Traumatic Brain Injury and Risk of Dementia and Alzheimer's Disease: A Systematic Review and Meta-Analysis

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Keywords

Traumatic brain injury · Dementia · Alzheimer's disease · Association · Meta-analysis

Abstract

Introduction: Previous studies have investigated the potential role of traumatic brain injury (TBI) in subsequent development of dementia and Alzheimer's disease (AD) but reported inconsistent results. We aimed to determine the association between TBI and subsequent occurrence of dementia and AD. **Methods:** We performed a systematic search in PubMed and Web of Science for studies that quantitatively investigated the association between TBI and risk of dementia and AD and were published on or before September 21, 2021. A random-effects model was used to combine the estimates. **Results:** Twenty-five eligible articles were included in this meta-analysis. The results suggested that TBI was associated with an increased risk of dementia (pooled odds ratio [OR] = 1.81, 95% confidence interval [CI] = 1.53–2.14). However, no association was observed between TBI and AD (pooled OR = 1.02, 95% CI = 0.91–1.15). In the subgroup analysis, TBI with loss of consciousness was not associated with risk of dementia (pooled OR = 0.96, 95%

CI = 0.84–1.09). Besides, Asian ethnicity, male gender, and mean age of the participants less than 65 years were associated with a higher risk of dementia. **Conclusion:** Our study suggests an increased risk of dementia among individuals with TBI, highlighting the need for more intensive medical monitoring and health education in individuals with TBI. Biological mechanisms linking TBI and the development of dementia are needed in future studies.

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Introduction

Traumatic brain injury (TBI) is the most common cause of death and disability worldwide, with various long-term outcomes in survivors [1]. Approximately, 23 million adults aged more than 40 years reported a history of TBI with loss of consciousness (LOC); in the USA alone, TBI cases grow by an alarming rate of 1.7 million annually [2–5]. The personal and societal costs are estimated to be USD 400 billion worldwide, accounting for 0.5% of the entire annual global output [6, 7]. In addition, higher rates of morbidity and mortality are seen in low-income and middle-income countries, making it a global health challenge [2].

Indeed, TBI is the most frequent cause of nervous tissue damage in the developed countries [8]. Neurological damage may occur not only at the moment of impact (primary injury) of TBI but also over patients' lifetime (secondary injury) [9]. Secondary damage is often linked to the molecular mechanisms that occur following TBI and results in neurotransmitter release, calcium-mediated damage, gene activation, mitochondrial dysfunction, excitotoxicity, neuroinflammation and cytokine damage, oxidative damage, and eventual cell death [10–12]. Interestingly, epidemiological evidence also showed correlation of TBI with an increased risk of neurodegenerative disease such as dementia [13–15], Alzheimer's disease (AD) [16–18], multiple sclerosis [19–21], Parkinson's disease [22–24], and amyotrophic lateral sclerosis [25–27].

As the most common neurodegenerative disorder, AD is the most common cause of dementia in old age [28]. It was reported that all-cause dementia risk was increased by around 1.5 times, of which, around 5% of all dementia cases worldwide may be attributable to TBI [29]. In particular, there is a long history linking TBI with the development of dementia, and an increasing number of articles have been published to explore the relationship between TBI and risk of dementia and AD in recent years. However, despite significant reservations, such as recall bias or concluding causality for TBI, the results were not all consistent. Several observational studies have suggested that TBI was associated with an increased risk of dementia or AD [14, 30], whereas others reported no association [31, 32].

In addition, Perry et al. [33] and Huang et al. [9] conducted meta-analyses but found no association between TBI and dementia or AD. Since most of the included studies in these meta-analyses were not cohort but case-control studies, the results might be confounded by various factors such as recall bias and selection bias. Besides, the exposure was yet a more broad head-injury definition, and the exposure assessment in these included studies was mainly based on self-report or questionnaire, making the effects stronger. Therefore, we performed an up-to-date meta-analysis to reevaluate this association based on published studies so as to determine whether TBI was a risk factor of dementia or AD.

Methods

This meta-analysis was performed according to the guidelines proposed by the PRISMA statement and Meta-analysis Of Observational Studies in Epidemiology [34, 35].

Literature Search

A comprehensive literature search of related studies was conducted using PubMed and Web of Science (published on or before September 21, 2021), with the following keywords “Alzheimer's disease or Alzheimer disease or dementia” and “Traumatic brain injury or craniocerebral trauma or craniocerebral injury” as query terms. The title and abstract of studies or the full text if necessary was reviewed to identify all relevant publications. In addition, reference lists of all included studies as well as reviews and meta-analyses were manually screened for extra potential studies.

Inclusion and Exclusion Criteria

Inclusion criteria were as follows: (1) cohort studies, case-control studies, or cross-sectional studies that quantitatively investigated the association between TBI and risk of dementia or AD; (2) exposure to TBI defined based on medical records, military records, questionnaires, or self-reports; (3) the outcome of interest was dementia or AD; (4) providing risk estimates with 95% confidence interval (CI) or data to calculate them; and (5) published in the English language. Exclusion criteria were as follows: (1) abstracts, reviews, letters, case reports, and studies that did not provide sufficient data to calculate the risk estimates and (2) exposure to head injury or head trauma which was not clearly defined as TBI. Two investigators independently selected studies, and any discrepancy was resolved through discussion.

Data Extraction and Quality Assessment

Data extraction was completed independently by two investigators, and any discrepancy was resolved by the third investigator. The following information was extracted from each study: first author, year of publication, country, ethnicity, study design, data source, exposure, assessment method of exposure, outcome, assessment method of outcome, the number of cases, the number of controls or sample size for cohort studies, odds ratio (OR), relative risk, hazard ratio (HR), or standardized incidence ratio and corresponding 95% CI. For each study, the fully adjusted risk estimates were extracted, and the age-adjusted risk estimates or univariate risk estimates and adjustments were used when the multivariate risk estimates were unavailable.

Quality assessment was performed using the Newcastle-Ottawa Scale (NOS) [36]. Individual studies were assessed based on three quality parameters: selection, comparability, and outcome. The maximum total score is nine points, with a score of seven points or higher indicating high study quality.

Statistical Analysis

Statistical analyses were done using Stata version 15 (Stata, College Station, TX, USA), and two-sided *p* values of 0.05 or less were considered statistically significant unless otherwise stated. Associations between TBI and risk of dementia and AD were evaluated by pooled OR and corresponding 95% CI using a random-effects model (DerSimonian-Laird) [37]. The significance of pooled OR was determined by the *Z* test.

Evaluation of meta-analysis included the test of heterogeneity, sensitivity analyses, and publication bias. The statistical heterogeneity among the studies was assessed by the Cochran *Q* statistic (*p* values <0.10 was considered indicative of statistically significant heterogeneity) and *I*² statistic (*I*² values less than 25% represented mild heterogeneity, values between 25% and 50% represented moderate heterogeneity, and values greater than 50% represented

Fig. 1. Literature search flowchart.

large heterogeneity) [38, 39]. In addition, sensitivity analyses were performed to investigate the influences of single studies on the overall risk estimate by removing one study each time. The potential publication bias was evaluated using both Begg's test and Egger's test, and p values <0.10 were considered to be statistically significant [40, 41].

Results

Literature Search Results and Study Characteristics

The literature search and selection process are presented in Figure 1. The comprehensive search generated 2,686 potentially relevant articles. After excluding 604 duplicated articles, we reviewed the title and abstract of 2,082 articles and excluded 2,043 of them. Then, full texts of the remaining 39 studies were examined, and we excluded 16 of them. To be specific, 12 articles with irrelevant topics, one article about the diagnosis of AD, one article about the mortality risk in patients with TBI, one

article in which the outcome of interest was TBI, and one article in which the outcome of interest was other disease were excluded. Additionally, two articles were included through previous review or reference lists of relevant studies. Finally, 25 articles met our inclusion criteria and were included in the meta-analysis, including 23 cohort studies [14, 15, 30–32, 42–59] and two case-control studies [60, 61].

The characteristics of the included studies are summarized in Table 1. Of these studies, 21 articles investigated the association between TBI and dementia with a total sample size of 8,684,485 and 411,310 cases, and seven articles investigated the association between TBI and AD with a total sample size of 2,820,181 and 11,487 cases. Among these studies, 14 were conducted in USA, six in Europe (two in Sweden, two in Denmark, one in the UK, and one in Finland), four in China, and one in Austria. TBI ascertainment was mainly based on International Classification of Diseases codes (68%). In addition, each

Table 1. Characteristics of the included studies

First author	Country	Ethnicity	Study design	Exposure type	TBI assessment	Outcome	Outcome assessment	Cases	Controls/ sample sizes	Follow-up (mean, years)	Or (95% CI)	Adjustments	Study quality
Stopa et al. [42]	USA	Caucasian	Cohort	TBI Mild TBI Moderate/severe TBI	ICD code	Dementia	ICD-9/10	936	24,846	≤10	2.2 (1.9–2.5) 2.3 (2.0–2.6) 1.3 (0.8–2.1)	Demographics, medical, psychiatric, and ISS	9
Jacob et al. [43]	UK	Caucasian	Cohort	TBI	ICD code	Dementia	ICD-10	710	9,520	10	M: 2.29 (1.64–3.19) W: 1.33 (1.07–1.64)	Unadjusted	7
Kornblith et al. [44]	USA	Caucasian	Cohort	TBI	ICD code	Dementia	ICD-9	63,312	999,642	4.3	M: 2.60 (2.54–2.66) W: 2.36 (2.08–2.69)	Demographics and comorbid conditions Demographics and comorbid conditions	7
Grasset et al. [45]	USA	Caucasian	Cohort	TBI with LOC	Self-reported	Dementia	Not reported	434	2,414	13	0.90 (0.65–1.26)	Sex, race, education, veteran status, marital status, depressive symptoms, ever have hypertension, diabetes, cancer, heart disease, stroke, lung disease, arthritis, and ever smoking	8
Osler et al. [46]	Denmark	Caucasian	Cohort	TBI	ICD code	Dementia	ICD-8 and 10	10,971	658,447	39.3	3.72 (3.49–3.97) ^a	TBI, cognitive ability, education, alcohol abuse, depression, and fractures	8
Sugarman et al. [47]	USA	Caucasian	Cohort	TBI with LOC	Self-reported	AD	Autopsy	2,822	4,761	3.8	1.10 (0.82–1.49)	NR	6
Yang et al. [48]	Taiwan	Asian	Cohort	TBI Mild TBI Moderate/severe TBI	ICD code	Dementia	ICD-9	1,406 4,451 1,409	501,889 399,058 149,475	≤10	3.04 (2.88–3.20) 1.78 (1.73–1.84) 2.18 (2.07–2.30)	SIR	8
Yaffe et al. [49]	USA	Mix	Cohort	TBI	ICD code	Dementia	ICD-9	4,125	109,140	4	1.49 (1.01–2.20)	Demographics and medical conditions	8
Gilsanz et al. [50]	USA	Mix	Cohort	TBI	ICD code	Dementia	ICD-9	212	4,049	5.8	3.03 (2.09–4.39)	Demographics, micro- and macrovascular complications, depression, HbA1c, and dysglycemic events	7
LoBue et al. [51]	USA	Caucasian	Cohort	TBI with LOC	Self-reported	AD	NINCDS/ADRDA	1,016	2,719	4	0.88 (0.69–1.12)	Age of MCI diagnosis, race, the presence of Apoe4 alleles, and family history of dementia	7
Barnes et al. [30]	USA	Mix	Cohort	TBI Mild TBI without LOC Mild TBI with LOC Moderate/severe TBI	ICD code	Dementia	ICD-9	15,533	357,558	4.2	3.45 (3.33–3.57) 2.36 (2.10–2.66) 2.51 (2.29–2.76) 3.77 (3.63–3.91)	Demographics and medical and psychiatric comorbidities	8

Table 1 (continued)

First author	Country	Ethnicity	Study design	Exposure type	TBI assessment	Outcome	Outcome assessment	Cases	Controls/ sample sizes	Follow-up (mean, years)	Or (95% CI)	Adjustments	Study quality
Fann et al. [14]	Denmark	Caucasian Cohort	Cohort	TBI	ICD code	Dementia	ICD-8 and 10	126,734	2,794,852	9.89	1.24 (1.21–1.27)	Age, sex, marital status, calendar period, and psychiatric comorbidities (i.e., depression, bipolar disorder, schizophrenia, and substance abuse)	9
				Severe TBI							1.35 (1.26–1.45)		
				Mild TBI							1.17 (1.13–1.20)		
				TBI	NA	AD					1.16 (1.12–1.22)	Unadjusted	
Cations et al. [60]	Australia	Other	Case-control	TBI with LOC	ICD code	Dementia	Clinical consensus	96	175		0.74 (0.41–1.34) ^b	Unadjusted	6
				Mild							0.65 (0.31–1.38)		
				Moderate/severe TBI							0.92 (0.35–2.44)		
Nordstrom et al. [52]	Sweden	Caucasian Cohort	Cohort	TBI	ICD code	Dementia	ICD-8, 9, and 10	21,963	491,252	15.3	1.81 (1.75–1.86)	Age, civil status, education, early retirement pension, and diagnoses at baseline	9
								1,204	93,940	18.8	1.89 (1.62–2.22)		
				Nested case-control				136,233	404,887		1.71 (1.66–1.76)		
Chu et al. [15]	Taiwan	Asian	Cohort	TBI	ICD code	Dementia	ICD-9	437	64,655	2.1	3.21 (2.65–3.90)	Age, gender, diabetes mellitus, chronic renal failure, chronic liver disease, thyroid disease, cardiovascular diseases, monthly income, geographic region, and urbanization level	8
				Repeat TB							3.62 (2.85–4.61)		
Crane et al. [31]	USA	Caucasian Cohort	Cohort	TBI with LOC	Self-reported	Dementia	DSM-IV	921	4,626	6.2	1.059 (0.876–1.280) ^c	Age at death; sex; years of education; and indicator terms for ROS, MAP, and three different enrollment groups for ACT	9
						Dementia		616	2,689	4.7	0.861 (0.614–1.208) ^c		
						AD	NINCDS-AD/DA	759	4,626		1.024 (0.823–1.274) ^c		
						AD		563	2,689		0.813 (0.565–1.170) ^c		
Mendez et al. [61]	USA	Caucasian Case-control	Case-control	TBI	NA	AD	Not reported	1,449	1,449		1.24 (0.99–1.55) ^d	Unadjusted	6
						AD		4,337	4,337		0.88 (0.75–1.02) ^d		
Gardner et al. [53]	USA	Mix	Cohort	TBI	ICD code	Dementia	ICD-9	10,971	164,661	6	1.26 (1.21–1.32)	Age, sex, race, comorbidities, trauma mechanism, health care use, and trauma severity	9
				Mild TBI							1.22 (1.13–1.32) ^a		
				Moderate/severe TBI							1.21 (1.14–1.28) ^a		
Barnes et al. [54]	USA	Mix	Cohort	TBI	ICD code	Dementia	ICD-9	18,451	188,764	7.44	1.57 (1.35–1.83)	Demographic, medical, and psychiatric factors	8

Table 1 (continued)

First author	Country	Ethnicity	Study design	Exposure type	TBI assessment	Outcome	Outcome assessment	Cases	Controls/ sample sizes	Follow-up (mean, years)	Or (95% CI)	Adjustments	Study quality
Nordstrom et al. [55]	Sweden	Caucasian	Cohort	TBI	ICD code	Dementia	ICD-8, 9, and 10	566	811,622	33	1.76 (1.36–2.28) ^b	Age, place, and year of conscription; weight, height; knee extension strength; TBI in parents; dementia in parents; income; educational level; systolic blood pressure; drug intoxication; depression; and cerebrovascular disease	9
				1 mild TBI							1.5 (1.1–2.0)		
				>1 mild TBI							1.8 (1.1–3.0)		
				1 severe TBI							2.3 (1.5–3.6)		
Lee et al. [56]	Taiwan	Asian	Cohort	Mild TBI	ICD code	Dementia	ICD-9	1,071	720,933		3.26 (2.69–3.94)	Age, gender, urbanization level, socioeconomic status, diabetes, hyperlipidemia, coronary artery disease, history of alcohol intoxication, ischemic stroke, intracranial hemorrhage, and Charlson comorbidity index	9
Dams-O'Connor et al. [32]	USA	Caucasian	Cohort	TBI with LOC	Self-reported	Dementia	DSM-IV	592	3,465	7.4	0.87 (0.60–1.27)	Age, age-squared, gender, and education	7
						AD	NINCDS-ADRA	510	3,465		0.95 (0.65–1.38)		
Wang et al. [57]	Taiwan	Asian	Cohort	TBI	ICD code	Dementia	ICD-9	4,635	269,550		1.68 (1.57–1.80)	Selected comorbidities in patients	8
Luuinen et al. [58]	Finland	Caucasian	Cohort	TBI	ICD code	Dementia	DSM-IV/MMSE	152	909		2.80 (1.35–5.81)	Low educational status and sex	8
Nemetz et al. [59]	USA	Mix	Cohort	TBI	Medical recodes	AD	Medical records	31	1,283		1.2 (0.8–1.7)	NA	7

DSM, diagnostic and statistical manual of mental disorders; ICD, International Classification of Diseases; M, men; MMSE, mini-mental state examination test; NR, not reported; SIR, standard incidence ratio; W, women. ^a The HR was a pooled HR based on HRs for the different time lags in the original article. ^b The HR was a pooled HR based on HRs for the different TBI (traumatic events and severity) in the original article. ^c The HR was a pooled HR based on HRs for TBI, with LOC <1 h and TBI, with LOC ≥1 h. ^d The risk estimates were calculated by 2 × 2 table.

Fig. 2. Forest plots of TBI and risk of dementia and AD. **a** TBI and risk of dementia. **b** TBI and risk of AD.

study included in our meta-analysis was carefully assessed according to the NOS. The quality scores ranged from 6 to 9 points, and 22 studies (88%) were scored 7 points or higher, indicating high quality.

Association between TBI and Risk of Dementia and AD

We found a moderate association between TBI and risk of dementia (pooled OR = 1.81, 95% CI = 1.53–2.14),

whereas no association was observed between TBI and AD risk (pooled OR = 1.02, 95% CI = 0.91–1.15) (Fig. 2). In the subgroup analyses, TBI with LOC was not associated with risk of dementia (pooled OR = 0.96, 95% CI = 0.84–1.09). Besides, we found that Asian ethnicity (pooled OR = 2.69, 95% CI = 1.84–3.94), male gender (pooled OR = 2.05, 95% CI = 1.43–2.95), and mean age less than 65 years (pooled OR = 2.13, 95% CI = 1.63–2.78) were associated with higher risk of dementia (Fig. 3).

Fig. 3. Subgroup analyses for risk of dementia in individuals with TBI.

Heterogeneity, Sensitivity Analysis, and Publication Bias

Large heterogeneity was found among studies concerning relationship between TBI and risk of dementia ($I^2 = 99.5\%$, $p < 0.001$) and AD ($I^2 = 64.2\%$, $p = 0.004$).

Meta-regression analyses suggested that study design ($p = 0.017$), ethnicity ($p = 0.046$), exposure variable ($p < 0.001$), and mean age of the participants ($p = 0.003$) might be the potential sources of heterogeneity of TBI and dementia risk ($p = 0.001$). Sensitivity analysis was

Fig. 4. Sensitivity analyses. **a** Dementia. **b** AD.

performed to evaluate the stability of results and showed that removing any single study could not significantly change the pooled relative risks and 95% CIs (Fig. 4). In addition, the funnel plot seemed symmetrical according to visual inspection (Fig. 5). Begg's test ($p = 0.941$) and Egger's test ($p = 0.985$) further confirmed that there was no potential publication bias in our meta-analysis.

Discussion

Our analysis comprehensively evaluated the relationship between TBI and subsequent risks of dementia and AD. The results suggested that TBI was associated with an increased risk of subsequent dementia, especially in individuals with Asian ethnicity, male gender, and mean age less than 65 years. We believe that these findings will highlight the need for more intensive medical monitoring

Fig. 5. Funnel plots.

and health education in patients with TBI. From a public health perspective, TBI prevention programs can help reduce the burden of dementia worldwide.

In this study, we found that TBI was associated with a 1.81-fold increased risk of dementia, which was consistent with previous meta-analyses and recent large cohort studies [9, 16, 30, 46, 48–50]. Possible mechanisms have been proposed to explain the positive association between TBI and dementia risk. It has been hypothesized that dysfunction of the blood-brain barrier might play a critical role in pathogenesis of dementia [62]. TBI can disrupt the blood-brain barrier, which could cause leukocyte infiltration and microglial activation. Besides, mitochondrial function, β -amyloid pathology, chronic neuroinflammation, tau deposition, vascular damage, and white-matter degeneration in patients with TBI have been implicated in development of neurodegenerative disease [63–70].

In our study, the risk of dementia was significantly elevated in patients with TBI. However, no association was found between TBI and subsequent AD. Alternatively, TBI may trigger a neuropathological process that more directly leads to dementia. Several studies have suggested that TBI-related dementia is distinct from AD both in the clinical presentation and the associated neuropathology [71]. Chronic traumatic encephalopathy, which is attributed to repeated head trauma, has become widely accepted to describe dementia syndrome [72, 73]. The neuropathology of chronic traumatic encephalopathy was reported to be different from the neuropathology of AD [74]. Otherwise, TBI was reported to be a risk factor of frontotemporal degeneration, which is one of the leading causes of neurodegenerative dementia [54, 75].

Nevertheless, our meta-analysis included not only cohort studies but also case-control studies. Therefore, subgroup analysis by the study design was conducted to explore the potential resource of heterogeneity. Pooled results from different study designs were inconsistent, which may cause biases. Results from case-control studies could have been somewhat biased by selective participation of TBI, and the information about TBI was recorded after dementia diagnosis, so the results might be confounded by recall bias.

In addition, we conducted subgroup analyses to determine whether TBI characteristics or methodological factors would influence our findings. Although TBI with LOC had no significant association with dementia, there were very limited studies on TBI with or without the LOC subgroup, making the subgroup results lack statistical power. Otherwise, our study suggested a comparable risk of dementia in patients with mild TBI or moderate to severe TBI. Therefore, whether the severity of TBI was associated with dementia was a puzzle. The assessment methods for TBI may also vary between the included studies, and the assessment of TBI in several included studies was based on a self-report, which could induce recall bias, especially for the patients with dementia or AD.

It is known that older age was a risk factor of dementia. Interestingly, we found a higher increased risk of dementia in TBI patients with a mean age less than 65 years compared with those older than 65 years (pooled OR: 2.13 vs. 1.55, $p = 0.003$), which may be explained by a couple of factors according to a previous study that reported dementia risk as the greatest in the middle-aged patients with TBI [42]. Although subgroup analysis by ethnicity suggested that TBI-related risk was higher in Asian populations, the data sources were all generated from a single database of Taiwan. Therefore, the participants may be largely overlapped, leading to overestimation of this association. Another important result of this study is the association between TBI and dementia differing between men and women. TBI-associated risk of dementia was higher (pooled OR: 2.05 vs. 1.54, $p = 0.019$) in men compared with women, and the results were similar with previous meta-analysis and recent nationwide cohort studies [14, 43, 76, 77].

Several limitations in this meta-analysis warrant consideration. First, many retrospective studies were included in our study; therefore, the results might be influenced by recall bias or selective bias. Besides, five studies included in our study reported unadjusted risk estimates, which could be confounded by other variables such as age and

gender. Second, although no evidence supports a positive association between TBI and AD in this study, the results should be explained with caution. On the one hand, the studies claiming to examine risk of AD specifically were often unadjusted. On the other hand, the outcome ascertainment of AD was usually different in the included studies (i.e., one autopsy study, a few relying on International Classification of Diseases codes, and the rest using National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer Disease and Related Disorders Association (NINCDS-ADRDA) for outcome ascertainment), and the risk of misascertainment (or at the very least, inconsistent ascertainment) of the outcome in the AD studies. Indeed, exact examination of all-case dementia and AD was needed since AD was in fact the cause of the dementia. Third, we could hardly perform subgroup analysis of TBI and AD due to the available data. Finally, although Begg's and Egger's tests confirmed no potential publication bias in our meta-analysis, there was potential publication bias since only English language studies were included in this study.

In conclusion, the current meta-analysis has confirmed that TBI is a potential risk factor for dementia, especially in individuals of Asian ethnicity, male gender, and mean age less than 65 years. Although no evidence supports a positive association between TBI and AD in this study, more well-designed studies with exact examination of all-case dementia and AD are needed to examine their relationship in the future.

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Statement of Ethics

An ethics statement is not applicable because this study is based exclusively on the published literature.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

G.L. and D.G. contributed to the conception and design of the study. D.G. and S.O. did the literature search, data extraction, and quality assessment. G.L. and D.G. did statistical analysis. D.G. wrote the first draft of the original manuscript with significant contributions from S.O. and G.L. All the authors read and approved the final manuscript.

Data Availability Statement

All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

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