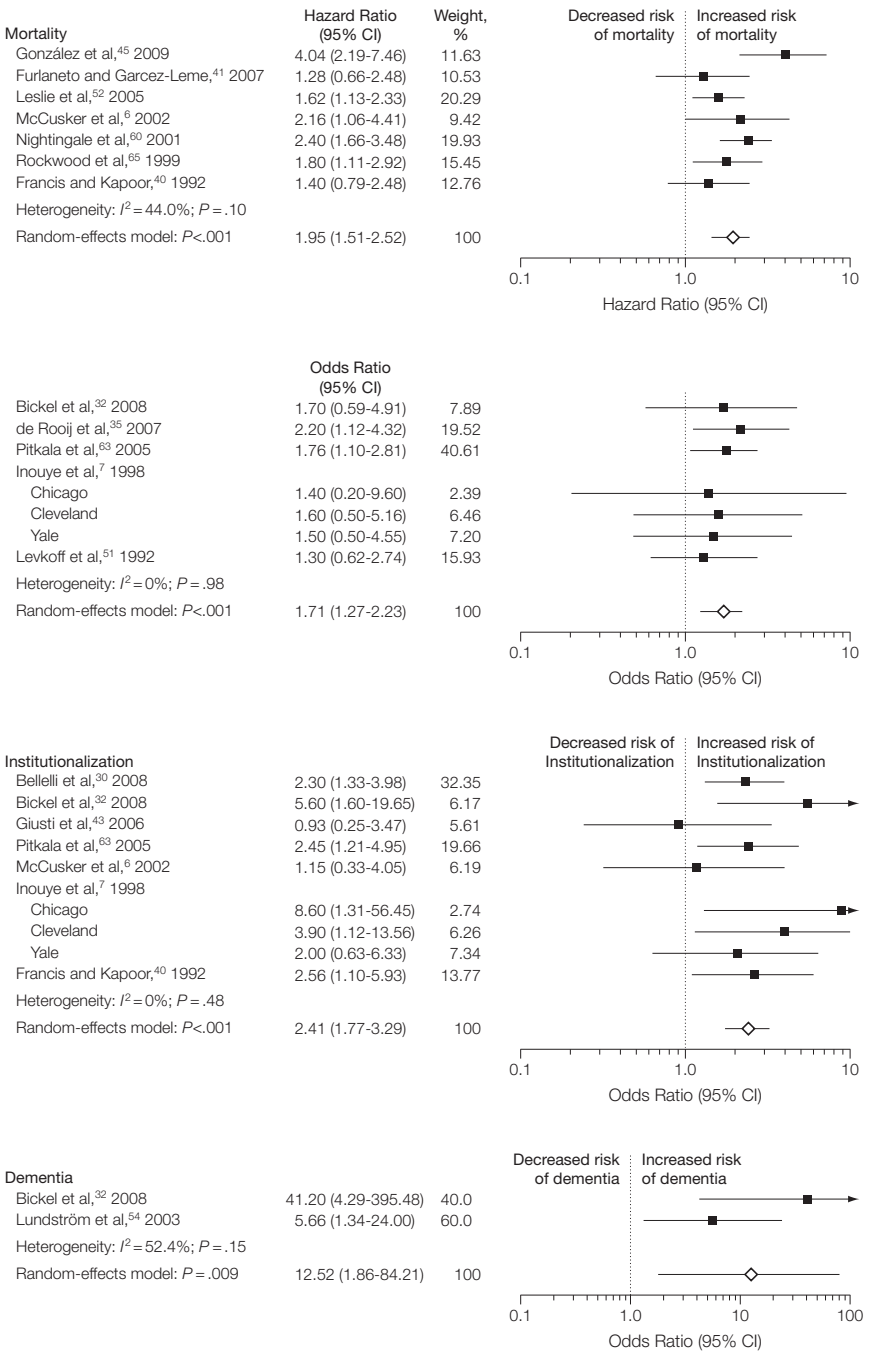
Secondary analyses with unadjusted ORs produced similar results (see the eFigure). Additional stratified analyses with unadjusted ORs showed that higher rates of institutionalization were present among individuals who experienced delirium regardless of the source of the study population (ie, inclusion of individuals with dementia, age, country of origin, and follow-up time; see eTable 5).

Our exploratory secondary analyses showed that delirium remained significantly associated with institutionalization when 80 of 174 patients with delirium superimposed on dementia (46.0%) were compared with 42 of 208 patients with dementia only (20.2%) (OR, 2.55 [95% CI, 1.56-4.18]; I^2, 0%), but the association was not significant when 24 of 108 patients with delirium only (22.2%) were compared with 29 of 237 patients with neither delirium nor dementia (12.2%) (OR, 3.25 [95% CI, 0.85-12.45]; I^2, 66.5%), although the number of patients in these study categories were small and power was limited (Table 2).

Dementia

The primary analysis of adequately adjusted ORs summarized the results of 2 studies and included 241 participants. Thirty-five of 56 patients with delirium (62.5%) had an increased risk of dementia at follow-up compared with 15 of 185 controls (8.1%) after 3.2 and 5.0 years of follow-up (OR, 12.52 [95% CI, 1.86-84.21]; I^2, 52.4%; Figure 2). Because only 2 studies were available for this primary analysis of adjusted risk estimates, no sensitivity or trim-and-fill analyses were performed. The secondary analysis confirmed the results of the primary analysis and showed that the association remained significant

Figure 2. Primary Analyses



Analyses of the association between delirium and mortality, institutionalization, and dementia adjusted for age, sex, comorbid illness or illness severity, and baseline dementia. CI indicates confidence interval. Weighting was assigned according to the inverse of the variance. Hazard ratios and odds ratios larger than 1 indicate increased risk of mortality, institutionalization, or dementia among participants who experienced delirium.

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when only incident cases of dementia (from studies that had the same method of ascertainment at baseline and follow-up) were included (see eTable 5).

COMMENT

The results of this meta-analysis provide evidence that delirium in elderly patients is associated with an increased risk of death, institutionalization, and dementia, independent of age, sex, comorbid illness or illness severity, and presence of dementia at base-

Table 1. Primary Analyses of the Association Between Delirium and Mortality, Institutionalization, and Dementia in Studies Adjusted for Age, Sex, Comorbid Illness or Illness Severity, and Baseline Dementia

	Delirium, No.		No Delirium, No.					
	Events	Total Patients[a]	Events	Total Patients[a]	k[b]	References	HR (95% CI)[c]	I^2, %
Mortality								
Fixed effects	271	714	616	2243	7	6, 40, 41, 45, 52, 60, 65	1.95 (1.62-2.34)	44.0
Random effects	271	714	616	2243	7	6, 40, 41, 45, 52, 60, 65	1.95 (1.51-2.52)	44.0
Postdischarge mortality only	160	414	318	1298	5	6, 40, 41, 52, 65	1.62 (1.29-2.04)	0
							OR (95% CI)	
Fixed effects	183	483	316	1583	7	7, 32, 35, 51, 63	1.71 (1.27-2.30)	0
Random effects	183	483	316	1583	7	7, 32, 35, 51, 63	1.71 (1.27-2.30)	0
Postdischarge mortality only	15	41	17	158	1	32	1.70 (0.59-4.91)	NA
Institutionalization								
Fixed effects	176	527	219	2052	9	6, 7, 30, 32, 40, 43, 63	2.41 (1.77-3.29)	0
Random effects	176	527	219	2052	9	6, 7, 30, 32, 40, 43, 63	2.41 (1.77-3.29)	0
Incident cases only	89	302	161	1829	7	6, 7, 30, 32, 40, 43, 63	2.37 (1.63-3.45)	12.7
Dementia								
Fixed effects	35	56	15	185	2	32, 54	10.06 (2.98-34.0)	52.4
Random effects	35	56	15	185	2	32, 54	12.52 (1.86-84.21)	52.4
Incident cases only	21	30	9	48	1	54	5.66 (1.34-24.0)	NA

Abbreviations: CI, confidence interval; HR, hazard ratio; NA, data not applicable; OR, odds ratio.
[a]The sum total of participants in each subgroup is an estimate because the event rates entered in statistically adjusted analyses were not consistently reported for all studies.
[b]Indicates the number of individual effect estimates in aggregated analyses.
[c]The HRs and ORs that are greater than 1 indicate increased risk of mortality, institutionalization, and dementia among participants who experienced delirium.

Table 2. Primary Risk-Adjusted Analyses and Secondary Unadjusted Analyses

	Delirium, No.		No Delirium, No.		Summary Estimates				Trim-and-Fill Estimates	
	Events	Total Patients	Events	Total Patients	k[a]	RR (95% CI)[b]	P Value	I^2, %	Missing Studies, No.	Adjusted OR (95% CI)[b]
Primary Analyses[c]										
Mortality										
HR	271	714	616	2243	7	1.95 (1.51-2.52)	<.001	44.0	0	1.95 (1.51-2.52)
OR	183	483	316	1583	7	1.71 (1.27-2.30)	<.001	0	0	1.71 (1.27-2.30)
Institutionalization	176	527	219	2052	9	2.41 (1.77-3.29)	<.001	0	1	2.32 (1.69-3.21)
Dementia	35	56	15	185	2	12.52 (1.86-84.21)	.009	52.4	NA	NA
Secondary Analyses										
Mortality[d]	783	2615	1015	7225	40	2.65 (2.34-3.01)	<.001	2.5	7	2.41 (2.08-2.80)
Institutionalization	331	869	338	2826	20	4.73 (3.46-6.47)	<.001	45.2	7	3.61 (2.57-5.07)
Dementia	38	70	66	381	6	9.42 (4.26-20.87)	<.001	23.8	0	9.42 (4.26-20.87)
With dementia										
Mortality	222	643	135	564	18	1.75 (1.30-2.36)	<.001	0.7	2	1.61 (1.16-2.24)
Institutionalization	80	174	42	208	5	2.55 (1.56-4.18)	<.001	0	0	2.55 (1.55-4.18)
Without dementia										
Mortality	168	575	266	1620	17	2.36 (1.82-3.05)	<.001	2.1	4	2.16 (1.56-3.00)
Institutionalization	24	108	29	237	6	3.25 (0.85-12.45)	.04	66.5	0	3.25 (0.85-12.45)

Abbreviations: CI, confidence interval; HR, hazard ratio; NA, data not applicable; OR, odds ratio; RR, risk ratio.
[a]Indicates the number of individual effect estimates in aggregated analyses.
[b]The HRs and ORs that are greater than 1 indicate increased risk of mortality, institutionalization, and dementia among participants who experienced delirium.
[c]The sum total of participants in each subgroup is an estimate because the event rates entered in the statistically adjusted analyses were not consistently reported for all studies.
[d]Edelstein et al[36] did not report event rates for the delirium and no delirium group. Therefore, this study was omitted in the sum total of participants for each subgroup.

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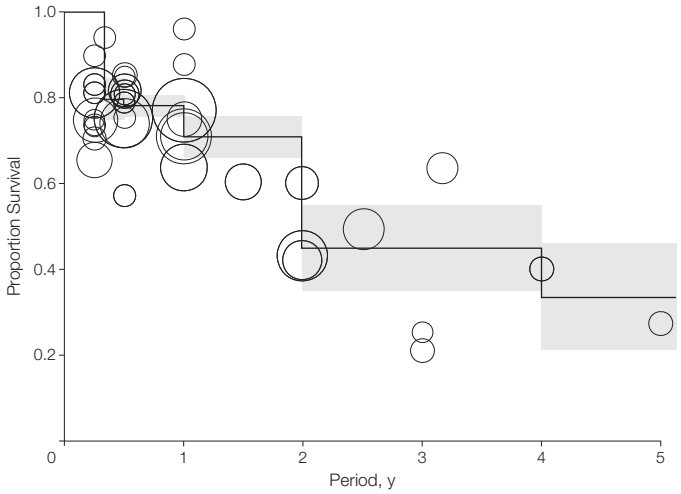
line. Moreover, our stratified models confirm that this association persists when excluding studies that included in-hospital deaths and patients residing in an institution at baseline.

The results of this meta-analysis can be instrumental in patient care. The low rate of survival and the high rates of institutionalization and dementia indicate that older people who experience delirium should be considered an especially vulnerable population (see FIGURE 3 and Table 2). The results of this meta-analysis gain special clinical relevance considering that delirium in some cases can be prevented.[8] However, once delirium is present, management of delirium has not been found to improve long-term mortality or need for institutional care.[67] Thus, identifying patients at high risk for delirium and implementing strategies aimed at preventing delirium may help to avert some of the delirium–associated poor outcomes these patients experience.

Figure 3. Meta-analytic Survival Curve



Based on mortality rates among patients that experienced delirium during hospitalization from studies listed in the eFigure at http://www.jama.com. Circles are proportional to study size and depict the proportion of surviving individuals. For specified periods, aggregated weighted estimates for survival are depicted by a horizontal line with corresponding 95% confidence intervals (gray area). For example, 2 to 4 years after delirium, 45% of individuals are still alive.

This, to our knowledge, is the first study to systematically summarize the risk of poor outcome in elderly patients who experienced delirium. We used a comprehensive search strategy and systematic review method, following recommendations from the MOOSE guidelines.[9] In our meta-analysis, we limited heterogeneity and potential sources of bias by including only high-quality studies in elderly patients in the hospital or postacute care settings, excluding population studies. We identified high-quality studies using individual methodological aspects because summary scores to identify trials of high quality can be problematic.[68] Furthermore, our approach subdivided poor outcome into several categories, thereby avoiding potential heterogeneity that may arise when a single summary estimate is used. Our primary analyses controlled for selected covariates that may influence the association between delirium and poor outcome. We also performed secondary analyses of unadjusted effect estimates and demonstrated that the associations persisted regardless of the study population, the inclusion of nursing home residents or patients with dementia, age, country of origin, and time of follow-up. Heterogeneity, potential outliers, and publication bias were examined and were not responsible for the associations identified.

There are several methodological limitations to our study. Given the nature of delirium, all studies in our meta-analysis are observational; diverse study designs and patient characteristics make interpretation of aggregated estimates challenging and causality cannot be inferred.[9] Nevertheless, delirium was associated with poor outcomes even after controlling for important covariates. Moreover, heterogeneity was low to moderate in the analyses of longer-term outcomes, suggesting that variations in findings are compatible with chance alone and not likely to be caused by genuine differences between studies.[13]

In our meta-analysis, studies were pooled irrespective of their definition of delirium. In most studies, delirium was diagnosed by experts based on criteria derived from the *Diagnostic and Statistical Manual of Mental Disorders*[1,10,69,70]; thus, broadly similar methods were used. With regard to the ascertainment of dementia, more variety was present. For instance, because of the high prevalence of delirium at hospital admission,[71] evaluation of cognitive function based on patient interviews may have overestimated the number of participants with preexisting dementia. Although no significant heterogeneity emerged when we pooled studies that adopted alternative definitions of delirium or dementia, differences in case ascertainment may have introduced some random error.

Only a small number of studies examined the risk of dementia after delirium. Importantly, sensitivity analyses restricted to incident cases of dementia yielded somewhat more conservative estimates of the association between delirium and dementia. Only 1 study[54] provided an adjusted OR based on incident cases, so no meta-analysis could be performed in this most stringent subgroup.

We restricted our search to English- and Dutch-language sources and we did not search gray literature or blind the data abstractors to the data sources. However, we believe that the

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magnitude and consistency of the observed effects render an important effect of bias unlikely in this respect. Moreover, we rigorously controlled for publication bias and used random-effects models that are generally better suited when studies are only gathered from the published literature.[14]

Several important clinical findings emerge from our meta-analysis. The persistence of the association between delirium and poor outcome years after the occurrence of delirium and presumably resolution of the precipitating factors suggests that delirium is not merely a marker of underlying disease. This is substantiated by our finding that the increased risk of poor outcome after delirium cannot readily be explained by predisposing factors, such as age, sex, comorbid illness or illness severity, and presence of baseline dementia. Moreover, the results of our stratified analyses suggest that even patients without the given risk factor analyzed experience adverse outcomes after delirium at least as often as do those with the risk factor. This somewhat counterintuitive finding may be because for vulnerable (eg, older, cognitively impaired) patients, relatively mild precipitating factors suffice to precipitate delirium, whereas in relatively healthier patients, a greater insult is required,[72] and those kinds of insults may be associated with a poorer long-term prognosis. Alternatively, the long-term detrimental effects of delirium in vulnerable populations may compete with other risks for poor outcome. Furthermore, delirium may be more difficult to detect in patients with dementia, resulting in misclassification and bias toward the null.

A number of potential explanations for the observed association between delirium and poor outcome can be hypothesized. Delirium may persist and a protracted course of delirium may contribute to increased morbidity and complications, exemplified by the association between delirium and the new concept of postoperative cognitive dysfunction.[73] In turn, the increased morbidity and complications may lead to poor outcome.[74] Persistence of symptoms can also be an indication that the underlying medical illness is still active or has deteriorated during the follow-up period. Alternatively, the factors that precipitated delirium may incite a detrimental sequence of events in the brain. Through overactivation of microglia and an aberrant stress response, the resulting uncontrolled neuroinflammation, elevation of cortisol levels, and neurotransmitter imbalances can persist for months, reducing the threshold for new episodes of delirium and potentially causing prolongation of neuropsychiatric symptoms.[75,76]

Delirium is a serious and common neuropsychiatric syndrome that may markedly affect outcome and long-term prognosis of elderly patients. Future studies will have to establish what exact mechanisms are responsible for the long-term poor outcomes after delirium and whether clinical characteristics of delirium itself (eg, duration or subtype) differentially influence prognosis. Moreover, clinical trials are needed to investigate whether the long-term sequelae associated with delirium can be averted.

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Study concept and design: van Gool, Witlox.
Acquisition of data: Witlox, Eurelings.
Analysis and interpretation of data: van Gool, Witlox, Eurelings, Eikelenboom, de Jonghe, Kalisvaart.
Drafting of the manuscript: Witlox, van Gool.
Critical revision of the manuscript for important intellectual content: van Gool, Witlox, Eikelenboom, de Jonghe, Eurelings, Kalisvaart.
Statistical analysis: Witlox, van Gool.
Administrative, technical, or material support: Witlox, van Gool, Eurelings.
Study supervision: van Gool, Eikelenboom, de Jonghe, Kalisvaart.
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