Physical performance and amyloid beta in humans: A systematic review and meta-analysis of observational studies

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Abstract

Background: Accumulation of amyloid beta (Aβ) plaques is one of the main features of Alzheimer's Disease (AD). Physical performance has been related to dementia risk and Aβ and it has been hypothesized as one of the mechanisms leading to greater accumulation of Aβ. Yet, no evidence synthesis has been performed in humans.

Objective: To investigate the association of physical performance with Aβ in humans, including Aβ accumulation on brain, and Aβ abnormalities measured in cerebrospinal fluid (CSF) and blood.

Method: A systematic review with multilevel meta-analysis was performed from inception to June 16th, 2022. Studies were eligible if they examined the association of physical performance with Aβ levels, including the measure of physical performance as a predictor and the measure of Aβ as an outcome in humans.

Results: 7 articles including 2,619 participants were included in the meta-analysis. The results showed that physical performance was not associated with accumulation of Aβ in the brain (ES= 0.01; 95% CI -0.21 to 0.24; I^2= 69.9%), in the CSF (ES= -0.28; 95% CI -0.98 to 0.41; I^2= 91.0%) or in the blood (ES=-0.19; 95% CI -0.61 to 0.24; I^2= 99.75%). Significant heterogeneity was found across the results suggesting possible effect moderation, but the limited number of studies hindered the opportunity to conduct a moderation analysis.

Conclusion: The association between physical performance and Aβ is inconclusive. This uncertainly arises from the limited number of studies, study design limitations, and heterogeneity of measurement approaches. More studies are needed to determine whether physical performance is related to Aβ levels in humans.

Keywords: Alzheimer's disease, Physical performance, Amyloid, Meta-analysis

INTRODUCTION

Alzheimer´s disease (AD) is one of the most prevalent medical conditions in older ages [1]. Accumulation of amyloid beta (Aβ) plaques is one of the main features of AD, which is related to neurodegeneration and increased risk for memory impairment [2]. The concentration of fibrillar Aβ plaques in the brain can be measured in vivo with Positron Emission Tomography (PET) and specific radiotracers. In addition, alterations in the concentration of Aβ species can be detected in cerebrospinal fluid (CSF) and, more recently, ultra-sensitive techniques have been developed to also measure them in plasma [3]. Typically, alterations in $A\beta_{1-42}$ or the ratio $A\beta_{1-42}/A\beta_{1-40}$ can be detected in CSF before soluble Aβ accumulates into plaques and can be detected through PET imaging.

Several factors have been identified that increase risk for Aβ accumulation, including genetic factors (i.e., APOE $\varepsilon 4$ carriers), level and quality of education, cardiometabolic conditions and lifestyle factors [1]. Identifying at-risk populations, such as APOE $\varepsilon 4$ carriers, persons with poorer education, poor cardiovascular health or poor lifestyle, is critical to understanding manifestation of clinical symptoms of AD and disease progression. Closely linked with lifestyle factors (e.g., physical activity) are physiological and behavioral measures of physical performance and function. In this review, we adopted the concept of physical performance including physical fitness or physical function tests, which are two interrelated concepts representing the capacity to carry out daily tasks with vigor and alertness, without undue fatigue and with ample energy to enjoy, involving sub-domains such as aerobic fitness, muscular strength, agility, flexibility, mobility, and dexterity, among others [4, 5]. In fact, there are many studies demonstrating an association between indices of better physical performance and greater brain health across the lifespan [6]. Further, higher levels of physical performance are associated with a reduced risk for several neurological diseases, including cognitive decline, AD, and dementia, but the mechanisms by which this occurs remains poorly understood [7, 8]. This is of relevance since physical performance is recognized as an

important marker for physical and brain health associated with several underlying conditions related to aging and AD [9, 10]. Moreover, there is a need to select easy and cheap measurements to implement into clinical practice, with the utility of identifying at-risk people [11].

One possible mechanism explaining the association between physical performance and reduced risk for dementia is that the better lifestyles and health behaviors that are associated with elevated physical performance led to reduced Aβ accumulation, which in turn could influence cognitive function and dementia risk [12]. Previous reviews have shown that physical exercise (the most effective approach for improving physical performance) reduces production of Aβ in animal models [12, 13]. In addition, recent evidence reinforces the idea that long-term exercise training attenuates Aβ accumulation, with the potential capacity to delay the progression of AD in rat models [14]. For instance, mice showing strength gains after exercise also had nearly a 30% reduction in Aβ in the hippocampus [15]. This is in line with two additional studies reporting a reduction of Aβ load in rat AD-like models after 6 weeks of exercise [16] and an Aβ load reduction in a dose-dependent manner by 12 weeks of exercise [17]. However, human studies examining physical performance and Aβ are scarce and conflicting. While several studies have shown that better physical performance is associated with lower Aβ accumulation in older adults [18], other studies have found no association [19, 20] or even the opposite association [21]. For instance, whereas several physical performance metrics such as aerobic performance and muscular performance have been negatively associated with blood $A\beta_{42}$ [18], others, such as gait speed, were not associated with blood markers of amyloid [22]. In addition, greater accumulation of brain Aβ, as measured by PET, was associated with lower gait speed in older adults without dementia. In contrast, no association with brain Aβ was found in patients with motor impairments [23]. One possible reason for these inconsistencies is that while animal models are more homogeneous, human studies have greater heterogeneity in physical performance components (i.e., aerobic performance, motor performance, muscular performance), Aβ measures

(i.e., PET, CSF or blood), and the characteristics of the study samples (e.g., cognitively normal or cognitively impaired). A systematic synthesis and meta-analysis of the existing evidence will contribute to a better understanding of the association of physical performance measures with Aβ, and it may help to confirm whether changes in physical performance is a risk factor for subsequent cognitive decline and AD.

Overall, two previous narrative reviews have explored the association of physical performance and Aβ accumulation in older adults [12, 13]. However, no previous systematic reviews have quantitatively synthesized these data in a meta-analysis or examined moderators (physical performance component, Aβ measurements and sample characteristics) of this relationship in humans. Therefore, the aim of this systematic review and meta-analysis was to investigate the association of physical performance with Aβ in humans. In addition, if there is enough evidence, we aimed to test the moderating role of physical performance components, Aβ measurements, and sample characteristics in the relationship between physical performance and Aβ.

METHOD

Information sources and study selection

The review protocol has been registered on PROSPERO (CRD42020184430). According to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [24], all potentially relevant articles were identified through a computerized search of the main electronic databases: PubMed, Web of Science, PsycINFO, Cochrane Central Register of Controlled Trials and SportDiscuss from inception to June 16th, 2022, without any filters being applied. The search strategy and search terms used for all databases is described in **Table S1.** Relevant articles were screened by titles and abstracts by two independent researchers (MAO and CAA) in EndNote. Full-text articles considered acceptable for review were examined to determine final eligibility by the same two

researchers (MAO and CAA). In case of disagreement, a consensus was achieved through discussion, and when required, the opinion of a third researcher (MRA) was considered. No language limitations were applied. In addition to the articles found in the search, reference lists of articles were reviewed.

Eligibility criteria

The review followed the PECOS framework (Population, Exposure, Comparator, Outcomes, Study design) framework. Briefly, inclusion criteria were : 1) Population: all ages; 2) Exposure/Comparator: a physical performance component; 3) Outcomes: Aβ accumulation assessed in the brain using PET, CSF, or in blood samples; 5) Study design: observational studies (i.e., cross-sectional and prospective cohort studies) and intervention studies (i.e., randomized controlled trial [RCT] and non-randomized controlled trials [non-RCT]) including a measure of association between physical performance (as predictor) and Aβ (as outcome) were considered eligible for inclusion.

Exclusion criteria were: 1) Population: non-human population; 2) Exposure/comparator: no measure of physical performance; 3) Outcomes: no Aβ measure; 4) Study design: case-control studies, review articles, letters to the editor, comments, gray literature, case reports, longitudinal, and intervention studies that did not report a cross-sectional association. Studies testing the inverse association (i.e., Aβ accumulation as exposure, and physical performance as outcome) were excluded. Missing data or necessary additional information were requested from the corresponding authors of the articles. When authors do not provide data to allow calculation of the effect size (ES) of the association of physical performance with Aβ accumulation, studies were excluded.

Data extraction

Two authors (MAO and PMG) independently extracted and double checked the data from each study. Disagreements were solved by a consensus meeting, and a third investigator (MRA) was consulted for any needed resolutions. The following data were extracted: first author and year of publication,

country of the sample, study design, age, sex, physical performance component, cognitive status, the outcome of interest, and details of adjustment for covariates in the multivariate model (when available).

Evaluation of the risk of bias

The risk of bias was evaluated independently by two authors (MAO and CMH) using the Joanna Briggs Institute Critical Appraisal Tool for Systematic Reviews, which has been used in previous reviews [25]. Any discrepancy was solved in a consensus meeting with PSU, MRA, and IEC. Each item was assigned one of four possible responses: "yes" (criterion met), "no" (criterion not met), "unclear" or "not applicable". The specific tools included thirteen items for RCTs, nine items for non-RCTs, eleven items for longitudinal studies, and eight items for cross-sectional studies. The studies were categorized with an overall risk of bias score as used in previous studies [25]. Specifically, the studies were considered as "low risk" when 75% of items were scored as "yes" (criterion met). The answer "not applicable" was excluded from the percentage calculation.

Multi-level Meta-analysis

A multi-level meta-analysis to study the association of physical performance and Aβ was performed, using R Statistical Software (version 4.2.2), and the *metafor* package version 3.8.1. For studies reporting associations between physical performance and Aβ, correlation coefficients were extracted, along with sample size. When correlation values were not provided, but studies met the inclusion criteria, correlation coefficients were calculated using the available data according to the analysis presented using *esc* package 0.5.1. Statistical significance was set at a p-value less than 0.05. Heterogeneity was assessed using the Q-statistic (with $p<0.10$ suggesting statistically significant heterogeneity) and I^2 statistic (the percentage of total variability attributed to between-study heterogeneity). Funnel plots of the ES against the standard error (SE) of ES were visually inspected

for small-sample bias, and Egger's test values with 95% CI for funnel plot asymmetry were calculated. Publication bias was considered to be present when the funnel plot appeared asymmetrical and the intercept of the Egger's test was significantly different from zero ($p<0.10$) [26, 27].

RESULTS

Studies retrieved

The systematic search yielded 2,012 references, of which 1,527 were unique. **Figure 1** shows the study selection process and literature search results. After screening titles and abstracts 1,443 documents were excluded and 84 full-text articles were retained for further screening. After revising the full-text of the studies, 7 unique studies were included for analysis. The specific reason for exclusion is shown in **Table S2**. No studies were excluded due to their methodological characteristics. No additional studies met the inclusion criteria after checking article's reference lists.

Study characteristics

Study characteristics are shown in **Table 1**. In total, 7 independent samples were included in the systematic review. Specifically, data from 2,619 participants were included in the meta-analysis. The sample size ranged from 20 [23] to 2,366 participants [22], and all studies included at least 35 % females [23], with the greatest percentage of female participation at 57.4 % [28]. Overall, the mean age ranged from 57.3 [18] to 92.4 years [29]. Additionally, 4 studies reported data of patients with any neurological condition/risk [18, 20, 23, 30], 2 studies included cognitively normal participants [22, 28], and 1 study included a mix of cognitively normal and cognitively impaired participants [29].

Most studies assessed physical performance using components of ambulation or motor ability. Six studies included motor ability [20, 22, 23, 28-30]. These studies assessed motor ability by gait speed [20, 22, 23, 28], global agility parameters [30], or the total score of the Short Physical Performance Battery, a commonly used measure in geriatric medicine to provide an index of physical

function and mobility [29]. One study included aerobic capacity using a fitness test (Rockport Fitness Walking Test) as a measure of physical performance [18]. Three studies included specific muscular strength measurements, both upper (i.e., handgrip strength test or arm curl test) and lower (chair stand test) body measurements, as indicators of physical performance [18, 22, 29].

Three studies assessed Aβ in the brain using a PET scan [23, 28, 29], using [18F]florbetapir or [18F]flutemetamol [23], [11C]PiB [28] and [18F]flutemetamol ligands [29]. While two studies used the distribution volume ratio values with the cerebellum gray matter as reference as outcome [28, 29], 1 study used centiloid values with the whole cerebellum as reference as outcome [23]. In addition, two studies assessed Aβ in CSF [20, 30] with one of these studies not reporting information related to the assay, and 1 was assayed using a high sensitivity ELISA technique. Finally, 2 studies assessed Aβ in blood [18, 22] using a high sensitivity ELISA technique in plasma [22] and serum [18] samples. None of the studies used Mass Spectrometry for measurement of Aβ in blood samples.

Finally, the most common confounding variables used as covariates in statistical models were age, sex, and educational level [22, 29, 30], and 4 studies reported unadjusted analyses without accounting for the potential influence of other variables [18, 20, 23, 28].

Risk of bias assessment

The risk of bias assessment is presented item by item in **Table S3**. Briefly, most studies met the criteria of clarity of a well-defined sample size. On the other hand, the criteria with the lowest compliance were those related to the validity and reliability of the outcome measurement. The risk of bias assessment for each study is presented in **Table S4**. Briefly, 5 studies were categorized as low risk, while 2 studies were categorized as high risk (25% of items were scored as “no” or “unclear”). The publication bias based on visual observation of the funnel plot and Egger’s tests is shown in

Figure 2, corresponding to brain (Coef: -0.057; p = 0.522; 95% CI: from -8.677 to 17.096), CSF (Coef: -34.641; p = 0.001; 95% CI: from - -55.781 to -13.500) and blood measures (Coef: -18.212; p = 0.001; 95% CI: from -29.147 to -7.276).

Meta-analysis of included studies

The association between physical performance and Aβ was investigated in 7 observational studies corresponding to 21 different ESs. From all ESs, 10 ESs corresponded to motor ability, 9 to muscular strength, and 2 corresponded to aerobic capacity. In addition, 5 ESs were derived from the brain (using PET), 13 were assessed in blood samples (6 of them Aβ42 isoform, 4 Aβ40 isoform, and 3 Aβ42/Aβ40), and 3 were derived from the CSF. **Figure 3, 4 and 5** shows the overall effect meta-analysis of physical performance on Aβ measurements corresponding to measures on brain (PET), CSF and blood, respectively. The overall effect was not significant on brain (**figure 3**; pooled standardized effect= 0.01; 95% CI -0.21 to 0.24; I^2= 69.9%), CSF (**figure 4**; pooled standardized effect= -0.28; 95% CI -0.98 to 0.41; I^2= 91.0%) or blood (**figure 5**; pooled standardized effect= -0.19; 95% CI -0.61 to 0.24; I^2= 99.75%). In addition, sensitivity analysis for the overall effect on blood excluding Aβ40 remains non-significant (pooled standardized effect= -0.15; 95% CI -0.66 to 0.36; I^2= 99.46%). Moderation analysis was not conducted due to the limited number of ESs.

DISCUSSION

The aim of the present work was to synthesize the current evidence and perform a systematic and quantitative review to determine the relationship between physical performance and Aβ in humans. Our main finding suggests that the association between measures of physical performance and Aβ levels is inconclusive, due to the limited number of studies included and the high heterogeneity in the measures. Additionally, there is insufficient data to test for various moderators (e.g., sample characteristics) of the association physical performance components and Aβ.

The amyloid pathway has been suggested as one possible mechanism explaining the association between physical performance measures and cognitive function in late adulthood [31, 32]. In humans, better physical performance could also influence Aβ changes [33]. Our review of the existing literature indicates that there is no consistent evidence that physical performance is associated with Aβ accumulation in the brain, and a small non-significant negative association with Aβ abnormalities in blood and CSF, respectively. The direction of the association between physical performance and Aβ seems to be controversial, with several methodological factors that likely contribute to the heterogeneity such as the measurement method for Aβ, the physical performance measurement, and sample characteristics. For example, an indirect laboratory measure of physical performance (e.g., energetic cost of walking, less is indictive of better performance) but not gait speed was positively linked with brain Aβ accumulation [28]. In patients with Parkinson's disease, lower levels of CSF Aβ42 predicted worse physical performance [34], while in patients with idiopathic normal pressure hydrocephalus, higher physical performance (gait velocity) was associated with lower CSF Aβ42 and Aβ40 levels [35]. However, there is insufficient and inadequate data to reach definitive conclusions due to the limited number of studies and heterogeneity of measurement approaches. Thus, well-controlled studies with larger sample sizes and standardized and harmonized measures in humans are needed to establish more definitive conclusions and to understand the clinical significance of any association between physical performance and Aβ.

In humans, the accumulation of Aβ in the brain as measured by PET is considered a gold-standard, but the results from measuring Aβ in CSF and blood are increasing [36-38]. Various factors, including assay methodologies and differences in clearance of Aβ from the brain, may contribute to these discrepancies. For instance, there is evidence of a positive association between plasma Aβ42 and CSF Aβ42, both showing lower levels in AD patients [39]. In contrast, there is also evidence showing that plasma Aβ42 was inversely correlated with CSF Aβ42 in AD patients [40],

which might be explained by differences in the influx of Aβ42 from the brain to the CSF and from the brain to the peripheral circulatory system [37, 38, 41-43]. Interestingly, it is also important to consider that other tissues may also contribute to peripheral Aβ production [42, 44]. Also, while blood biomarkers may be more sensitive to changes in Aβ than CSF biomarkers [42], different detection methods have different levels of sensitivity and specificity [40]. For example, high-performance mass spectrometry analysis provides better sensitivity and specificity than commercial ELISAs [45]. Specifically, our results show a high variability of approaches for assessing Aβ accumulation and Aβ abnormalities in terms of ligands, processing and assays. Thus, these methodological factors may provide an explanation for the heterogeneous results of our analysis.

Regarding physical performance measures, most were "walking" or "gait" tests and were included in all studies, while muscular strength was included only in 3 different studies. Regarding study sample characteristics, there is high variability in amyloid accumulation between cognitively normal and cognitively impaired individuals, and amyloid clearance is more efficient in patients with higher Aβ baseline levels [46]. In addition, Tsai et al., explored the interaction of APOE ε4 carriers in the relationship between physical performance and Aβ, and found that the association of physical performance with Aβ42 was only significant in APOE ε4 carriers [18]. However, we could not perform moderation analysis in this review due to the limited number of studies in each assessment of Aβ, the small sample sizes include in the studies, the lack of power due to the limited number of ESs in the cognitively impaired group, and the high variability in genetic, disease, and baseline amyloid status. Therefore, further studies are needed to test whether physical performance is associated with brain, blood, and CSF biomarkers of amyloid, including studies with larger sample sizes and more homogeneous sample and measurement methods. This is particularly important for blood biomarkers, since they might be more clinically available, less invasive, and more conducive for clinical trials than CSF and PET biomarkers [42].

This systematic review and meta-analysis has several limitations. First, only 7 studies met the inclusion criteria and were included. Further, we focused our inclusion criterion to studies examining the association in only one direction (physical performance as a predictor of Aβ levels), but there is evidence suggesting the opposite association - that amyloid accumulation could influence physical performance measures. In this regard, while acknowledge that physical performance detrimental might be a consequence of amyloid pathology, our main interest is investigating the physical performance measures as potential preventive and therapeutic strategies for cognitive decline. Further studies are needed with focus in reveal the reverse causality in these measures. Furthermore, the lack of consistency across studies, such as variations in sample sizes, hinders the reliability of the results and restricts the extent of the conclusions. For instance, Jacob et al. [22] conducted their research on physical function and plasma biomarkers with a notably larger sample size compared to the other studies. However, despite this limitation, our review specifically concentrates on the relationship between physical performance and Aβ, encompassing all tissues. In consideration of these mixed findings, more standardized research protocols are needed to understand the role of physical performance in modulating Aβ levels in middle-aged and older adults. Finally, motor ability as a measure of functional mobility, was the physical performance component most considered in the included studies, and the associations for the other physical performance components (i.e., aerobic capacity and muscular strength) were based on a small number of subjects. Considering that aerobic capacity and muscular strength are the most important components related to health [47], more evidence including these components is needed. The strength of the present systematic review is that we provided a synthesis of the association of several physical parameters with measures of amyloid across several tissues (brain, blood, CSF), and provided a comprehensive overview of the available evidence with a focus on understanding the role of physical performance on amyloid accumulation.

Literature gaps and future research

- More studies are needed to test the association of physical performance with Aβ levels, with larger sample sizes and including clearly articulated measurements of physical performance and Aβ levels.
- Due to the possibility of bi-directionality, longitudinal cohort studies with physical performance measures and Aβ for at least two-time points are needed to determine the possibility of reverse causality and to confirm the predictive value of physical fitness on AD progression.
- More studies are needed to disambiguate whether sample characteristic such as cognitive status or type of tissue or assay, might moderate the association of physical performance and Aβ levels.
- In addition to the Aβ path, more research is needed to unravel the potential mechanisms linking physical performance with cognitive decline trajectories in the elderly.

In conclusion, the results suggest that the association between physical performance and Aβ levels in humans remains inconclusive. This uncertainty arises from the limited number of studies, design limitations, and heterogeneity of measures; which in turn precludes the exploration of potential moderating variables (i.e., physical performance measures, Aβ measurements and sample characteristics). This information might be considered in further studies investigating the association of physical performance and Aβ levels in humans.

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Conflict of Interest

JDG has received research support from GE Healthcare, Roche Diagnostics, Hoffmann-La Roche and has received speaker/consultant fees from Biogen, Roche Diagnostics, Philips Nederlands and Life-Molecular Imaging.

Data availability

The data utilized in the analysis can be requested from the corresponding authors.

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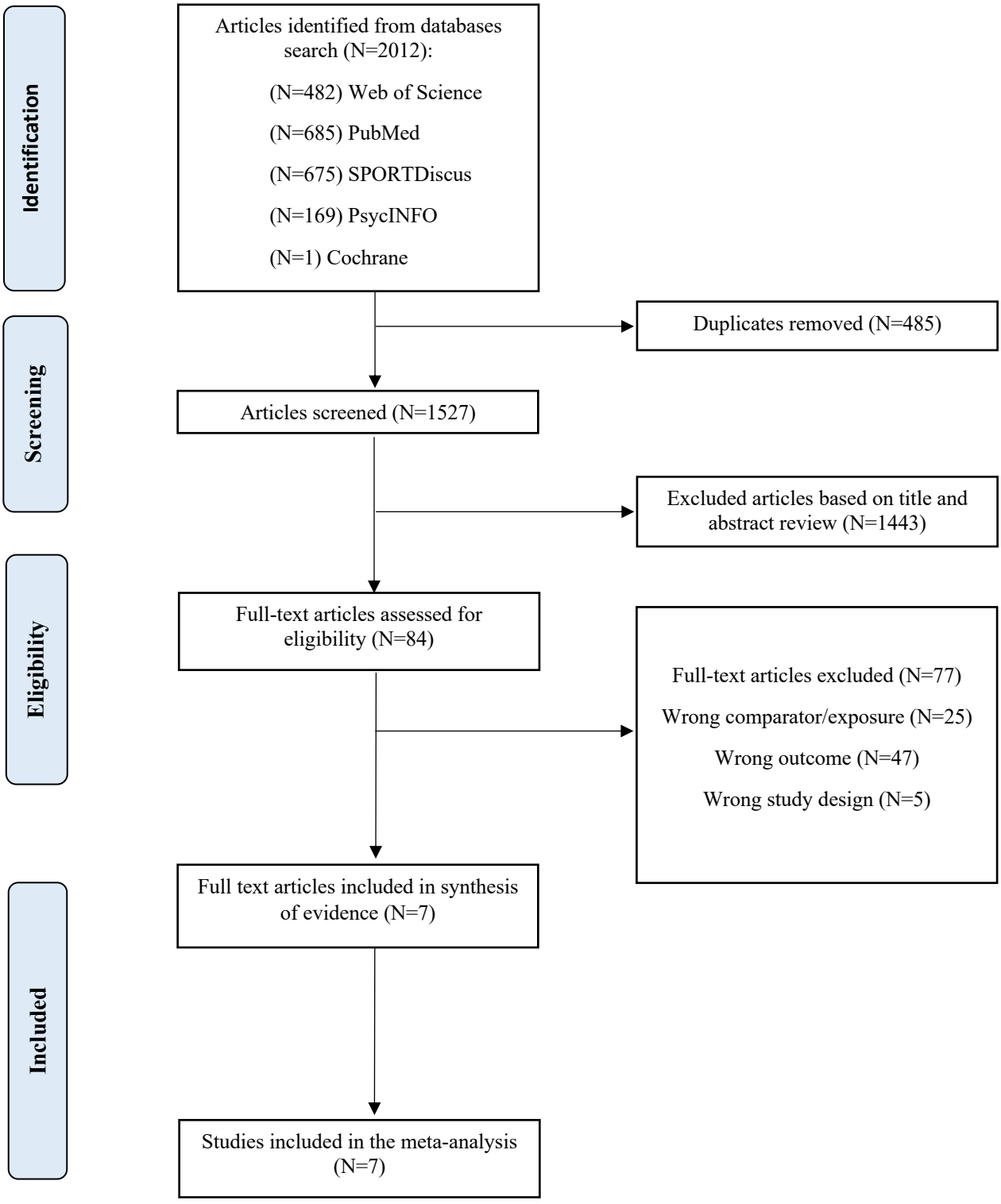

Figure 1. Flow diagram for study selection

Table 1. Summary of studies investigating the association of physical performance and amyloid beta accumulation (n= 7).

First author, Year; Country	Risk of bias	Study design	Target population (Age [range])	N (% females)	Physical function/fitness; Assessment instruments	Aβ markers	Method; Instrument/tracer	Covariates
Bommarito et al. 2022; Switzerland	Low	Cross-sectional	Participants with cognitive complains (73.2±6.4) [Older adults]	20 (35%)	Gait speed; Normal walking using 12-camera optoelectronic system	Aβ	PET; [18F]florbetapir or [18F]flutemetamol	Age
Dougherty et al. 2021; USA	Low	Cross-sectional	Cognitively normal participants without dementia (77.5±8.4) [Older adults]	149 (56%)	Gait speed and energetic cost of walking; Usual gait over a 6-m course in an uncarpeted corridor, Usual comfortable pace 20-m	Aβ	PET; [11C]PiB	Age, sex, years of education, race height, body composition, comorbid conditions, and APOE ε4 carrier status
Hatcher-Martin et al. 2021; USA	High	Cross-sectional	Parkinson disease patients with FoG (70.7 ± 8.3); without FOG (70.4 ± 10.1); healthy controls (74.4 ± 10.0) [>18]	12 (67%); 19 (37%); 12 (8%); All: 43 (37.2%)	FoG; levodopa challenge paradigm; Timed Up & Go; MDS-UPDRS-III criteria	Aβ42	CSF; INNO-BIA AlzBio3, Luminex technology;	Age, sex and duration of disease
Jacob et al. 2022; USA	Low	Cross-sectional	Cognitively normal participants (60.55 ± 9.34) [34-88]	2366 (54%)	Fast walking speed, and muscular strength; 4-meter walk, 5 chair stand test, hand dynamometer	Aβ42, Aβ40, Aβ42/Aβ40	Plasma; INNO-BIA AlzBio3, Luminex xMap technology;	Age, sex, diabetes, cardiovascular disease, atrial fibrillation, smoking, APOE ε4 carrier status, systolic blood pressure, waist-to-hip ratio, total cholesterol level, PA index and plasma homocysteine levels
Knapstad et al. 2019; Norway	Low	Cross-sectional	The participants with a recent onset of cognitive symptoms (64 ± 9) [40-80]	69 (52%)	Usual and fast gait speed; 10-m dynamic walking speed test	Aβ42	CSF; ND	Age, sex, years of education and BMI
Legdeur et al. 2021; 11 cohorts in Europe	Low	Cross-sectional	84 cognitively normal and 38 cognitively impaired participants (92.4 ± 2.8) [90+]	84 (53.6%); 38 (65.8%); All 122 (57.4%)	General physical performance, muscular strength; SPPB, hand dynamometer	Aβ	PET; [18F]flutemetamol	Age, sex and education
Tsai et al. 2021; USA	Low	Cross-sectional	Individuals with a family history of Alzheimer disease: Non-APOE-4 (59.73 ± 5.69); APOE-4 (57.32 ± 7.26) [38-73]	22 (50%); 22 (50%)	Aerobic fitness, muscular strength; Rockport Fitness Walking Test, Arm Curl and 30-s chair stand test (from SFPF battery)	Aβ42, Aβ40	Serum; Single Molecule Counting (SMC®) Immunoassay Technology	Age

Abbreviations: APOE-4: Apolipoprotein E; **Aβ**: amyloid beta; **BMI**: body mass index; **CSF**: Cerebrospinal fluid; **FoG**: Freezing of gait; **SPPB**: Short Physical Performance Battery; **GXT**: Physician-supervised graded exercise test; **HABCPPB**: Health ABC Physical Performance Battery; **MAPT:** The Multidomain Alzheimer Preventive Trial; **MDS-UPDRS**: Revised Unified Parkinson's Disease Rating Scale; **MMSE**: Mini Mental State Examination; **ND**: Not disclosed; **NFOG-Q:** New Freezing of Gait Questionnaire**; PD**: Parkinson disease; **PET**: Positron Emission Tomography; **PIB**: Pittsburgh Compound B; **REM:** Rapid eye movement; **RSEGCD:** The Rating Scale for Gait Evaluation in Cognitive Deterioration; **SPPB**: Short Physical Performance Battery; **SUVR**: standardized uptake value ratio; **TUGT:** Timed Up and Go Test; **UPDRS**: Unified Parkinson's Disease Rating Scale. **MDS**: Meso Scale Discovery; **SFPF:** Senior Functional Physical Fitness; **PA:** Physical activity.

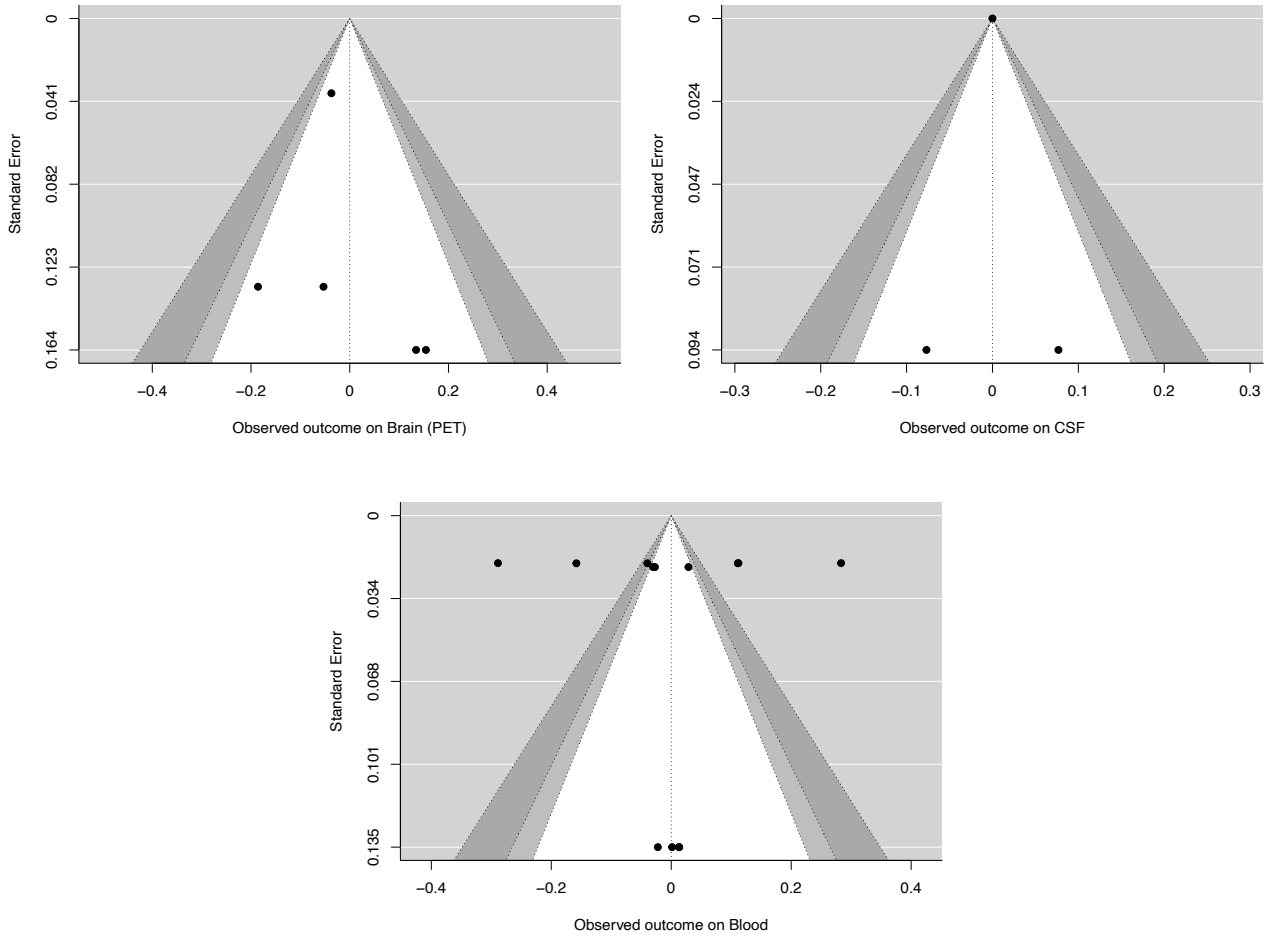

Figure 2. Funnel plots to show publication bias in the association of physical performance with amyloid beta on Brain (PET), CSF and blood. Diagonal lines represent pseudo-95% confidence intervals. The y-axis represents the standard error (weight in the pooled analysis). The x-axis shows the effect size; thus, the vertical line represents the calculated estimated effect of amyloid beta.

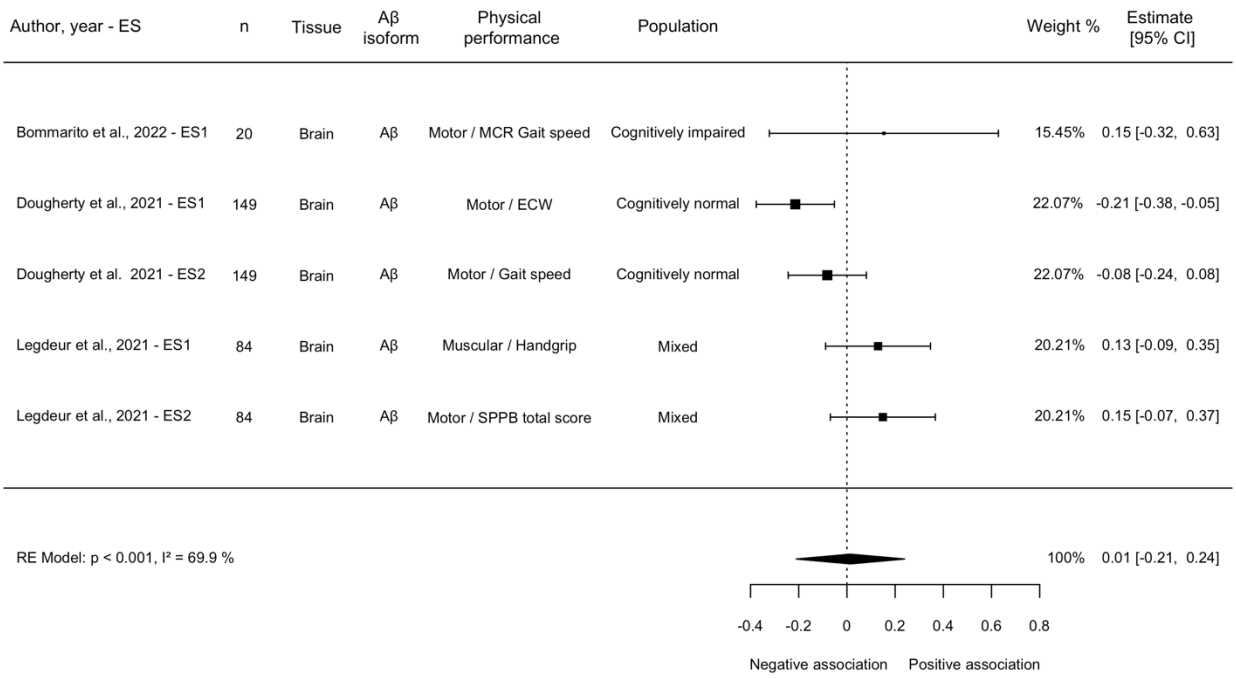

Figure 3. Overall effect meta-analysis of physical performance on amyloid beta accumulation on Brain (PET). Aβ: Amyloid beta. I^2: Heterogeneity. ECW: Energetic cost of walking. SPPB: Shor physical performance battery. MCR: Motoric Cognitive Risk classified with gait speed.

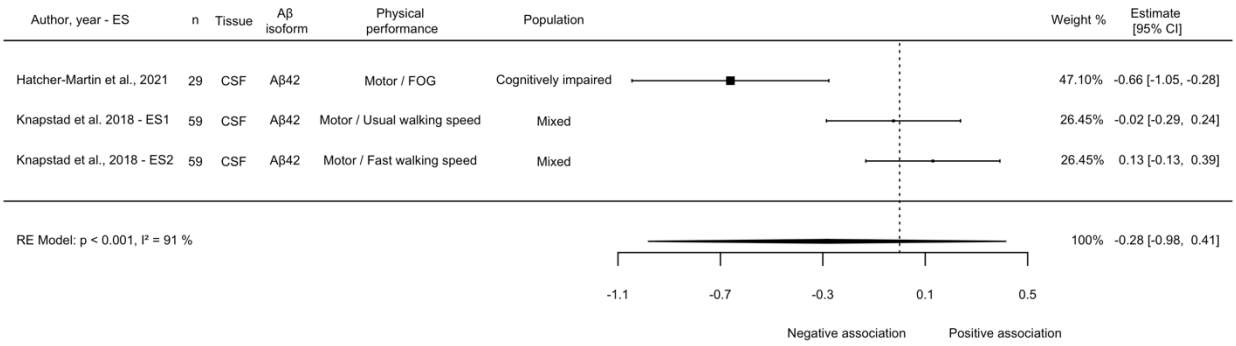

Figure 4. Overall effect meta-analysis of physical performance on amyloid beta abnormalities in CSF. Aβ: Amyloid beta. I^2: Heterogeneity. FOG: Freezing of gait.

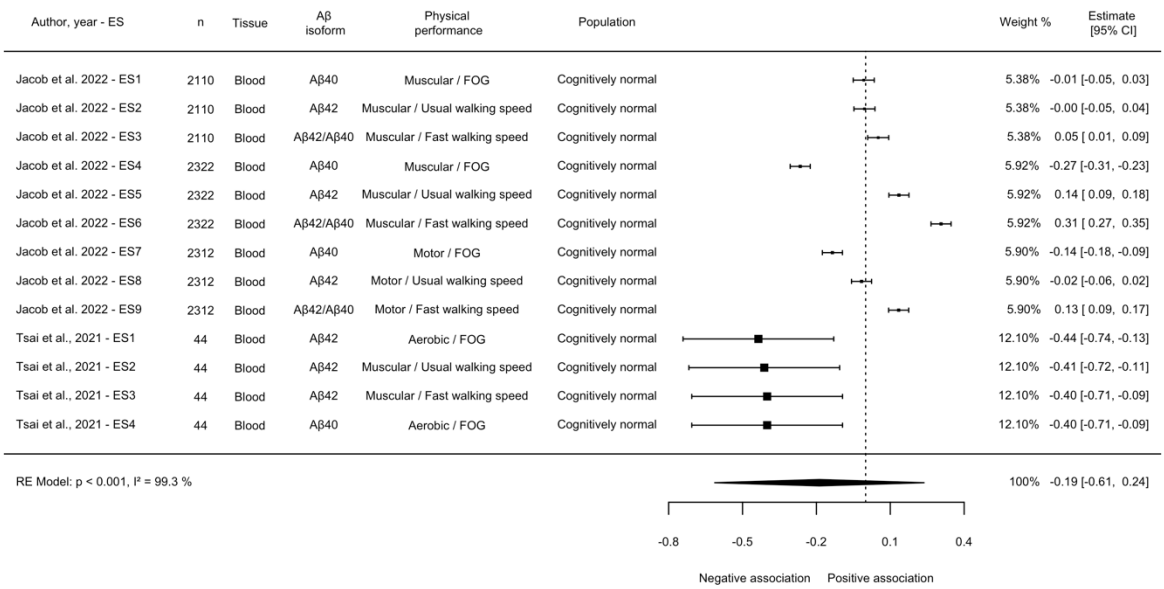

Figure 5. Overall effect meta-analysis of physical performance on amyloid beta abnormalities in blood. Aβ: Amyloid beta. I^2: Heterogeneity. FOG: Freezing of gait.

Table S1. Search strategy.

Databases	Search strategy
Web of Science, PubMed, SPORTDiscuss PsycINFO, Cochrane Central Register of Controlled Trials, until 16 June 2022.	(“A-beta” OR “amyloid” OR “Aβ” OR “beta-Peptide” OR “beta- Protein*” OR “β-protein” OR Amyloidosis) AND ("Physical Fitness" OR "Physical Conditioning" OR "Muscle Strength" OR “Muscular strength” OR “Muscular fitness” OR “Musculoskeletal fitness” OR "Range of Motion" OR "Postural Balance" OR “Musculoskeletal Equilibrium” OR “Postural Equilibrium” OR “Joint range of motion” OR “Joint flexibility” OR “Range of motion” OR "Cardiorespiratory fitness" OR "Cardiovascular fitness" OR "Aerobic fitness" OR "Aerobic capacity" OR "Maximal oxygen consumption" OR "VO2max" OR "Running Speed" OR "Agility" OR “Motor Fitness” OR “Motor ability” OR gait OR “standing balance” OR “motor slowing” OR “functional mobility” OR “physical function” OR “physical functioning” OR “physical performance” OR “physical ability” or “intrinsic capacity”)

Table S2. Excluded articles (N=77)

Reasons	Number of articles	References
Wrong predictor	25	Allali et al., 2018; Dunkelmann et al., 2018; Lacroix et al., 2017; Lalonde et al., 2012; Law et al., 2019; Lilamand et al., 2018; Lilamand et al., 2016; Mollica et al., 2019; Mukhamedyarov M et al., 2009 ; Stover et al., 2015; Tsai et al., 2019; Wagner et al.,2019; Xu et al., 2007; Yuan Q et al., 2017; Min et al., 2021; Snitz et al., 2020; Rattay et al., 2022; Hyang-Beum et al., 2021; Wu et al., 2020; Conejero et al., 2021; Jang et al., 2022; Babulal et al., 2020; Said et al., 2022; Tsai et al., 2021; Wallon et al., 2021;
Wrong outcome	47	Delrieu et al., 2020; Ngwa et al., 2021; Nilsson et al., 2021; Stein et al., 2021; Mueller-Schmitz et al., 2020; Zagatt et al., 2022; Sullivan et al., 2021; Ngwa et al., 2022; Nadkarni et al., 2017; Villas-Boas et al., 2021; Ahn et al., 2020; Skillback et al., 2022; Lauretani et al., 2020; D'Souza et al., 2021; Lukkarinen et al, 2022; Cohelo et al., 2022; He et al., 2020a; Goncalves et al.., 2020; He et al, 2020b; Shaaban et al., 2022; Chou et al., 2021; Bedada et al., 2021; Chelban et al., 2021; Taghdiri et al., 2020; Padilla et al., 2022; Craig et al., 2020; Rodziewiccz-Flis et al., 2022; Morel et al., 2020; Kanemoto et al., 2021; Kim et al. 2020; Darrow et al., 2022; Dadar et al., 2021; Barreto et al., 2017; Bohnen et al., 2014; Dao et al., 2016; Del campo et al., 2016; Koychev et al., 2018; Leahey et al., 2007; Muller et al., 2013; Rochester et al., 2017; Schirinzi et al., 2018; Schultz et al., 2017; Schultz et al., 2015; Tian et al., 2017; Tian et al., 2018; Wennberg et al., 2016; Wennberg et al., 2017; Yoon et al., 2018
Wrong study design	5	Mayor et al., 2015; Komiyama et al., 1991; Vidoni et al, 2021; Ribeiro et al., 2021; Willis, 2020

Table S3. Criteria for the methodological risk of bias assessment of included articles and percentage of studies meeting these criteria.

Criteria items	Percentage of studies meeting criterion (%)
1. Were the criteria for inclusion in the sample clearly defined?	100
2. Were the study subjects and the setting described in detail?	71.4
3. Was the exposure measured in a valid and reliable way?	100
4. Were objective, standard criteria used for measurement of the condition?	-
5. Were confounding factors identified?	71.4
6. Were strategies to deal with confounding factors stated?	71.4
7. Were the outcomes measured in a valid and reliable way?	42.8
8. Was appropriate statistical analysis used?	85.6

Adapted from the Joanna Briggs Institute Critical Appraisal Tool for Systematic Reviews;
- : Not applicable criterion

Table S4. Risk of bias assessment of included articles.

Study	Item 1	Item 2	Item 3	Item 4	Item 5	Item 6	Item 7	Item 8	Quality Score %	Risk Category
Bommarito et al. (2022) [1]	✓	✓	✓	-	✓	✓	✓	✓	100	Low Risk
Dougherty et al. (2021) [2]	✓	✓	✓	-	✓	✓	✓	✓	100	Low Risk
Hatcher-Martin et al. (2021) [3]	✓	×	✓	-	×	×	×	×	28	High Risk
Jacob et al. (2022) [4]	✓	✓	✓	-	✓	✓	×	✓	85	Low Risk
Knapstad et al. (2019) [5]	✓	✓	✓	-	✓	✓	×	✓	85	Low Risk
Legdeur et al. (2021) [6]	✓	✓	✓	-	✓	✓	✓	✓	100	Low Risk
Tsai et al. (2021) [7]	✓	×	✓	-	×	×	×	✓	57	High Risk
Criterion Score %	100	71.4	100	-	71.4	71.4	42.8	85.6	-	-

Note that the total risk of bias score was calculated by dividing the number of criteria met in one study by the total number of criteria (i.e., 7). ✓: meet the methodological quality criterion; ×: not meet the methodological quality criterion; the studies were considered as "low risk" when 75% of items were scored as "yes" (criterion met); Adapted from the Joanna Briggs Institute Critical Appraisal Tool for Systematic Reviews; -:Not applicable criterion. Item 1: Were the criteria for inclusion in the sample clearly defined?; Item 2: Were the study subjects and the setting described in detail?; Item 3: Was the exposure measured in a valid and reliable way?; Item 4: Were objective, standard criteria used for measurement of the condition?; Item 5: Were confounding factors identified?; Item 6: Were strategies to deal with confounding factors stated?; Item 7: Were the outcomes measured in a valid and reliable way?; Item 8: Was appropriate statistical analysis used?

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