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Review Article

Anticholinergic Drug Burden and Delirium: A Systematic Review

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A B S T R A C T

Objectives: To investigate the association between anticholinergic drug burden (ADB), measured with anticholinergic drug scales, and delirium and delirium severity.
Design: Systematic review.
Setting and Participants: All available studies.
Methods: A systematic literature search was performed in Medline, Embase, PsycINFO, Web of Science, CINAHL, Cochrane library, and Google Scholar. Studies evaluating the association between ADB (measured as a total score) and delirium or delirium severity, published in English, were eligible for inclusion.
Results: Sixteen studies, including 148,756 persons, were included. Fifteen studies investigated delirium. ADB was measured with the Anticholinergic Risk Scale (ARS, n = 5), the Anticholinergic Cognitive Burden Scale (ACB, n = 6), the list of Chew (n = 1), the Anticholinergic Drug Scale (ADS, n = 5), a modified version of the ARS (n = 1), and a modified version of the ACB (n = 1). A high ADB, measured with the ARS, was associated with delirium (5/5). Also with the modified version of the ARS and ACB, an association was found between a high ADB and delirium during 3-month (1/1) and 1-year follow-up (1/1), respectively. When ADB was assessed with other scales, the results were inconclusive, with only 1 positive association for the ACB (1/6) and ADS (1/5) each. The possible association between ADB and delirium severity has also been investigated (ADS n = 2, Summers Drug Risk Number n = 1). One study found an association between a high ADB, measured with the ADS, and an increase in severity of delirium.
Conclusions and Implications: ADB assessed with the ARS is consistently associated with delirium. The association found between the modified versions of the ARS and ACB and delirium needs confirmation. When ADB was assessed with other scales, the findings were inconclusive. The current findings suggest that the ARS might be a useful tool to identify patients at increased risk for delirium.

Delirium is very common among older patients and is associated with poor outcomes, such as functional and cognitive decline and increased mortality.[1] Despite the high prevalence and clinical impact, this syndrome is still poorly understood. Knowledge about the underlying pathophysiology and identification of modifiable risk factors are of paramount interest.

The neurotransmitter acetylcholine is implicated in several processes that are impaired during delirium, such as attention, sleep, and memory, and this has led to the hypothesis that a cholinergic deficiency might be involved in the pathogenesis of delirium.[2,3] Drugs with anticholinergic properties are commonly prescribed in older persons, and the use of these drugs can cause some degree of cholinergic deficiency by blocking the effects of acetylcholine.[4] Therefore, use of anticholinergic drugs could be a risk factor for delirium.

Previous studies have investigated the possible association between anticholinergic drugs and delirium, but the findings are conflicting.[5,6] Discrepancies in the results might be caused by the methods used to assess anticholinergic drug use, which differ

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substantially among studies.[7] In some studies, anticholinergic drug use is assessed with crude measures such as "exposed or not exposed" or the total number of anticholinergic drugs taken. Other studies use the anticholinergic drug burden (ADB), which takes into account the specific anticholinergic load of the drugs used by a person. The ADB can be calculated with anticholinergic drug scales and is defined as the sum of scores assigned to the drugs. In the last decade, different anticholinergic drug scales have been developed, but these scales differ substantially from each other in number and ranking of drugs, and the question rises whether the use of all these scales results in comparable associations with delirium. Therefore, the aim of the present review was to investigate the possible association between ADB, measured with anticholinergic drug scales and delirium.

Methods

This review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The checklist is added as Supplementary Data (Appendix 1).

Data Sources and Search Strategy

A systematic literature search was performed in Medline Ovid, Embase, PsycINFO, Web of Science, CINAHL, Cochrane library, and Google Scholar covering the period up until January 31, 2020 using relevant terms for anticholinergic drugs and delirium. The search queries were developed with the assistance of an experienced biomedical information specialist and can be found in the Supplementary Data, Appendix 2. Reference lists of review articles and included studies were manually screened to identify additional eligible studies.

Eligibility Criteria

Studies that met each of the following criteria were eligible for inclusion: (1) the association between ADB and delirium or delirium severity was investigated; (2) ADB was measured with an anticholinergic drug scale and expressed as a total score; and (3) the study was published in the English language. In case full text articles were not available, the corresponding authors were contacted and whenever answers were not obtained despite reminders, articles were excluded. Case studies, case series, review articles, commentaries, letters, editorials, conference abstracts, and studies that used the Drug Burden Index without stratification into the anticholinergic and sedative components were excluded.

Study Screening and Selection

All references identified by the search queries were downloaded in Endnote X9 (Clarivate Analytics, Philadelphia, PA) and duplicates were removed. Three reviewers (A.E., R.M.G., and H.A.) independently screened titles and abstracts for potentially eligible studies, and assessed full-text articles against the eligibility criteria. Disagreements at any stage were resolved through consensus.

Data Extraction

Data from all studies that met the inclusion criteria were independently extracted by 2 authors (A.E. and F.M.R.) using a predefined extraction table, including author, year of publication, study design, population and setting, sample size, participant age and sex, number of persons with delirium, methods of measuring ADB, tools used to assess delirium and delirium severity, type of delirium (prevalent or incident), information on the statistical analyses, and the results with regard to the possible association between ADB and delirium (odds ratios, hazard ratios, relative risks, differences in proportions or regression coefficients). When studies used multiple models to investigate the association between ADB and delirium, the results of the model including the most covariates were extracted. Authors were contacted when study details were missing and data were considered unattainable if no answer was obtained despite several reminders. Any uncertainties were resolved through discussion.

Quality Assessment

Two reviewers (A.E. and G.Z.) independently assessed the methodological quality of the included studies using the Newcastle-Ottawa Scale for cohort and case-control studies.[8] The scale used for case-control studies was additionally used for cross-sectional studies.[9] The Newcastle-Ottawa Scale evaluates 3 aspects of the study methodology: the selection of study groups (score range 0–4), comparability of the groups (score range 0–2), and the quality of outcome/exposure ascertainment (score range 0–3). The total score ranges from 0 to 9 (highest quality). Disagreements were resolved through discussion.

Data Synthesis

The association between ADB and delirium was investigated separately for prevalent and incident delirium. To explore any variations in results across the studies and anticholinergic drug scales, the results were additionally grouped based on the clinical settings where the studies were performed, regardless of delirium type. Furthermore, we planned to perform subgroup analyses to explore the influence of potential confounding factors, such as dementia and severity of illness.[3] Furthermore, the association between ADB and delirium severity was investigated.

Results

Study Selection

The primary literature search resulted in 3085 records. After exclusion of duplicates, 1960 records remained; of these, 1829 were excluded based on titles and abstracts. In total, 131 records were assessed for eligibility. Sixteen studies met the inclusion criteria and were included in the final review. An overview of the study selection process is presented in Figure 1.

Study Characteristics

The characteristics of the sixteen included studies are presented in Table 1. There were 8 prospective cohort studies,[10–13,16,17,21,26] 5 retrospective cohort studies,[14,18,23–25] 1 nested case-control study,[19] and 2 retrospective cross-sectional studies.[20,22] A total of 148,756 persons were studied (sample size range 90–118,750; mean = 9297.25; median = 420.5). Thirteen studies were conducted in the hospital setting,[10–14,17–22,25,26] of which 10 on a medical ward[10,12–14,17–20,22,26] and 3 on a surgical ward,[11,21,25] 1 study was performed in nursing homes,[16] 1 study was performed in community-dwelling patients with dementia,[23] and 1 study was performed in the general population.[24] Delirium was assessed with the *Diagnostic and Statistical Manual of Mental Disorders* (4^{th} and 5^{th} edition) criteria,[19,20] the Confusion Assessment Method,[10,11,13,16,17,25,26] the Nursing Delirium Scale,[25] the Delirium Rating Scale,[12] codes for delirium according to the *International Classification of Diseases, 9^{th} and 10^{th} edition*,[18,23,24] the 4 'A's test,[22] and a validated chart-based instrument developed by Inouye et al[15] for the identification of delirium[14] and documented diagnoses of delirium in discharge summaries.[21] Delirium severity was assessed with the Delirium Index[10] and the Memorial Delirium Assessment

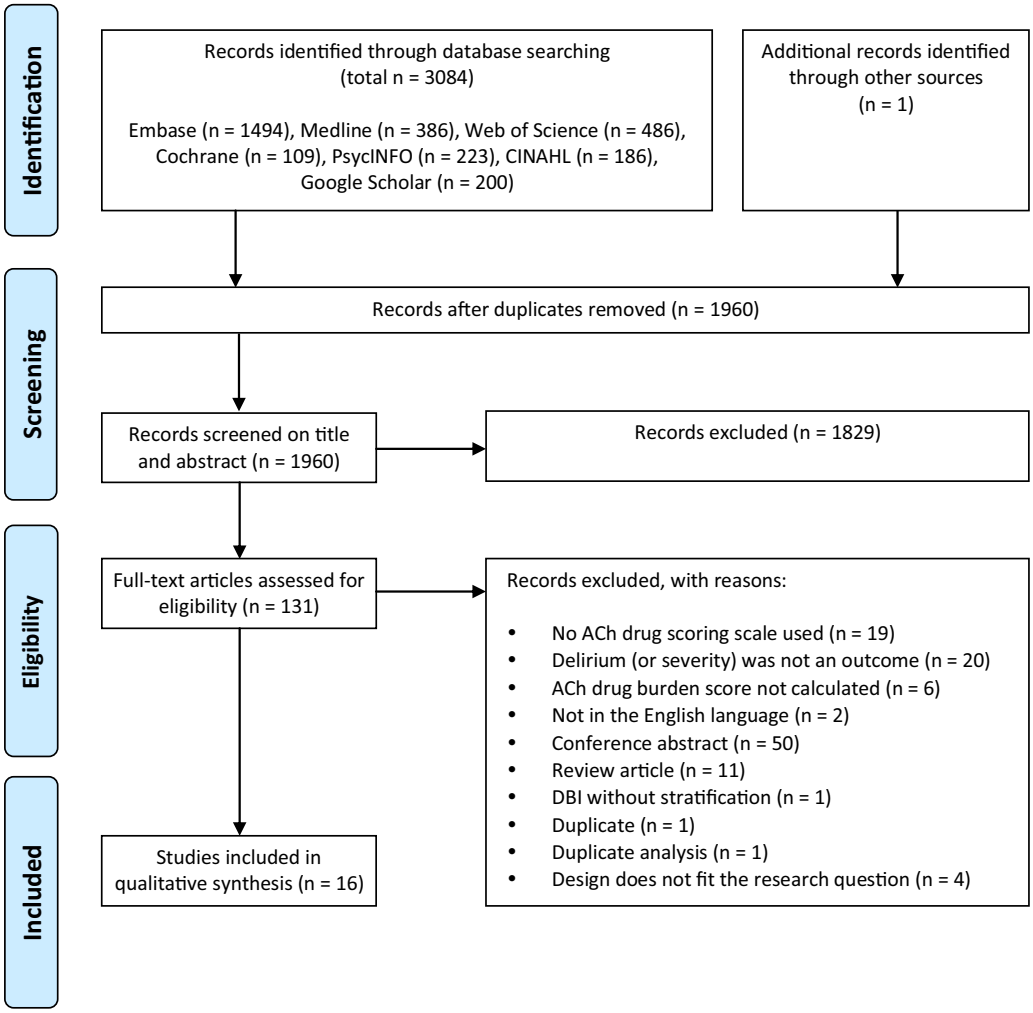

Fig. 1. PRISMA flow diagram of the study selection process.

Scale.[12] ADB was measured with the Anticholinergic Risk Scale (ARS),[14,16–18,20] the Anticholinergic Cognitive Burden scale (ACB),[13,19–22,26] the list of Chew,[20] the Anticholinergic Drug Scale (ADS),[10–12,17,19,25] a modified version of the ARS,[24] and a modified version of the ACB.[23] Characteristics of these anticholinergic drug scales are outlined in Table 2. Studies were performed in the United States,[12–14,18] the Netherlands,[17,20] Italy,[16,22] Canada,[11,21] Korea,[23,24] Norway,[10] the United Kingdom,[19] Germany,[25] and Portugal.[26]

Quality of the Studies

Details on the methodological quality of the included studies according to the Newcastle-Ottawa Scale are provided as Supplementary Data (Appendix 3). Quality scores ranged from 5 to 9 stars (median 8 stars). One study scored the maximum 4 stars for the study selection criteria. Fourteen out of 16 studies scored the maximum 2 stars for the comparability of the study groups, and 14 studies achieved the maximum 3 stars for the outcome/exposure criteria.

Anticholinergic Drug Burden and Delirium

The possible association between ADB and delirium was investigated in 15 of the 16 studies.[11–14,16–26] Four studies investigated prevalent delirium,[11,19,20,22] 7 studies incident delirium,[11–14,17,21,25] 2 studies delirium at some point during the hospital stay (combination of prevalent and incident delirium),[18,26] 1 study delirium during 3 months follow-up,[24] and 2 studies delirium during 1-year follow-up.[16,23] The studies investigating incident delirium, delirium at some point during the hospital stay, and delirium during follow-up are combined in this review.

Prevalent Delirium

Four studies reported on the possible association between ADB and prevalent delirium (delirium on admission in 3 studies[19,20,22] and preoperative delirium in 1 study[11]). A total of 1993 persons were studied (659 with delirium). Three studies were performed in acutely ill patients admitted to the hospital[19,20,22] and 1 study in patients admitted with a hip fracture.[11] In all 4 studies, the median or mean age was >80 years. Delirium was assessed with the *Diagnostic and Statistical Manual of Mental Disorders* (4th and 5th edition),[19,20] the 4 'A's test,[22] and the Confusion Assessment Method.[11] ADB was assessed with the ARS,[20] the ACB,[19,20,22] the ADS,[11,19] and the list of Chew.[20] The study results are presented in Table 3. Only a moderate and high ADB, measured with the ARS, was associated with delirium on admission.[20] No associations were found with the other anticholinergic drug scales.

Table 1
Study Characteristics

References	Study Design	Setting	Country	Study Population	Sample Size, n	Age, y, Mean ± SD	Men, %	Delirium, n (%)*	Delirium Assessment Method	Delirium Severity Assessment Tool
Han et al, 2001[10]	Prospective cohort	Hospital	Norway	Acutely ill patients with delirium age ≥65	278	83.4 ± 7.3	38.8	278	CAM	Delirium Index
Juliebø et al, 2009[11]	Prospective cohort	Hospital	Canada	Patients admitted with a hip fracture age ≥65	364	Unknown, median (IQR): 84 (79-88)	24.2	168 (46.2)	CAM	-
Fann et al, 2011[12]	Prospective cohort	Hospital	USA	Patients with malignancies admitted for myeloablative HSCT	90	41.5 ± 9.9	48.9	45 (50)	DRS	MDAS
Campbell et al, 2011[13]	Prospective cohort	Hospital	USA	Patients with cognitive impairment age ≥65	147	76.5 ± 7.9	36.7	33 (22.4)	CAM	-
Zimmerman et al, 2014[14]	Retrospective cohort	Hospital	USA	Palliative inpatients	217	72.9 ± 12.8	96.8	67 (30.9)	Validated chart-based instrument developed by Inouye et al[15]	-
Landi et al, 2014[16]	Prospective cohort	Nursing homes	Italy	Nursing home residents age ≥65	1490	83.5 ± 8.0	28.5	Not defined	NH-CAM	-
Wolters et al, 2015[17]	Prospective cohort	Hospital	The Netherlands	Critically ill patients (ICU)	1112	60 ± 16	60.4	535 (48)	CAM-ICU	-
Crispo et al, 2016[18]	Retrospective cohort	Hospital	USA	Patients with Parkinson disease age ≥40	16302	Unknown, 82.4% ≥70 y	52.6	362 (2.2)	ICD-9 codes	-
Moorey et al, 2016[19]	Nested case control	Hospital	UK	Acutely ill patients age ≥70	247	84.0 ± 6.6	32.7	125	DSM-IV-TR	-
Egberts et al, 2017[20]	Retrospective cross-sectional	Hospital	The Netherlands	Acutely ill patients age ≥65	905	81.0 ± 7.0	48.3	215 (23.8)	DSM-IV-TR DSM-V	-
Hussain et al, 2018[21]	Prospective cohort	Hospital	Canada	Patients undergoing TAVI	90	83 ± 6	61.1	7 (8.0)	Clinical charts	-
Pasina et al, 2019[22]	Retrospective cross-sectional	Hospital	Italy	Acutely ill patients age ≥65	477	83.9 ± 6.5	41.9	151 (31.7)	4-'A's Test	-
Ah et al, 2019[23]	Retrospective cohort	Population-based	Korea	Patients with dementia age >60 who started a cholinesterase inhibitor	7438	Unknown, 60.9% ≥75 y	34.4	298 (4.0)	ICD-10 codes	-
Hwang et al, 2019[24]	Retrospective cohort	Population-based	Korea	Persons age ≥65	118,750	75.4 ± 6.6	43.6	66 (0.05)†	ICD-10 codes	-
Mueller et al, 2019[25]	Retrospective cohort	Hospital	Germany	Cancer patients undergoing surgery age ≥65	651	71.8 ± 4.9	68.5	66 (10.1)	CAM-ICU and Nu-DESC	-
Rigor et al, 2020[26]	Prospective cohort	Hospital	Portugal	Acutely ill patients age ≥65	198	79.9 ± 7.5	53.5	56 (28.3)	Short-CAM	-

CAM, Confusion Assessment Method; DRS, Delirium Rating Scale; DSM (TR), Diagnostic Statistical Manual of Mental Disorders (Text Revision); HSCT, hematopoietic stem-cell transplantation; ICD, *International Classification of Diseases*; ICU, intensive care unit; IQR, interquartile range; MDAS, Memorial Delirium Assessment Scale; NH, nursing home; Nu-DESC, Nursing Delirium Scale; SD, standard deviation; TAVI, transcatheter aortic valve implantation; UK, United Kingdom; USA, United States of America.

*Percentage not provided for case-control (matched) studies and studies that included only patients with delirium.

†Emergency department visits for delirium.

Table 2
Characteristics of the Anticholinergic Drug Scales

Anticholinergic Drug Scale (Publication Year)	Basis of Scale Concept	Number of Drugs with a Score >0	Grading System
ARS (2008)[27]	Pharmacological principles of 500 drugs and expert opinion. Grading based on anticholinergic potential. Scale attempts to predict peripheral and central effects.	49	1-2-3
ACB (2008,[28] updated in 2012)[29]	Literature review of drugs with anticholinergic activity and expert opinion. Grading based on the potential to cause cognitive effects.	2008: 88 2012: 99	1-2-3
ADS (2002)[30]	A pre-existing anticholinergic drug scale (clinician-rated anticholinergic scale), literature review and expert opinion. Grading based on anticholinergic activity and the potential to cause adverse effects.	117	1-2-3
Chew (2008)[31]	In vitro serum anticholinergic activity of 107 drugs commonly used by older adults.	39	0/+, +, ++, +++
Modified ACB (2018)[23]	A pre-existing anticholinergic drug scale (ACB). A literature search and expert opinion were used to add and rank drugs available in Korea.	169 (9 drugs from the updated ACB scale were excluded and 79 drugs were added)	1-2-3
Modified ARS (2019)[24]	A pre-existing anticholinergic drug scale (ARS). A Delphi process involving 7 experts was used to add and rank drugs available in Korea.	103 (6 drugs from the original ARS were excluded and 60 drugs were added)	1-2-3

Incident Delirium

Twelve studies reported on the possible association between ADB and incident delirium.[11–14,16–18,21,23–26] A total of 146,849 persons were studied (1703 with delirium; in 1 study, the number of patients with delirium was not defined[16]). Nine studies were performed in patients admitted to the hospital (palliative inpatients,[14] patients with cognitive impairments,[13] patients admitted to the Intensive Care Unit,[17] patients with a hip fracture undergoing surgery,[11] patients with Parkinson's disease,[18] patients undergoing transcatheter aortic valve implantation,[21] patients with malignancies,[12] cancer patients undergoing surgery,[25] and acutely ill patients[26]), 1 study in nursing home patients,[16] 1 study in community-dwelling patients with dementia,[23] and 1 study in the general population.[24] In 9 studies, the median or mean age was >70 years,[11,13,14,16,18,21,24–26] in 1 study 60.9% of the patients were 75 years or older,[23] in 1 study the mean age was 60 years,[17] and in 1 study the mean age was 41.5 years.[12] Delirium was assessed with the Confusion Assessment Method,[11,13,16,17,25,26] the Nursing Delirium Scale,[25] the Delirium Rating Scale,[12] *International Classification of Diseases, 9th and 10th edition* codes for delirium,[18,23,24]

Table 3
Study Results—Prevalent Delirium

ACh Drug Scale	Reference	Drug Exposure	Adjustments	Outcome	Results OR/HR/RR/β(95% CI) or Proportions with *P* Value
ARS	Egberts et al, 2017[20]	Categories of ADB	Age, sex, CCI, number of non-ACh drugs	Prevalent delirium	Total ADB score 1-2: **OR 1.70 (1.16 – 2.49)** Total ADB score ≥3: **OR 1.83 (1.06 – 3.15)**
ACB	Moorey et al, 2016[19]	Total ADB score (continuous)	Age	Prevalent delirium	OR ns
	Egberts et al, 2017[20]	Categories of ADB	Age, sex, CCI, number of non-ACh drugs	Prevalent delirium	Total ADB score 1-2: OR 0.99 (0.67 – 1.46) Total ADB score ≥3: OR 1.39 (0.89 – 2.18)
	Pasina et al, 2019[22]	Categories of ADB	Age, sex, tumors, dementia, Mini Nutritional Assessment score	Prevalent delirium	Total ADB score 1: OR 0.93 (0.49 – 1.79) Total ADB score 2: OR: 1.01 (0.47 – 2.16) Total ADB score 3: OR 1.81 (0.74 – 4.47) Total ADB score 4: OR 2.19 (0.87 – 5.53) Total ADB score ≥5: OR 2.73 (0.85 – 8.77)
ADS	Juliebø et al, 2009[11]	Categories of ADB	None*	Preoperative delirium	Total ADB score ≥3: Delirium: 20% No delirium: 19.8% *P* = .97
	Moorey et al, 2016[19]	Total ADB score (continuous)	Age	Prevalent delirium	OR ns
Chew	Egberts et al, 2017[20]	Categories of ADB	Age, sex, CCI, number of non-ACh drugs	Prevalent delirium	Total ADB score 0.5-1: OR 1.00 (0.71 – 1.43) Total ADB score ≥1.5: OR 1.34 (0.85 – 2.11)

ACh, anticholinergic; CCI, Charlson Comorbidity Index; CI, confidence interval; HR, hazards ratio; ns, not significant; OR, odds ratio; RR, risk ratio.
Values in bold are statistically significant ($P < .05$).
*ADB was not statistically significantly different between the groups and therefore not included in the multivariate analysis.

Table 4
Study Results—Incident Delirium

ACh Drug Scale	Reference	Drug Exposure	Adjustments	Outcome	Results OR/HR/RR/β(95% CI) or Proportions with *P* Value
ARS	Zimmerman et al, 2014[14]	Increase in total ADB score during admission: no/yes	Age, APACHE-III, brain metastasis, ICU admission	Incident delirium	**OR: 1.4 (1.0–1.9)**
	Landi et al, 2014[16]	Total ADB score at baseline (continuous)	Age, sex, CIRS, CPS, schizophrenia, depression	Delirium during 1-y follow-up	**OR: 1.16 (1.02–1.32)**
	Wolters et al, 2015[17]	Daily total ADB score (continuous)	Age, sex, CCI, type of admission, APACHE-IV, use of mechanical ventilation, length of ICU stay until transition, SOFA score without neurologic component	Incident delirium	**OR: 1.12 (1.03–1.22)**
	Crispo et al, 2016[18]	Categories of ADB	Age, sex, race, length of stay, Elixhauser comorbidity score, census region, urban/rural status, hospital size, hospital teaching status	Delirium at some point during the during hospital stay[†]	Total ADB score 1: OR: 1.05 (0.69–1.61) Total ADB score 2-3: **OR: 2.14 (1.46–3.15)** Total ADB score ≥4: **OR: 1.61 (1.08–2.40)**
ACB	Campbell et al, 2011[13]	Total ADB score (continuous)	Age, sex, African American vs other, SPMSQ score, CCI.	Incident delirium	OR: 0.95 (0.80–1.13)
	Hussain et al, 2018[21]	Total ADB score (continuous)	Age, history of stroke, atrial fibrillation, diabetes, general anesthesia	Postoperative delirium	OR: 1.62 (0.81–3.24)
	Rigor et al, 2020[26]	Total ADB score (continuous)	Age, sex, number of comorbidities, CCI, dementia, number of outpatient drugs, number of outpatient anticholinergics	Delirium at some point during the hospital stay[†]	**OR: 1.65 (1.09–2.51)**
ADS	Juliebø et al, 2009[11]	Categories of ADB on admission	None[*]	Postoperative delirium	Total ADB score ≥3: Delirium: 25% No delirium: 16,8% $P = .18$
	Fann et al, 2011[12]	Total ADB score in the previous 48 h	Pain, lagged pain, opioids, alkaline phosphatase, blood urea nitrogen	Post-transplantation delirium	HR: ns
	Wolters et al, 2015[17]	Daily total ADB score (continuous)	Age, sex, CCI, type of admission, APACHE-IV, use of mechanical ventilation, length of ICU stay until transition, SOFA score without neurologic component	Incident delirium	OR: 1.05 (0.99–1.10)
	Mueller et al, 2019[25]	Total ADB score on admission (continuous)	Age, ASA status, ICU stay	Postoperative delirium	**OR: 1.50 (1.09–2.05)**
Modified ARS	Hwang et al, 2019[24]	Average daily ADB score during the first 3 mo (categories)	Age, sex, insurance type, comorbid conditions, polypharmacy, excessive polypharmacy, exposure to sedative drugs, warfarin, insulin, digoxine	ED visits for delirium during 3 mo follow-up	Total ADB score ≥2: **HR: 2.05 (1.13–3.73)**
Modified ACB	Ah et al, 2019[23]	Average daily ADB score during the first 3 mo (categories)	Age, sex, diabetes, hypertension, dyslipidaemia, stroke, depression, schizophrenia, Parkinson's disease, use of ginkgo extract, high sedative load	Delirium during 1-y follow-up	Total ADB score >3: **HR: 1.52 (1.17–1.96)**

ACh, anticholinergic; *APACHE*, Acute Physiology and Chronic Health Evaluation; *ASA status*, American Society of Anesthesiologists Physical Status; *CCI*, Charlson Comorbidity Index; *CI*, confidence interval; *CIRS*, Cumulative Illness Rating Scale; *CPS*, Cognitive Performance Scale; *ED*, emergency department; *ICU*, intensive care unit; *HR*, hazards ratio; *ns*, not significant; *OR*, odds ratio; *RR*, risk ratio; *SOFA*, Sequential Organ Failure Assessment; *SPMSQ*, Short Portable Mental Status Questionnaire
Values in bold are statistically significant ($P < .05$).
[*]ADB was not statistically significantly different between the groups and, therefore, not included in the multivariate analysis.
[†]Includes prevalent and incident delirium.

and a validated chart-based instrument developed by Inouye et al[15] for the identification of delirium[14] and documented diagnoses of delirium in discharge summaries.[21] ADB was assessed with the ARS,[14,16–18] the ACB,[13,21,26] the ADS,[11,12,17,25] a modified version of the ARS,[24] and a modified version of the ACB.[23] The study results are presented in Table 4. In all 4 studies using the ARS, an association was found between ADB and incident delirium. A moderate and high ADB as well as an increase in burden during the hospital stay, measured with the ARS, was associated with an increased risk of developing delirium. In addition, with the modified versions of the ARS and ACB, an association was found between a high ADB and delirium during follow-up. Conflicting results were found when the ADB was assessed with the ACB or ADS.

Subgroup Analyses

The studies included in this review are performed in different patient populations, which might influence the association. The outcomes of the studies were therefore additionally grouped based on the clinical setting (Supplementary Data, Appendix 4). Only in acutely ill hospitalized patients was the association investigated more than 2 times (6 studies in total[13,18–20,22,26]): the ARS was used in 2 studies,[18,20] the ACB in 5,[13,19,20,22,26] and the ADS[19] and Chew[20] in 1. Both studies that used the ARS found an association,[18,20] and only 1 study that used the ACB did.[26]

In addition, the included studies used a wide range of variables in the multivariate models. Dementia and severity of acute illness might have a large impact on the association between ADB and delirium.[3] Only 2 studies adjusted for dementia[22,26] and 3 for severity of acute illness as defined by the Acute Physiology and Chronic Health Evaluation (APACHE) score and the American Society of Anesthesiologists Physical (ASA) status.[14,17,25] Because of the small number of studies adjusting for these variables, no subgroup analyses could be performed.

Anticholinergic Drug Burden and Delirium Severity

Two studies reported on the possible association between ADB and delirium severity.[10,12] A total of 368 persons were studied (323 with delirium). One study was performed in acutely ill patients admitted to the hospital[10] and 1 study in patients with malignancies.[12] Mean ages in these studies were 84.3 years and 41.5 years, respectively. Delirium was diagnosed with the Confusion Assessment Method[10] and the Delirium Rating Scale.[12] The study results can be found in the Supplementary Data, Appendix 5. Both studies used the ADS and 1 study[10] found an association between an increase in ADB and an increase in delirium severity.

Discussion

The findings of this systematic review demonstrate consistent evidence that ADB measured with the ARS is associated with delirium. In addition, with a modified version of the ARS and ACB an association was found between high ADB and delirium. The findings were conflicting when ADB was assessed with other scales, with more negative than positive studies.

This systematic review has evaluated the association between anticholinergic drugs and delirium in more depth than previous reviews.[5,6] In the present review, we specifically included studies in which the ADB score was calculated with a scale and this has highly increased the ability to compare the findings. Previous reviews have reported conflicting findings and these discrepancies can be caused by the fact that the included studies were quite heterogeneous in their quantification of the anticholinergic load. Moreover, the review of Welsh et al included only other systematic reviews about ADB tools and was not designed to investigate the association between anticholinergic drugs and delirium.[32]

The 16 studies included in the present review have used 6 different anticholinergic drug scales (ie, the ARS, ACB, ADS, the list of Chew, a modified version of the ARS, and a modified version of the ACB), and only the ARS was consistently associated with delirium (5 out of 5 studies found a positive association). Also, in the 2 studies that used a modified version of the ARS and ACB, an association was found between a high ADB and delirium during the 3-month[24] and 1-year follow-up,[23] respectively. The modified version of the ARS includes 60 more drugs,[24] and the modified version of the ACB includes 79 more drugs[23] than the original ARS[27] and ACB scale.[29] Moreover, in both studies, the authors also took into account the daily drug dose and, therefore, the findings cannot be compared with findings found with the original scales. When ADB was assessed with other scales, the results were inconclusive, with only 1 positive association for the ACB[26] (1 out of 6 studies) and 1 for the ADS[25] (1 out of 5 studies). An explanation for the discrepancies in findings might be the large differences in the total number and ranking of drugs between the available anticholinergic drug scales as well as the different methods used to develop the scales. A previous study has evaluated the agreement between the ARS, ACB, ADS, and the anticholinergic subscale of the Drug Burden Index for measuring ADB, and found a poor agreement between the 4 scales. Only the ACB and ADS showed a good agreement,[33] and these findings were confirmed in another study.[34] Previous systematic reviews have already highlighted that the association between anticholinergic drug scales and outcomes, such as mortality and physical function, can be different depending on which scale is used.[35–37] Therefore, the large differences in the measurement of the ADB among the available anticholinergic drug scales can also have a high impact on finding an association with delirium.

In addition, the ARS attempts to predict both peripheral and central effects,[27] in contrast to the ACB in which the grading of drugs is based on the potential to cause cognitive effects.[28] It might be possible that in delirium not only central, but also peripheral anticholinergic effects may play a role. Blurred vision, urinary retention, and constipation, known peripheral adverse effects of anticholinergic drugs,[4] are risk factors for delirium[38] and might explain why the ARS was associated with delirium. However, because the individual studies did not report on adverse effects, this remains speculative.

Furthermore, it might be possible that the differences in findings among the anticholinergic drug scales are caused by the variety in patient populations and the diversity in variables for which has been adjusted in multivariate models. Unfortunately, no conclusions can be drawn because some patient populations have only been studied once. Only in acutely ill older patients has the association between ADB and delirium been investigated several times.[13,18–20,22,26] Five studies used the ACB (with almost comparable mean age and delirium prevalence),[13,19,20,22,26] and only 1 study found an association.[26] Moreover, the included studies did not adjust for the same confounding factors. Factors that might influence the association, such as dementia and baseline severity of illness,[3] were not always included in the analyses and, therefore, no conclusions can be drawn for the effect of possible confounders.

Based on the findings of the present review, it can be concluded that the ARS could be a suitable instrument to identify patients at increased risk of delirium. Previous studies have shown that medication reviews can be effective in reducing ADB scores (based on the ARS) in persons age 65 years and older.[39,40] Therefore, it would be interesting to investigate whether regular medication reviews with the ARS as an additional tool, in both the community and hospital setting, will reduce delirium.

Limitations and Strengths

This systematic review has some limitations. First, our search was limited to articles published in the English language. As far as we are aware, there is 1 study published in Spanish in which the association between the ARS, ACB, and ADS and delirium was investigated in patients admitted to a geriatric ward of a hospital.[41] The results are in line with our findings: a significant association was found between the ARS and incident delirium and no association was found with the other anticholinergic drug scales. Second, one might speculate that publication bias could have played a role, considering that 50 conference abstracts were excluded. Of these 50 abstracts, 8 abstracts explicitly described that they have investigated the association between ADB, measured with a scale, and delirium. Two of these abstracts are included as full-text studies in the present review. Of the remaining abstracts, 3 have used the ARS, of which 2 have found an association and 1 not; 4 abstracts have used the ACB and none have found an association; and the ADS was used in 1, and also this abstract found no association. These findings are in line with the results of the present review, and therefore, we think that publication bias has not influenced the results. Third, there was considerable heterogeneity among the studies. However, considering that the evidence for the ARS is consistent among the studies despite the different settings and populations, we do not believe that this has influenced our findings. Fourth, the studies included in this review used the ARS, ACB, ADS, and the list of Chew. Although these are the most frequently used scales in research, other scales exist and it is not known whether these scales are associated with delirium. Moreover, the list of Chew and the modified versions of the ACB and ARS were only used in 1 study each[20,23,24]; therefore, confirmation of the findings is warranted. Fifth, this review identified only 2 studies investigating the possible association between ADB and the severity of delirium,[10,12] which hampers the ability to draw conclusions. More studies in this field are needed.

Major strengths of this review are the comprehensive search, which was performed in multiple databases, and the inclusion, which was limited to studies in which the ADB score was calculated.

Conclusions and Implications

The findings of this systematic review demonstrate consistent evidence that ADB measured with the ARS is associated with delirium. Also, with the modified versions of the ARS and ACB, an association was found between high ADB and delirium, but these findings need confirmation. The current findings suggest that the ARS might be a useful tool to identify persons at increased risk for delirium. Future studies are needed to investigate whether regular medication reviews with the ARS in both the community and hospital settings will reduce delirium.

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Supplementary Data

Appendix 1. PRISMA Checklist

Section/Topic	#	Checklist Item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2-3
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	4
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (eg, Web address), and, if available, provide registration information including registration number.	Not available
Eligibility criteria	6	Specify study characteristics (eg, PICOS, length of follow-up) and report characteristics (eg, years considered, language, publication status) used as criteria for eligibility, giving rationale.	5
Information sources	7	Describe all information sources (eg, databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	5
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Appendix 2
Study selection	9	State the process for selecting studies (ie, screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	6
Data collection process	10	Describe method of data extraction from reports (eg, piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	6
Data items	11	List and define all variables for which data were sought (eg, PICOS, funding sources) and any assumptions and simplifications made.	6
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	6-7
Summary measures	13	State the principal summary measures (eg, risk ratio, difference in means).	6
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (eg, I2) for each meta-analysis.	Not applicable
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (eg, publication bias, selective reporting within studies).	Not applicable
Additional analyses	16	Describe methods of additional analyses (eg, sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	7
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	8, Figure 1
Study characteristics	18	For each study, present characteristics for which data were extracted (eg, study size, PICOS, follow-up period) and provide the citations.	8-9, Table 1
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	9, appendix 3
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	9-12, Tables 3 and 4, appendix 4-5
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	Not applicable
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	Not applicable
Additional analysis	23	Give results of additional analyses, if done (eg, sensitivity or subgroup analyses, meta-regression [see Item 16]).	11-12
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (eg, healthcare providers, users, and policy makers).	13-15
Limitations	25	Discuss limitations at study and outcome level (eg, risk of bias), and at review-level (eg, incomplete retrieval of identified research, reporting bias).	15-16
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	16
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (eg, supply of data); role of funders for the systematic review.	Title page

Appendix 2. Search Strategy

embase.com

('cholinergic receptor blocking agent'/mj OR 'anticholinergic effect'/de OR 'anticholinergic syndrome'/de OR (((cholinerg* OR acetylcholin*-receptor* OR AChR OR parasympath*) NEAR/3 (block* OR anti* OR inhibitor*)) OR anticholinergic* OR cholinolytic* OR parasympatholytic*):kw,ab,ti) AND ('delirium'/exp OR confusion/exp OR 'delusion'/de OR 'delusional disorder'/de OR 'somatic delusion'/de OR (delier OR delir* OR delusion* OR confusion*):kw,ab,ti) NOT ('case report'/de OR ((case NEAR/3 report)):kw,ab,ti) AND [english]/lim

Medline Ovid

(Cholinergic Antagonists/ OR Anticholinergic Syndrome/ OR (((cholinerg* OR acetylcholin*-receptor* OR AChR OR parasympath*) ADJ3 (block* OR anti* OR inhibitor*)) OR anticholinergic* OR cholinolytic* OR parasympatholytic*).kw,ab,ti.) AND (exp confusion/ OR Delusions/ OR (delier OR delir* OR delusion* OR confusion*).kw,ab,ti.) NOT (case report/ OR ((case ADJ3 report)).kw,ab,ti.) AND english.la.

Web of science

TS=(((((cholinerg* OR acetylcholin*-receptor* OR AChR OR parasympath*) NEAR/2 (block* OR anti* OR inhibitor*)) OR anticholinergic* OR cholinolytic* OR parasympatholytic*)) AND ((delier OR delir* OR delusion* OR confusion*)) NOT (((case NEAR/2 report)))) AND LA=(english)

Cochrane CENTRAL

((((cholinerg* OR acetylcholin* NEXT/1 receptor* OR AChR OR parasympath*) NEAR/3 (block* OR anti* OR inhibitor*)) OR anticholinergic* OR cholinolytic* OR parasympatholytic*):kw,ab,ti) AND ((delier OR delir* OR delusion* OR confusion*):kw,ab,ti) NOT (((case NEAR/3 report)):kw,ab,ti)

PsycINFO Ovid

(Cholinergic Blocking Drugs/ OR (((cholinerg* OR acetylcholin*-receptor* OR AChR OR parasympath*) ADJ3 (block* OR anti* OR inhibitor*)) OR anticholinergic* OR cholinolytic* OR parasympatholytic*).ab,ti.) AND (Delirium/ OR Delusions/ OR (delier OR delir* OR delusion* OR confusion*).ab,ti.) NOT (case report/ OR ((case ADJ3 report)).ab,ti.) AND english.la.

CINAHL EBSCOhost

(MH Cholinergic Antagonists OR TI (((cholinerg* OR acetylcholin*-receptor* OR AChR OR parasympath*) N2 (block* OR anti* OR inhibitor*)) OR anticholinergic* OR cholinolytic* OR parasympatholytic*) OR AB (((cholinerg* OR acetylcholin*-receptor* OR AChR OR parasympath*) N2 (block* OR anti* OR inhibitor*)) OR anticholinergic* OR cholinolytic* OR parasympatholytic*)) AND (MH confusion+ OR TI (delier OR delir* OR delusion* OR confusion*) OR AB (delier OR delir* OR delusion* OR confusion*)) NOT (MH Case Studies OR TI ((case N2 report)) OR AB ((case N2 report))) AND LA english

Google scholar

"cholinergic|acetylcholine receptor blocker|inhibitor":|anticholinergic|cholinolytic|parasympatholytic delirium|delusion|confusion

Appendix 3

Quality Assessment

Study	Selection				Comparability	Outcome			
	Representative of Exposed Cohort	Selection of Nonexposed Cohort	Ascertainment of Exposure	Demonstration - Outcome not Present at start	Adjustment	Ascertainment of Outcome	Was Follow up long Enough	Adequacy of Follow up of Cohorts	Total
Cohort Studies									
Han et al, 2001[10]	0	1	1	0	2	1	1	0	6
Juliebø et al, 2009[11]	0	1	1	1	2	1	1	1	8
Fann et al, 2011[12]	0	1	1	1	1	1	1	1	7
Campbell et al, 2011[13]	0	1	1	1	2	1	1	1	8
Zimmerman et al, 2014[14]	0	1	1	1	2	1	1	1	8
Landi et al, 2014[16]	1	1	1	1	2	1	1	1	9
Wolters et al, 2015[17]	0	1	1	1	2	1	1	1	8
Crispo et al, 2016[18]	0	1	0	0	2	1	1	1	6
Hussain et al, 2018[21]	0	1	0	0	2	0	1	1	5
Ah et al, 2019[23]	1	1	1	0	2	1	1	1	8
Hwang et al, 2019[24]	1	1	1	0	2	1	1	1	8
Mueller et al, 2019[25]	0	1	1	1	2	1	1	1	8
Rigor et al, 2020[26]	0	1	1	0	2	1	1	1	7

Study	Selection				Comparability	Exposure			Total
	Case definition	Representativeness of cases	Selection of controls	Definition of controls	Adjustment	Ascertainment of exposure	Same method cases and controls	Non-response rate	
Case-control									
Moorey et al, 2016[19]	1	1	0	1	1	1	1	1	7
Cross-sectional									
Egberts et al, 2017[20]	1	1	0	1	2	1	1	1	8
Pasina et al, 2019[22]	1	1	0	1	2	1	1	1	8

Supplementary Table A1
Study Results Stratified on Study Population

Ach Drug Scale	Reference	Sample Size, n	Age in y, Mean ± SD	Delirium, n (%)*	Results OR, HR or Proportions with *P* Value
Acutely ill					
ARS	Egberts et al,[20]	905	81.0 ± 7.0	215 (23.8)	Total ADB score 1-2: **OR 1.70 (1.16–2.49)** Total ADB score ≥3: **OR 1.83 (1.06–3.15)**
	Crispo et al.[18]	16,302	Unknown, 82.4% ≥70 years	362 (2.2)	Total ADB score 1: OR 1.05 (0.69–1.61) Total ADB score 2-3: **OR 2.14 (1.46–3.15)** Total ADB score ≥4: **OR 1.61 (1.08–2.40)**
ACB	Egberts et al.[20]	905	81.0 ± 7.0	215 (23.8)	Total ADB score 1-2: OR 0.99 (0.67–1.46) Total ADB score ≥3: OR 1.39 (0.89–2.18)
	Moorey et al.[19]	247	84.0 ± 6.6	125	OR ns
	Pasina et al.[22]	477	83.9 ± 6.5	151 (31.7)	Total ADB score 1: OR 0.93 (0.49–1.79) Total ADB score 2: OR 1.01 (0.47–2.16) Total ADB score 3: OR 1.81 (0.74–4.47) Total ADB score 4: OR 2.19 (0.87–5.53) Total ADB score ≥5: OR 2.73 (0.85–8.77)
	Rigor et al.[26]	198	79.9 ± 7.5	56 (28.3)	**OR 1.65 (1.09–2.51)**
	Campbell et al.[13]	147	76.5 ± 7.9	33 (22.4)	OR 0.95 (0.80–1.13)
ADS	Moorey et al.[19]	247	84.0 ± 6.6	125	OR ns
Chew	Egberts et al.[20]	905	81.0 ± 7.0	215 (23.8)	Total ADB score 0.5-1: OR 1.00 (0.71–1.43) Total ADB score ≥1.5: OR 1.34 (0.85–2.11)
Critically ill					
ARS	Wolters et al.[17]	1112	60 ± 16	535 (48)	**OR 1.12 (1.03–1.22)**
ADS	Wolters et al.[17]	1112	60 ± 16	535 (48)	OR 1.05 (0.99–1.10)
Surgical					
ACB	Hussain et al.[21]	90	83 ± 6	7 (8.0)	OR 1.62 (0.81–3.24)
ADS	Juliebø et al.[11]	364	Unknown, median (IQR): 84 (79-88)	168 (46.2)	Preoperative delirium: Total ADB score ≥3: Delirium: 20% No delirium: 19.8% *P* = .97 Postoperative delirium: Total ADB score ≥3: Delirium: 25% No delirium: 16,8% *P* = .18
Cancer and/or cancer-related surgery					
ADS	Fann et al.[12]	90	41.5 ± 9.9	45 (50)	HR: ns
	Mueller et al.[25]	651	71.8 ± 4.9	66 (10.1)	**OR 1.50 (1.09–2.05)**
Palliative					
ARS	Zimmerman et al.[14]	217	72.9 ± 12.8	67 (30.9)	**OR 1.4 (1.0–1.9)**
Community					
Modified ARS	Hwang et al.[24]	1,18,750	75.4 ± 6.6	66 (0.05)	Total ADB score ≥2: **HR: 2.05 (1.13–3.73)**
Modified ACB	Ah et al.[23]	7438	Unknown, 60.9% ≥75 years	298 (4.0)	Total ADB score >3: **HR: 1.52 (1.17–1.96)**
Nursing home					
ARS	Landi et al.[16]	1490	83.5 ± 8.0	Not defined	**OR 1.16 (1.02–1.32)**

Values in bold are statistically significant ($P < .05$).
ACh, anticholinergic; *CI*, confidence interval; *HR*, hazards ratio; *ns*, not significant; *OR*, odds ratio.
*Percentage not provided for case-control (matched) studies and studies that included only patients with delirium.

Supplementary Table A2
Study Results—Delirium Severity

ACh Drug Scale	Reference	Drug Exposure	Type of Analysis	Results OR/HR/RR/β (95% CI)
ADS/clinician-rated	Han et al, 2001[10]	Daily total ADB score	Multivariate	**β = 0.20 (0.03–0.38),** $P = .02$
ACh scale	Fann et al, 2011[12]	Total ADB score in the previous 48 h	Multivariate	β = 0.03 (−0.06 to 0.11), $P = .52$
Summers Drug Risk Number	Han et al, 2001[10]	Daily total ADB score	Multivariate	β = 0.07 (−0.07 to 0.21), $P = .35$

ACh, anticholinergic; *CI*, confidence interval; *HR*, hazards ratio; *OR*, odds ratio; *RR*, risk ratio.
Values in bold are statistically significant ($P < .05$).