Frailty and Delirium in Older Adults: A Systematic Review and Meta-Analysis of the Literature

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OBJECTIVES: To evaluate the relationship between frailty and delirium.

DESIGN: Systematic review and meta-analysis.

SETTING: MEDLINE, EMBASE, PubMed, Scopus, Web of Science, and Google Scholar databases were searched for articles on frailty and delirium published on or before October 31, 2017.

PARTICIPANTS: Individuals aged 65 and older.

MEASUREMENTS: Two authors independently reviewed all English-language citations, extracted relevant data, and assessed studies for potential bias. Articles involving pediatric or neurosurgical populations, alcohol or substance abuse, psychiatric illness, head trauma, or stroke, as well as review articles, letters, and case reports were excluded. Studies underwent qualitative or quantitative analysis according to specified criteria. Using a random-effects or fixed-effects model, relative risk (RR) was calculated for the effect of frailty as a predictor of subsequent delirium. Heterogeneity was tested using Q and I² statistics.

RESULTS: We identified 1,626 articles from our initial search, of which 20 fulfilled the selection criteria (N=5,541 participants, mean age 77.8). Eight studies were eligible for meta-analysis, showing a significant association between Q2 frailty and subsequent delirium (RR = 2.19, 95% confidence interval = 1.65–2.91). There was low variability among studies in the measures of association between frailty and delirium (I² 2.24, p-value Q-statistic = .41) but high heterogeneity in the methods used to assess the two conditions.

CONCLUSION: This systematic review and meta-analysis supports the existence of an independent relationship between frailty and delirium, although there is notable methodological heterogeneity between the methods used to assess the 2 conditions. Future studies are needed to better delineate the dynamics between these syndromes. J Am Geriatr Soc 66:2022–2030, 2018.

Key words: frailty; delirium; geriatric assessment; cognition; review

Frailty is a clinical condition that may be considered the result of a progressive decline in homeostatic capacity and a vicious cycle in which multiple causes and contributors are directly involved.1,2 Frailty implies vulnerability to endogenous and exogenous stressors that exposes the individual to risk of negative health-related outcomes, including medical complications, disability, and death.1,2 Delirium is a serious, potentially preventable, neuro-psychiatric disorder occurring in association with other underlying medical conditions.3 It is characterized by acute onset, fluctuating course, inattention, cognitive dysfunction, abnormal arousal, and behavioral abnormalities.3 Delirium is highly prevalent (affecting 20% of hospitalized older adults)4 and involves enduring adverse effects, including long hospital stay, significant healthcare costs, worsening of functional and cognitive performance, and death.5–8 Delirium is also associated with distress for patients, caregivers, and healthcare professionals.9,10 Although in specific circumstances a single factor may cause delirium, it is commonly accepted that its pathogenesis is multifactorial, depending on complex interactions between predisposing and precipitating factors.7 In particular, the higher the
severity of predisposing conditions, the higher the risk of developing delirium.5

It is hypothesized that frailty underlies and predisposes people to delirium, although no systematic review focusing on this relationship has been conducted. It is important to establish whether frailty and subsequent delirium are associated and to evaluate all available evidence to better understand the nature of this relationship. Therefore, the primary aims of our study were to perform a systematic review of currently available literature focusing on the association between frailty and delirium in older adults and to conduct a meta-analysis to determine whether frailty predisposes individuals to delirium.

METHODS

Search strategy and selection criteria

The systematic review was conducted according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses recommendations.11 The MEDLINE, EMBASE, PubMed, Scopus, Web of Science, and Google Scholar electronic databases were searched for the period from 1966 to October 31, 2017, using the search and corresponding Medical Subject Heading terms “frail*,” OR “vulnerab*,” OR “resilien*” AND “delirium” OR “organic brain syndrome” OR “acute confusion” appearing in the title or in the abstract of published articles. We also manually searched the bibliographies of relevant articles and performed a forward citation search in the databases for all studies examined.

Articles included in the systematic review were written in English and investigated any type of relationship between frailty and delirium, independent of the type of assessment method used. Articles studying children, alcohol or substance use disorders, psychiatric illness, head trauma, stroke, or individuals undergoing neurosurgery were excluded. Review articles, opinion letters, and case reports were also excluded. When data were published more than once, the most recent and complete publication was considered.

The search was restricted to observational studies (cohort, case-control, cross-sectional) because of the absence of meaningful data from randomized clinical trials. Studies were included if they investigated frailty as an exposure, assessed delirium as an outcome, and reported crude or adjusted estimates of the association between frailty and delirium (relative risk (RR), odds ratio, hazard rate ratio, or prevalence ratio and corresponding 95% confidence interval (CI) or p-value) or sufficient raw data to allow their calculation. To be included in the meta-analysis, studies also had to have evaluated frailty and delirium using validated instruments in a precise chronological order (assess frailty after excluding simultaneous presence of delirium), to avoid potential misclassifications of both conditions and reduce heterogeneity between studies.

Data extraction

Two researchers (IP, JH) independently searched for and identified articles for full-text review. Included studies were agreed upon by consensus of three researchers (IP, JH, GB), who also extracted the data. The following data were recorded: name of first author, publication year, study location, and design; study setting and participant population (sample size, mean age, proportion female); methods used to assess frailty and its prevalence; methods used to diagnose delirium and its prevalence or incidence; association estimates with 95% CIs; and variables of adjustment.

Assessment of study quality

Three authors (IP, AZ, GB) independently assessed study quality and reached consensus. Studies eligible for the systematic review were examined for methodological quality using the Newcastle-Ottawa Scale (NOS)12 (Supplementary Table S1 and S2).

Data analysis

The studies were analyzed using a qualitative approach, stratifying for type of outcome (incident vs nonincident). The studies reporting association measures of incident delirium were also analyzed using a meta-analytical approach.

If a study used several methods to classify frailty, only 1 method was included in the meta-analysis, according to the prevalence of frailty reported (excluding methods that yielded extreme prevalence of frailty) and the range of CIs (association estimates with narrow range were considered). We dichotomized frailty into 2 levels (frailty, nonfrail) if it was reported as a continuous variable.

The summary RR of delirium associated with frailty was the measure of interest. Whenever possible, we pooled the adjusted estimates from the original studies; otherwise raw data and computed unadjusted RRs were used. Forest plots were used to appreciate variation in RR estimates that expressed the strength of association between frailty and delirium. We pooled the original estimates using fixed- or random-effects models. Heterogeneity was tested using Q and I² statistics.13 When significant heterogeneity was found, results from the random-effects model were presented.

An analysis was also conducted according to subgroup, considering the strata defined according to study quality level. Heterogeneity among strata levels was assessed using Q statistics, with chi-square distribution and degrees of freedom = number of strata-1.

Publication bias

A funnel plot was used to check for publication or other reporting biases for the studies included in the meta-analysis. The Egger test and “trim and fill” methods were applied to assess the effect of publication bias on the pooled estimates.14,15

For all tests, significance was set at p<.05, and 95% CIs were presented. The corresponding calculations and graphical visualizations of forest and funnel plots were conducted using R system statistical software (version 3.4.3) https://www.r-project.org/about.html.

RESULTS

A total of 1,626 articles constituted the original database (1,599 articles from searched databases and 27 additional
After removal of duplicates, there were 1,207 relevant articles (Figure 1). Upon application of the eligibility criteria, the number of relevant articles was further reduced to 46. These articles were then scrutinized in depth and subsequently reduced to 20, which defined the basis of this work. Overall, 5,541 participants (minimum 35, maximum 1,418) were considered in the present systematic review. Their mean age was 77.8 (range 62–86), and the mean proportion of women was 51.3% (range 24.0–83.0%). The majority of the studies were from European populations (10 studies), followed by North American (6 studies), Australian (3 studies), and Asian (1 study) populations.

The main characteristics of the selected studies are reported in Tables 1 and 2 and Supplementary Table S3. Twelve studies were evaluated only qualitatively because they were determined to be ineligible for meta-analysis, leaving the remaining 8 studies to be evaluated qualitatively and meta-analytically.

Of studies not included in the meta-analysis, 9 did not evaluate delirium as an incident phenomenon, 2 did not specify the method used to classify delirium, and 1 used an ambiguous method to define frailty (used to classify frail participants was not mutually exclusive to other participants in the study).

**Studies analyzed using a qualitative evaluation**

Eleven studies were conducted in acute hospital wards, and 1 involved individuals at home after discharge from an acute hospital. One study focused on individuals with atrial fibrillation; 1 on individuals admitted to a vascular surgical ward; 2 on individuals with cancer, organ failure, or mixed conditions; 1 on individuals admitted to intensive care units (ICU); 3 on individuals with a mix of geriatric, medical, and surgical conditions; and 2 on individuals with hip fracture; studies did not specify the main diagnoses.

To assess frailty, 3 studies used tools based on the deficit accumulation hypothesis (Frailty Index), defined frailty based upon the results of the Comprehensive Geriatric Assessment, used the Edmonton Frailty Scale, 1 used a modified Frailty Phenotype,
1 used the Clinical Frailty Scale, and 1 used the results of the 5-question Frail Scale.

To assess delirium, 5 studies used the Confusion Assessment Method (CAM), – 21, 22, 23, 31, 32 1 the CAM for the ICU (CAM-ICU), 26 1 the Delirium Rating Scale (DRS)-R98, 35 1 the interRAI- Acute Care for Comprehensive Geriatric Assessment (with 2 items used as a screening tool for delirium) 34, and 1 the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) criteria; 20 3 studies did not specify the delirium assessment method, 24, 30, 33. The prevalence of frailty in these studies ranged from 23% to 78%. The prevalence of delirium ranged from 7.9% to 72%. It was 100% in 1 study for which the presence of delirium was a criterion for entry.

Six studies – 20, 21, 24, 30, 32, 34 reported a significant association between frailty and delirium, with measures of association or Relative Risk ranging from 1.46 to 6.7. In 1 study, the RR of 1.46 (95% CI=1.19–1.80) was obtained using 1,418 participants, 34 but no adjustment for confounders was performed. The study for which the presence of delirium was a criterion for entry reported a significant association between frailty and subsyndromal delirium (RR=4.1, 95% CI=2.1–8.2).

Studies analyzed using qualitative and meta-analytical evaluations

All studies included in the meta-analysis were conducted in acute hospital wards and investigated individuals.

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**Table 1. Characteristics of Studies Selected for Qualitative Analysis**

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Participants, n</th>
<th>Frailty Assessment</th>
<th>Score Indicating Frailty</th>
<th>Frail, %</th>
<th>Delirium Assessment</th>
<th>Delirium, %</th>
<th>Relative Risk (95% Confidence Interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kristjansson, 2009</td>
<td>178 24</td>
<td>Comprehensive Geriatric Assessment</td>
<td>2a</td>
<td>42.7</td>
<td>Unspecified</td>
<td>7.9</td>
<td>4.92 (1.42–17.03)</td>
</tr>
<tr>
<td>Eeles, 2012</td>
<td>273</td>
<td>Frailty Index (33 items)</td>
<td>≥ 0.25</td>
<td>40.6</td>
<td>Diagnostic and Statistical Manual for Mental Disorders, 4th Edition, criteria</td>
<td>37.3</td>
<td>3.62 (2.53–5.18)</td>
</tr>
<tr>
<td>Joosten, 2014</td>
<td>220</td>
<td>Modified Frailty Phenotype Study of Osteoprotic Fractures criteria (3 items)</td>
<td>≥ 3/5</td>
<td>40.5</td>
<td>CAM</td>
<td>10.9</td>
<td>0.64 (0.25–2.08)</td>
</tr>
<tr>
<td>Huijtberts, 2015</td>
<td>306</td>
<td>Frailty condition</td>
<td>3b</td>
<td>18.6</td>
<td>CAM</td>
<td>36.8</td>
<td>2.36 (1.84–3.02)</td>
</tr>
<tr>
<td>Kistler, 2015</td>
<td>35</td>
<td>Modified Frailty Phenotype Scale</td>
<td>≥ 3/5</td>
<td>51.4</td>
<td>CAM, chart review</td>
<td>40</td>
<td>2.36 (0.91–6.11)</td>
</tr>
<tr>
<td>Brummel, 2016</td>
<td>1,040</td>
<td>Clinical Frailty Scale</td>
<td>≥ 5/7</td>
<td>30</td>
<td>CAM for the Intensive Care Unit</td>
<td>72</td>
<td>1.02 (0.93–1.10)</td>
</tr>
<tr>
<td>Nguyen, 2016</td>
<td>302</td>
<td>Modified Edmonton Frailty Scale</td>
<td>≥ 8/9</td>
<td>53.3</td>
<td>Unspecified</td>
<td>9.9</td>
<td>1.00 (0.51–1.98)</td>
</tr>
<tr>
<td>Verloo, 2016</td>
<td>114</td>
<td>Edmonton Frailty Scale</td>
<td>≥ 6/9</td>
<td>78</td>
<td>CAM</td>
<td>17.5</td>
<td>2.53 (0.63–10.17)</td>
</tr>
<tr>
<td>McRae, 2016</td>
<td>110</td>
<td>Summary Frailty score</td>
<td>4c</td>
<td>39</td>
<td>CAM</td>
<td>20</td>
<td>6.7 (2.0–22.1)</td>
</tr>
<tr>
<td>Hubbard, 2017</td>
<td>1,418</td>
<td>Frailty Index</td>
<td>InterRAI-Acute Care for Comprehensive Geriatric Assessment score &gt; 0.4</td>
<td>23</td>
<td>InterRAI delirium screen</td>
<td>23</td>
<td>1.46 (1.19–1.80)</td>
</tr>
<tr>
<td>Chew, 2017</td>
<td>234</td>
<td>Frailty Index (20 items)</td>
<td>≥0.25</td>
<td>68</td>
<td>DRS-R98</td>
<td>62.0 5d</td>
<td>4.1 (2.1–8.2) 5d</td>
</tr>
<tr>
<td>Gleason, 2017</td>
<td>175</td>
<td>FRAIL scale</td>
<td>≥ 3</td>
<td>41.7</td>
<td>Unspecified</td>
<td>20</td>
<td>2.10 (1.14–3.84)</td>
</tr>
</tbody>
</table>

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*a Personal Activities of Daily Living (PADL) score <19; instrumental activity of daily living score ≤43; Cumulative Illness Rating Scale: any grade 4 comorbidity, >3 grade 2 comorbidities, or >2 grade 3 comorbidities; ≥7 medications/d; Mini Nutritional Assessment score <17; Mini-Mental State Examination (MMSE) score ≤24; Geriatric Depression Scale score >13.

*b Living in nursing home or other shelter or combination of MMSE score ≤24 and modified Katz ADL score ≤8.

*c Baseline dependency in ≥1 ADLs, Abbreviated Mental Test score ≤7, or Malnutrition Screening Tool score ≥2.

*d For residual subsyndromal delirium, CAM = Confusion Assessment Method.

Further explanations are given in the Supplementary Table S3.
undergoing elective cardiac or vascular surgery\textsuperscript{16,18,19,25,28,29} or noncardiac surgery.\textsuperscript{17,27}

The criteria for measuring frailty in these studies were highly heterogeneous. Two studies used the frailty phenotype model,\textsuperscript{27,29} 1 the Edmonton Frailty Scale,\textsuperscript{25} and 1 the Groningen Frailty Index.\textsuperscript{16} Two studies used 2 different methods (1 used clinical judgment and a summary score from baseline Comprehensive Geriatric Assessment components,\textsuperscript{18} 1 used the Groningen Frailty Index and rated the ones own physical fitness), 1 study\textsuperscript{28} used 3 methods (modified Frailty Phenotype, Short Physical Performance Battery, 35-item Frailty Index), and 1 study\textsuperscript{19} used 6 methods (5-m walking test, Canadian Study of Health and Aging, Katz index, handgrip strength, Identification of Seniors at Risk).

The criteria for measuring delirium were equally heterogeneous. Three studies used a chart-based method for the retrospective identification of delirium,\textsuperscript{17,19,29} two studies used the Confusion Assessment Method (CAM),\textsuperscript{25,27} one study used the CAM-ICU in addition to the CAM,\textsuperscript{28} and one study used the DSM-IV criteria.\textsuperscript{18} Additionally, another study used the Delirium Observation Scale as a screening tool to inform the DSM-IV, Text Revision, criteria.\textsuperscript{16} The prevalence of frailty in these studies ranged

\begin{longtable*}{|l|l|c|c|c|c|c|}
\hline
\textbf{Author, Year} & \textbf{Participants, n} & \textbf{Frailty Assessment} & \textbf{Score Indicating Frailty} & \textbf{Frail, \%} & \textbf{Delirium Assessment} & \textbf{Delirious, \%} & \textbf{Relative Risk (95\% Confidence Interval)} \\
\hline
Leung et al., 2011\textsuperscript{27} & 63 & Modified Frailty Phenotype & \(\geq 3/5\) & 27 & CAM & 30 & 1.96 (0.86–4.45) \\
\hline
Pol et al., 2011\textsuperscript{16} & 142 & Groningen Frailty Index & \(\geq 4/15\) & 35.2 & Delirium Observation Scale plus DSM-IV & 7 & 3.18 (0.98–10.32) \\
\hline
Jung et al., 2015\textsuperscript{28} & 133 & Frailty Index & \(\geq 0.3/35\) & 35.3 & CAM, CAM for the Intensive Care Unit & 18 & 3.72 (1.39–9.92) \\
 & & Modified Frailty Phenotype & \(\geq 3/7\) & 54.1 & & & 5.06 (1.58–16.13) \\
 & & Short Physical Performance Battery\textsuperscript{a} & \(\leq 9\) & 52 & & & 2.39 (0.90–6.38) \\
 & & Short Physical Performance Battery\textsuperscript{b} & 4–6 & 35 & & & 8.26 (2.23–30.64) \\
\hline
Hempenius et al., 2015\textsuperscript{17} & 251 & Groningen Frailty Index & \(\geq 4/15\) & 28.3 & Chart based & 18.3 & 1.78 (1.06–3.0) \\
 & & Rating Physical Fitness\textsuperscript{c} & \(\leq 6/10\) & 26 & & & (0.73–3.25) \\
\hline
Partridge et al., 2015\textsuperscript{25} & 125 & Edmonton Frailty Scale & \(\geq 6.5/9\) & 52 & CAM & 19.2 & 1.54 (0.73–3.25) \\
\hline
Brown et al., 2016\textsuperscript{29} & 55 & Modified Frailty Phenotype & \(\geq 3/5\) & 30.9 & Chart-based & 16.4 & 18.30 (2.10–161.80) \\
\hline
Assmann et al., 2016\textsuperscript{18} & 89 & Clinical judgment & & 53 & DSM-IV & 28 & 3.10 (1.14–8.46) \\
 & & Summary frailty score & & \textsuperscript{a} & & & 3.78 (2.12–6.72) \\
Bagienski et al., 2017\textsuperscript{19} & 141 & 5-m walking test & \(\geq 6\) seconds & 10.6 & Chart based & 20.5 & 4.35 (2.48–7.64) \\
 & & Elderly Mobility Scale\textsuperscript{d} & \(\geq 7\) & 3.5 & & & 4.50 (2.64–7.67) \\
 & & Canadian Study of Health and Aging Katz index & \(\geq 5\) & 7.8 & & & 0.35 (0.18–0.66) \\
 & & Grip strength & \(< 9\) & 90.1 & & & 6.04 (5.33–6.86) \\
 & & Identification of Seniors at Risk score & \(< 2\) & 33.3 & & & 2.14 (1.13–4.06) \\
\hline
\end{longtable*}

\textsuperscript{a}Summary score from baseline components: Mini-Mental State Examination score \(\leq 27/30\), activity of daily living score \(\leq 1\), instrumental activity of daily living score \(\leq 1\), Mini Nutritional Assessment score \(< 12\), impaired mobility (gait speed over 4 m \(< 0.75\) m/s and Timed Up & Go test \(\geq 12.5\) seconds).

CAM = Confusion Assessment Method; DSM-IV = Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition; nr = not reported.

Further explanations provided in Supplementary Table S3.
from 2.8% when using grip strength as the reference method\textsuperscript{19} to 90.1%, which was reported in the same study using the Katz Index as the reference method.\textsuperscript{19} The incidence of delirium ranged from 7.0%\textsuperscript{16} to 30.0%.\textsuperscript{27}.

According to the above-mentioned criteria, if there was more than 1 definition of frailty, only 1 was selected (as determined a priori) to conduct the necessary calculations; in 1 study,\textsuperscript{17} the selected method was the Rating Physical Fitness, and in another,\textsuperscript{18} the selected method was clinical judgment, because these variables were presented as dichotomous. In another study,\textsuperscript{19} we chose the Identification of Seniors at Risk because of the prevalence of frailty.

Quality of methodology of studies in systematic review

The quality of methodology was evaluated for all the studies included in the systematic review with qualitative or quantitative analysis (Supplementary Tables S1, S2, S4). None of the studies was assigned 9 points (the maximum score), suggesting overall suboptimal quality. Of the studies evaluated for the qualitative analysis, 1 was assigned 8 points,\textsuperscript{35} 3 were assigned 7,\textsuperscript{22,23,34} 3 were assigned 6,\textsuperscript{21,26,32} 4 were assigned 5,\textsuperscript{20,30,31,33} and 1 was assigned 4,\textsuperscript{24} suggesting insufficient methodological quality. Of the studies selected for quantitative evaluation, 2 were assigned 8 points,\textsuperscript{28,29} 3 were assigned 7,\textsuperscript{19,25,27} 2 were assigned 6,\textsuperscript{17,18} and 1 was assigned 4,\textsuperscript{16} suggesting insufficient methodological quality.

Meta-analytical results and funnel plot

The meta-analytical summary association estimate between frailty and subsequent delirium was based on a fixed-effects model, showing a significant association (RR=2.19, 95% CI = 1.65–2.91) (Figure 2). There was low heterogeneity among estimates (I\textsuperscript{2} 29.87, p-value Q-statistic=.22; low-quality studies, I\textsuperscript{2} 0, p-value Q-statistic=.87).

The funnel plot and the Egger test (p <.001) suggested systematic bias in reporting (Supplementary Figure S1), although the summary RR estimate corrected using the “trim and fill” approach (RR=1.94, 95% CI=1.49–2.53) was marginally lower than the original summary estimate reported in the main analysis.

DISCUSSION

To the best of our knowledge, this is the one of first systematic reviews and meta-analyses to investigate the relationship between frailty and delirium in older adults. We found a small amount of available evidence, with only 20 studies published on this topic and 8 that qualified for the meta-analysis. Furthermore, these studies were of fair to good (but not excellent) quality and were heterogeneous in the makeup of their study populations and the definitions of the variables of interest (frailty and delirium). Nevertheless, our findings show that frailty significantly predisposes individuals to subsequent delirium. The quality levels of the evaluated studies did not influence the association between frailty and subsequent delirium, but the risk of bias was relevant because many studies did not adjust for confounders.

The paucity of studies that evaluated frailty as a predisposing factor for delirium was an unexpected finding of this work, given that the relationship between these conditions is generally assumed and accepted in clinical practice.\textsuperscript{36} We therefore hope that our article spurs new research in this field.

We found notable heterogeneity between methods used to assess frailty and delirium in the selected studies. Frailty was assessed in most studies using common, well-accepted methods,\textsuperscript{23,27–29,33} whereas other studies used instruments based on relatively arbitrary evaluations or questionnaires meant to assess self-reported complaints.\textsuperscript{30} Delirium too was assessed using several, often suboptimal, approaches.
A key statement outlining common guidelines is that delirium should be assessed using standardized procedures and validated screening tools, if not, the risk of underdetecting delirium is substantial, although this was not the case in some of the studies included in our systematic review. For example, in one study, delirium was assessed on alternate days from admission to discharge, and in another study, a geriatrician screened for and subsequently diagnosed delirium only when the nursing staff highly suspected its presence. Other studies evaluated delirium without using any method, which is probably why the incidence of postoperative delirium was lower in these studies than in others that used a standardized approach.

Assessing frailty and delirium using various instruments is a common practice, which probably reflects the lack of standardization and specific guidelines for these conditions in the field. Future studies and, it is hoped, a consensus conference should be considered to define the most appropriate approaches to evaluating these conditions. This step is probably a prerequisite for larger multicenter studies with the aim of assessing the true relationship between these conditions.

Despite the small number of studies available and the variability in the methods used to assess frailty and delirium, our meta-analysis found a significant association between frailty and delirium. In particular, the risk of developing delirium was 2.2 times as great in individuals who were frail, and the quality of the studies seemed not to influence the nature of this relationship.

Frailty and delirium are multifactorial conditions that share many common aspects. Both conditions are associated with negative health-related events, and a common pathophysiology has been hypothesized that involves chronic inflammation, the endocrine and vascular systems, oxidative stress, and nutritional deficiencies. Nevertheless, frailty and delirium should also be considered distinct phenomena. Frailty may be considered to be the result of chronic decline in various biological functions, whereas delirium is an acute condition. Therefore, frailty should be regarded as a predisposing factor for delirium, because it contributes to one’s homeostatic reserves and susceptibility to negative outcomes. At the same time, delirium may be a syndromic presentation of an overt clinical manifestation of underlying frailty.

Our study has several noteworthy strengths. First, we used a comprehensive search strategy and systematic review method, consulting several databases in the process. Second, we controlled for potential sources of bias by adopting

### Table 1: Relative Risk Estimates

<table>
<thead>
<tr>
<th>Author, year</th>
<th>RR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>High quality studies</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>JUNG, 2015</td>
<td>3.72</td>
<td>[1.39, 9.94]</td>
</tr>
<tr>
<td>LEUNG, 2011</td>
<td>1.96</td>
<td>[0.86, 4.45]</td>
</tr>
<tr>
<td>BROWN, 2016</td>
<td>18.30</td>
<td>[2.08, 160.63]</td>
</tr>
<tr>
<td>BAGIENSKI, 2017</td>
<td>2.14</td>
<td>[1.13, 4.06]</td>
</tr>
<tr>
<td>PARTRIDGE, 2015</td>
<td>1.54</td>
<td>[0.73, 3.25]</td>
</tr>
<tr>
<td>FE Estimate</td>
<td>2.24</td>
<td>[1.53, 3.27]</td>
</tr>
<tr>
<td><strong>Low quality studies</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HEMPENIUS, 2015</td>
<td>1.78</td>
<td>[1.06, 3.00]</td>
</tr>
<tr>
<td>POL, 2011</td>
<td>3.18</td>
<td>[0.98, 10.32]</td>
</tr>
<tr>
<td>ASSMANN, 2016</td>
<td>3.10</td>
<td>[1.14, 8.44]</td>
</tr>
<tr>
<td>FE Estimate</td>
<td>2.13</td>
<td>[1.39, 3.27]</td>
</tr>
</tbody>
</table>

Figure 3. Forest plots of relative risk (RR) estimates found for effect of frailty as predictor of subsequent delirium according to quality of study. High-quality studies: $I^2 = 29.87248$, test for heterogeneity between strata: $Q$ (degrees of freedom $df=1$) = 5.70, $p=.22$. Low-quality studies: $I^2 = 0$; test for heterogeneity between strata: $Q$ ($df=1$) = 0.02, $p=.87$. CI = confidence interval; FE=fixed-effects model used to calculate estimate.
clear, predetermined selection criteria, and we evaluated the quality of the studies using a well-validated, commonly used approach (NOS). Third, the meta-analysis allowed us to extend conclusions beyond cohorts included in a specific study, particularly given the limited number of studies and the small study sizes. Fourth, the criteria to qualify for meta-analysis were rigorous, trying to control for heterogeneity among studies. Fifth, the quality of the studies did not influence the meta-analytical results.

Several limitations of our study should also be considered. First, the studies included in this analysis had very heterogeneous study populations, variable methods for collecting information on outcome variables, and in at least one case, inadequate methods for assessing a critical outcome variable. Thus, the conclusions reached must be considered carefully. Second, the final number of selected studies was small, and many had small sample sizes. Third, many studies did not mention whether assessors were blinded to the predisposing factor or the outcome, which is a potential source of bias. Fourth, many studies evaluated frailty and delirium only in specific populations, such as individuals with cardiovascular problems, neoplasms, or atrial fibrillation. Fifth, there were differences in how primary outcomes were measured. Most studies assessed frailty and delirium using a dichotomous approach (present vs absent). This approach may have biased the study results and thus the interpretation of our review, given that both conditions are gradable in terms of severity. Moreover, some studies assessed delirium on a single day and did not consider the possibility that the presentation of delirium may fluctuate during the course of the day or week. Therefore, it is possible that a higher-than-reported proportion of participants might have had delirium in some of the selected studies. Sixth, a possible publication bias cannot be excluded, although it did not seem to have influenced the measures of association between frailty and delirium (or the relative risk) among studies of estimates substantially. A final possible limitation is that we limited our search strategy to studies published in English, although only 3 additional articles in other languages (1 Dutch, 1 French, 1 German) were published during the same period in peer-reviewed indexed journals.

In conclusion, this study is the first to quantify the relationship between frailty and delirium. These results should be interpreted with caution, given the small number of studies available and the presence of considerable methodological heterogeneity. More research is needed to better delineate the dynamic relationship between frailty and delirium—2 geriatric conditions that severely burden individual quality of life and the healthcare system.

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REFERENCES


SUPPORTING INFORMATION

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

Figure S1: Funnel plot to check for publication bias of selected studies.

Table S1: Original Newcastle Ottawa Scale and Survey Questions for Cohort Studies

Table S2: Adapted Newcastle Ottawa Scale and Survey Questions for Cross-Sectional Studies

Table S3: Characteristics of Studies Included in Systematic Review

Table S4: Summary of Assessment of Risk of Bias (Using Newcastle Ottawa Quality Assessment Scale) for Studies Included in Systematic Review