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Post-Operative Delirium and Its Relationship with Biomarkers for Dementia: A Meta-Analysis

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Abstract

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Objectives—This paper seeks to identify Alzheimer's and related dementias (ADRD) biomarkers associated with post-operative delirium (POD) via meta-analysis.

Design—A comprehensive search was conducted. Studies met the following inclusion criteria: ≥18 years of age, identified POD with standardized assessment, and biomarker measured in the AT(N)-X (A=amyloid, T=tau, (N)=neurodegeneration, X-Other) framework. Exclusion criteria: focus on prediction of delirium, delirium superimposed on dementia, other neurologic or psychiatric disorders, or terminal delirium. Reviewers extracted and synthesized data for the meta-analysis.

Setting—Meta-analysis.

Participants—Patients with POD.

Measurements—Primary outcome: association between POD and ATN-X biomarkers. Secondary outcomes involved sample heterogeneity.

Results—28 studies were included in this meta-analysis. Studies focused on inflammatory and neuronal injury biomarkers; there were an insufficient number of studies for amyloid and tau biomarker analysis. Two inflammatory biomarkers (IL-6, and CRP) showed a significant relationship with POD (IL-6 $n = 10$, SMD: 0.53, 95% CI: 0.36 to 0.70; CRP $n = 14$, SMD: 0.53, 95% CI: 0.33 to 0.74). Two neuronal injury biomarkers (blood based S100B and NfL) were positively associated with POD (S100B $n = 5$, SMD: 0.40, 95% CI: 0.11 to 0.69; NFL $n = 2$, SMD: 0.93, 95% CI: 0.28 to 1.57). Of note, many analyses were impacted by significant study heterogeneity.

Conclusions—This meta-analysis identified an association between certain inflammatory and neuronal injury biomarkers and POD. Future studies will need to corroborate these relationships and include amyloid and tau biomarkers in order to better understand the relationship between POD and ADRD.

Keywords

delirium; post-operative delirium; Alzheimer's disease; biomarkers; inflammation

INTRODUCTION

Post-operative delirium (POD) affects up to 15–50% of older adults undergoing major surgery.[1] It is defined by an acute change in mental status and is characterized by fluctuating levels of consciousness and inattention.[2] A bidirectional relationship between POD and cognitive dysfunction is reported; pre-existing cognitive impairment is both a risk factor for, and a consequence of POD.[3–6] Growing evidence suggests that POD is associated with the development of subsequent mild cognitive impairment (MCI) and Alzheimer's disease and other related diseases (ADRD).[7–11] It is not well understood how underlying neuropathology contributes to POD and how the mechanisms of POD such as dysregulation of inflammation and vascular processes may lead to new or further neurodegenerative disorders. However, the underlying pathophysiology for POD is still an active area of research.[12] Biomarker characterization of this interrelationship between POD and ADRD could provide a deeper understanding of the pathophysiology which may link these two disorders.[13]

One approach to systematically characterize the relationship between disease state markers of POD and those of ADRD is to use the National Institute on Aging-Alzheimer's Association (NIA-AA) Diagnostic Framework.[14] This framework characterizes disease state biomarkers to detect the pathophysiology of ADRD even before clinical symptoms of present. These disease state biomarkers are categorized into amyloid (A), tau (T), and neurodegeneration (N). Biomarkers that do not fit into these categories, namely non-AD etiologies (*e.g.* vascular, inflammation, TDP-43), are placed into category X. We synthesized the literature on POD and ADRD biomarkers by conducting this meta-analysis of disease state biomarkers which aligned with the AT(N)-X categories in post-operative delirium biomarker studies.

METHODS

Eligibility and Search Strategy

Details about the search strategy are described in an earlier systematic review characterizing delirium biomarker studies using the NIA-AA Framework.[15] In brief, PRISMA guidelines were followed to search Ovid MEDLINE, PsycInfo, Embase, and the Cochrane Library were searched from January 1, 2000, through February 20, 2020, using a combination of controlled vocabulary and keyword terms developed in collaboration with a medical librarian and content experts in ADRD and delirium. The overall search strategy was designed to ensure citations included both the concept of delirium and AT(N)-X (X = other) biomarkers.

Study inclusion criteria were: 1) age ≥ 18 years old, 2) used standardized delirium screening tools or diagnostic assessments, and 3) biomarker measurements listed in NIA-AA framework. Study exclusion criteria were: 1) delirium not included or measured using standardized screening tools or diagnostic assessments, 2) age < 18 years old, 3) biomarker measurements not aligned with AT(N)-X categories, 4) primary focus on delirium in the following contexts: 4a) premorbid or comorbid ADRD (*i.e.* delirium superimposed on dementia); 4b) psychiatric disorders (e.g. alcohol dependence, alcohol withdrawal, major depressive disorder, bipolar disorder, and psychotic disorders) 4c) central nervous system disorders other than ADRD; 4d) terminal illness (palliative care or hospice services); 4e) persistent delirium (etiology may be different); 4f) long-term care settings; 5) non-human studies; and 6) non-English articles. Of note, the meta-analysis did not include studies which focused only on biomarker levels to predict delirium.

Details of the study selection and data extraction are described elsewhere.[15] The study selection procedures including data extraction were conducted with independent, blinded reviewers, and discrepancies were evaluated by consensus panels. A predetermined data extraction list was used to extract data for this meta-analysis. In total, 61,256 studies were retrieved from the literature search. We included 113 articles after abstract review and full-text evaluation. Out of these remaining 113 delirium biomarker studies, there were 56 total articles that examined POD. Thirty of these studies are described in this article. (Supplementary Table 1 contains the references of 26 articles not included in this article because they either did not contain enough studies to conduct a meta-analysis or they focused on EEG, functional connectivity, or other biomarkers not easily compared in this

format.) The quality of these articles were graded independently with the Newcastle-Ottawa Scale (NOS)[16] and REMARK Scale. The following quantitative data were extracted from the included studies: the means and standard deviations of biomarkers and the sample sizes of delirium cases and controls, separately. For studies that only reported the median, the minimum and maximum values, and/or the inter-quartile ranges (IQRs), means and SDs were estimated from these quantities using the formulae proposed by Wan and colleagues.[17] When mean (SD) value of biomarker levels could not be provided by the authors but data were available in the articles in graph format, values were extracted using the ImageJ software (version 1.53a, National Institutes of Health, Bethesda, Maryland), which is a free, downloadable, public domain image processing software program (http://rsbweb.nih.gov/ij/download.html). Following our pre-specified inclusion and exclusion criteria, we included the one-time point results if they were only available from individual studies. For a few studies with available data on multiple time points, we included the data with significant results or larger sample sizes for the purpose of hypothesis testing.

Statistical Analysis

The standardized mean difference (SMD) and 95% confidence interval (95% CI) were calculated for each biomarker as a continuous outcome using both fixed and random effect models. The classical DerSimonian and Laird's random-effects meta-analysis method using inverse variance weights were preferred if significant heterogeneity was expected as they assumed and accounted for between-study variance.[18] We presented the results of the random effects meta-analysis in the results section. We estimated SMDs using Hedges's g, a standardized mean difference score corrected for inflation due to small sample sizes. A Q-statistic was calculated using a chi-squared test to quantify the heterogeneity among combined results.[19] Inconsistency was calculated using the I^2 Index to determine the impact of heterogeneity.[20] I^2 is a percentage and its values lie between 0% and 100%. A value of 0% indicates no observed heterogeneity. The presence of heterogeneity can be quantified as low, moderate, high, and considerably high with ranges of 0–25%, 25–50%, 50–75%, and 75–100% for I^2, respectively. Publication bias was examined by funnel plots and the Egger test. All analyses were conducted using STATA/SE version 16.1 for Windows (STATACorp, College Station, TX). *P* values are based on two-sided hypothesis tests. A *p* value of less than .05 was considered statistically significant.

RESULTS

We included 28 POD biomarker studies in the meta-analysis. The overall age of participants ranged from 50 to 83 years old (Control mean: 71.35, SD: 8.56; Delirium mean: 74.71, SD: 7.08). Table 1 depicts the demographics and clinical characteristics of the twenty-eight studies.[21–48] Sample sizes of the studies were highly variable (mean number of delirious subjects = 57.96, SD = 54.68; mean number of non-delirious subjects = 140.36, SD = 201.72). Combined, cardiac surgeries ($n = 9$) and hip fracture repair ($n = 10$) represented 2/3 of the studies.

The mean (SD) NOS and REMARK scores were 6.83 (SD: 1.73) and 16.13 (3.78), respectively, suggesting these articles were of moderate quality. Figure 1 and Table 2

depict the results from meta-analysis of the association between biomarkers and POD. These included blood-based biomarkers (interleukin (IL)-1B, IL-6, IL-8, IL-10, C-reactive protein (CRP), tumor necrosis factor (TNF)-α, S100B, neuron specific enolase (NSE), and neurofilament light chain (NfL)) and cerebrospinal fluid (CSF) biomarkers (IL-8 and S100B). Although there was an insufficient number of studies for amyloid ($n = 3$) and tau ($n = 1$) biomarkers to conduct a meta-analysis, the findings of these studies are briefly summarized below.

Amyloid and Tau Biomarkers

Three articles examined amyloid biomarkers, CSF Aβ1–42, amyloid PET scan, and the blood-based biomarker Aβ1–40. Idland *et al.* found that CSF Aβ1–42 levels were lower in non-demented patients who had delirium than those who did not have delirium.[49] CSF was collected at the time of spinal anesthesia; the results of amyloid biomarkers, however, were from patients those who had delirium pre-operatively and then developed delirium post-operatively. Rolandi *et al.* found that the post-operative amyloid PET scan in 5 patients with POD were all negative, although it was positive in 6 out of 11 patients who did not develop POD.[50] Finally, Sun *et al.* found that at post-operative day 2, blood-based levels of Aβ1–40 were significantly more elevated.[51] Of note, although the blood-based biomarker Aβ1–40 was intended by the authors to measure the role of amyloid pathogenesis in POD, this was not listed as a widely accepted biomarker to measure aggregated Aβ. Due to the types of amyloid biomarkers collected and the methodological issues noted, a meta-analysis of the amyloid biomarkers was not conducted.

In the one article which measured tau biomarker, CSF P-tau was slightly elevated in non-demented patients who had delirium compared to those without delirium, although this was of borderline significance ($P = 0.06$).[46] However, the results of phosphorylated tau biomarkers in delirium group combined findings from patients those who had delirium pre-operatively and then developed delirium post-operatively. Since there was only one tau biomarker study, a meta-analysis of the tau biomarker was not conducted.

Inflammatory Biomarkers

Analyses identified two inflammatory biomarkers to be positively associated with POD. Specifically, IL-6 and CRP showed a significant relationship to delirium incidence (IL-6 $n = 10$, SMD: 0.53, 95% CI: 0.36 to 0.70; CRP $n = 14$, SMD: 0.53, 95% CI: 0.33 to 0.74). In contrast, analyses did not identify a significant association between POD and other inflammatory biomarkers. Specifically, no relationships were observed with IL-1B ($n = 3$, SMD: 0.00; 95% CI: −0.43 to 0.44), IL-8 blood-based levels ($n = 7$, SMD: 0.85; 95% CI: −0.14 to 1.84), and IL-10 ($n = 4$, SMD: 0.12; 95% CI: −0.14 to 0.37).

Neuronal Injury Biomarkers

The analyses identified two neuronal injury biomarkers that were positively associated with POD. Specifically, S100B blood-based levels and NfL showed a significant relationship to delirium prevalence (S100B blood-based $n = 5$, SMD: 0.40, 95% CI: 0.11 to 0.69; NfL $n = 2$, SMD: 0.93, 95% CI: 0.28 to 1.57). In contrast, no significant relationships were observed with TNF-α ($n = 5$, SMD: −0.20; 95% CI: −0.61 to 0.20), S100B CSF levels ($n = 2$, SMD:

0.37; 95% CI: −0.52 to 1.25), and NSE (n = 3, SMD: 0.42; 95% CI: −0.07 to 0.91). Of note, for the purposes of this study, S100B was utilized as a neuronal injury biomarker, though it has been linked to a variety of neuronal biomarkers, included blood-brain barrier breakdown.

Heterogeneity of Studies

As shown in Table 2, a majority of analyses were impacted by significant study heterogeneity. Namely, studies of IL-8 levels (I^2= 96.4%, p < 0.001), CRP (I^2 < 82.0%, p = 0.001), TNF-α (I^2 = 62.6%, p = 0.030), blood-based S100B levels (I^2 = 63.9%, p = 0.026) and CSF levels (I^2 = 77.1%, p = 0.036), NSE (I^2 = 71.8%, p = 0.029), and NfL (I^2 = 85.9%, p = 0.008).

DISCUSSION

The ATN(X) framework was developed as a conceptual biological framework to categorize both current and future disease state biomarkers.[14] Our meta-analysis suggests that we are still in the early stages of using the ATN(X) framework to characterize the complex relationship between POD and ADRD. One major gap identified through our project is the relatively small number of studies measuring amyloid and phosphorylated tau as disease state markers of POD. Meta-analysis could not be conducted on the amyloid biomarker category studies since they measured different biomarkers from this category. The data that were available for the amyloid biomarkers were concerning for methodological issues. One of the studies that found a difference in amyloid biomarkers between the non-delirious and delirious patients but had methodological concerns in terms of its approach for POD and timing of the CSF in relation to the development of delirium,[49] and the other studies that found a difference did not collect an amyloid biomarker listed in the Jack et al. paper.[46] The third paper which did collect the amyloid PET scan during the post-operative phase did not find a difference between non-delirious and delirious patients.[50]

The most well-studied disease state biomarkers in the POD literature have focused predominantly on neuronal injury (N) and inflammation (X) categories, but even these findings are inconsistent. Several inflammatory biomarkers (IL-6 blood-based and CRP blood-based levels) and neuronal injury biomarkers (S100B blood-based and NfL blood-based levels) were significantly elevated in those patients with POD compared to those without POD. Of note, three of these biomarkers IL-6, CRP, and NfL have moderate to large-size effects. While the evidence for IL-6 and CRP is fairly consistent with the current hypothesis that inflammation being a contributor to neurodegeneration after POD, the examination of NfL as a marker of post-operative neurodegeneration from delirium requires further investigation. However, not all inflammatory (blood-based levels for IL-1β, IL-8, IL-10, and TNF-α) and neuronal injury biomarkers (S100B CSF and NSE blood-based levels) were significantly associated with POD. This suggests that although the processes of inflammation and neuronal injury are key to the pathophysiology of POD and subsequent ADRD, only specific disease state biomarkers may be altered in POD.

The current model of POD proposes that surgery triggers inflammation, in which tissue macrophages and blood monocytes become activated and secrete various mediators, such as IL-1, IL-1β, IL-6, and tumor necrosis factor-α (TNF-α).[51] Peripheral inflammation leads to

microglial activation, and this state of neuroinflammation can lead to neuronal dysfunction, which clinically manifests as delirium. Our findings only partially support this model; the strongest evidence is for certain peripheral inflammatory (IL-6 and CRP) and blood brain barrier breakdown (S100B blood-based levels) being linked to POD. Our meta-analysis also supported the importance of neurodegeneration (NfL) in POD, but this finding was compromised by the small number of studies.

The connection between POD and ADRD is even less well understood. It is hypothesized that persistent neuronal dysfunction leads to persistent neuronal injury, which then manifests clinically as ADRD. Nevertheless, it is not well understood whether the pathophysiology of POD, most notably the dysregulated inflammatory response, trigger, accelerate, or unmask an underlying neurodegenerative process which may eventually lead to ADRD. The use of the ATN-(X) framework to characterize the interrelationship between POD and ADRD can lay the foundation for a systematic process to answer these complex relationships.

Figure 2 depicts possible mechanisms about the interrelationship between the pathophysiology of POD and ADRD—which could possibly co-exist in the AT(N)-X framework. The first possible mechanism is that there is underlying vulnerability to ADRD (such as pre-existing amyloid plaques) and with an outside stressor, such as surgery, the neurodegeneration manifests as POD, and subsequent post-operative cognitive decline reflects the pre-episode trajectory of cognitive decline leading to ADRD that would have occurred independent of the episode of POD.[51] The second possible mechanism is that POD may be associated with an increase in the pre-existing neurodegenerative process or a de novo neurodegenerative process happening during the episode of delirium. Hypothetical examples include transient elevation of Aβ from anesthesia during surgery or new-onset inflammation causing neuronal injury and death, leading to ADRD.[52,53] The third possible mechanism is that POD may accelerate a pre-existing neurodegenerative process (such as faster post-operative deposition of neurofibrillary tangles).[54,55] Figure 2 outlines how studies can test these models by using concomitant collection of cognitive data and biomarkers using the AT(N) framework during the pre-operative, intra-operative (or within 24 hours post-operative), post-operative, and long-term recovery phases. Based on our Table 1, we can see that many studies included pre-operative biomarkers, only a few articles examined the long-term recovery phase, approximately one month or longer after surgery ($n = 2$). These findings suggest that having delirium biomarker studies with an extended timeline beyond the usual pre-hospital or in-hospital phases are crucial to deeper understanding of POD and ADRD.

Earlier studies have examined the relationship between pre-operative ADRD biomarkers and POD. While some studies suggest a role for pre-existing Aβ and tau pathology (both phosphorylated and total tau measurements) increasing the risk of POD, this has not been a consistent finding.[56,57] Likewise, various studies ($n = 18$) have examined whether a preoperative inflammatory state may predispose to POD, but a previous systematic review found that in non-cardiac surgical patients, only pre-operative CRP was associated with POD.[58] There were too few studies to comment on other blood-based or neuroimaging biomarkers. Our meta-analysis of ADRD biomarkers as “disease state markers for delirium” showed findings similar to the literature for pre-operative ADRD biomarkers. CRP appears

to be both a marker of increased risk of delirium as well as a disease state marker for delirium. The finding of IL-6 as a disease state marker for delirium is consistent with our other meta-analysis of ICU delirium studies which also showed IL-6 was associated with ICU delirium. On the other hand, the role of neuronal injury markers appears to be more complicated. Although blood-based levels of S100B were associated with POD, S100 CSF levels were not, possibly because there were so few studies.

One particularly promising category of biomarker in the ATN(X) framework which will be especially crucial to understanding the relationship between POD and ADRD is the neuronal injury category. Two additional studies published after the timeframe of this meta-analysis supported our initial findings about the importance of neurodegeneration biomarkers in POD.[59,60] One study found that NfL remained persistently elevated in those with long-term post-operative decline,[59] whereas another study found that total tau levels correlated with severity of delirium and then resolved with the delirium episode.[60] Understanding whether certain neuronal injury markers could be disease state biomarkers for POD, post-operative ADRD, or both will be advance our understanding of the pathophysiology which is unique to POD.

Strengths and Limitations

The major strength of our study is that it is the first meta-analysis of POD biomarker studies using the AT(N)-X framework. This analysis points to the need to collect more data about amyloid and tau biomarkers, as well as certain neuronal injury biomarkers (such as GFAP, NfL, and total tau) that are well-known to be linked to ADRD. Indeed, since the majority of the studies were conducted prior to the proposed framework, many of them do not concurrently measure all of AT(N) biomarkers within a single cohort.

There were a number of limitations to this study. First, due to the lack of random allocation, the influence of confounding variables cannot be completely ruled out and thoroughly assessed. Second, there were significant discrepancies in study numbers, with most analyses limited to only a few studies. This means that analyzing subsets of surgical populations (cardiac vs non-cardiac) was not possible, which limits our understanding as to whether specific types of surgeries may be predisposed to certain pathologies, *e.g.* vascular pathology with cardiac surgeries. Third, there is the possibility of type 1 error due to multiple outcome assessments.

As mentioned previously, the heterogeneity of study methodologies may have impacted some overall outcomes, particularly with our analyses for blood-based IL-8, CRP, TNF-α, S100B blood based and CSF, NSE, and NFL levels. One issue could be the analysis of the time points. There were inconsistent reporting of time points, making a meta-analysis of the time-dependent data very difficult. Since certain studies reported the results at only one time point, we aimed to maximize statistical power to identify potential predictors based on overall results as the main study purpose. For a few studies with available data on multiple time points, we included the only one time point data with significant results or larger sample sizes in the final meta-analysis for the hypothesis testing purpose. Also, while timing of the blood draw may have contributed to the heterogeneity, other factors such as differences in clinical characteristics also likely contributed. For example, inflammatory

markers may also be affected by other factors, including timing of the blood draw in relationship to delirium severity and circadian rhythms (with inflammatory levels being higher in the evening).

The methodologies for longitudinal sampling of biomarkers in relation to delirium were of variable quality in the studies we included for meta-analysis. Most studies only looked at the presence or absence of POD, but only a few examined the association of biomarkers with delirium severity or duration. Demonstration of a dose-response relationship (*i.e.* correlation of biomarker levels with delirium severity or duration) would have strengthened our analyses. Likewise, there were limitations in terms of the pre-operative data. Since we did not have enough data to measure pre- and post-operative change, our observational evidence only indicates a causal relation but cannot demonstrate causality, particularly between delirium and inflammation. Also, we cannot exclude the possibility that some of our observations may be due to the presence of preclinical ADRD pathology prior the episode of delirium. Conversely, there were not enough studies which measured biomarkers one month or later after surgery to provide much needed data about whether ADRD disease state biomarkers in those affected by POD are distinct. It is worth noting that in the proposed best practices for examining delirium biomarkers, biomarker assessment should be timed to be collected at delirium onset and resolution, and in the case of populations who are at risk for delirium (such as post-operative delirium populations), prior to delirium onset.[61]

CONCLUSION

In summary, this meta-analysis identified biomarkers associated with neuroinflammation and neuronal injury that were positively associated with POD. Specifically, higher blood-based levels of IL-6, CRP, S100B, and NfL were associated with POD. As with previous literature on this topic, this meta-analysis identified several limitations to current post-operative delirium biomarker research, including a need for more systematic methodology in biomarker identification and collection, as well as delirium documentation. Concurrent characterization of delirium biomarkers within a single cohort using the AT(N)-X framework may help future researchers understand the complex, bidirectional interrelationship between delirium and ADRD. Finally, future studies could incorporate multimodal measurements such as neuroimaging and electroencephalography methods outlined by the AT(N) framework with blood and CSF-based biomarkers to provide a multidimensional evaluation of brain function and neuronal injury throughout the perioperative timeframe.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Data availability:

Data supporting the results reported in the manuscript can be available upon request.

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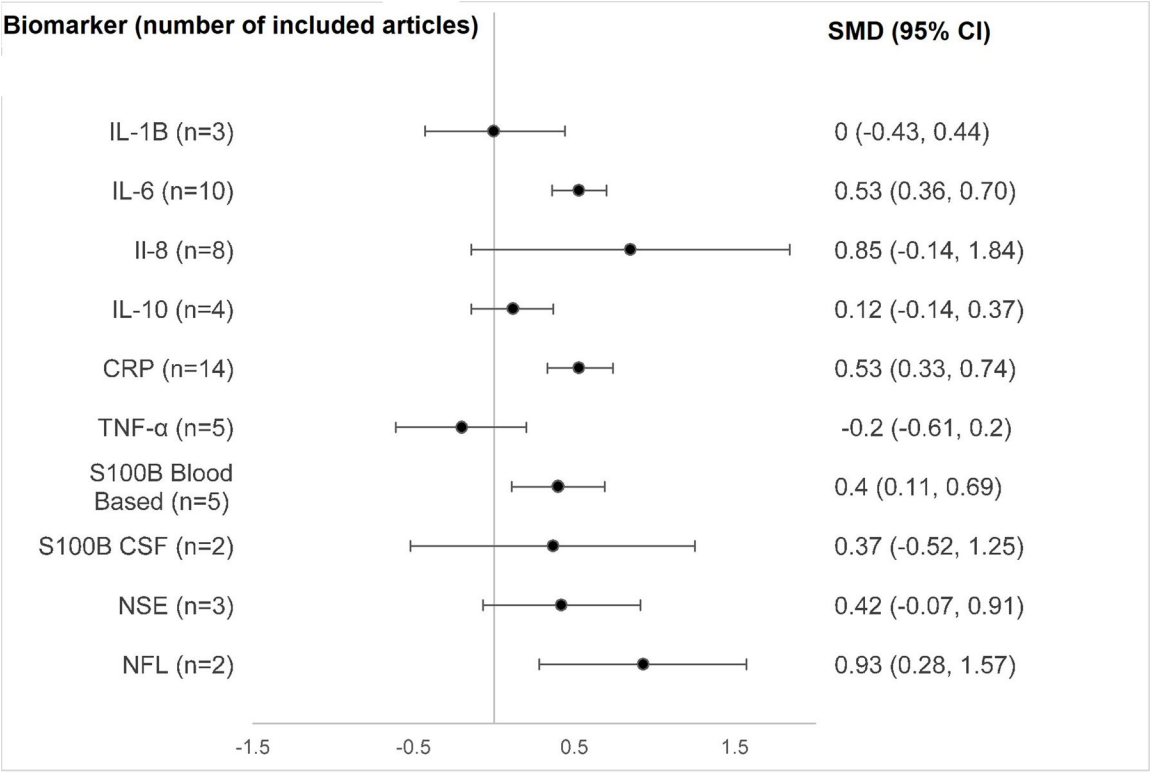

Random-effects meta-analyses were performed to calculate the pooled standardized mean difference (SMD) of each biomarker comparing post-operative delirium cases to non-delirium controls. The black circle indicates the pooled SMD per biomarker. Horizontal lines represent the 95% confidence interval. The vertical line represents the null hypothesis. The number (n) in the parentheses indicates the number of included studies in the meta-analysis.

Abbreviation: CI, confidence interval; IL, interleukin; CRP, C-reactive protein; TNF-α, tumor necrosis factor; S100β, S100 calcium-binding protein B; NSE, neuron specific enolase; NFL, neurofilament light

Figure 1.
Meta-analysis of the Association between Biomarkers and Post-Operative Delirium

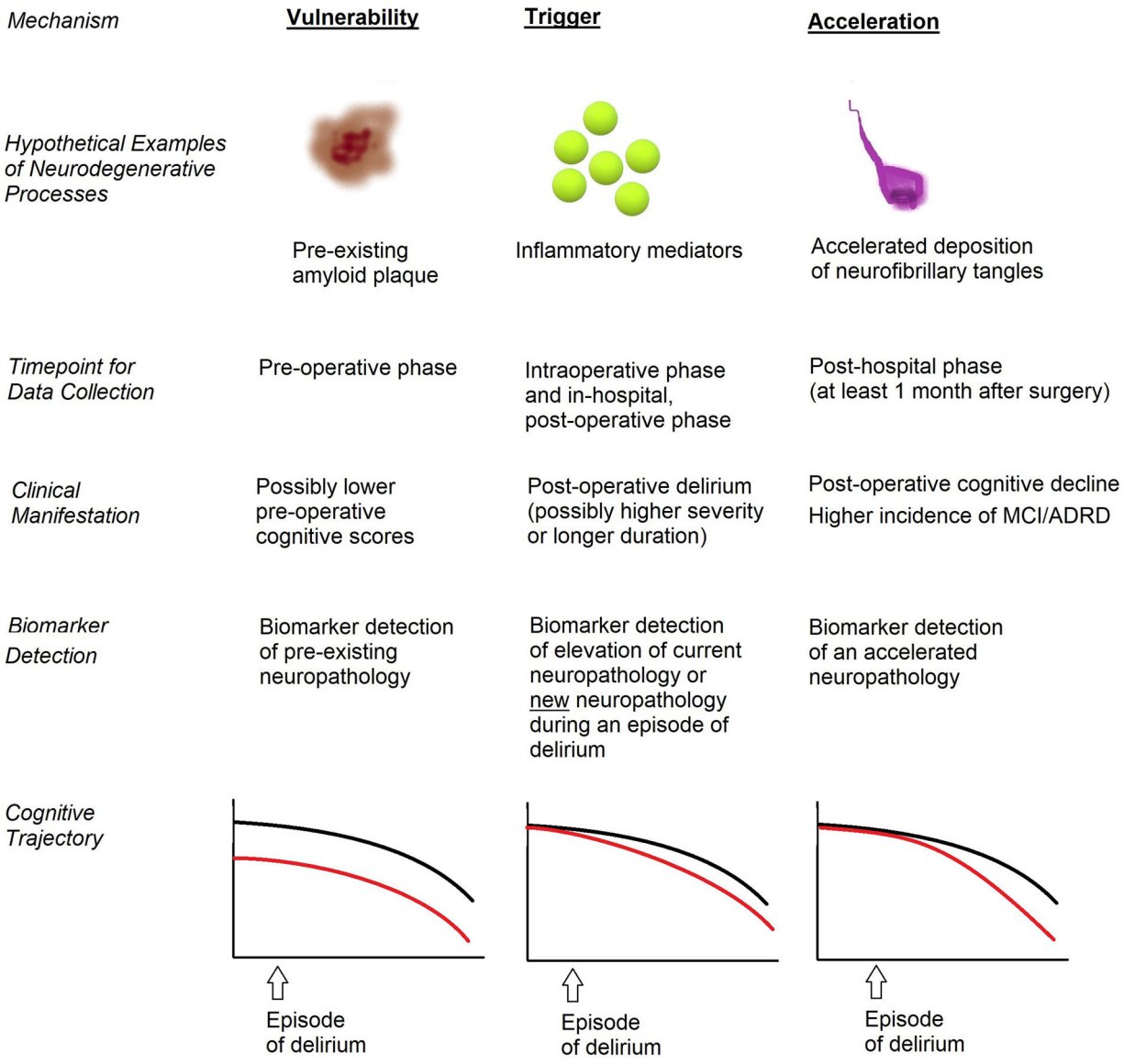

Figure 2.

Use of ATN-(X) Framework Characterize Interrelationship between Post-Operative Delirium and ADRD

Table 1.

Characteristics of Post-Operative Delirium Biomarker Studies

Author	Title	Surgery Type	*N* (% Delirium)	Biomarkers measured	Time of draw	Pre-Op Cognition assessed	Motoric subtype measured
Al Tmimi 2016	Serum protein S100 as marker of postoperative delirium after off-pump coronary artery bypass surgery: secondary analysis of two prospective randomized controlled trials	CABG	92 (20.7%)	S100B	Pre-Op Post-Op 1d	Yes: MMSE	Yes
Anderson 2018	Incidence, risk factors, and clinical implications of post-operative delirium in lung transplant recipients	Lung Transplant	155 (36.8%)	NSE	Post-Op 24h	No	No
Baranyi 2012	The impact of intra- and postoperative albumin levels as a biomarker of delirium after cardiopulmonary bypass: results of an exploratory study	Cardiopulm. Bypass	34 (32.4%)	CRP	Pre-Op Intra-Op Post-Op 24h, 48h	Yes: SKT	No
Beishuizen 2017	Unraveling the Relationship Between Delirium, Brain Damage, and Subsequent Cognitive Decline in a Cohort of Individuals Undergoing Surgery for Hip Fracture	Hip Fracture	64 (20.3%)	S100B (CSF and Blood-Based)	Pre-Op Post-Op within 8d	Yes: IQCODE	No
Beloosesky 2007	Cytokines and C-reactive protein production in hip-fracture-operated elderly patients	Hip Fracture	41 (41.4%)	IL-1B, IL-6, IL-8, TNF-α, IL-10, CRP	Pre-Op Post-Op 10h, 48–60h, 7d, 30d	Yes: MMSE	No
Casey 2020	Postoperative delirium is associated with increased plasma neurofilament light	Multiple (non-cardiac)	108 (36.1%)	IL-1B, IL-6, IL-8, NFL	Pre-Op Post-Op 1d, 2d, 3d, 4d	No	No
Cereghetti 2017	Independent Predictors of the Duration and Overall Burden of Postoperative Delirium After Cardiac Surgery in Adults: An Observational Cohort Study	Cardiac	618 (39.0%)	CRP	Post-Op not specified	No	No
Cerejeira 2012	The cholinergic system and inflammation: common pathways in delirium pathophysiology	Multiple (non-cardiac, non-hip fracture)	101 (36.6%)	IL-1B, IL-6, IL-8, TNF-α, IL-10, CRP	Pre-Op Post-Op 1d	Yes: MMSE	No
Cerejeira 2013	The stress response to surgery and postoperative delirium: evidence of hypothalamic-pituitary-adrenal axis hyperresponsiveness and decreased suppression of the GH/IGF-1 Axis	Hip (no fracture)	101 (36.6%)	IL-6, IL-8, IL-10, CRP	Pre-Op Post-Op 1d	Yes: MMSE	No
Chen 2019	Change in Serum Level of Interleukin 6 and Delirium After Coronary Artery Bypass Graft	CABG	266 (32.0%)	IL-6	Pre-Op Post-Op 6h, 12h, 18h	Yes: MMSE	No

Author	Title	Surgery Type	*N* (% Delirium)	Biomarkers measured	Time of draw	Pre-Op Cognition assessed	Motoric subtype measured
Cinar 2014	Role of CRP, TNFa, and IGF-1 in Delirium Pathophysiology	Cardiac	35 (42.9%)	TNF-α, CRP	Pre-Op Post-Op 2d	Yes: MMSE	No
Cizginer 2017	The Cognitive Reserve Model in the Development of Delirium: The Successful Aging After Elective Surgery Study	Multiple (non-cardiac)	556 (24.1%)	CRP	Post-Op 2d	Yes: WTAR	No
Dillon 2017	Higher C-Reactive Protein Levels Predict Postoperative Delirium in Older Patients Undergoing Major Elective Surgery: A Longitudinal Nested Case-Control Study	Multiple (non-cardiac)	150 (50.0%)	CRP	Pre-Op, PACU Post-Op 2d and 1m	Yes: Medical record	No
Gailiusas 2019	Association between serum biomarkers and postoperative delirium after cardiac surgery	Cardiac	44 (18.2%)	NSE	Pre-Op Post-Op not specified	No	No
Halaas 2018	Neurofilament light in serum and cerebrospinal fluid of hip fracture patients with delirium	Hip Fracture	314 (51.6%)	NFL	Pre-Op Post-Op not specified	Yes: IQCODE	Yes
Hov 2017	Cerebrospinal Fluid S100B and Alzheimer's Disease Biomarkers in Hip Fracture Patients with Delirium	Hip Fracture	62 (25.8%)	S100B (CSF and Blood-Based)	Pre-Op Post-Op 2–5d	Yes: IQCODE	No
Kazmierski 2014	Raised IL-2 and TNF-α concentrations are associated with postoperative delirium in patients undergoing coronaryartery bypass graft surgery	CABG	113 (36.3%)	TNF-α	Post-Op 1d	Yes: MoCA	No
Knaak 2019	C-reactive protein for risk prediction of postoperative delirium and post-operative neurocognitive disorder	Multiple (non-cardiac)	314 (22.9%)	CRP	Pre-Op Post-Op 1d-7d	Yes: IQCODE	No
Kudoh 2005	Postoperative interleukin-6 and cortisol concentrations in elderly patients with postoperative confusion	Abdominal	80 (21.3%)	IL-6, CRP	Pre-Op Post-Op 24h, 48h	Yes: MMSE	No
Lee 2011	Early assessment of delirium in elderly patients after hip surgery	Hip Surgery	65 (27.7%)	CRP	Pre-Op Post-Op <24h, 2–3d, 7d	Yes: MMSE	No
Lee 2018	Preoperative statins are associated with a reduced risk of postoperative delirium following vascular surgery	Vascular	1132 (11.5%)	CRP	Post-Op unspecified	No	No
Plaschke 2013	The role of interleukin-6 in postoperative delirium	Cardiac	114 (28.1%)	IL-6	Post-Op 24h	No	No
Rudolph 2009	Chemokines are associated with delirium after cardiac surgery	Cardiac	24 (50.0%)	IL-1B, IL-6, TNF-α, IL-10	Pre-Op Post-Op 6h, 4d	No	No
Sun 2016	Production of inflammatory cytokines, cortisol, and Aβ1–40 in	Oral Cancer	112 (50.0%)	IL-6, CRP	Pre-Op Post-Op end of surgery, 12h	Yes: Medical record	No

Author	Title	Surgery Type	*N* (% Delirium)	Biomarkers measured	Time of draw	Pre-Op Cognition assessed	Motoric subtype measured
	elderly oral cancer patients with postoperative delirium						
Van Munster 2008	Time- course of cytokines during delirium in elderly patients with hip fractures	Hip Fracture	95 (49.5%)	IL-1B, IL-6, IL-8, TNF-α, IL-10	Pre-Op Post-Op 1–8d	Yes: IQCODE	Yes
Van Munster 2009	Markers of cerebral damage during delirium in elderly patients with hip fracture	Hip Fracture	115 (49.6%)	NSE	Pre-Op Post-Op 1–8d	Yes: IQCODE	Yes
Van Munster 2010	Cortisol, interleukins and S100B in delirium in the elderly	Hip Fracture	48 (52.1%)	IL-6, IL-8, S100B	Pre-Op Post-Op 1–6d	Yes: IQCODE	No
Vasunilashorn 2017	High C-Reactive Protein Predicts Delirium Incidence, Duration, and Feature Severity After Major Noncardiac Surgery	Multiple (non-cardiac)	560 (23.9%)	CRP	Pre-Op Post-Op 2	Yes: Medical record	No

Table 2.

Random-effects meta-analysis of studies regarding the association between post-operative delirium and biomarkers

		Delirium			Control						Heterogeneity *I*-Squared (p)
Study	**Time of Post-Op Biomarker**	**Mean**	**SD**	**N**	**Mean**	**SD**	**N**	**Weight (%)**	**SMD**	**95% CI**	
IL-1B											
Beloosesky 2007	10 hours	0.94	0.87	12	0.65	0.59	29	28.03	0.42	−0.26, 1.10	
Rudolph 2009	6 hours	−0.50	0.80	12	0.00	1.00	12	21.44	−0.53	−1.35, 0.28	
Cerejeira 2012	24 hours	0.40	0.30	37	0.40	0.29	64	50.53	0.00	−0.40, 0.40	
Total (95% CI)								**100**	**0.00**	**−0.43, 0.44**	**35.2% (0.214)**
IL-6											
Kudoh 2005	24 hours	83.20	30.50	17	58.00	37.50	63	7.52	0.69	0.14, 1.24	
Beloosesky 2007	10 hours	68.59	38.17	12	38.46	29.83	29	4.97	0.91	0.21, 1.62	
Van Munster 2008	≤24 hours	55.96	45.89	47	36.00	33.63	48	11.46	0.49	0.08, 0.90	
Rudolph 2009	6 hours	0.50	0.90	12	0.00	1.00	12	3.85	0.51	−0.31, 1.32	
Van Munster 2010	≤24 hours	84.30	133.80	25	84.30	127.07	23	7.11	0.00	−0.57, 0.57	
Cerejeira 2012	24 hours	117.39	114.20	37	93.18	75.27	64	11.54	0.26	−0.14, 0.67	
Cerejeira 2013	24 hours	113.21	147.21	37	76.09	110.56	64	11.52	0.29	−0.11, 0.70	
Plaschke 2013	24 hours	293.32	113.12	32	214.71	72.78	82	10.84	0.91	0.48, 1.34	
Sun 2016	End of surgery	158.70	71.09	56	97.90	77.08	56	12.34	0.81	0.43, 1.20	
Chen 2019	6 hours	853.60	1146.30	85	489.80	407.80	181	18.85	0.50	0.24, 0.76	
Total (95% CI)								**100**	**0.53**	**0.36, 0.70**	**30.8% (0.163)**
IL-8											
Beloosesky 2007	10 hours	48.14	23.28	12	26.68	10.66	29	13.80	1.37	0.63, 2.12	
Van Munster 2008	≤24 hours	20.31	22.18	47	10.42	9.17	48	14.59	0.58	0.17, 0.99	
Rudolph 2009	6 hours	0.40	0.80	12	0.00	1.00	12	13.59	0.40	−0.41, 1.21	
Van Munster 2010	≤24 hours	84.30	133.80	25	84.30	127.07	23	14.26	0.00	−0.57, 0.57	
Cerejeira 2012	24 hours	18.83	13.34	37	16.59	8.53	64	14.60	0.21	−0.19, 0.62	

		Delirium			Control						Heterogeneity *I*-Squared (p)
Study	**Time of Post-Op Biomarker**	**Mean**	**SD**	**N**	**Mean**	**SD**	**N**	**Weight (%)**	**SMD**	**95% CI**	
Cerejeira 2013	24 hours	7.57	13.31	37	7.04	12.58	64	14.60	0.04	−0.36, 0.45	
Casey 2020	24 hours	4.92	4.44	39	1.59	0.83	69	14.56	3.33	2.90, 3.75	
Total (95% CI)								**100**	**0.85**	**−0.14, 1.84**	**96.4% (<0.001)**
IL-10											
Beloosesky 2007	10 hours	8.23	8.73	12	5.64	3.88	29	13.60	0.45	−0.23, 1.13	
Rudolph 2009	6 hours	0.40	0.80	12	0.00	1.00	12	9.58	0.40	−0.41, 1.21	
Cerejeira 2012	24 hours	3.17	2.49	37	3.18	2.92	64	38.42	−0.00	−0.41, 0.40	
Cerejeira 2013	24 hours	1.27	3.80	37	1.11	3.10	64	38.41	0.05	−0.36, 0.45	
Total (95% CI)								**100**	**0.12**	**−0.14, 0.37**	**0.0% (0.609)**
CRP											
Kudoh 2005	24 hours	6.10	1.80	17	5.70	2.10	63	5.90	0.19	−0.34, 0.73	
Beloosesky 2007	10 hours	23.32	6.93	12	13.85	5.92	29	4.20	1.49	0.74, 2.24	
Lee 2011	≤24 hours	12.11	5.76	18	7.88	3.87	47	5.61	0.94	0.37, 1.51	
Baranyi 2012	24 hours	16.92	6.80	11	14.15	6.92	23	4.38	0.39	−0.33, 1.12	
Cerejeira 2012	24 hours	18.31	9.12	37	15.89	11.61	64	7.18	0.22	−0.18, 0.63	
Cerejeira 2013	24 hours	15.35	15.33	37	14.62	13.71	64	7.20	0.05	−0.35, 0.46	
Cinar 2014	48 hours	5.40	1.10	15	5.40	1.30	20	4.78	0.00	−0.67, 0.67	
Sun 2016	End of surgery	9.88	2.53	56	5.52	2.18	56	6.80	1.83	1.39, 2.28	
Cereghetti 2017	Unspecified	23.67	8.50	241	18.46	7.44	377	9.49	0.66	0.50, 0.83	
Cizginer 2017	48 hours	19.68	7.12	134	17.45	7.81	422	9.26	0.29	0.10, 0.49	
Dillon 2017	48 hours	19.85	6.74	75	13.99	7.32	75	7.93	0.83	0.50, 1.16	
Vasunilashorn 2017	48 hours	20.05	7.27	134	17.56	7.52	426	9.26	0.33	0.14, 0.53	
Lee 2018	Unspecified	14.32	7.72	130	11.43	8.31	1002	9.36	0.35	0.17, 0.53	
Knaak 2019	1–7days	10.36	9.07	72	8.24	6.19	242	8.64	0.31	0.04, 0.57	
Total (95% CI)								**100**	**0.53**	**0.33, 0.74**	**82.0% (<0.001)**

		Delirium			Control						Heterogeneity *I*-Squared (p)
Study	**Time of Post-Op Biomarker**	**Mean**	**SD**	**N**	**Mean**	**SD**	**N**	**Weight (%)**	**SMD**	**95% CI**	
TNF-alpha											
Beloosesky 2007	10 hours	14.12	10.95	12	12.12	3.37	29	17.42	0.30	−0.37, 0.98	
Rudolph 2009	6 hours	−0.50	1.00	12	0.00	1.00	12	14.33	−0.48	−1.30, 0.33	
Cerejeira 2012	24 hours	1.50	1.18	37	1.50	1.78	64	25.19	0.00	−0.40, 0.40	
Cinar 2014	48 hours	28.20	28.30	15	28.20	48.50	20	17.59	0.00	−0.67, 0.67	
Kazmierski 2014	24 hours	10.25	3.78	41	13.54	4.76	72	25.47	−0.74	−1.13, −0.34	
Total (95% CI)								**100**	**−0.20**	**−0.61, 0.20**	**62.6% (0.030)**
S100B (Blood Based)											
Van Munster 2009	≤24 hours	0.17	0.11	57	0.11	0.05	58	21.35	0.67	0.30, 1.05	
Van Munster 2010	≤24 hours	0.18	0.15	25	0.12	0.04	34	14.43	0.52	−0.06, 1.10	
Al Tmimi 2016	24 hours	0.12	0.07	19	0.08	0.06	73	16.31	0.67	0.16, 1.19	
Hov 2017	2–5 days	0.08	0.05	36	0.07	0.04	59	19.77	0.26	−0.16, 0.67	
Beishuizen 2017	≤8 hours	0.10	0.06	126	0.09	0.05	258	28.14	0.06	−0.15, 0.28	
Total (95% CI)								**100**	**0.40**	**0.11, 0.69**	**63.9% (0.026)**
S100B (CSF)											
Hov 2017	2–5 days	1.36	0.44	16	1.09	0.28	46	50.42	0.81	0.23, 1.40	
Beishuizen 2017	≤8 hours	0.88	0.48	13	0.91	0.35	51	49.58	−0.09	−0.70, 0.52	
Total (95% CI)								**100**	**0.37**	**−0.52, 1.25**	**77.1% (0.036)**
NSE											
Van Munster 2009	≤24 hours	11.70	3.80	57	11.70	4.70	58	38.44	0.00	−0.37, 0.37	
Anderson 2018	24 hours	12.96	5.25	57	10.23	3.91	98	39.87	0.61	0.28, 0.95	
Gailiusas 2019	Unspecified (“Early post-op period”)	12.42	6.35	8	8.48	4.66	36	21.68	0.79	0.01, 1.58	
Total (95% CI)								**100**	**0.42**	**−0.07, 0.91**	**71.8% (0.029)**
NFL											
Halaas 2018	1–5 days	101.17	147.36	162	34.03	28.44	152	53.99	0.62	0.40, 0.85	

		Delirium			Control						Heterogeneity *I*-Squared (p)
Study	**Time of Post-Op Biomarker**	**Mean**	**SD**	**N**	**Mean**	**SD**	**N**	**Weight (%)**	**SMD**	**95% CI**	
Casey 2020	24 hours	3.08	2.10	39	1.38	0.47	69	46.01	1.28	0.85, 1.71	
Total (95% CI)								**100**	**0.93**	**0.28, 1.57**	**85.9% (0.008)**

Studies are ordered by the year of publication.

SD = standard deviation; SMD = standardized mean difference; CI = confidence interval.