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FEATURED ARTICLE

The economic cost of delirium: A systematic review and quality assessment

Irina Kinchin[1,2] | **Eileen Mitchell**[1] | **Meera Agar**[2] | **Dominic Trépel**[1]

[1] Trinity College Institute of Neuroscience, School of Medicine, Trinity College Dublin, the University of Dublin, Dublin, Ireland

[2] University of Technology Sydney, Sydney, New South Wales, Australia

Correspondence
Irina Kinchin, Trinity College Dublin, the University of Dublin, Dublin D02 PN40, Ireland.
E-mail: kinchini@tcd.ie

[Correction added on May 25, 2021, after first online publication: An typographical error in Table B.1 was removed.]

Abstract

Introduction: This review aims to systematically identify and appraise the methodological quality of claims on the cost of delirium; and discuss challenges and opportunities for improvements in the precision of the estimates.

Methods: Searches of scientific papers and gray literature were performed up until June 2020. The Larg and Moss checklist was used to assess the methodological quality of the included studies.

Results: After deduplication, the search identified 317 potentially relevant articles, of which 17 articles were eligible for inclusion. After adjusting for inflation and common currency, the cost of delirium ranged between $806 and $24,509 (in 2019 US$).

Discussion: This review found significant variation among the cost estimates and methodological quality. There has been limited focus on dementia as a sequela of delirium in terms of economic implications, but recent evidence suggests cost implications of delirium may be 52% higher when dementia is considered.

KEYWORDS
cost, cost of illness, delirium, economic impact, methodology, quality assessment, systematic review

1 | INTRODUCTION

1.1 | Background on delirium

Delirium is an acute and often fluctuating syndrome characterized by a decline in cognitive functioning, typically triggered by sudden and severe illness, surgery, hospitalization, or by medications.[1–3] The development of delirium has been associated with increased morbidity;[4] persistent functional decline;[5] increased frailty;[6] and higher demand for overall health care including increased nursing time per patient,[7] increased length of hospital stay and associated cost,[8] higher subsequent rates of nursing home placement,[9] and mortality.[10]

Apart from these general economic implications, delirium is increasingly being recognized as an important risk factor and a possible trigger for many brain aging disorders.[3,11,12] Delirium is linked to the acceleration of cognitive decline, and it may also reveal vulnerability due to pre-existing dementia pathology in non-demented or mildly impaired individuals, reducing time to dementia diagnoses.[11,12] Due to the recognition of delirium as a risk factor for dementia, there is currently unprecedented public health potential to lessen the cognitive and physical burden of delirium. This includes a better understanding of the true economic impact of this condition.[3]

In a global health blueprint for actions, Khachaturian et al.[3] call to advance the field of delirium along five pillars: diagnosis, awareness, burden, biology, and policy. This article aims to understand the economic burden of delirium and its additional cost, the magnitude of the cost in different health-care settings, and specific cost drivers to guide the policy development aimed at reducing the risk of delirium.

1.2 | Background on cost of illness studies

Evidence suggests that delirium is avoidable in 30% to 40% of cases[13,14] and thus holds substantial relevance as a target for

cost-effective measures aimed at reducing the risk of delirium.[15] In this context, cost of illness studies can be sought to help prioritize the relative importance of specific disease areas[16] and, where estimates are considered accurate, can provide a basis for further economic evaluations, such as cost-effectiveness, cost-utility, and cost-benefit analysis.[17,18] Such information, it is argued, "can help to determine research and funding priorities by highlighting areas where inefficiencies may exist and savings be made."[19,20]

Cost of delirium is reported over several varying sources, though, to the best of our knowledge, no study has systematically appraised the methodological quality of these claims. Lacking, poor quality, or inconsistent information can be a case of accuracy to inform investment decisions or may unfairly motivate investment into areas with limited reassurance of return on the investment, or indeed benefit, to the end user.[21]

To ensure appropriate policy response, readers must query the validity of cost-of-illness studies.[16,20] The level and the magnitude of the cost variation raise significant questions on methodological quality and the basis for delirium policy. "Area of high expenditure does not provide enough information to suggest inefficiency and waste and so should not automatically take precedence for further scrutiny."[20] Cost-of-illness studies are often restricted to a certain country, deal with small patient groups, or present only a part of all illness costs. A systematic assessment of the quality of evidence generated by cost-of-illness studies for delirium is warranted in identifying cost drivers, contextualizing the substantial variation in findings, as well as in identifying opportunities for improvements in the precision of the burden.

RESEARCH IN CONTEXT

1. Systematic Review: The authors reviewed Embase, MEDLINE, PsychInfo, PsycARTICLES, Econlit, and the NHS Economic Evaluation Database sources plus article reference lists. To our knowledge, this is the first review that systematically identified and appraised the methodological quality of claims on the costs attributable to delirium against best-practice guidelines; and discussed challenges and opportunities for improvements in the precision of the estimates.
2. Interpretation: This review found significant variation among cost estimates and differences in the methodological quality.
3. Future Directions: Efforts should be made to facilitate standardization of cost of illness terminology for delirium and delirium case detection to allow benchmarking and re-use of results from subsequent evaluation studies. Further research to better understand the economic relationship between delirium and dementia is warranted.

2 | METHODS

2.1 | Aims and objective

This review aims to systematically review published claims on the cost of delirium in different settings, to apply established tools to assess their quality and validity, and to identify challenges with conducting such studies. The goal of this review is to draw attention to sound economic arguments. This review addresses the following research questions (RQ):

RQ1: What is the additional economic cost of delirium in different settings?

RQ2: Does the cost differ, why, and which estimates should be cited?

RQ3: How does the cost and the quality of studies change over time?

RQ4: What proportion of the cost of delirium studies consider cost associated with sequela dementia, and to what degree might dementia increase cost implications of delirium?

2.2 | Protocol and registration

This review conforms to the evidence-based guidelines in the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines.[22] The systematic review was registered in the PROSPERO database (CRD42020188487).

2.3 | Eligibility criteria and study selection

Using the PICO model, we searched for primary studies that estimated the cost of delirium as a primary or secondary Outcome (PICO). Due to the investigative nature of this review, we did not put any limits on Population (PICO) or Comparison (PICO). We excluded full economic evaluations of Interventions (PICO), which deserve an independent review.[23]

We excluded studies with no cost data associated with, or attributable to, delirium; and non-English language studies, due to the lack of access to an interpreter. We excluded conference abstracts, posters, and studies without full text available. We excluded studies on delirium tremens (ie, among patients with alcohol withdrawal) due to specific etiology and associated clinical management.

2.4 | Information sources

Studies were identified by searching electronic databases and supplemented with backward snowballing, ie, identifying articles from the reference lists. The search was applied to Embase, MEDLINE, PsychInfo, PsycARTICLES, Econlit, and The NHS Economic Evaluation Database. Additional gray literature was identified using Google Advanced Search. The final search was run on June 4, 2020.

Each database was searched using the keywords "Delirium" and "Cost" and associated medical subject heading (MeSH) terms for the MEDLINE/PubMED. The MEDLINE search strategy is reported in Appendix A. All references were imported into EndNote software

where duplicates were removed. Eligibility assessment was performed in an unblinded standardized manner by two reviewers (IK and EM).

2.5 | Data collection process

To provide a comprehensive understanding of the included studies, we developed a data extraction sheet, pilot tested it on five randomly selected included studies, and refined accordingly. Information was extracted from each included study on the country of origin, publication year, study size, costing as a primary focus (Y/N), epidemiological approach, method of resource quantification, study period and the cost reference year, perspective, study design, mean age of participants/study subjects, setting, currency, cost category and cost components, the number of citations, main data source, the definition of delirium, and delirium assessment tools. When the epidemiological approach, method of resource quantification, or the cost reference year were not clearly specified, a consensus was achieved by discussion among the investigators.

2.6 | Quality assessment in individual studies

The Larg and Moss checklist[19] was used to ascertain the validity of the included studies as a quality criterion. Key elements of quality that were considered: (1) analytical framework: what costs should have been measured? (2) methodology and data: how well were resource use and productivity losses measured? (3) analysis and reporting: how well were the analysis and reporting performed?

Quality assessment was performed independently by two investigators (IK and EM). The investigators compared results and resolved discrepancies through discussion. The investigators assigned a global quality score to each individual study derived as a proportion of "Yes" answers out of the total 17 questions in the checklist. Cohen's kappa statistics ranged between 0.7 and 0.8, which is consistent with a substantial agreement.[24]

2.6.1 | Cost versus quality versus citations

To explore variability in study results (heterogeneity), we specified the following hypotheses before conducting the analysis. We hypothesized that the average number of citations per year might differ according to the methodological quality of the studies and the magnitude of the reported cost.

2.7 | Summary of evidence and adjustment to aid comparison

The primary outcome measure was to extract the additional cost associated with delirium, ie, an "incremental cost" of delirium. In cases in which the incremental cost of delirium was not reported, ie, costs were reported separately for delirium (C_1) and non-delirium groups (C_2), these costs were converted into the cost difference by subtracting the cost of the non-delirium group from the cost of the delirium group ($C_1 - C_2$).

To allow for comparability among varying years and local currencies, reported costs were transferred from the local currency in the year of the costs to the inflated values in local currency for the year 2019, for which the latest statistics are available.[25] To allow for international comparison of costs, country costs of delirium were further converted to U.S. dollars by using the gross domestic product purchasing power parity (PPP;[26] Appendix D). Due to heterogeneity of the cost estimates and the lack of essential statistics being reported (eg, standard error, variance, or confidence interval), a meta-analysis was not performed.

3 | RESULTS

3.1 | Literature search

The PRISMA flowchart (Figure 1) outlines the search and retrieval process. The search identified 632 studies. We removed 315 duplicate articles after merging the citations from all databases. Screening of article titles and abstracts resulted in 41 potentially eligible studies. Full texts of these studies were retrieved and reviewed for inclusion. Finally, 24 potentially eligible studies were excluded[9,27-49], leaving 17 studies for inclusion (Appendix B). Table 1 provides an overview of the included studies.

3.2 | Cost estimates

The cost of delirium estimates varied considerably depending on the settings and the methodology used (Figure 2). All studies measured the direct cost of delirium associated with a prolonged inpatient stay, but one[50] also measured funeral expenses borne by family and friends of people with delirium and the deadweight loss due to lost taxation revenue. This study adapted a societal perspective, and in addition to the direct costs associated with delirium, estimated indirect and intangible costs. Indirect costs included productivity losses associated with absenteeism and informal care. Intangible costs were described as the loss of well-being, including pain, suffering, and premature mortality, all measured in terms of disability adjusted life years.

Two studies out of 15 considered costs associated with sequela dementia. Pezzullo et al.[50] further estimated 10.6% of dementia cases were associated with delirium. The total costs of dementia due to delirium were estimated to be £2.2 billion in Australia in 2016-17 out of the total cost of delirium of £4.3 billion. In other words, the cost of dementia attributable to delirium accounted for 52% of the total cost of delirium. According to Fick et al.,[51] delirium led to a 50% and 37% higher health-care cost among those diagnosed with delirium superimposed on dementia or dementia only, respectively.

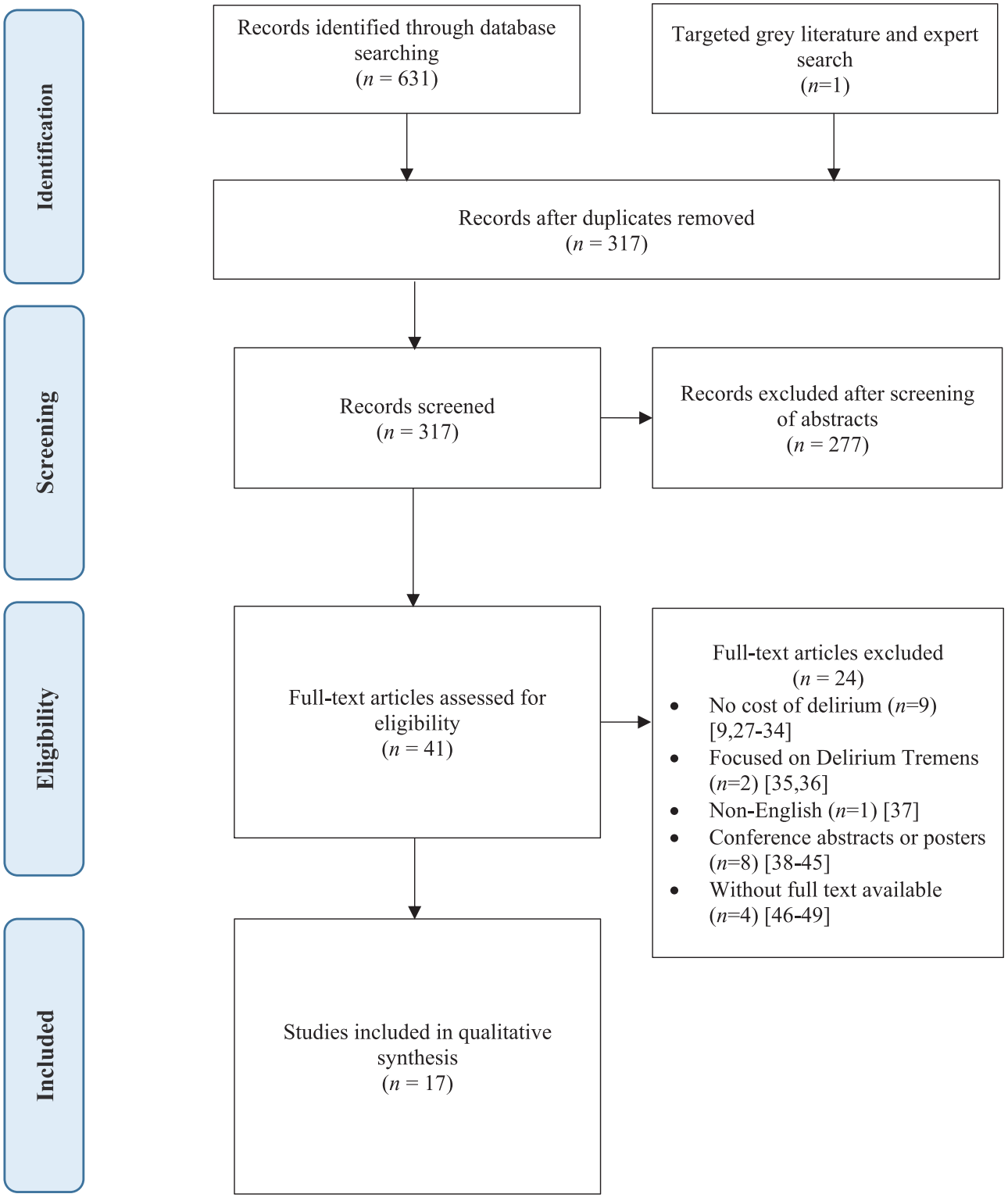

FIGURE 1 Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) flowchart of the literature search strategy

3.3 | Quality critique

The quality of the included studies was generally poor to moderate according to the Larg and Moss quality assessment checklist[19] (Appendix C). Seven studies (41%) were rated below 50%.[52–58] Seven studies (41%) met 51% to 79% of the quality checklist criteria.[51,59–64] Only three studies (18%) were in the top 80 and over of the quality checklist criteria.[50,65,66]

The reasons for deductions resulted from the lack of sensitivity analysis (82%); cost perspective (71%), hence the inability of an evaluator

TABLE 1 Summary characteristics of the included studies (n = 17)

Characteristic	Number (%)	Reference
Country of origin		
United States	10 (59%)	51,52,54,59–64,66
Australia, Canada, Germany, Spain, Switzerland, Korea, China	1 each (44%)	50,53,55–58,65
Costing as primary focus		
Yes	15 (88%)	50–56,59–66
No	2 (13%)	57,58
Health-care setting that patient cohort originated from		
Inpatient	15 (88%)	
Community	3 (18%)	50,51,64
Inpatient type		
Surgical	8 (53%) out of 15	52,54–56,60–62,65
Medical	2 (13%) out of 15	53,64
Medical and Surgical	1 (7%) out of 15	57
ICU	4 (27%) out of 15	58,59,63,66
Inpatient health area		
Cardiac	2 (13%) out of 15	61,62
Cancer	2 (13%) out of 15	52,60
Non-cardiac	2 (13%) out of 15	54,56
Orthopedic	2 (13%) out of 15	55,65
Palliative	1 (7%) out of 15	57
General	2 (13%) out of 15	53,64
ICU	4 (27%) out of 15	58,59,63,66
Study design		
Prospective	9 (53%)	52,54,57–59,62,63,65,66
Retrospective	7 (41%)	51,53,55,56,60,61,64
Secondary data analysis	1 (6%)	50
Delirium assessment tool*		
CAM	6 (35%)	53,54,56,62,64,65
CAM-ICU	4 (24%)	58,62,63,66
RASS	3 (18%)	58,63,66
CAPD	1 (6%)	59
DOS-13	1 (6%)	57
Delirium Rating Scale-Revised-98	1 (6%)	62
ICD-9 diagnosis codes	4 (24%)	51,55,60,61
Perspective		
Hospital	3 (18%)	63,65,66
Pediatric ICU	1 (6%)	59
Societal	1 (6%)	53
Not specified	12 (71%)	50–52,54–58,60–62,64
Data sources		
A hospital electronic system	9 (53%)	52–55,59,62,63,65,66
US Medicare	2 (12%)	61,64
US Health system claims data	1 (6%)	51
US Premier Hospital Database	1 (6%)	60
Australian Independent Hospital Pricing Authority	1 (6%)	50
Not stated	3 (18%)	56–58
Top-down or bottom-up costing methodology		
Bottom-up	17 (100%)	50–66
Mixed: top-down and bottom-up	1 (6%)	50
Cost reported		
Direct	17 (100%)	50–66
Inpatient	17 (100%)	50–66
Outpatient	3 (18%)	50,51,64
Indirect	1 (6%)	50
Intangible	1 (6%)	50

Abbreviations: CAM, confusion assessment method; CAPD, Cornell Assessment for Pediatric Delirium; DOS-13, 13-item delirium observation screening scale; ICD-9, International Classification of Diseases, Ninth revision; ICU, intensive care unit; RASS, Richmond Agitation Sedation Scale. *One study can use a combination of assessment tools.

to assess the relevance of cost components; omission of incremental or additional disease-attributable (excess) cost (59%); application of suitable ratios to convert prices to more accurate values of resource use, such as cost-to-charge ratios (53%);[67] and unclear timeframe (47%). These were the areas with the most quality variation (refer to supporting information 1 for an extended summary of quality critique). Among other resource quantification issues were lack of discussion of the generalizability to other settings; issues with the identification of delirium; failure to account for baseline differences and skewed costing data; adjustment for discounting for a study over 1 year.

3.4 | Cost versus quality versus citations

Spearman correlation analyses found weak/fair positive correlations between the methodological quality of the studies and the cost (r_s[18] = 0.443, P = 0.065), the cost and the average number of citations per year (r_s([18] = 0.154, P = 0.541), the methodological quality of the studies, and the average number of citations per year (r_s[18] = 0.378, P = 0.121). These associations were not statistically significant[68] (Figure 3).

3.5 | Change in cost and quality over time

When analyzed over time, the magnitude of the cost of delirium seemed to increase though not statistically significantly] (Figure 4).

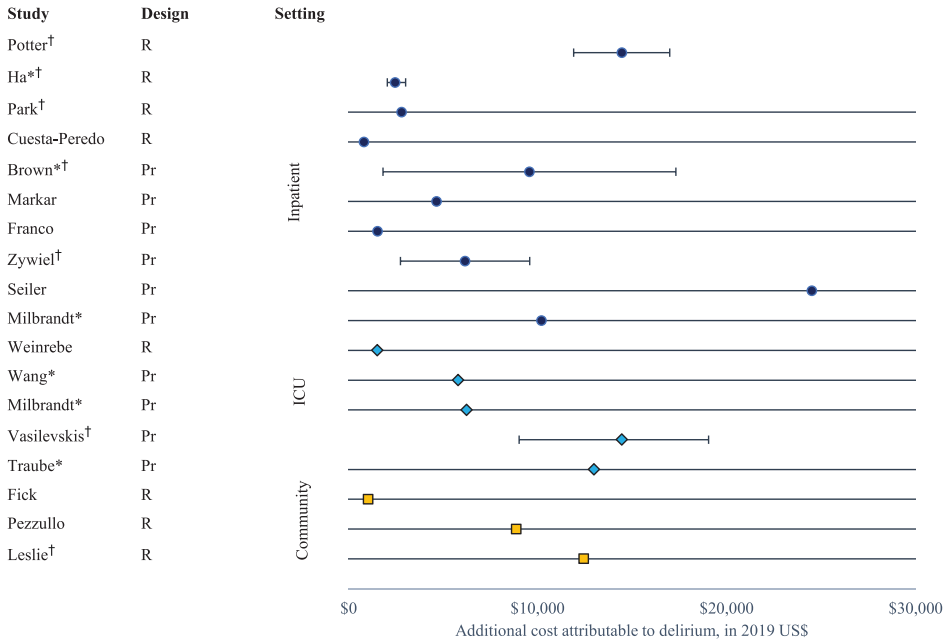

FIGURE 2 Distribution of the cost attributable to delirium by setting, in 2019 US$. Dots represent the mean/median cost attributable to delirium. Whiskers represent uncertainty around the mean/median as reported (95% confidence intervals) or not reported in the study (iInfinite whiskers). Inpatient settings are represented by circle; diamond, intensive care unit; square, community. R, retrospective. Pr, prospective. *Median cost. †Adjusted cost

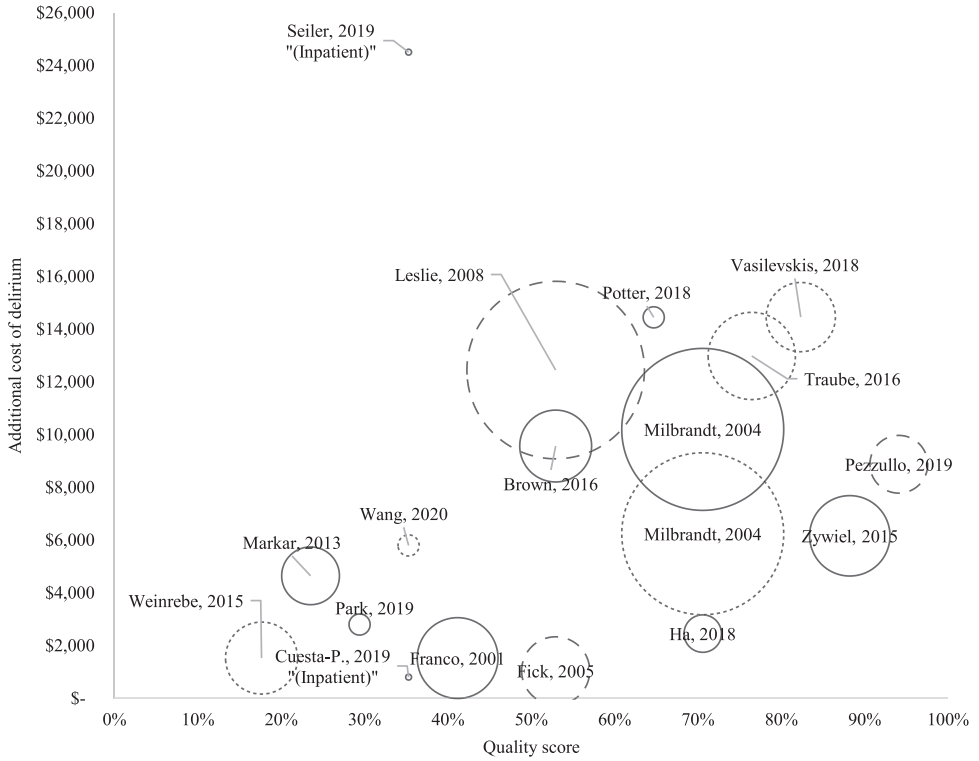

FIGURE 3 Association among the cost, quality, and the average number of citations per year. The bubble size represents the average number of citations per year. Solid lines represent inpatient setting; dotted line, intensive care unit ; dashed line, community. The quality score was derived using the Larg and Moss checklist. Citations were extracted from Google Scholar between 9 and 10 June 2020

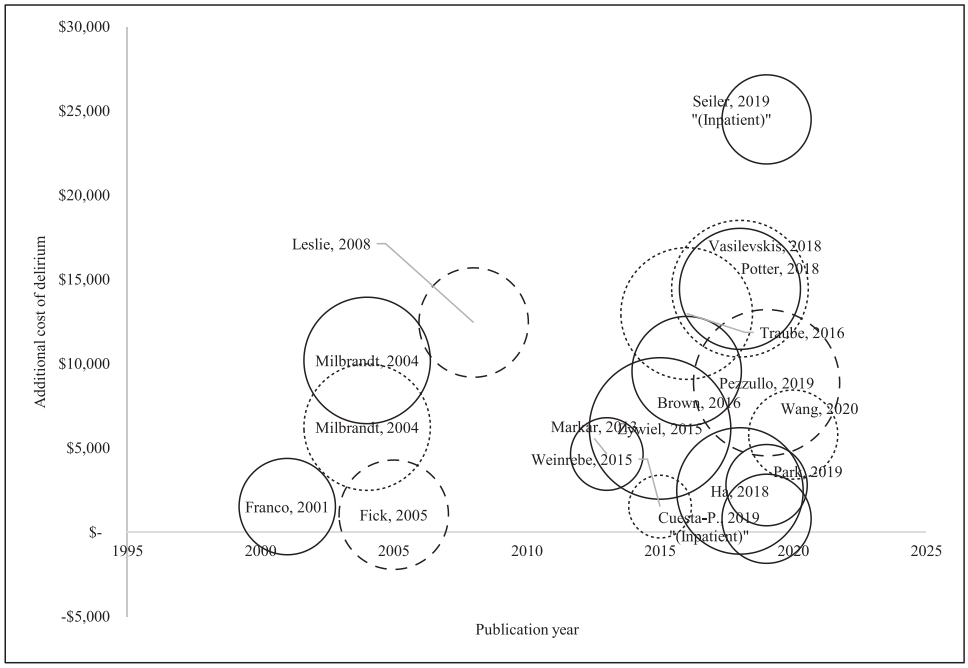

FIGURE 4 Change in cost and quality over time. The bubble size represents the quality score derived using the Larg and Moss checklist. Solid line represents inpatient setting; dotted line, intensive care unit; dashed line, community

Spearman correlation showed weak/fair positive association between the cost and publication year ($r_s[18] = 0.128$, $P = 0.613$). On the other hand, the quality of evidence seemed to decrease slightly, but again not significantly. Spearman correlation showed weak/fair negative association between the quality score derived using the Larg and Moss checklist[19] and publication year ($r_s[18] = -0.096$, $P = 0.704$).

An albeit somewhat tenuous observation that warrants further investigation, we noted that studies rated as having higher quality were those that also considered longer term sequela (specifically, dementia).

4 | DISCUSSION

This study evaluates and compares the economic cost of delirium through a systematic review and assessment of the quality of published research. The economic cost of delirium was reported over a number of varying sources, with the estimated additional cost ranging from $806 to $24,509 (in 2019 US$). The lowest cost increment was observed in Spain ($806) and the highest in Switzerland ($24,509), both in the inpatient setting. The economic cost of delirium in the inpatient setting ranges between $806 and $24,509, in the intensive care unit between $1,529 and $14,462, and among community-based residents between $1,045 and $12,452.

The magnitude of the cost was somewhat positively, but not statistically significantly, associated with the average number of citations per year, suggesting that a higher cost might attract a greater number of citations. The magnitude of the cost of delirium increased over time slightly, but again not significantly. On the other hand, the quality of evidence somewhat decreased.

To illustrate potential budgetary impact at a national level, inpatient delirium would cost somewhere between $6.6 billion and $82.4 billion in the United States alone (in 2019 US$). This cost assumed a fixed prevalence of delirium (31%[69]) among adults 65 years and older (with 13,956,300 hospital discharges per year[70]) and the additional cost of delirium ranging between $1,529 and $19,050 per hospital stay (refer to Table D.1 in Appendix D). This profound difference in costs could be attributed to several factors.

Similar to Caplan et al.'s narrative review of the financial and social costs of delirium, we found wide variability in identification and measurements of costs, analytical approaches, and presentation of results.[71] Clinical differences in identification of delirium and its types, as well as country-specific health-care system financing and the effect of costs exerted by different payers could further explain variability in the cost estimates. Costs may be included in the data or imputed by study authors by assigning unit costs to types of health-care use. Even when costs are included, such as they are in several U.S. claims databases, the specific type of costs can vary and may be subject to the payer (ie, commercial, Medicare, or Medicaid). While differences in costs would remain, it is important for the cost assumption to be explicitly stated.

Efforts should be made to establish a common methodology for cost-of-illness studies for delirium. Given the plethora of advice available regarding the conduct of economic studies, there is little reason for authors to ignore fundamental issues such as stating the perspective of the study, transparent reporting of the types of resource use identified, and sources of cost information. Limited reporting provides insufficient information to assist decision makers and hinders comparison. A standardization of terminology will facilitate comparison across

studies and allow pooling and re-use of results from subsequent, longer term evaluation studies.

Khachaturian et al.,[3] in the global blueprint for action to illuminate delirium, highlighted that "delirium is poorly recognized in practice, in part because of lack of a unifying definition … and a lack of consistent application of clinically effective assessment tools." Our analysis reinforces this statement. We observed a range of delirium assessment tools often applied with little to no justification (refer to supporting information 1 for an extended summary of delirium assessment tools). As with standardization of cost-of-illness terminology, there needs to be an international consensus on the definition of the reference standard that defines an episode of delirium. The inconsistent definition can lead to inconsistent case detection, or over- or underestimation of the economic impact of delirium.

When citing a cost estimate, it is essential to recognize key challenges in conducting cost-of-illness studies, including the identification of delirium, narrow scope in the cost perspective, inadequate or lack of generalizability to other settings. For the extended summary of the identified challenges related to cost estimation procedure refer to supporting information 1. We encourage readers to carefully consider the methodological quality of the estimates before relying on the magnitude of the cost or the number of citations.

Delirium has been linked with the acceleration of cognitive decline and dementia.[11,12] As part of this review, we were interested in understanding to what degree might dementia increase cost implications of delirium. We found a limited focus on dementia as a sequela of delirium (2 out of 15 studies) in terms of economic implications. Pezzullo et al. suggested that 52% of the overall cost of delirium in community settings could be attributed to dementia.[50] Further, Fick et al.[51] found that delirium increased the health-care cost by 50% and 37% among those diagnosed with delirium superimposed on dementia and dementia only, respectively.

Given the strong association of delirium with cognitive decline,[11,12] there may be considerable opportunities to reduce some of the worldwide burdens of dementia and improve the fiscal sustainability of health systems in the face of aging populations. Further research to better understand the economic relationship between delirium and dementia is warranted.

Best-practice recommendations to establish a common methodology for cost-of-illness studies for delirium. Cost-of-illness studies warrant different analytical considerations than cost-effectiveness or cost-utility analyses.[19] Cost of illness studies the overall societal cost of health problems, which is different from estimating the incremental per-patient cost of specific health interventions in cost-effectiveness or cost-utility analyses. Larg and Moss[19] synthesized best practice recommendations for conducting cost-of illness-studies, which we discuss below in the context of our review findings.

The best practice recommends that "readers should be able to identify the analytical framework underpinning the study, as this should determine the selection of cost components, the appropriate measurement method, and the reporting requirements." The analytical framework encompasses the motivation for conducting the study; the perspective of the study; and the epidemiological approach, such as the incidence-based or prevalence-based approach, all of which should be made clear. In our review, 29% of the studies ($n = 5$) specified the perspective and only 6% ($n = 1$) specified the epidemiological approach.

"It is imperative to have a clearly defined research question stated in an answerable form." Elements that should be specified include cost components, the time frame of the study, case definition of the disease or risk factor, and counterfactual population occurrence (ie, hypothetical alternative incidence or prevalence). While all studies had a defined objective, only half specified the necessary time frame, such as the base year and endpoint in incidence-based studies and a period over which costs are measured, usually a year, in prevalence-based studies.

"Readers need to be able to identify which methods were used to quantify resource use and to understand the limitations of each of these methods." Methods are commonly categorized into "top-down" (population-based) and "bottom-up" (person-based) approaches. Only one study (6%) explicitly stated the method they used to quantify resource use.

The accuracy of estimates of the cost of disease-specific health-care services rely on the type and accuracy of data used for cost allocation. Use of health-care claims data may not provide the same level of accuracy as clinical records in terms of disease diagnoses.[19] Conversely, disease classifications used in administrative and research databases may preclude an exact match with the cost of illness case definition adopted.[19] While four studies (24%) used cost-to-charge ratio, three (18%) distinguished between charges and costs, though it is unclear how and whether the adjustment was made in the analysis.

There are many uncertainties surrounding cost-of-illness estimates, and it is important that the main sources are disclosed, and their implications discussed. It is of importance that both univariate and multivariate (multi-way) sensitivity analyses that consider alternative values for all important parameters and key assumptions are conducted in cost-of-illness studies. The results of such analyses must be reported and evaluated. Only three studies (18%) explored the robustness of the results in the sensitivity analysis.

"The overall cost-of illness estimates should be expressed as confidence intervals or at least as credible ranges, rather than point estimates, to reflect the range of feasible costs discovered through sensitivity analyses." Less than half (35%; $n = 6$) explicitly reported incremental or additional cost of delirium, and only three (18%) expressed the incremental cost as confidence intervals. Sufficient documentation of data, sources, all assumptions, and estimation methods should be explicitly stated, along with main limitations. It is good practice to report costs in a disaggregated fashion, by cost category and cost component. Five (29%) of the included studies specified cost categories or cost component and/or reported costs in a disaggregated fashion.

Last, "a justification should be given for the cost types included, along with some discussion of the expected effects of excluded costs." In addition to direct health care, efforts should be made to incorporate the downstream costs of delirium and their impact on lifespan and post-hospital survivorship, including caregiving cost, as well as myriad indirect costs due to new disability and/or accelerated

cognitive decline, and that are potentially related to or a consequence of delirium. We echo the recommendation by Khachaturian et al.[3] "to improve the measurement and valuation of the informal care invariably delivered to patients with delirium or post-delirium sequelae provided by family caregivers." This is an important avenue for methodological development, given the substantial variation in both terminology and methodology.

4.1 | Strengths and limitations

To our knowledge, this is the first review that critically appraised the methodological quality of review-published claims on the costs of delirium against best-practice guidelines. The extensive search strategy used to capture the concepts of delirium and costs is a major strength of this review. A second strength is that our checklist was adapted from the Larg and Moss[19] assessment guidelines, which were developed by experts in the field for the purpose of optimizing the reporting of cost-of-illness studies.

However, this review should be interpreted in the context of several limitations. While we adopted a comprehensive search strategy, it is still possible that this review might have missed some articles. Second, the checklists provided a guiding framework for critically reviewing the methodology reported by the articles. There was room for subjective interpretation, which may have biased the scoring. We attempted to address this bias through two raters independently appraising the articles against the checklist, with disagreements resolved by consensus. The study investigators had carried out discussions to reach a consensus while deciding on the epidemiological approach, method of resource quantification, or the cost reference year, which might have resulted in some bias by not having an expert outside of the study team. Assigning costs to the last year of the study period or the article submission year might not accurately reflect the true cost year. No attempt was made to combine individual study costs in an aggregate average cost estimate due to heterogeneity of the study designs, methodologies, and included cost components.

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CONFLICTS OF INTEREST

The authors have no conflicts of interest to declare. There was no requirement for this study to undergo a review by a Human Research Ethics Committee.

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AUTHOR CONTRIBUTIONS

Irina Kinchin conceived the study and wrote the manuscript. Eileen Mitchell was involved in data extraction and quality assessment as second rater. Dominic Trépel and Meera Agar were involved in resolving questions regarding the interpretation of the analysis and manuscript preparation. All authors read and approved the final version of the manuscript.

ORCID

Irina Kinchin https://orcid.org/0000-0003-0133-2763

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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APPENDIX A

Search conducted by Liz Chinchen on 04.06.2020

Database: Embase < 1974 to 2020 June 03 > , Ovid MEDLINE and Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Daily and Versions <1946 to June 03, 2020>

Search Strategy: ——————————————————————————

0 *"Cost of Illness"/ (17924)
2 *delirium/ (17091)
3 1 and 2 (12)
4 remove duplicates from 3 (10)
5 "cost of illness".mp. (48447)
6 delirium.mp. (52640)
7 5 and 6 (72)
8 remove duplicates from 7 (60)
9 limit 8 to itatio language (54)
10 from 9 keep 3,11,15,17,38,48 (6)
11 4 or 10 (14)
12 economic evaluation/or economic evaluation.mp. (108621)
13 cost-utility analysis/or cost-utility analysis.mp. (92077)
14 Cost-Benefit Analysis/or Cost-Benefit Analysis.mp. (168776)
15 cost-minimization analysis/or cost-minimization analysis.mp. (52617)
16 "costs and cost analysis"/or cost*.mp. (1767856)
17 12 or 13 or 14 or 15 or 16 (1773496)
18 6 and 17 (2778)
19 remove duplicates from 18 (2155)
20 limit 19 to itatio language (2068)
21 limit 20 to humans (1976)
22 (editorial or letter or note or comment).de,pt. (4455395)
23 21 not 22 (1825)
24 limit 23 to y = "2019 -Current" (264)
25 from 24 keep 11,30,43,53,66,68,72-73,81,90,98,107,118-119, 125,137,139,144,149-150,157,163,168,174,189,192,206,209,223, 229,240,255-256 (33)
26 25 not 22 (33)
27 remove duplicates from 26 (33)

APPENDIX B

TABLE B.1 Study characteristics and quality score

Reference	Setting	Type	Currency	Ref year	Cost category						Costing period	Cost result (in local currency)	Av. citation/ year	Quality score[e]
					Inp	Outp	Med	NonM	Ind	Intang				
Potter[61]	Inpatient: Surgical	Cardiac	US dollars	2015	+	–	–	–	–	–	DHS	Regression-adjusted incremental mean cost of postprocedure delirium $15,592 (95% CI: $12,849–$18,334)	1	65%
Brown[62]	Inpatient: Surgical	Cardiac	US dollars	NS	+						DHS	Propensity score model adjusted incremental median cost of $10,339 (95% CI: $1,969–$18,709), $P = 0.02$	11	53%
Markar[52]	Inpatient: Surgical	Cancer	US dollars	2000-08	+	–	–	–	–	–	DHS	Delirium group (mean ± SD): $28,222.8 ± 13,017.7; Nondelirium group (mean ± SD): $22,702.2 ± 9,689.2, $P < 0.05$	7	24%
Ha[60]	Inpatient: Surgical	Cancer	US dollars	2013	+	–	–	–	–	–	DHS	Patients with delirium experienced a $2,697(95%CI: $2,250–$3,314), $P < 0.001$ increase in direct hospital admission costs compared to those without delirium (regression adjusted)	3	71%
Franco[54]	Inpatient: Surgical	Non-cardiac	US dollars	NS	+	–	–	–	–	–	DHS	Delirium group (mean ± SD): technical cost[c] 6,745.89 ± 4065; professional cost[d] 2,637.30 ± 1561; nursing 5,333.62 ± 3,326.09. Non-delirium group (mean ± SD): technical cost[d] 5330.90 ± 3,933, $P = 0.015$; professional cost[d] 2,224.33 ± 1,487, $p = 0.063$; nursing 4,353.08 ± 3,009.45, $P = 0.023$	14	41%
Park[56]	Inpatient: Surgical	Non-cardiac	Won	NS	+						DHS	Regression-adjusted incremental mean cost of postprocedure delirium $2474 × 10^3$, $P < 0.001$	1	29%
Zywiel[65]	Inpatient: Surgical	Orthopedic	CAN dollars, US dollars and Euro	2012	+[a]	–	–	–	–	–	Episode-of-care	Propensity score model adjusted mean episode-of-care cost $8,286 (95% CI $3,690–$12,881), $P < 0.001$	13	88%
Cuesta-Peredo[55]	Inpatient: Surgical	Orthopedic	Euro	NS	+						DHS	Mean differences between patients with and without the adverse events were €532.8 for delirium, $P < 0.001$	0	35%
Seiler[57]	Inpatient: Surgical and medical	Palliative	Swiss franc	NS	+						DHS	Medical costs per delirium case (mean, SD) 51,832 CHF (70,417 CHF); non-delirium case (mean, SD) 23,457 CHF(22,505 CHF), $P < 0.001$	0	35%
Weinrebe[53]	Inpatient: Medical	General	Euro	NS	+[b]	–	–	–	–	–	DHS	Mean €1,200 per delirium patient	11	18%
Wang[58]	Inpatient: ICU	Neurosurgical	Chinese Yuan/ 10,000	NS	+						DHS	Postoperative delirium group, median [IQR]: ¥7.1 [5.4 to 10.4]; postoperative non-delirium group, median [IQR] ¥4.6 [4.0 to 5.9], $P < 0.001$	1	35%

(Continues)

TABLE B.1 (Continued)

Reference	Setting	Type	Currency	Ref year	Cost category						Costing period	Cost result (in local currency)	Av. citation/ year	Quality score[e]
					Inp	Outp	Med	NonM	Ind	Intang				
Milbrandt[63]	Inpatient: ICU	Medical	US dollars	2001	+	–	–	–	–	–	ICU day and DHS	ICU costs (median, IQR) were significantly higher for those with at least one episode of delirium ($22,346, $15,083–$35,521) vs those with no delirium ($13,332, $8,837–$21,471, $P < .001$). Total hospital costs were also higher in those who developed delirium ($41,836, $22,782–$68,134 vs $27,106, $13,875–$37,419, $P = .002$)	54	71%
Vasilevskis[66]	Inpatient: ICU	Medical and surgical	US dollars	2007	+	–	–	–	–	–	30-day ICU stay	Mean incremental cumulative ICU cost related to persistent delirium in survivors $17,838 (95% CI $11,132–$23,497)	10	82%
Traube[59]	Inpatient: ICU	Paediatric	US dollars	2014	+	–	–	–	–	–	ICU stay; by additional day	Median total PICU costs were higher in patients with delirium than in patients who were never delirious ($18,832 vs $4,803, $P < 0.0001$). Costs increased incrementally with number of days spent delirious (median cost of $9,173 for 1 day with delirium, $19,682 for 2–3 days with delirium, and $75,833 for > 3 days with delirium, $P < 0.0001$); this remained highly significant even after adjusting for PICU length of stay ($P < 0.0001$)	16	76%
Fick[51]	Community	–	US dollars	98-2000	+	+	+	–	–	–	3 y	Total cost – delirium group (mean, SD): $9422 ($23341); control (mean, SD): $4766 ($6644). Facility cost – delirium group (mean, SD): $5312 ($18751); control (mean, SD): $2471 ($4565). Provider cost – delirium group (mean, SD): $2407 ($3497); control (mean, SD): $1630 ($2070). Prescription cost – delirium group (mean, SD): $1368 ($3581); control (mean, SD): $424 ($1497)	10	53%
Pezzullo[50]	Community	–	UK pounds	2016-17	+	+	+	+	+	+	1 y	The total cost associated with delirium (excluding dementia) in Australia £2034.9 million; health system and aged care cost £844.2 million, other financial costs £196.6 million, loss of well-being £994.1 million	7	94%
Leslie[64]	Inpatient: Medical & Community	–	US dollars	2005	+	+		+			DHS and up to 1 year follow-up after discharge	Total cost estimates attributable to delirium ranged from $16,303 to $64,421 per patient per year, implying that the national burden of delirium on the health care system ranges from $38 billion to $152 billion each year	64	53%

Abbreviations: CI, confidence interval; DHS, duration of hospital stay; Ind, indirect; Int, inpatient; Intang, intangible; IQR, interquartile range; Med, medications; N, no; NonM, non-medical; NS, not stated; Outp, outpatient; SD, standard deviation; Y, yes.

[a] Excluding surgeon, anesthetist, or other consulting physician billings, which in Canada are typically billed to the insurer by individual providers without any involvement of the hospital.

[b] Including. an intensive care unit (ICU), stroke unit, geriatric medicine.

[c] Not clearly stated in the study, consensus by discussion.

[d] Professional cost (ie, relating to services provided by physicians); technical cost (ie, remaining, non-physician services).

[e] Quality assessment was undertaken using the checklist by Larg and Moss[19] for the critical evaluation of cost-of-illness studies.

APPENDIX C

TABLE C.1 Larg and Moss's checklist quality assessment of the included studies ($n = 17$)

	Franco (2001)[54]	Milbrandt (2004)[63]	Fick (2005)[51]	Markar (2013)[52]	Weinrebe (2015)[53]	Zywiel (2015)[65]	Traube (2016)[59]	Ha (2018)[60]
(1) Analytical framework: What costs should have been measured?								
(a) What was the motivation and perspective of the study?	**Not clear**	**Yes**	**Not clear**	**Not clear**	**Not clear**	**Yes**	**Yes**	**Not clear**
(b) Was the appropriate epidemiologic approach taken?	**Yes**	**Yes**	**Yes**	**Yes**	**Yes**	**Yes**	**Yes**	**Yes**
€ Was the study question well specified?								
(i) Were all relevant, non-trivial cost components and their stakeholders identified?	Not clear	Yes	Not clear	Not clear	Not clear	Yes	Yes	Not clear
(ii) Were necessary timeframes specified?	No	Yes	Yes	Not clear	No	Yes	Yes	Yes
(iii) Was a case of disease or risk factor adequately and appropriately defined?	Yes	Yes	Yes	Not clear	Yes	Yes	Yes	Yes
(2) Methodology and data: How well were resource use and productivity losses measured?								
(a) Was an appropriate method(s) of quantification used, such that additional, or excess, costs were measured?	**No**	**No**	**No**	**No**	**Not clear**	**Yes**	**No**	**Yes**
(b) Was the resource quantification method(s) well executed?								
(i) For population-based studies, were cost allocation methods, data, and assumptions valid?	Not appropriate	Not appropriate	Not appropriate	Not appropriate	Not appropriate	Not appropriate	Not appropriate	Yes
(ii) For person-based studies, were appropriate statistical tests performed and reported?	Not clear	Yes	Yes	Yes	No	Yes	Yes	Yes
(iii) Were data representative of the study population?	Not clear	Not clear	Not clear	Not clear	Not clear	Not clear	Not clear	Yes
€ Were health-care resources valued appropriately?	**Yes**	**Yes**	**Not clear**	**Not clear**	**Yes**	**Yes**	**Yes**	**Yes**
(3) Analysis and reporting								
(a) Did the analysis address the study question?	**Yes**	**Yes**	**Yes**	**Yes**	**Yes**	**Yes**	**Yes**	**Yes**
(b) Was a range of estimates presented?	**Yes**	**Yes**	**Yes**	**Yes**	**No**	**Yes**	**Yes**	**Yes**
€ Were the main uncertainties identified?	**Yes**	**Yes**	**Yes**	**Yes**	**No**	**Yes**	**Yes**	**Yes**
(d) Was a sensitivity analysis performed?	**No**	**No**	**Yes**	**No**	**No**	**Yes**	**No**	**No**
€ Was adequate documentation and justification given for cost components, data and sources, assumptions and methods?	**Not clear**	**Yes**	**Not clear**	**Not clear**	**Not clear**	**Yes**	**Yes**	**Not clear**
(f) Was uncertainty around the estimates and its implications adequately discussed?	**Yes**	**Yes**	**Yes**	**Not clear**	**Not clear**	**Yes**	**Yes**	**Yes**
(g) Were important limitations discussed regarding the cost components, data, assumptions, and methods?	**Yes**	**Yes**	**Yes**	**No**	**No**	**Yes**	**Yes**	**Yes**
(h) Were the results presented at the appropriate level of detail to answer the study question (cost components; disease subtypes, severity, stage; subpopulation groups, cost bearers)?	**Not clear**	**Not clear**	**Not clear**	**Not clear**	**No**	**Yes**	**Yes**	**Yes**
Total (*n* yes)	7	12	9	4	3	15	13	12
Total (% yes)	41%	71%	53%	24%	18%	88%	76%	71%

TABLE C.2 Larg and Moss's checklist quality assessment of the included studies ($n = 17$)

	Potter (2018)[61]	Vasilevskis (2018)[66]	Pezzullo (2019)[50]	Brown (2016)[62]	Cuesta-Peredo (2019)[55]	Park (2019)[56]	Seiler (2019)[57]	Wang (2020)[58]	Leslie (2008)[64]
(1) Analytical framework: What costs should have been measured?									
(a) What was the motivation and perspective of the study?	**Not clear**	**Yes**	**Yes**	**Not clear**	**Not clear**	**Not clear**	**Not clear**	**Not clear**	**Yes**
(b) Was the appropriate epidemiologic approach taken?	**Yes**	**Yes**	**Yes**	**Not clear**	**Not clear**	**Not clear**	**Not clear**	**Not clear**	**Not clear**
€ Was the study question well specified?									
(i) Were all relevant, non-trivial cost components and their stakeholders identified?	Not clear	Yes	Yes	Not clear	Not clear	Not clear	Not clear	Not clear	Not clear
(ii) Were necessary time frames specified?	Yes	Yes	Yes	Not clear	Not clear	Not clear	Not clear	Not clear	Yes
(iii) Was a case of disease or risk factor adequately and appropriately defined?	Yes	Yes	Not clear	Yes	Not clear	Yes	Yes	Yes	Yes
(2) Methodology and data: How well were resource use and productivity losses measured?									
(a) Was an appropriate method(s) of quantification used, such that additional, or excess, costs were measured?	**Yes**	**Yes**	**Yes**	**Yes**	**Yes**	**No**	**No**	**No**	**Yes**
(b) Was the resource quantification method(s) well executed?									
(i) For population-based studies, were cost allocation methods, data and assumptions valid?	Not appropriate	Yes	Yes	Not appropriate	Not appropriate	Not appropriate	Not appropriate	Not appropriate	Not appropriate
(ii) For person-based studies, were appropriate statistical tests performed and reported?	Yes	Not appropriate	Not appropriate	Yes	Yes	Yes	Yes	Yes	Yes
(iii) Were data representative of the study population?	Not clear	Not clear	Yes	Not clear	Not clear	Not clear	Not clear	Not clear	Not clear
€ Were health-care resources valued appropriately?	**Yes**	**Yes**	**Yes**	**Yes**	**No**	**Not clear**	**Not clear**	**Not clear**	**Not clear**
(3) Analysis and reporting									
(a) Did the analysis address the study question?	**Yes**	**Yes**	**Yes**	**Yes**	**Yes**	**Yes**	**Yes**	**Yes**	**Yes**
(b) Was a range of estimates presented?	**Yes**	**Yes**	**Yes**	**Yes**	**Not clear**	**No**	**Yes**	**Yes**	**Yes**
€ Were the main uncertainties identified?	**Yes**	**Yes**	**Yes**	**Yes**	**Yes**	**Yes**	**Yes**	**Yes**	**Not clear**
(d) Was a sensitivity analysis performed?	**No**	**No**	**Yes**	**No**	**No**	**No**	**No**	**No**	**Not clear**
€ Was adequate documentation and justification given for cost components, data and sources, assumptions and methods?	**Not clear**	**Yes**	**Yes**	**Not clear**	**Not clear**	**Not clear**	**Not clear**	**Not clear**	**Yes**
(f) Was uncertainty around the estimates and its implications adequately discussed?	**Yes**	**Yes**	**Yes**	**Yes**	**Yes**	**Yes**	**Yes**	**Yes**	**Not clear**
(g) Were important limitations discussed regarding the cost components, data, assumptions and methods?	**Yes**	**Yes**	**Yes**	**Yes**	**Yes**	**Not clear**	**No**	**No**	**Yes**
(h) Were the results presented at the appropriate level of detail to answer the study question (cost components; disease subtypes, severity, stage; subpopulation groups, cost bearers)?	**Yes**	**Yes**	**Yes**	**No**	**Not clear**	**Not clear**	**Not clear**	**Not clear**	**No**
Total (n yes)	11	14	16	9	6	5	6	6	9
Total (% yes)	65%	82%	94%	53%	35%	29%	35%	35%	53%

APPENDIX D

TABLE D.1 Cost conversion

First author	Country	Cost year/ published	Mean/ Median	Cost as reported in local currency	Costing period	National index in cost/ published year[a]	National index in 2019[a]	Local currency in 2019	PPP for GDP 2019[b]	US$ in 2019
Potter	US	2015	Mean	$15592 (95% CI: $12849–$18334)	DHS	237.0	255.7	14452 (95% CI: 11910–16994)	1	14452 (95% CI: 11910–16994)
Ha	US	2013	Median	$2697 (95% CI: $2250–$3314)	DHS	233.0	255.7	2458 (95% CI: 2051–3020)	1	2458 (95% CI: 2051–3020)
Park	Korea	2016	Mean	2474×10^3	DHS	101.0	104.9	2382021	850	2801
Cuesta-Peredo	Spain	2016	Mean	€533	DHS	100.0	104.4	511	0.63	806
Brown	US	2014	Median	$10339 (95% CI: $1969–$18709)	DHS	236.7	255.7	9571 (95% CI: 1823–17319)	1	9571 (95% CI: 1823–17319)
Markar	US	2008	Mean	$5,521	DHS	215.3	255.7	4649	1	4649
Franco	US	1999	Mean	$2347	DHS	166.6	255.7	1529	1	1529
Zywiel	Canada	2012	Mean	$8286 (95% CI $3690-$12881)	Episode-of-care cost	121.7	136.0	7415 (95% CI: 3303–11527)	1.20	6166 (95% CI: 2746–9586)
Seiler	Switzerland	2014	Mean	28375 CHF	DHS	101.8	102.0	28319	1.16	24509
Milbrandt	US	2001	Median	$14730 (Hospital)	DHS	177.1	255.7	10202	1	10202
Weinrebe	Germany	2014	Mean	€1200	DHS	99.5	105.3	1134	0.74	1529
Wang	China	2018	Median	¥25000	DHS	105.8	108.8	24311	4.19	5801
Milbrandt	US	2001	Median	$9014 (ICU)	DHS	177.1	255.7	6243	1	6243
Vasilevskis	US	2007	Mean	$17838 (95% CI $11132–23497)	30-day cumulative	207.3	255.7	14462 (95% CI: 9025–19050)	1	14462 (95% CI: 9025–19050)
Traube	US	2014	Median	$14029	DHS	236.7	255.7	12987	1	12987
Fick	US	2000	Mean	$4656 over 3 y or $1552 over 1 y	Y/person	172.2	255.7	1045	1	1045
Pezzullo	UK	2017	Average	£6367	Y/person	103.6	107.8	6119	0.69	8879
Leslie	US	2005	Mean	$16303	Y/person	195.3	255.7	12452	1	12452

Abbreviations: CI, confidence interval; DHS, duration of hospital stay; GDP, gross domestic product; ICU; intensive care unit; PPP, purchasing power parity; Y, year.

[a] Consumer Price Index, Organisation for Economic Co-operation and Development (OECD),[25] accessed 10 June 2020.

[b] Purchasing Power Parities, National currency per US dollar, Organisation for Economic Co-operation and Development (OECD),[26] accessed 10 June 2020.