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RESEARCH ARTICLE

Physical activity, biomarkers of brain pathologies and dementia risk: Results from the Memento clinical cohort

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Abstract

INTRODUCTION: This study aims to examine whether physical activity moderates the association between biomarkers of brain pathologies and dementia risk.

METHODS: From the Memento cohort, we analyzed 1044 patients with mild cognitive impairment, aged 60 and older. Self-reported physical activity was assessed using the International Physical Activity Questionnaire. Biomarkers of brain pathologies com-

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prised medial temporal lobe atrophy (MTA), white matter lesions, and plasma amyloid beta (Aβ)42/40 and phosphorylated tau181. Association between physical activity and risk of developing dementia over 5 years of follow-up, and interactions with biomarkers of brain pathologies were tested.

RESULTS: Physical activity moderated the association between MTA and plasma Aβ42/40 level and increased dementia risk. Compared to participants with low physical activity, associations of both MTA and plasma Aβ42/40 on dementia risk were attenuated in participants with high physical activity.

DISCUSSION: Although reverse causality cannot be excluded, this work suggests that physical activity may contribute to cognitive reserve.

KEYWORDS
brain changes, cognitive reserve, dementia, physical activity

Highlights

- Physical activity is an interesting modifiable target for dementia prevention.
- Physical activity may moderate the impact of brain pathology on dementia risk.
- Medial temporal lobe atrophy and plasma amyloid beta 42/40 ratio were associated with increased dementia risk especially in those with low level of physical activity.

1 | BACKGROUND

With the rapid aging of the population, a growing number of individuals will be at risk of developing neurodegenerative diseases.[1] In the absence of effective treatments against dementia, identifying protective factors of cognitive decline that could therefore delay dementia onset is of utmost importance. Physical activity represents an interesting modifiable target for prevention strategies, and intervention could be implemented in the elderly population. Indeed, in addition to its global benefits for health,[2–4] a high level of physical activities may lower dementia risk and attenuate cognitive decline, even at older ages.[5–8] Interestingly, it has also been shown that higher levels of physical activity are related to better cognitive performance among individuals at higher risk of dementia such as individuals with mild cognitive impairment (MCI).[9–11] Therefore, physical activity should also be explored as a potential target for delaying conversion to dementia in symptomatic older persons with MCI.

Brain pathologic changes, such as small vessel disease, Alzheimer's disease (AD) neuropathology (amyloid plaques and neurofibrillary tangles), and brain atrophy can develop decades prior to dementia diagnosis, and accelerate its clinical onset. There is growing evidence that older adults being physically more active may preserve longer their brain health assessed with brain volume, cortical thickness, or functional activity.[12–14] A few studies have also reported reduced AD pathology or lower load of cerebrovascular disease with higher physical activity.[15–18] However, whether physical activity may contribute to cognitive reserve and modify the negative impact of these brain changes on dementia risk remains unclear, especially for individuals already experiencing some cognitive impairment.[19] Cognitive reserve is a concept referring to the ability to maintain adequate cognitive functions despite development of brain pathologies.[20] Individuals with higher cognitive reserve may thus be able to compensate for the negative effects of brain pathologies. A factor contributing to cognitive reserve will moderate the impact of brain pathologies on cognitive decline.[21] Some studies, mainly among cognitively normal individuals, have reported that physical activity moderates the association between some brain pathologies (AD pathology, cerebrovascular injury, or brain atrophy) and cognitive function or decline, which is consistent with the concept of cognitive reserve.[20,22–27] However, results from some other studies did not support the contribution of physical activity to cognitive reserve.[22,25,28,29] Inconsistent findings across studies can be explained by selection biases (various sample sizes, convenience sampling, and different study settings) as well as lack of comparability of selected biomarkers of brain pathologies. Moreover, most previous studies were conducted among cognitively healthy older adults, and whether similar relationships are present in cognitively impaired persons, such as MCI participants, remains uncertain. Evidencing a moderating effect of physical activity on brain pathologies over conversion from MCI to dementia would be of interest to delay symptom worsening for individuals at higher risk of dementia.

For this work, we thus aimed to investigate the contribution of physical activity to cognitive reserve among consecutively enrolled MCI patients followed over up to 5 years from a large clinical cohort. In particular, we assessed the moderating effect of physical activity on the association between selected magnetic resonance imaging (MRI) and plasma biomarkers of brain pathology and conversion to dementia.

2 | METHODS

2.1 | Study population

The Memento cohort is a prospective clinic-based study aiming to better understand the natural history of AD and related disorders. Details of the study have been previously published.[30] Briefly, 2323 participants consulting within 26 French memory clinics and presenting with either isolated cognitive complaints or recently diagnosed MCI were recruited from April 2011 to June 2014. Clinical MCI was defined as having a Clinical Dementia Rating (CDR) = 0.5. Participants were examined at baseline and followed every 6 to 12 months up to 5 years. Baseline data collection during face-to-face interview included socio-demographic characteristics, lifestyle factors, neurological and physical examination, and a full neuropsychological battery. Baseline brain MRI was mandatory for Memento participants but only 2183 had an MRI due to either post-consent refusal or contraindication. Of the 2183, 86% of participants included in the Memento cohort had a 3.0 Tesla MRI scan (1.5 Tesla for the others). Plasma samples were also obtained at baseline for all participants.

Among the 2323 Memento participants, 1194 participants were ≥ 60 years and had clinical MCI at baseline. We then excluded those without follow-up (n = 15), as well as participants with missing physical activity status at baseline (n = 135), leaving a final analytical sample of 1044 participants.

2.2 | Physical activity definition

Physical activity data were collected using the short version of the International Physical Activity Questionnaire (IPAQ).[31] It consists of seven questions self-assessing intensity of physical activity (vigorous, moderate, and walking) that people had been doing as part of their daily lives over the past 7 days. It estimates total physical activity in metabolic equivalent of task (MET)-minutes/week by multiplying the number of minutes dedicated to each activity class over a week by the specific MET score for that activity (walking = 3.3 METs, moderate = 4.0 METs, and vigorous = 8.0 METs). In addition, physical activity was also categorized as low, moderate, and high according to the IPAQ scoring protocol[32]: (1) high intensity was defined as engaging in either vigorous intensity activity on at least 3 days achieving a minimum total physical activity of at least 1500 MET minutes a week, or 7 or more days of any combination of walking, moderate intensity, or vigorous intensity activities achieving a minimum total physical activity of at least 3000 MET minutes a week; (2) moderate intensity was defined as engaging in either 3 or more days of vigorous intensity activity and/or walking of at least 30 minutes per day, or 5 or more days of moderate intensity activity and/or walking of at least 30 minutes per day, or 5 or more days of any combination of walking, moderate intensity, or vigorous intensity activities achieving a minimum total physical activity of at least 600 MET minutes a week; (3) participants who did not meet the above criteria were classified as having low level of physical activity.

RESEARCH IN CONTEXT

1. **Systematic Review**: We searched PubMed for all articles investigating the interactions between physical activity and biomarkers of Alzheimer's disease and related dementias in relation to dementia risk or cognitive function or decline published up to October 1, 2022. Few studies investigated the moderating effect of physical activity on the associations between markers of brain pathology and dementia risk.
2. **Interpretation**: In this prospective clinic-based cohort of participants with mild cognitive impairment (MCI), physical activity modified the association with dementia risk of both medial temporal lobe atrophy (MTA) and plasma amyloid beta (Aβ)42/40 ratio. Indeed, strengths of the associations between MTA and plasma Aβ42/40 ratio and dementia risk were attenuated for participants with higher levels of physical activity.
3. **Future Directions**: Physical activity in late life may be an interesting modifiable target to reduce the negative impact of brain pathology on conversion from MCI to dementia.

2.3 | Neuroimaging biomarkers of brain pathology

All neuroimaging acquisitions and analyses were coordinated by the Center for Acquisition and Treatment of Images (CATI; cati-neuroimaging.com), a platform dedicated to the management of multicenter neuroimaging studies.[33] Scans were harmonized across centers, centralized, quality checked, and postprocessed to obtain standardized acquisitions. Medial temporal lobe atrophy (MTA) was rated visually by two trained physicians from the CATI team, using Scheltens' scale.[34] MTA was dichotomized according to validated cut-offs: high MTA was defined as a Scheltens' scale score of 2 in either of the two hemispheres in individuals < 75 years, or a MTA score of 3 in individuals aged ≥ 75 years.[35] White matter lesion (WML) severity was also rated by visual assessment of whole brain deep and periventricular lesions done centrally by two trained raters using the Fazekas scale.[36,37] A score of 0 to 3 was assigned separately to periventricular and subcortical WML (sum 0–6), and severe WML was defined as a Fazekas sum score of 4 to 6.

We investigated baseline measurement of MTA as a marker of hippocampal atrophy, a key structure in AD-related neurodegeneration, and WML as a marker of small vessel disease.

2.4 | Plasma biomarkers of brain pathology

Plasma amyloid beta (Aβ)42, Aβ40, phosphorylated tau 181 (p-tau181) concentrations were measured using Simoa technology with

commercial kits on a Quanterix HD-1 analyzer. Measures were performed in the same laboratory for all participants (Bordeaux University Hospital), blinded of clinical outcomes. Plasma Aβ42/40 ratio and p-tau181 were used as markers of amyloid and tau pathology, respectively.

2.5 | Outcome definition

During a 5-year follow-up period, patients underwent a clinical and neurologic evaluation every 6 to 12 months. Incident cases of dementia were then assessed by trained neurologist according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Revision (DSM-IV) criteria. AD dementia was ascertained using criteria from the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA). In addition, all dementia cases were reviewed and validated by an independent endpoint review committee composed of expert neurologists/geriatricians based on individuals' case files.

2.6 | Additional covariables

Education level was categorized as lower versus higher than high school level. Apolipoprotein E (*APOE*) ε4 status was defined as at least one ε4 allele carried versus none. Smoking status, as well as diabetes status and cardiovascular disease history, were self-reported at baseline. Hypertension was defined as either arterial pressure ≥ 140/90 mmHg or antihypertensive drug use. Body mass index (BMI) was objectively measured at baseline examination.

2.7 | Statistical analysis

Participants' characteristics at baseline were compared across physical activity levels using Kruskal–Wallis and $\chi 2$ tests, as appropriate. Associations between physical activity and each marker of brain pathology were tested using logistic regression for MTA and severe WML, and linear regression for plasma Aβ42/40 ratio and p-tau181 level, adjusted for age at baseline, sex, *APOE* ε4 status, education level, hypertension, and BMI.

To estimate dementia risks associated with physical activity, we performed Cox models with delay between study entry and event or censoring being the time scale. Participants who remained free of dementia were censored at the age of their last known dementia-free visit or at age of death. Aβ42/40 ratio was reverse coded so that higher levels represented greater amyloid pathology. Aβ42/40 ratio and p-tau181 were log-transformed and standardized. First, we evaluated the association between physical activity intensity (modeled either as log-transformed MET-minutes/week, or as categorical physical activity levels [low, moderate, and vigorous]) and dementia risk, without or with adjustments for the four different markers of brain pathologies. These models were additionally adjusted for age at baseline, sex, *APOE* ε4 status, education level, hypertension, and BMI.

Then, we generated dementia incidence rates according to levels of physical activity and of each marker of brain pathology using Poisson models adjusted for age at baseline, sex, *APOE* ε4 status, education level, hypertension, and BMI. For continuous plasmatic biomarkers, incidence rates are presented for both low and high (+/− 1 standard deviation [SD]) pathology (Aβ42/40 or p-tau181).

Moreover, interactions between physical activity levels and biomarkers of brain pathologies on dementia risks were added and tested within the initial Cox models (also adjusted for age at baseline, sex, *APOE* ε4 status, education level, hypertension, and BMI) to investigate the moderating effect of physical activity. Hazard ratios of the associations between each biomarker and dementia risk were presented for the three levels of physical activity. Similar models were performed with AD dementia as the outcome (non-AD dementia cases were censored at the end of the follow-up). In a post hoc analysis, we also tested whether the moderating effect of physical activity differed by biological sex.

Sensitivity analyses were performed to assess the robustness of our findings. The main results reported were based on a complete case analysis under the assumption that missing data for biomarkers and covariates ($n = 134$) were missing completely at random (MCAR). Multiple imputation by chained equations with a fully conditional specification (20 imputed data sets) was used to impute missing data to assess the plausibility of the MCAR assumption. Then, an alternative categorization for physical activity was used based on guidelines for physical activity, with a cut-off of at least 500 MET-minutes/week considered high physical activity. Finally, as plasma AD biomarker variability depend on kidney disease function,[38] all models that included AD blood biomarkers either as exposure of interest or as potential confounder were adjusted for the glomerular filtration rate (using the Chronic Kidney Disease Epidemiology Collaboration definition).

Analyses were conducted using R (version 4.1.3).

3 | RESULTS

Analytical sample characteristics are presented in Table 1. Participants were 72.7 years old on average, and more often women (59%). Half of the participants had a high education level, and 30% were *APOE* ε4 carriers. Compared to participants with low physical activity, those with moderate and high physical activity were more often *APOE* ε4 carriers, had higher education level, less often had hypertension, and had a lower BMI on average. Table S1 in supporting information shows associations between physical activity and biomarkers of brain pathologies. Globally, we found no differences according to physical activity, with only a trend toward less severe WML and higher levels of p-tau181 with higher levels of physical activity. Participants with missing biomarkers or covariates had higher levels of plasma amyloid pathology and less often severe WML (Table S2 in supporting information).

TABLE 1 Description of population characteristics according to physical activity levels, the Memento cohort.

	Total *N* = 1044	Low *N* = 199	Moderate *N* = 422	High *N* = 423	*P*-value
Female	616 (59.0)	131 (65.8)	247 (58.5)	238 (56.3)	0.07
Age at baseline	72.7 (6.9)	73.1 (7.5)	73.0 (6.7)	72.1 (6.6)	0.09
APOE ε4 carriers	317 (30.4)	50 (26.3)	120 (30.0)	147 (36.7)	0.02
High education level	521 (49.9)	84 (42.2)	216 (51.2)	221 (52.2)	0.05
Smoker	74 (7.1)	17 (8.5)	31 (7.4)	26 (6.1)	0.53
Diabetes	129 (12.4)	32 (16.1)	45 (10.7)	52 (12.3)	0.16
Hypertension	657 (62.9)	139 (70.9)	271(65.5)	247 (59.5)	0.02
CVD history	164 (15.7)	32 (16.1)	77 (18.2)	55 (13.0)	0.11
BMI	25.6 (4.3)	26.8 (4.8)	25.6 (4.5)	25.0 (3.7)	<0.01
MET-minute/week	2373 [1052–4568]	495 [244–884]	1646 [1074–2313]	5040 [3906–7383]	<0.01
Aβ42/40 ratio	0.05 [0.05–0.06]	0.06 [0.05–0.06]	0.06 [0.05–0.06]	0.06 [0.05–0.06]	0.60
P-tau181	0.95 [0.60–1.45]	0.91 [0.57–1.38]	0.95 [0.60–1.45]	0.98 [0.64–1.50]	0.31
High MTA	208 (19.9)	35 (18.4)	76 (18.7)	97 (23.9)	0.13
Severe WML	292 (28.0)	58 (29.1)	126 (29.9)	108 (25.5)	0.34

Note: Categorical variable: N (%) ; Continuous variable: mean (sd) or median [IQR] as appropriate. (Missing data: APOE-ε4 = 53, Smoker = 1, Hypertension = 19, BMI = 13, Aβ4240 ratio = 28, P-tau181 = 17, MTA = 42).
Abbreviations: Aβ, amyloid beta; *APOE*, apolipoprotein E; BMI, body mass index; CVD, cardiovascular disease; MCI, mild cognitive impairment; MET, metabolic equivalent of task; MTA, medial temporal lobe atrophy; p-tau181, phosphorylated tau; WML, white matter lesions.

TABLE 2 Associations between baseline physical activity and dementia (all and Alzheimer's disease) risks over 5-year follow-up.

	All dementia		Alzheimer's disease dementia	
N = 910[a]	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
Model 1				
Physical activity (per 1 log MET increase)	0.90 (0.82–0.98)	0.02	0.92 (0.83–1.02)	0.13
Physical activity				
Moderate versus low	0.72 (0.49–1.06)	0.09	0.75 (0.49–1.16)	0.20
High versus low	0.75 (0.51–1.10)	0.14	0.85 (0.56–1.31)	0.46
Model 2				
Physical activity (per 1 log MET increase)	0.83 (0.76–0.92)	0.0002	0.85 (0.7–0.95)	0.003
Physical activity				
Moderate versus low	0.64 (0.44–0.94)	0.02	0.67 (0.43–1.03)	0.07
High versus low	0.58 (0.39–0.86)	0.007	0.66 (0.42–1.02)	0.06

Note: Model 1: adjusted for age at baseline, sex, education level, *APOE* ε4 status, hypertension, and BMI. Model 2: Model 1 + additionally adjusted for markers of brain changes (medial temporal lobe atrophy, white matter lesions, and plasma levels of Aβ42/40 ratio and p-tau181).
[a]A total of 134 had missing data (*APOE* ε4 = 53, hypertension = 19, BMI = 13, Aβ4240 ratio = 28, p-tau181 = 17, MTA = 42).
Abbreviations: Aβ, amyloid beta; *APOE*, apolipoprotein E; BMI, body mass index; CI, confidence interval; HR, hazard ratio; MET, metabolic equivalent of task; MTA, medial temporal lobe atrophy; p-tau181, phosphorylated tau.

Over the 5-year follow-up, 202 dementia cases were diagnosed. Increasing physical activity (measured as continuous) was associated with lower risk of dementia, without (hazard ratio [HR] for 1 log MET-minute/week = 0.90 [95% confidence interval (CI): 0.82–0.98]) and with (HR = 0.83 [95% CI: 0.76–0.92]) adjustment for markers of brain pathologies (Table 2). Similarly, when studying physical activity as categorical exposure, compared to low physical activity, moderate and high physical activity tended to be associated with decreased dementia risk, although the association did not reach statistical significance (HR = 0.72 [95% CI: 0.49–1.06] and HR = 0.75 [95% CI: 0.51–1.10], respectively). After further adjustment for markers of brain pathologies, compared to low physical activity, the HRs for dementia declined and became statistically significant toward protective association (HR = 0.64 [95% CI: 0.44–0.94] for moderate physical activity

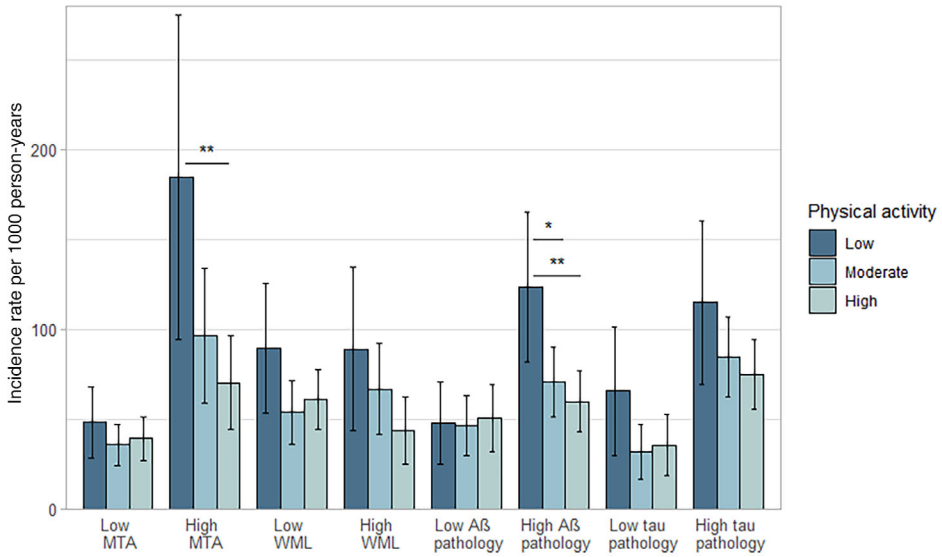

FIGURE 1 Incidence rates of dementia per 1000 person-years according to physical activity and markers of cerebral lesion status. Aβ, amyloid beta; MTA, medial temporal lobe atrophy; WML, white matter lesions.

and HR = 0.58 [95% CI: 0.39–0.86] for high physical activity). Strengths of the associations between moderate physical activity and risk of AD dementia were similar to the ones of dementia risk, while associations between high physical activity and AD dementia risk were weaker (Table 2).

Incidence rates of dementia per 1000 person-years according to physical activity level and to biomarkers of brain pathologies are displayed in Figure 1. We observe a trend for decreased incidence rates of dementia with increasing levels of physical activity, more marked in participants with higher levels of brain pathology. For high MTA and Aβ pathology, incidence rates of dementia were statistically significantly lower in people with high physical activity compared to those with low physical activity.

The study of the interactions between physical activity levels and biomarkers of brain pathologies on dementia risk are displayed in Table 3. In the group of participants with high level of physical activity, dementia risks associated with MTA and plasma Aβ42/40 ratio were statistically significantly weaker compared to the corresponding risks in the group of participants with low physical activity. As physical activity level increases, associations between MTA or amyloid pathology and dementia risk decreased. For instance, for an increase of 1 SD of Aβ42/40 ratio level (reverse coded; i.e., higher pathology levels), HRs for dementia were 1.64 (95% CI: 1.33–2.03) in persons with low physical activity compared to 1.23 (95% CI: 1.03–1.46) in persons with moderate physical activity and 1.09 (95% CI: 0.88–1.33) in persons with high physical activity. There were no statistically significant interactions between severe WML or plasma p-tau181 and physical activity on dementia risk. Regarding AD dementia, physical activity moderated the association between dementia risk and plasma Aβ42/40 (but not MTA). In addition, biological sex interacted with physical activity to moderate the associations between MTA or Aβ42/40 ratio and dementia risk, but not severe WML or p-tau181 level. MTA and Aβ42/40 ratio were more strongly associated with dementia risk in men compared to women. The moderating effect of physical activity on the association between MTA or Aβ42/40 ratio and dementia risk appeared to be stronger among men than women (Table S3 in supporting information).

Results from sensitivity analyses showed that our results were consistent both after imputing missing data under missing at random scenario and after adjusting for renal function (Table S4 in supporting information). When using a binary categorization of IPAQ (at least 500 MET-minutes/week: yes vs. no) based on physical activity recommendations, the moderating impact of higher physical activity on the association between MTA and dementia risk was attenuated whereas the moderating effect on other brain biomarkers was fairly consistent (Table S5 in supporting information).

4 | DISCUSSION

In this prospective study of MCI patients, higher physical activity levels were associated with reduced risks of developing dementia when controlling for biomarkers of brain pathologies. In addition, physical activity moderated the relationship between biomarkers of both neurodegeneration and amyloid pathology and risk of dementia, leading to attenuated associations of both MTA and plasma Aβ42/40 ratio level with dementia risk for participants with the highest level of physical activity. We did not show evidence of a moderating effect of physical activity on the association between biomarkers of WML or tau pathologies on dementia risk. These results suggest that greater engagement in physical activity may contribute to cognitive reserve in specific ways and delay dementia onset in symptomatic older adults.

With the increasing prevalence of dementia, research focusing on modifiable factors promoting resilience, even for individuals at higher risk, is necessary to attempt to reduce the global burden related to dementia. Our findings are somewhat consistent with the rich literature suggesting a protective effect of physical activity on dementia

TABLE 3 Associations between biomarkers of brain pathologies and risk of dementia stratified by levels of physical activity.

	Low PA *N* = 178 HR (95% CI)	Moderate PA *N* = 365 HR (95% CI)	High PA *N* = 367 HR (95% CI)	Moderate versus low *P*-value*	High versus low *P*-value*
All dementia					
Medial temporal lobe atrophy	4.48 (2.40–8.33)	2.90 (1.79–4.67)	1.85 (1.18–2.90)	0.28	0.02
Severe white matter lesions	1.01 (0.53–1.90)	1.26 (0.65–2.47)	0.71 (0.44–1.16)	0.56	0.39
Aβ42/40 ratio	1.64 (1.33–2.03)	1.23 (1.03–1.46)	1.09 (0.88–1.33)	0.04	0.007
P-tau181	1.33 (0.95–1.85)	1.64 (1.29–2.10)	1.46 (1.14–1.88)	0.31	0.64
Alzheimer's disease dementia					
Medial temporal lobe atrophy	3.21 (1.54–6.71)	3.87 (2.29–6.54)	1.87 (1.15–3.04)	0.69	0.23
Severe white matter lesions	0.84 (0.40–1.76)	1.36 (0.80–2.30)	0.68 (0.40–1.15)	0.29	0.63
Aβ42/40 ratio	1.71 (1.35–2.17)	1.19 (0.97–1.46)	1.11 (0.89–1.46)	0.02	0.008
P-tau181	1.82 (1.23–2.69)	1.71 (1.30–2.26)	1.42 (1.08–1.86)	0.81	0.31

Note: Models adjusted for age at baseline, sex, education level, *APOE* ε4 status, hypertension, BMI, and the three other markers of brain changes. MTA and WML are visually rated from MRI (Scheltens and Fazekas scales respectively), while Aβ42/40 ratio and p-tau181 levels are plasma measures. Plasma Aβ42/40 ratio was reverse coded so that higher levels represented greater amyloid pathology. Plasma Aβ42/40 ratio and p-tau181 were standardized and units correspond to 1 SD increase. HR for MTA and severe WML are presented for presence versus absence, while HR for plasma Aβ42/40 ratio and p-tau181 are presented for 1 SD increase.

**P*-values of the interactions between physical activity and each biomarker.

Abbreviations: Aβ, amyloid beta; *APOE*, apolipoprotein E; BMI, body mass index; CI, confidence interval; HR, hazard ratio; MET, metabolic equivalent of task; MRI, magnetic resonance imaging; PA, physical activity; MTA, medial temporal lobe atrophy; p-tau181, phosphorylated tau; SD, standard deviation; WML, white matter lesions.

risk.[5,39] These results also add knowledge on the impact of physical activity on the conversion from MCI to dementia.[9,40,41] They also complement evidence showing better cognitive and functional outcomes following exercise interventions among dementia patients.[42,43] Yet, we did not evidence relationships between physical activity and brain pathologies consistent across the markers investigated. These results do not support the hypothesis that physical activity reduces dementia risk by preventing or delaying brain changes related to dementia development. This hypothesis would still need to be tested further in a setting in which the associations between physical activity and brain pathologies can be studied longitudinally.

Neuropathological and neuroimaging studies have suggested that many people may tolerate considerable cerebral changes without expressing clinical symptoms, consistent with the cognitive reserve concept.[20] Our results support this body of literature, as participants with higher physical activity experienced lower dementia risk while presenting with similar levels of brain pathologies. Cognitive reserve can be influenced by the interaction of innate individual differences and lifetime exposures such as lifestyle factors. The biological mechanisms underlying cognitive reserve lie in the adaptability of functional brain processes. Physical activity, by contributing to cognitive reserve, may allow physically active individuals with MCI to compensate, through increased synaptogenesis, for the negative effect of amyloid pathology and atrophy in the brain, thus tolerating more damage before developing cognitive impairment.[19] Late-life physical activity may also enhance efficiency, capacity, or flexibility of brain networks when performing cognitive functions.[44]

To appropriately investigate cognitive reserve mechanisms, a cognitive reserve–related factor, a brain measure, and a cognitive measure are required.[21] Up to date, only a few studies have explored the contribution of physical activity to cognitive reserve while accounting for brain pathology.[22,24–26,28,29,45] They yielded heterogeneous findings. Our work evidenced weaker associations of MTA and plasma Aβ42/40 ratio level with dementia risk across increasing levels of physical activity. Two studies from the Chicago Health and Aging Project showed a non-significant trend toward slower cognitive decline with higher physical activity, even for participants with high levels of serum neurofilament light chain and total tau.[25,26] Another study reported that greater engagement in physical activity was protective against Aβ-related cognitive decline and neurodegeneration in 182 asymptomatic older adults.[24] In addition, from the Rush Memory and Aging Project study that used objectively measured physical activity, it was reported that within-person increase in physical activity attenuated the association between AD pathology and cognition.[27] Unlike our results, two other studies reported a moderating effect of physical activity on the associations of white matter hyperintensities with cognition.[22,46] Memel et al. also reported that baseline physical activity attenuated the association between cerebrovascular pathology and cognition.[27] The absence of an interaction between physical activity and severe WML in our work may be due to characteristics of our study sample, as severe WML were not significantly associated with higher dementia risk in our study. However, two studies did not show an association between physical activity and markers of cognitive reserve using a residual approach for cognitive reserve.[28,29] In addition, although physical activity was associated with better cognition after controlling for different brain pathologies, Buchman et al. did not evidence that a more active lifestyle modified the associations of brain pathologies with cognitive function proximate to death.[45] Only a few studies

investigated the moderating effect of physical activity on tau pathology with dementia risk or cognition. The absence of interaction we found may be due to the fact that individuals with high tau pathology may be too advanced in the disease process to benefit from physical activity's effects. In addition, only a few studies have looked at tau pathology and cognitive reserve;[47,48] thus, future studies are needed to validate our results. Taken together, our results and others' support the hypothesis that different lifestyle factors may only moderate specific, but not all, markers of brain pathologies on cognition.

In addition to the type of pathology, both physical activity measurement and population characteristics may contribute to differences in results. Most studies investigating the contribution of physical activity to cognitive reserve used self-reported physical activity measures assessed through standardized questionnaires, which may be unreliable. However, questionnaires allow us to collect information on physical activity intensity and frequency. In our work, moderate physical activity was associated with a lower risk of dementia after adjustment for brain pathologies, but it was not significantly moderating the association between MTA and dementia risk. It seems that only higher levels of physical activity are required to significantly mitigate the negative association between brain atrophy and dementia risk. A few studies also used objective measures through pedometers or accelerometers, yet assessed physical activity over a limited period of time.[24,27,45] Finally, regarding population characteristics, most studies were realized among population-based clinically normal older adults. This work thus extends previous findings to persons with MCI who are at risk of developing dementia. Moreover, our results suggest that physical activity may contribute to cognitive reserve more strongly in men than in women, potentially due to stronger associations between biomarkers of brain pathologies and dementia risk among men in the Memento cohort. Additional studies are required to confirm these sex differences.

This study has some limitations. First, physical activity exposure was self-reported at baseline, thus misclassification may have occurred and could have conferred to biased results. Moreover, low engagement in physical activity may be due to reverse causation, that is, people may become less physically active during the years preceding dementia onset, and biomarkers of brain pathologies were only measured once at baseline, thus causal interpretations must be drawn with caution. In addition, our physical activity questionnaire allowed us to assess physical activity within the past 7 days. Although this issue is common in studies assessing physical activity, it may not be representative of long-term physical activity habits. Participants excluded due to missingness had higher plasma amyloid levels and less severe WML; thus, our results may be specific to our study population. The sensitivity analysis using multiple imputation to account for selection yielded similar results, suggesting that the characteristics of the excluded participants in this study did not influence the moderation results. Finally, we used plasmatic markers of AD-related cerebral lesions, which may be less reliable than positron emission tomography or cerebrospinal fluid amyloid/tau markers. Still, plasmatic markers have been shown to associate with AD-related pathology and dementia risk[49] and our sensitivity analysis accounting for renal function yielded consistent results. In addition, the Simoa platform was used for plasma AD biomarker quantification. It would be interesting to further assess the robustness of our results using alternative quantification of plasma AD biomarkers such as mass spectrometry-based methods that have been suggested to be stronger predictors of amyloid positivity.[50] It should also be noted that plasma biomarkers were not measured in duplicate. Nevertheless, several controls of reproducibility were realized on subsets throughout the study, leading to very satisfactory results.

This study also has important strengths and contributes to our understanding of the influence of physical activity with dementia risk. The Memento study provides an adequate setting to investigate, within a large sample size, the contribution of physical activity to cognitive reserve, due to the large availability of various neuroimaging and plasmatic AD-related markers. Additionally, this work relies on well-defined dementia cases, as each case was reviewed by a validation committee. Although self-reported, physical activity was assessed by a standardized and validated questionnaire, allowing us to investigate different levels of activity.

In conclusion, this work suggests that, in persons with MCI, higher levels of physical activity may attenuate the impact of cerebral atrophy and amyloid pathology on the risk of developing dementia. These results suggest potential pathways for modifying the effect of amyloid pathology and cerebral atrophy on cognition and dementia. They also suggest that promoting engagement in physical activity in persons at risk of developing dementia could delay dementia onset. Future studies adding longitudinal measures of markers of brain pathologies are needed to confirm the mechanisms involved in the association between physical activity and dementia.

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CONFLICT OF INTEREST STATEMENT

The authors have nothing to report. Author disclosures are available in the supporting information.

CONSENT STATEMENT

All participants provided written informed consent.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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APPENDIX

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