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Review

Physical activity and amyloid beta in middle-aged and older adults: A systematic review and meta-analysis

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Abstract

Background: One of the pathological hallmarks distinguishing Alzheimer's disease from other dementias is the accumulation of amyloid beta (Aβ). Higher physical activity is associated with decreased dementia risk, and one potential path could be through Aβ levels modulation. We aimed to explore the relationship between physical activity and Aβ in middle-aged and older adults.

Methods: A systematic search of PubMed, Web of Science, PsycINFO, Cochrane Central Register of Controlled Trials, and SPORTDiscus was performed from inception to the 28th of April 2022. Studies were eligible if they included physical activity and Aβ data in adults aged 45 years or older. Multi-level meta-analyses of intervention and observational studies were performed to examine the role of physical activity in modulating Aβ levels.

Results: In total, 37 articles were included (8 randomized controlled trials, 3 non-randomized controlled trials, 4 prospective longitudinal studies, and 22 cross-sectional studies). The overall effect size of physical activity interventions on changes in blood Aβ was medium (pooled standardized mean difference = −0.69, 95% confidence interval (95%CI): −1.41 to 0.03; $I^2 = 74.6\%$). However, these results were not statistically significant, and there were not enough studies to explore the effects of physical activity on cerebrospinal fluid (CSF) and brain Aβ. Data from observational studies were examined based on measurements of Aβ in the brain using positron emission tomography scans, CSF, and blood. Higher physical activity was positively associated with Aβ only in the CSF (Estimate $r = 0.12$; 95%CI: 0.05–0.18; $I^2 = 38\%$).

Conclusion: Physical activity might moderately reduce blood Aβ in middle-aged and older adults. However, results were only near statistical significance and might be interpreted with caution given the methodological limitations observed in some of the included studies. In observational studies, higher levels of physical activity were positively associated with Aβ only in CSF. Therefore, further research is needed to understand the modulating role of physical activity in the brain, CSF, and blood Aβ, as well as its implication for cognitive health.

Keywords: Aging; Cognitive impairment; Dementia; Exercise; PET

1. Introduction

Life expectancy is increasing globally in tandem with the number of people living with dementia and cognitive impairment. In particular, Alzheimer's disease (AD) is the major cause of cognitive decline and dementia worldwide.[1] AD is characterized by severe progressive memory impairments related to deposition

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of amyloid beta (Aβ) plaques in brain extracellular spaces causing cortical dysfunction and neuronal loss.[2] Aβ accumulation can be detected in a preclinical stage of AD, before clinical symptoms emerge,[3] and can be measured in the brain and the cerebrospinal fluid (CSF) via positron emission tomography (PET) and lumbar puncture, respectively.[4] Several studies indicated an inverse correlation between global cortical amyloid PET and CSF Aβ levels.[5–7] One of the hypotheses is that Aβ levels gradually decrease in the CSF in AD because of the preferential sequestration as insoluble deposits in brain.[5] Recently, an increasing number of studies have also explored blood Aβ as a blood biomarker for AD. However, the published results regarding the correlation of blood Aβ with brain and CSF Aβ are conflicting, and many factors have been reported to impact blood Aβ levels and their association with AD biomarkers.[8]

Potentially modifiable factors (e.g., lifestyle factors) have garnered increased attention as possible approaches for reducing Aβ accumulation in the brain and, in turn, delaying the progression of AD.[9] Animal models indicate that physical activity may delay, prevent, or treat AD by impacting Aβ plaque deposition.[10–12] In humans, researchers have used several measurements of Aβ in the brain, CSF, and blood to explore the effects of physical activity on Aβ levels. However, the results obtained were inconsistent.[13–17] For instance, some intervention studies have found that the level of Aβ in the brain does not change after a physical activity intervention.[13,14] Similar results were found by Jensen et al.,[15] who concluded that physical activity did not affect CSF Aβ after a 16-week intervention. In contrast, other studies established that physical activity reduces the levels of blood circulating Aβ.[16,17] There are several possible explanations for these inconsistencies, including the study design, population characteristics, or Aβ measurement. Therefore, a systematic synthesis of the current evidence that considers potential moderators is needed to confirm or refute the hypothesis that physical activity modulates Aβ levels. Clarity on this issue would improve our understanding of whether Aβ modulation is one of the mechanisms through which physical activity might decrease dementia risk. This knowledge would no doubt contribute to the development of more effective physical activity interventions for reducing cognitive decline in older adults.

Two previous narrative reviews have explored the relationship between physical activity and Aβ.[18,19] Specifically, Ebrahimi et al.[18] suggested that physical activity could improve cognitive function by reducing Aβ levels. In contrast, Brown et al.[19] concluded that although evidence in animals seems consistent, evidence of the influence of physical activity on Aβ in humans is still scarce. While these reviews contributed important insights to the field, the absence of objective and systematic study selection criteria arguably leads to a number of methodological biases (e.g., the author's interpretation and conclusions). In 2015, de Souto Barreto et al.[20] performed a systematic review to explore the association of physical activity and AD biomarkers, including Aβ, in humans. However, evidence at that time was limited. Only 5 cross-sectional studies were included, and their results were contradictory (i.e., 3 positive and 2 null associations). In 2019, Frederiksen et al.[21] carried out a systematic review of observational studies to explore the association of physical activity with AD biomarkers. In brief, they concluded the majority of the identified studies did not find a significant association between physical activity and Aβ.[21] This, together with the lack of quantitative synthesis of data (e.g., a meta-analysis), and the fact that literature in the field has grown substantially over the past few years, has limited the ability of prior work to draw solid conclusions about the effect of physical activity on Aβ in humans. Consequently, an updated systematic review is needed to understand the role of physical activity on Aβ levels—and it must include both intervention studies, to provide causal evidence, and observational studies, to provide complementary information in an emerging field that is still in its infancy.

Therefore, the aim of the current systematic review was to determine the overall effect of physical activity on Aβ by conducting a systematic review and meta-analysis of available intervention studies (including randomized controlled trials (RCTs) and non-RCTs). Due to the expected lack of intervention studies, we also aimed to synthesize the observational evidence by conducting a meta-analysis of observational studies (including cross-sectional and prospective longitudinal studies) testing the association between physical activity and Aβ in middle-aged and older adults.

2. Methods

This study was conducted in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[22] Additionally, the systematic review protocol was registered in the international Prospective Register of Systematic Reviews (PROSPERO) (CRD42020184203).

2.1. Search strategy

The literature search was carried out from inception to 28th April 2022 in PubMed, Web of Science, PsycINFO, Cochrane Central Register of Controlled Trials, and SPORTDiscus. The search strategy used for all databases is described in Table 1. We extracted all studies from the different databases into an EndNote Library (Version X7, Clarivate, Philadelphia, PA, USA). Relevant articles were screened by titles and abstract by 2 independent researchers (CAA and MÁO). Full-text articles considered acceptable for review were examined to determine final eligibility by the same 2 researchers (CAA and MÁO). In case of disagreement, consensus was achieved through discussion and, when required, the opinion of a third researcher (MRA) was considered.

2.2. Eligibility criteria

Overall, the inclusion criteria were: (a) age criterion: adults aged 45 years and older; (b) language criterion: no restrictions; (c) exposure: physical activity; for experimental studies, physical exercise interventions (a form of physical activity that is planned, structured, repetitive, and performed to improve health or fitness) not combined with another type of intervention (e.g., cognitive/diet interventions) were included; for observational studies,

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Table 1
Search strategy.

Databases	Search strategy	Limits
PubMed, Web of Science, PsycINFO, Cochrane Central Register of Controlled Trials, SPORTDiscus	("A-beta" OR "amyloid" OR "Aβ" OR "beta-Peptide" OR "beta-Protein*" OR "β-protein" OR "Amyloidosis") AND ("Exercise" OR "Sports" OR "physical exercise" OR "Aerobic exercise" OR athletic OR "Motor Activity" OR "Physical activity" OR "Locomotor activity" OR "Training" OR "Moderate physical activity" OR "Vigorous physical activity" OR "Moderate-to-vigorous physical activity" OR "MVPA" OR "Sedentary" OR "Inactivity" OR "Aerobic activities" OR "Aerobic activity" OR "Cardiovascular activities" OR "Cardiovascular activity" OR "Endurance activities" OR "Physical activities" OR "Physical conditioning" OR "Resistance training" OR "strength training" OR "Lifestyle activities" OR "Lifestyle activity" OR "Recreational activities" OR "Recreational activity" OR "Tai chi" OR "Tai ji" OR "Yoga" OR "Chi kung" OR "Qigong" OR "dance" OR "dancing" OR "Balance training" OR "Functional training" OR "stretching" OR "Walk" OR "Walking") AND (adult OR adults OR adulthood OR elderly OR "Oldest Old") PubMed (Filters activated: Humans, Middle Aged + Aged: 45+ years)	Publication date from inception to 2022/04/28.

objective or self-reported physical activity measurements were included; (d) control group criterion, understood as "treatment as usual" or "stretching": intervention studies should have either an inactive, active, or no control group (we considered a control group as active when participants from the control group practiced any type of exercise but stretching; only the primary subset of studies (i.e., physical exercise group *vs*. control group) were included in the meta-analyses); (e) outcome: Aβ in the brain using PET, CSF, or blood; Aβ ratios (Aβ42/40 or Aβ40/42) were also included in this review; (f) study design: we included cross-sectional studies, longitudinal cohort studies and intervention studies (RCTs and non-RCTs).

2.3. Data extraction

Two researchers (CAÁ and PSU) extracted data from the selected studies to a customized data extraction form developed and piloted a priori by the review team. We extracted the following items: study background (name of the first author, year, and country), total risk of bias score, sample characteristics (target population, number of participants, participants' age, and sex), design, measures and instruments used to assess both Aβ and physical activity. For intervention studies, we also extracted intervention details (exercise type, frequency in number of sessions per week, session duration, intervention duration in weeks, exercise intensity) together with control conditions. Information extracted in the tables was double-checked by 3 experienced researchers (IEC, PMG, and MRA). Possible disagreements were discussed by the researchers until a consensus was reached. Lastly, in cases of incomplete/missing data, we contacted the corresponding authors for data requests.

2.4. Risk of bias

The risk of bias was evaluated independently by 2 researchers (CAA and MAO) and disagreements were resolved in a consensus meeting with IEC, PMG, MRA, and CMH. The risk of bias was evaluated using the Joanna Briggs Institute Critical Appraisal Tool for Systematic Reviews,[23] which has been used in previous reviews.[24–26] The studies were categorized with an overall risk of bias score as used in previous studies.[24] Specifically, the studies were considered as "low risk" when 75% of items were scored as "yes" (criterion met).

2.5. Synthesis of the evidence

Multi-level meta-analyses of intervention and observational studies were performed using *R* Statistical Software (Version 4.2.2; https://www.r-project.org/contributors.html) and the *metafor* package Version 3.8.1 (Wolfgang Viechtbauer, Maastricht University, Netherlands). A separate synthesis of the evidence was performed for studies that assess Aβ in the CSF, brain and blood. Statistical significance was set at a p value of less than 0.05.

2.5.1. Multi-level meta-analysis for intervention studies

Standardized mean differences (SMD) between the exercise and control groups were computed. Weighted mean differences were calculated using a random effects model. Heterogeneity was measured using the I^2 statistic (the percentage of total variability attributed to between-study heterogeneity). SMD was calculated using Hedges' adjusted g (similar to Cohen's d). ESs of 0.2, 0.4, and 0.8 were considered small, medium, and large, respectively. The publication bias was assessed by a funnel plot and the Egger's regression asymmetry test, considering the level of significance of <0.1.[27] To run the Egger's test, the random-effects model was modified to include the standard error of the effect size as a moderator.

Posteriori exploratory moderation analyses were performed using sex and type of intervention (aerobic interventions *vs*. others) as categorical variables and mean of age and total intervention duration (weeks × sessions × minutes/session) as continuous moderators (meta-regression). In addition, exploratory subgroup comparisons were calculated for categorical variables (i.e., sex and type of intervention).

2.5.2. Meta-analysis for observational studies

For studies reporting associations between physical activity and Aβ, correlation coefficients were extracted along with

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sample size. Wherever 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 (Daniel Lüdecke, University Medical Center Hamburg, Germany). Heterogeneity was assessed using the Q statistic (with $p < 0.10$ suggesting statistically significant heterogeneity). A *posteriori* moderator analysis was performed. Specifically, a mixed-effects model was fitted to examine the moderators described below as potential sources of variance. Separate models were fitted to determine the main effects for population characteristics (cognitively normal *vs*. cognitively impaired). The analysis of main effects was interpreted using the 95% confidence interval (95%CI) for the point estimates of each level of a moderator and the statistical significance of the omnibus test.

Funnel plots of the effect size against the standard error of the effect size were visually inspected for small-sample bias, and Egger's test values with 95%CI for funnel plot asymmetry were calculated.[28−30] To run the Egger's test, the random-effects model was modified to include the standard error of the effect size as a moderator. Small-sample 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 ($p < 0.10$).[28,29]

2.6. Data sharing statement

The data that support the findings of this study are available from the corresponding authors upon reasonable request.

3. Results

3.1. Study selection and characteristics

The database search revealed a total of 2261 articles, of which 450 were duplicates. Finally, a total of 71 articles were identified for full-text screening. After the full-text screening, 8 RCTs, 3 non-RCT intervention, 4 prospective longitudinal studies, and 22 cross-sectional studies met the inclusion criteria and were subsequently included in this systematic review. Further details about the selection process are shown in Fig. 1. The excluded articles and corresponding reasons for exclusion are shown in Supplementary Table 1. Detailed descriptions of the included intervention and observational studies are provided in Supplementary Tables 2 and 3, respectively.

3.2. Study characteristics of the intervention studies

Sample sizes of included intervention studies ranged from 14[17] to 109[14] participants (Supplementary Table 2). Participants ranged from 55 to 85 years of age.[31] Five studies included only females.[17,32−35] In another study, 92% of the total sample was female.[16] Six of 11 studies included cognitively impaired participants (from patients with AD to patients with mild cognitive impairments).[13,15,31,32,34,36] Most interventions (6 of 11 studies) included aerobic exercise,[13−15,31,33,36] while 3 studies included a combination of aerobic and resistance exercises,[16,17,34] another included resistance exercise using bands,[32] and another Taekwondo.[35] Interventions ranged from 8[33] to 52 weeks,[13,14] and the majority implemented 60-min exercise sessions between 3 and 5 times per week. Only 3 studies reported data on intervention adherence,[14−16] which ranged from 69%[15] to 90%.[16] Most studies did not specify the control group criteria.[17,32−34] In the studies whose criteria were described, participants from the control group continued their usual routines,[15] received educational sessions,[14] or participated in an active control group (e.g., stretching and balance exercises).[13,16,36,31] Lastly, 3 studies measured Aβ in the brain by PET,[13,14,36] 1 study measured Aβ in CSF by lumbar puncture,[15] and 7 studies measured Aβ in the blood (i.e., 4 in plasma,[16,31,33,34] 2 in serum,[17,35] and 1 study did not specify plasma or serum[32]).

3.3. Study characteristics of the observational studies

3.3.1. Longitudinal studies

Sample sizes ranged from 65[37] to 515,[38] and participants were aged up to 94 years[38] (Supplementary Table 3). Two studies included cognitively normal individuals;[38,39] another 2 included cognitively impaired participants.[37,40] Physical activity was assessed by validated self-reported questionnaires[37−39] or through an interview.[40] No studies assessed physical activity with objective measures (e.g., accelerometry). Regarding the outcome, one study assessed brain Aβ levels with carbon 11−labeled Pittsburgh compound B PET,[37] one assessed CSF Aβ with an enzyme-linked immunoassay (ELISA) kit (Fujirebio (formerly Innogenetics), Ghent, Belgium),[40] and one assessed both brain Aβ, with carbon 11−labeled Pittsburgh compound B PET, and CSF Aβ, with an ELISA kit (Innotest; Fujirebio (formerly Innogenetics)).[39] Lastly, one of the studies assessed blood Aβ in plasma using a combination of mouse monoclonal antibody 6E10 and two different antibodies specific for Aβ1-40 and Aβ1-42, in a double antibody sandwich ELISA.[38] Finally, follow-up ranged from 2[39,40] to 3 years.[38,40]

3.3.2. Cross-sectional studies

Sample sizes ranged from 40[41] to 1108,[42] and participants were aged up to 97 years[43] (Supplementary Table 3). Most of the studies assessed physical activity by self-report questionnaires (80%). The remaining studies utilized interviews,[44] pedometers,[45,46] and accelerometry[43] to measure physical activity. Regarding the measurements of Aβ, 9 studies used only PET to measure brain Aβ,[44−52] 4 studies included both PET and CSF measures,[53−56] and 2 studies used both PET and plasma measurements of Aβ.[57,58] Additionally, 3 studies included only CSF samples,[41,42,59] 2 studies used only plasma samples,[60,61] and 1 study used postmortem brain samples.[43] Only 2 studies used mass-spectrometry assays for assessing Aβ in CSF[62] and blood.[58]

3.4. Risk of bias assessment

The percentage of studies that met the criteria for reporting a "low risk of bias" item-by-item is presented in Supplementary Tables 4−7 according to their study design (RCT, non-RCTs, longitudinal cohort studies, and cross-sectional studies, respectively). In addition, the overall risk of bias assessment study-by-study is presented in Supplementary Tables 8−11.

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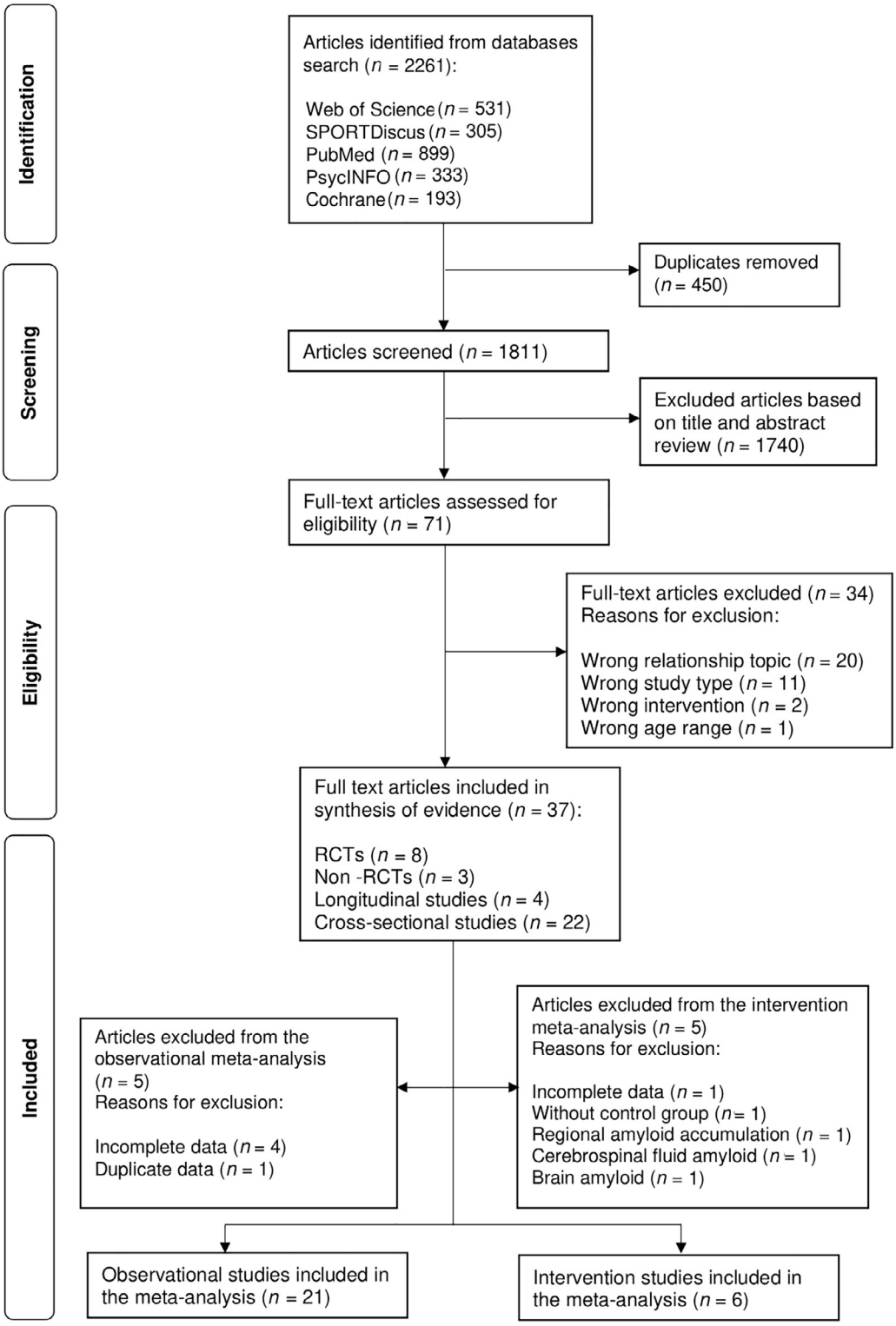

Fig. 1. Flow diagram for study selection. RCT = randomized controlled trial.

In brief, most of the included studies presented a "high risk" (25% of items were scored as "no" or "unclear"). Specifically, a high risk of bias was detected in 6 of 8 (75%) RCTs, 3 of 3 (100%) non-RCTs, 2 of 4 (50%) longitudinal studies, and 7 of 22 (32%) cross-sectional studies.

3.5. Synthesis of the evidence

3.5.1. Meta-analysis of intervention studies

A meta-analysis of intervention studies conducted on 131 participants is presented in Fig. 2. Compared to the control

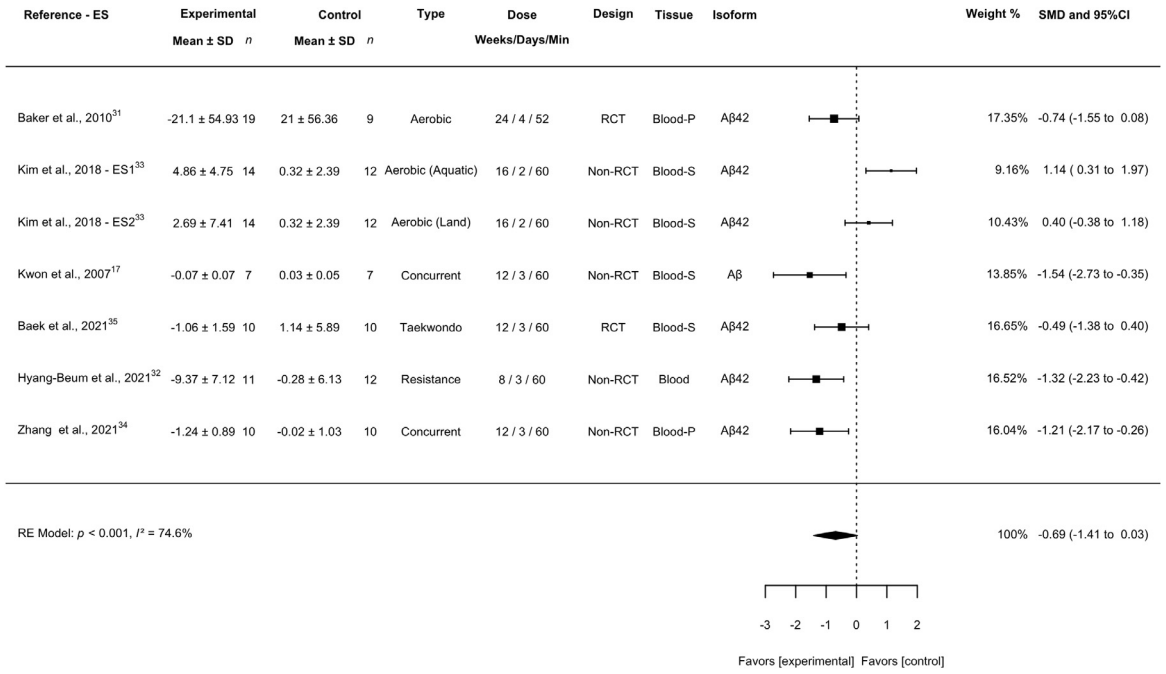

Fig. 2. Forest plot of pooled effect size and confidence intervals of intervention studies analyzing the effect of physical activity on blood Aβ. Kim et al.[33] did not report the isoform assessed. 95%CI = 95% confidence interval; Aβ = amyloid beta; Blood-P = blood-plasma; Blood-S = blood-serum; RCT = randomized controlled trials; RE = random effect; SMD = standardized mean difference.

group, exercise interventions had a medium effect on reducing blood Aβ in middle-aged and older adults (pooled SMD = −0.69, 95%CI: −1.41 to 0.03; I^2 = 74.6%). However, only a few interventions achieved the criteria for being meta-analyzed, and the results were not statistically significant. Two intervention studies were excluded from the meta-analysis due to incomplete data[36] and the absence of a control group.[16] Tarumi et al.[13] was the only study to assess Aβ locally instead of in the whole brain. In addition, Jensen et al.[15] was the only study to assess Aβ in the CSF. Lastly, Vidoni et al.[14] was the only study to assess Aβ in the brain. Therefore, we performed our analyses excluding these 5 studies from the pool. Consequently, only studies that assessed Aβ in the blood were included in the meta-analysis. Of note, 1 study[33] assessed Aβ 30 min after the last session in the 16th week. This complicates the interpretation of the results because it combines into a single measure the acute and chronic effects of the exercise program on Aβ. Therefore, we ran a sensitivity analysis excluding this study from the general pool and observed the overall effect became significant (pooled SMD = −0.99, 95%CI: −1.41 to −0.58; I^2 = 0%). Due to the limited number of studies included in the meta-analysis, sensitivity analyses (e.g., excluding plasma/serum Aβ) could not be performed. Lastly, we did not find evidence of publication bias based on visual observation of the funnel plot and Egger's tests (Supplementary Fig. 1).

Moderation analyses showed that participants who attended a combined (i.e., aerobic + resistance training) or non-aerobic (e.g., taekwondo intervention) exercise intervention had larger effects on Aβ (Omnibus test of moderators = 8.85, p = 0.01; aerobic: SMD = 0.079, 95%CI: −0.844 to 1.002; combined or non-aerobic: SMD = −1.114, 95%CI: −1.853 to −0.375). In addition, subgroup analysis including only females revealed that results remain consistent according to the general effect (SMD = −0.695, 95%CI: −1.570 to 0.181).

Finally, meta-regression analyses (including continuous moderators) showed large effects on older participants (Omnibus test of moderators = 5.291, p = 0.021), and no differences were observed according to the total time of the intervention (Omnibus test of moderators = 0.000, p = 0.984) (Supplementary Fig. 2).

3.5.2. *Meta-analysis of observational studies*

The meta-analysis of observational studies assessing Aβ in the brain is shown in Fig. 3. In brief, the overall association of physical activity with brain Aβ was not significant (ES = −0.06, 95%CI: −0.11 to 0.00, I^2 = 49.92%). Results did not change when longitudinal studies were excluded from the general pools (ES = −0.06, 95%CI: −0.12 to 0.00, I^2 = 51.81%) (data not shown). The meta-analysis of observational studies that assessed Aβ in the CSF is summarized in Fig. 4. Specifically, the overall effect of physical activity on CSF Aβ was significant (ES = 0.12, 95%CI: 0.05−0.18, I^2 = 38%). All studies included in this pool had a cross-sectional design. Lastly, the overall effect of physical activity on blood Aβ is presented in Fig. 5. Briefly, the association between physical activity and blood Aβ was not significant (ES = −0.06, 95%CI: −0.15 to 0.03, I^2 = 68.02%). When only studies with a cross-sectional design were included, the results remained consistent (pooled SMD = −0.04, 95%CI: −0.141 to 0.070, I^2 = 74.72%) (data not shown). Results did not change when we explored separately the association between physical activity and the ratio Aβ42/Aβ40 (pooled SMD = −0.083, 95%CI: −0.216 to 0.049, I^2 = 79.85%),

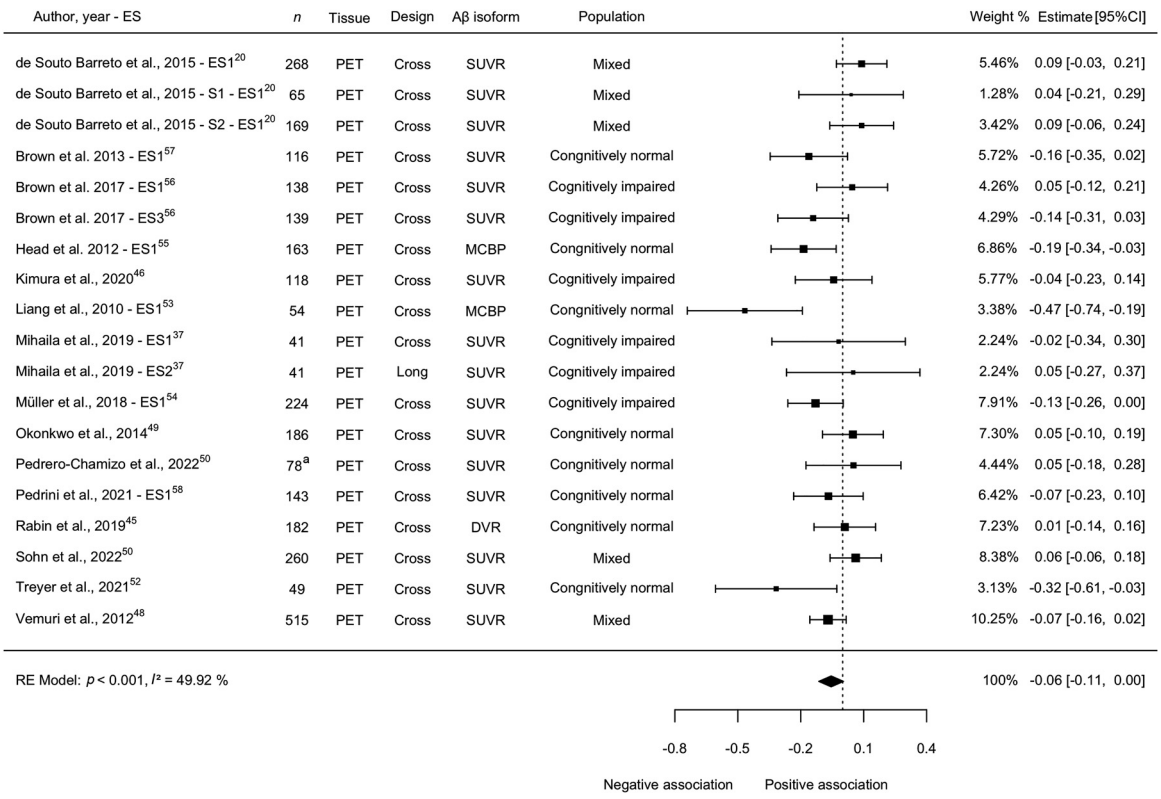

Fig. 3. Forest plot of pooled effect size and confidence intervals of observational studies exploring the association between physical activity and brain Aβ. [a] Sample represents the number of participants in the extreme group. 95%CI = 95% confidence interval; Aβ = amyloid beta; cross = cross-sectional studies; DVR = distribution volume ratio; ES = effect sizes; long = longitudinal cohort studies; MCBP = mean cortical blinding potentials; PET = positron emission tomography; RE = random effect; SUVR = standardized uptake value ratio.

Aβ42 (pooled SMD = −0.091, 95%CI: −0.190 to 0.009, I^2 = 54.45%), and Aβ40 (pooled SMD = −0.046, 95%CI: −0.163 to 0.071, I^2 = 66.57%). Only a single study reported the ratio Aβ40/Aβ42.[58] Therefore, these data were excluded from the general pool, and we were not able to meta-analyze them separately.

Moderation analysis by population (cognitively normal *vs.* cognitively impaired) revealed no moderation effect in CSF

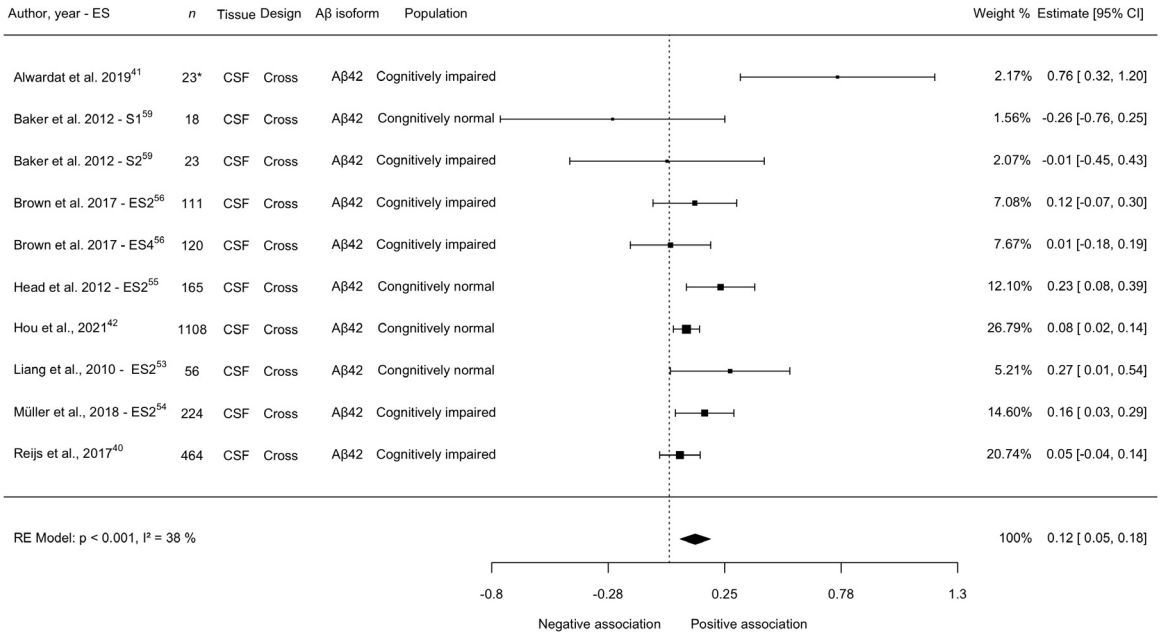

Fig. 4. Forest plot of pooled effect size and confidence intervals of observational studies exploring the association between physical activity and CSF Aβ. * = Sample represents the number of participants in the extreme groups (low vs. high PA groups). 95%CI = 95% confidence interval; Aβ = amyloid beta; CSF = Cerebrospinal fluid; cross = cross-sectional studies; ES = effect sizes; long = longitudinal cohort studies; RE = random effect.

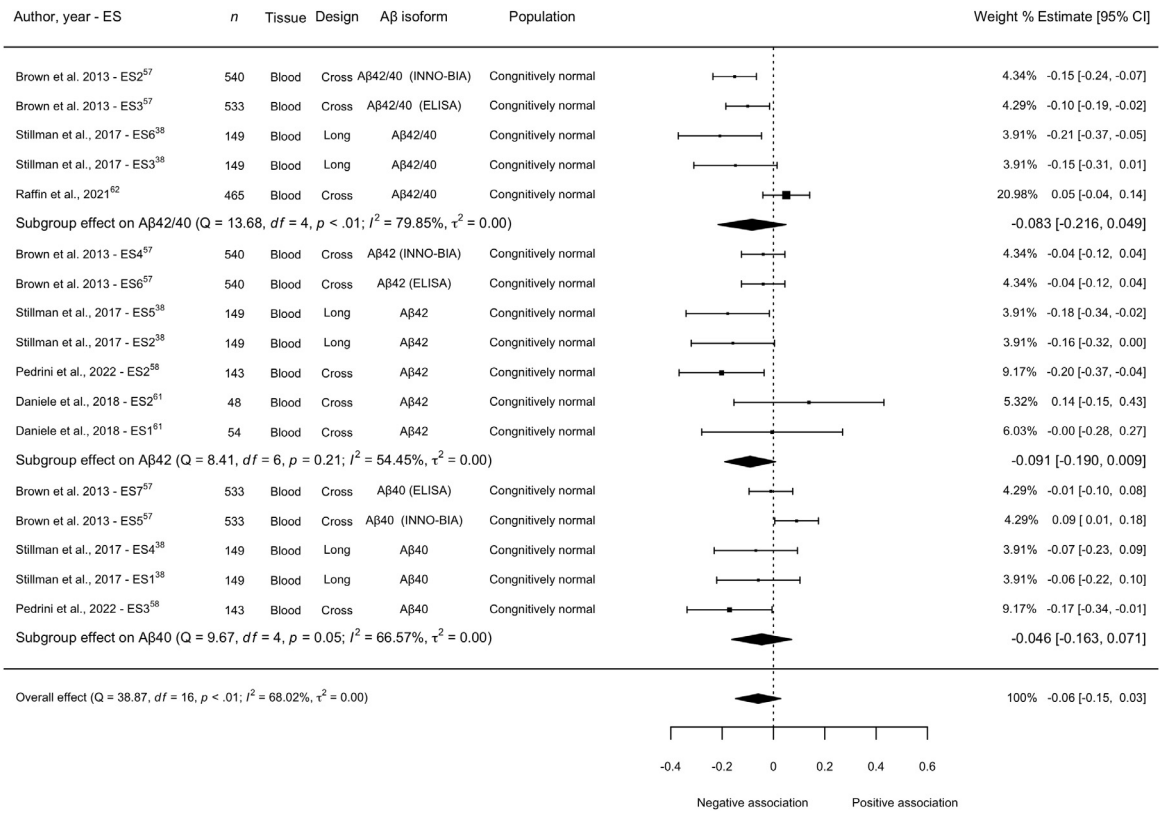

Fig. 5. Forest plot of pooled effect size and confidence intervals of observational studies exploring the association between physical activity and blood Aβ. 95%CI = 95% confidence interval; Aβ = amyloid beta; cross = cross-sectional studies; ES = effect sizes; ELISA = enzyme-linked immunoassay; long = longitudinal cohort studies; *Q* = the *Q* test is typically used to test the homogeneity of effect sizes as well as the impact of moderators; INNO-BIA = a commercial kit to assess Aβ (Innogenetics, Inc., Gent, Belgium).

analysis (Omnibus test of moderators = 8.44, $p = 0.88$) and brain (Omnibus test of moderators = 6.68, $p = 0.2$) analysis (see Fig. 6). We did not run moderation analyses by population in blood because all participants were cognitively normal. Lastly, we did not find evidence of publication bias based on visual observation of the funnel plots and Egger's tests (Supplementary Figs. 3−5).

4. Discussion

The main findings of this review suggest that exercise interventions of 12−52 weeks have a medium effect on blood Aβ levels in middle-aged and older adults. Notably, only a few studies were included in the meta-analysis, and the results were not statistically significant. Therefore, caution is needed in interpreting these findings. In addition, there were not enough studies in the literature to meta-analyze the effects of physical activity on the brain and CSF Aβ. In observational studies, the association of physical activity with brain and blood Aβ was not significant, but higher levels of physical activity were positively associated with Aβ in the CSF.

4.1. Meta-analysis of intervention studies: The effects of physical activity on Aβ

Our intervention meta-analysis identified that physical activity moderately reduces the levels of blood Aβ in middle-aged and older individuals. However, the results were not

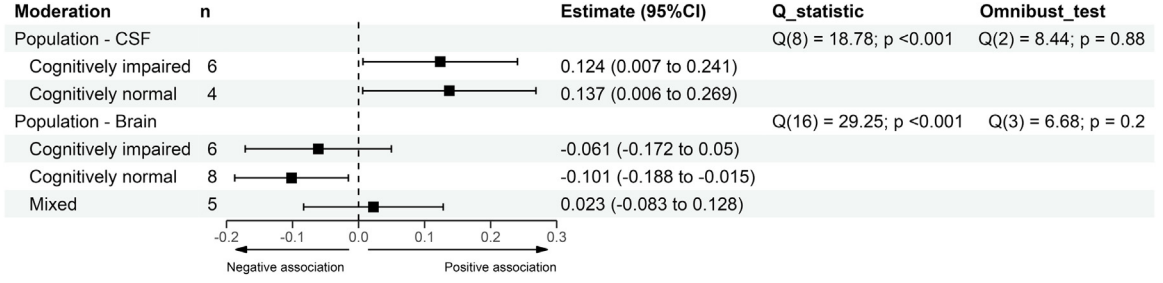

Fig. 6. Forest plot of moderation analysis of observational studies by population. All studies included in these analyses used the isoform Aβ42 when they assessed Aβ in the CSF. 95%CI = 95% confidence interval; Aβ = amyloid beta; CSF = cerebrospinal fluid. *Q* = the *Q* test is typically used to test the homogeneity of effect sizes as well as the impact of moderators.

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statistically significant, and the number of studies assessing Aβ only in the blood in the final meta-analyses was limited. The published results regarding the correlation of blood Aβ with brain and CSF Aβ are conflicting, and its effect on other AD biomarkers is still unclear.[8] Altogether these findings make it difficult to conclude whether physical activity could be a protective factor for AD through its effect on Aβ. We are not suggesting that physical activity does not positively affect cognitive health in older adults, just that there are other possible mechanisms, such as exercise-induced changes in the expression of neurotrophic factors and neurotransmitters, that might explain the protective role of physical activity in neurocognitive health during late adulthood.[63] Additionally, it is important to note that several questions remain unanswered at present. First, the effect of physical activity on Aβ might differ between cognitively normal and cognitively impaired people as well as in younger and older adults. In this regard, animal studies[19] suggest that physical activity might only be effective in reducing Aβ accumulation within an early preclinical stage. Accordingly, individuals who are already experiencing deterioration in cognitive function may be too advanced in the disease course for physical activity to modify Aβ deposition. However, in our meta-analysis, we were surprised to observe higher effects in older people, which is out of line with this hypothesis. Altogether, due to the contradictory findings, the heterogeneity between studies, and the low number of studies included in our meta-analysis, more intervention studies are needed to develop a full picture of the role of age and cognitive health status in the effects of physical activity on Aβ in both middle-aged and older adults. Second, the measurements of Aβ were heterogeneous (only a single study used brain Aβ,[14] one used CSF Aβ,[15] and 6 used blood Aβ[17,31–35]). Because of the heterogeneity between studies, only studies that assessed Aβ in the blood were included in the meta-analysis. Thus, additional well-designed RCTs with a standardized Aβ measurement protocol are needed to confirm or refute the effects of physical activity on brain, CSF, and blood Aβ levels in cognitively normal and cognitively impaired individuals. Third, the effects of physical activity on Aβ became significant and the total effect size increased when the study carried out by Kim et al.[33] (which assessed Aβ 30 min after the final session in the 16th week) was excluded from the meta-analysis. Consequently, future studies might explore the acute and chronic effects of physical activity on Aβ by standardizing the time interval between the final session of the physical activity intervention and the post-intervention Aβ assessment. Lastly, our meta-analysis also suggested the type of intervention (i.e., aerobic *vs*. others) might affect Aβ differently. Therefore, further studies might explore whether the effect of physical activity on Aβ varies by type of intervention.

*4.2. Meta-analyses of observational studies: The associations between physical activity and A*β

Meta-analyses of observational studies in middle-aged and older individuals indicated that physical activity was significantly associated only with CSF Aβ. However, these results should be interpreted with caution because most studies included in the meta-analyses were of a cross-sectional design. Of the 4 longitudinal cohort studies included in this systematic review, 2 were performed in cognitively normal older adults,[38,39] while the other 2 were carried out in individuals with mild cognitive impairment[40] or Down syndrome.[37] Notably, the 2 studies focused on individuals with cognitive impairments did not find any significant association.[37,40] A possible explanation for this could be that physical activity is less influential in individuals whose accumulation of Aβ in the brain reaches a certain threshold. Of note, longitudinal PET studies in humans have demonstrated that Aβ accumulates slowly and plateaus at the onset of clinical symptoms.[64–66] The plateau of Aβ may indicate that amyloid pathology reaches dynamic equilibrium or inactivity at the clinical stage of dementia. Although we observed a tendency in favor of this hypothesis, population characteristics of included studies (cognitively normal *vs*. cognitively impaired) did not moderate the relationship between physical activity and Aβ in our meta-analysis. Overall, further prospective population-based cohort studies are needed to provide greater insight on the longitudinal association between physical activity and Aβ by comparing (a) preclinical and clinical stages of AD, and (b) individuals of different ages and cognitive characteristics.

In addition to the participants' characteristics, other differences (e.g., the instrument used to assess Aβ measurements in the brain, CSF, or blood) might be considered. For instance, gold-standard measurements, such as PET, offer the most accurate way of evaluating the relationship between physical activity and brain Aβ levels antemortem. However, despite its advantages, PET scanning is not able to quantify small changes in brain Aβ, especially over short periods, which could partially explain the null associations.[67] In contrast, other Aβ biofluid markers in the CSF seem to be more sensitive and dynamic indicators of the relationship between physical activity and Aβ in human populations,[68] which could partially explain our findings. In addition to CSF and brain Aβ, there has been a growing interest in developing new techniques to measure blood Aβ due to its being a less expensive and invasive approach. However, until recently, most studies exploring the association between physical activity and blood Aβ have used ELISA kits, which showed high variability.[19] This issue might be attenuated by using high-performance blood-based Aβ assays, such as mass spectrometry.[4] Remarkably, differences were also found in the direction of the associations between physical activity and the various measurements of Aβ. Specifically, the relationship between physical activity and CSF Aβ was positive, which is contrary to what was expected in the brain. Although more accurate assays are needed to understand whether physical activity differentially modulates Aβ levels in the brain, CSF, or blood, previous studies showed that Aβ levels increase in AD when it is assessed in the brain with PET[69] and decrease when measured in the CSF.[70] One possible explanation for this is that aggregation of Aβ into plaques and greater retention of the peptide in the brain results in reduced diffusion of Aβ into the CSF. Lastly, although most studies suggest higher levels of brain

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and blood Aβ are predictive of AD, there are still some inconsistencies between studies.[8] Therefore, more replication within cohorts and more standardization with respect to analytical procedures focusing on Aβ are necessary to understand the relationship between physical activity and blood Aβ.

4.3. Literature gaps and future research

- There is a need to determine whether the effect of physical activity on Aβ varies by type, duration, intensity, or frequency of physical activity.
- Intervention studies might assess Aβ in the blood, the brain, and the CSF to explore whether the effect of exercise on Aβ might vary by type of tissue.
- Future intervention studies might compare the exercise group with a standardized non-active control group (e.g., participants who continued their usual routines) to avoid any effect-size bias.
- More large-scale multicenter intervention studies are needed to test the effectiveness of physical activity for modulating Aβ levels.
- Long-term physical activity interventions are needed to more definitively test the effect of physical activity on PET-quantified brain Aβ. For CSF and blood Aβ, the use of high-performance blood-based Aβ assays is needed to reduce the variability in previous studies.
- Future interventions should standardize the time interval between the final session of the intervention and the brain, blood, and CSF Aβ post-intervention assessment since results may differ (e.g., positive or negative direction) when assessing Aβ in acute *vs*. chronic conditions.
- Longitudinal population-based studies are needed to explore the long-term associations between physical activity and Aβ, and to compare the general population with preclinical and clinical stages of AD.
- Due to the possibility of bi-directionality, longitudinal cohort studies with physical activity and Aβ data at 2 time points are needed to determine the possibility of reverse causality.
- More studies are needed to disambiguate populations most affected by physical activity as well as set the key stages for appreciating Aβ changes (e.g., cognitively normal *vs*. cognitively impaired).
- In addition to the Aβ path, more research is needed to unravel the potential mechanisms linking physical activity with cognition in the elderly.

4.4. Limitations and strengths

Our review has some limitations. First, there were not sufficient studies in each population (i.e., cognitively normal and cognitively impaired) to identify individuals most affected by physical activity. Second, we could not explore the moderating roles of several variables that might have influenced the meta-analytic results (e.g., Apolipoprotein E (APOE) genotype). Third, our search was limited to middle-aged and older adults. Since amyloid deposition can occur in an earlier stage of life,[71] future studies can include younger populations to explore whether physical activity might affect Aβ differently in earlier stages of life. Lastly, given the scarcity of studies in the meta-analysis, future RCTs on this topic are needed.

This systematic review also has some strengths. First, it follows the PRISMA guidelines for systematic review methodology. Second, we registered the study in PROSPERO databases before starting the specific search. Third, we organized a list of excluded articles and the reasons for exclusion. Finally, we included different databases and all types of study designs.

5. Conclusion

Research in the field of cognitive aging has attempted to understand the reasons for individual variability in cognitive decline. This body of work is highly convinced that physical activity affects cognitive and brain health outcomes.[72] However, more research is needed to understand how physical activity shapes the aging brain.[72] In this context, the present systematic review suggests physical activity might moderately reduce blood Aβ, which is one possible mechanism for delivering the benefits of physical activity, in older people. However, since the results neared but did not reach statistical significance, they should be interpreted with caution, especially given the methodological limitations observed in some of the included studies. Moreover, increased physical activity was associated with higher levels of Aβ only when it was assessed in the CSF. Overall, due to the small number of intervention studies included in the meta-analysis, and to the equivocal findings provided by the observational studies, more studies are needed to understand the role of physical activity in modulating brain, CSF, and blood Aβ levels, as well as the implications for cognitive health. Additionally, future studies should continue exploring the potential mechanisms responsible for the positive effects of physical activity on cognition to spur the development of more effective interventions and stimulate the identification of cost-efficient alternative therapies for preventing and treating AD. Finally, although our systematic review and meta-analysis cannot provide direct clinical practice changes, we identified gaps in the literature as well as future perspectives that might guide new research directions in the cognitive aging field.

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Authors' contributions

MRA participated in the design/conception, data analysis, interpretation, manuscript preparation, and revision; PSU participated in the design, data analysis, interpretation, and manuscript revision; CAÁ participated in the design, data analysis, and manuscript preparation; PMG participated in the data analysis, interpretation, and manuscript preparation and revision; MÁO participated in the data analysis; CMH participated in the data analysis; manuscript preparation, and revision; MGR, BB, and KIE participated in the interpretation and manuscript revision; IEC participated in the design/conception, data analysis, interpretation, manuscript preparation, and revision. All authors agreed to be accountable for all aspects of the work, contributed to the manuscript writing. All authors have read and approved the final version of the manuscript, and agree with the order of presentation of the authors.

Competing interests

The authors declare that they have no competing interests.

Supplementary materials

Supplementary materials associated with this article can be found in the online version at doi:10.1016/j.jshs.2023.08.001.

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