Journal of the International Neuropsychological Society (2015), **21**, 861–867.

doi:10.1017/S1355617715000831

Physical Activity as Protective Factor against Dementia: A Prospective Population-Based Study (NEDICES)

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(RECEIVED April 2, 2015; FINAL REVISION July 22, 2015; ACCEPTED August 25, 2015)

Abstract

The aim of this study was to analyze whether physical activity (PA) is a protective factor for the incidence of dementia after 3 years of follow-up. The Neurological Disorders in Central Spain (NEDICES) is a prospective population-based survey of older adults (age 65 years and older) that comprised 5278 census-based participants at baseline (1994–1995). A broad questionnaire was used to assess participants' sociodemographic characteristics, health status, and lifestyle. Subsequently, a modified version of Rosow-Breslau questionnaire was applied to classify individuals' baseline PA into groups (i.e., sedentary, light, moderate, and high). Cox regression models adjusted for several covariates (age, sex, education, previous stroke, alcohol consumption, hypertension, health related variables) were carried out to estimate the association between the PA groups and risk of dementia at the 3-year follow-up (1997–1998). A total of 134 incident dementia cases were identified among 3105 individuals (56.6% female; mean age = 73.15 ± 6.26) after 3 years. Hazard ratios (HRs) of the light, moderate, and high PA groups (*vs*. sedentary group) were 0.40 (95% confidence interval {CI} [0.26, 0.62]; $p < .001$), 0.32 (95% CI [0.20, 0.54]; $p < .001$) and 0.23 (95% CI [0.13, 0.40]; $p < .001$), respectively. Even after controlling for covariates and the exclusion of doubtful dementia cases, HRs remained significant. However, a supplementary analysis showed that the dose-effect hypothesis did not reach statistical significance. PA is a protective factor of incident dementia in this population-based cohort. (*JINS*, 2015, *21*, 861–867)

Keywords: Aging, Alzheimer's disease, Risk factors, Lifestyle, Exercise, Reserve

INTRODUCTION

Dementia is one of the most disabling and burdensome health conditions worldwide (Bermejo-Pareja, Benito-León, Vega, Medrano, & Román, 2008; Ferri et al., 2005). Unfortunately, no cure has yet been discovered, and many scientific studies focus on seeking strategies to delay the onset and progression of this devastating syndrome (Larson et al., 2014). In this context, physical activity (PA) has been consistently associated with a reduced risk of cognitive decline and dementia (Beeri & Middleton, 2012), but the mechanisms implicated in this effect are unclear (Lautenschlager, Cox, & Kurz, 2010; Tortosa-Martínez & Clow, 2012).

Several prospective surveys have shown a lower incidence of dementia and Alzheimer's disease (AD) in people who carry out PA (Buchman et al., 2012; Larson et al., 2014; see Hamer & Chida, 2009, and Sofi et al., 2010, for a review and meta-analysis). However, some prospective randomized trials have shown contradictory results (Denkinger, Nikolaus, Denkinger, & Lukas, 2012; Snowden et al., 2011; Wang, Xu, & Pei, 2012). Moreover, the type and intensity of PA as a protective factor for dementia needs further investigation (Rolland, Abellan Van Kan, & Vellas, 2008), and the presence of possible dose-effects is controversial (Scarmeas et al., 2009; Wilson et al., 2002).

The aim of this study is to analyze whether PA is a protective factor against dementia after 3 years in a population-based sample of Spanish older people. In these terms, individuals were classified according to the intensity of PA (slight, moderate, or high), and dose effect was tested in a supplementary analysis.

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METHODS

Participants

Data were collected from the Neurological Disorders in Central Spain (NEDICES), a population-based survey of older people's (age 65 years and older) main age-related conditions, including Parkinson's disease, essential tremor, stroke, and dementia. A signed informed consent was obtained from all participants at the time of enrolment. Ethical standards committees on human research at the University Hospitals "12 de Octubre" (Madrid) and "La Princesa" (Madrid) approved the protocol of the study as complying with the Declaration of Helsinki (World Medical Association, 1989).

A detailed account of the background, study population, and methods of the survey were previously reported (Bermejo et al., 2001; Morales et al., 2004). Briefly, the NEDICES study was carried out in three well-defined geographic areas of central Spain to obtain a representative cohort of older people with different socioeconomic backgrounds. Thus, participants were collected from population censuses of three communities: Las Margaritas, a working-class neighborhood in Getafe (Greater Madrid); Lista, a professional-class neighborhood in the Salamanca district (Central Madrid); and 38 villages from the agricultural region of the Arévalo county (125 km northwest of Madrid). In Margaritas and Arévalo, every eligible subject was to be screened. However, because of the large number of older residents in Lista, proportionate stratified random sampling procedure was used to select subjects for screening.

Currently, two complete cross-sectional surveys have been performed: baseline wave (1994–5) and incidence wave (1997–8). At the time of their baseline assessment (1994–1995), 5278 census-based older people (57.6% women with a mean age of 74.31 ± 6.97; 53,1% without a primary studies certificate) were interviewed face-to-face using a 500-item screening questionnaire that assessed demographic data, medical conditions, current medication, and lifestyle (e.g., consumption of alcohol, smoking habits, physical activity, self-reported health). Self-rated health was assessed with one question (*"In general terms, how would you describe your health: very good, good, fair, poor, or very poor?"* rated with 1 (*very good*) to 5 (*very poor*) points). Meanwhile, the comorbidity index was calculated based on the Romano's adaptation (Romano, Roos, & Jollis, 1993). A short form of the questionnaire was mailed to participants who were unavailable for face-to-face or telephone screening.

Measures and Testing Procedure

a) Assessment of cognitive function and diagnosis of dementia

The NEDICES study was carried out in two phases: door-to-door screening (Phase 1) of eligible people and a neurologist's examination of the individuals who screened positive (Phase 2).

The screening instruments for dementia included the Spanish adaptation of a 37-item version of the Mini-Mental State Examination (Prieto, Contador, Tapias-Merino, Mitchell, & Bermejo-Pareja, 2012; Tapias-Merino et al., 2010) and an adapted Spanish version of Pfeffer's Functional Activities Questionnaire (FAQ; Olazarán, Mouronte, & Bermejo, 2005). This screening protocol for dementia was designed and validated in a World Health Organization (WHO) Aging Study demonstrating sensitivity greater than 90% (Baldereschi, Meneghini et al., 1994). Participants were considered to have screened positive for dementia if: (1) they scored <24 points on the 37-item version of the MMSE and >5 points on the Spanish version of Pfeffer's FAQ; or (2) there were missing values (i.e., subject failed to provide an answer for any reason, or information was not available) on these screening instruments; or (3) the participants themselves or through their proxies reported of a history of cognitive decline (e.g., spontaneously during the interview or when checking the available information).

Every person who screened positive for dementia underwent a neurological examination at National Health Service clinics or at home. Institutionalized persons who were recruited in the study were also screened with the same procedure. The diagnosis of dementia was made by consensus of two neurologists using the Diagnostic and Statistical Manual of Mental Disorders-IV (DSM-IV) criteria. In this survey, the etiologic diagnosis of dementia were AD according to NINCDS-ADRDA criteria (including both possible and probable categories), vascular dementia (VaD), using DSM-IV criteria; dementia associated with Parkinson's disease (PD), dementia with Lewy bodies or longstanding Parkinsonism (more than 6 months); and secondary dementia (known or probable specific dementia cause). Finally, the diagnosis of doubtful dementia (DD) was established in accordance with the categorization of the WHO program for research on aging (Baldereschi, Amato et al., 1994), which is comparable to the Clinical Dementia Rating (CDR) of 0.5 (Morris, 1993). This category was assigned to persons with evidence of cognitive impairment in memory or other cognitive domains, but whose functional or social impairment were too slight to meet the criteria for dementia.

The methods for the diagnosis of dementia were similar in both waves. In addition, regardless of their screening results, reachable participants at follow-up underwent a short neuropsychological battery composed of different tasks: Trail Making Test-A (Army Individual Test Battery, 1944), naming and pictures recall (Peña-Casanova, Guardia, Bertran-Serra, Manero, & Jarne, 1997), logical memory (Cornoni-Huntley, Brock, Ostfeld, Taylor, & Wallace, 1986; Bermejo et al., 1994), and semantic fluency (Isaacs & Kennie, 1973). The neuropsychological assessment at follow-up was independent of the clinical diagnosis (Serna et al., 2015).

b) Assessment of daily physical activity

The PA of individuals was collected at baseline (1994–1995) using an adapted modified version (four items) of the Rosow-Breslau physical function measure (Rosow & Breslau, 1966). The measure assesses usual tasks faced by community-dwelling older adults (e.g., walk a half mile, walk up to the second floor and down, perform heavy

https://doi.org/10.1017/S1355617715000831 Published online by Cambridge University Press

housework) and its test–retest reliability ($r = 0.81$) has been assessed in the Established Populations for Epidemiologic Studies of the Elderly (Smith et al., 1990). Therefore, the measure seems sufficiently stable for longitudinal analyses, and concurrent validity was previously established (Reuben & Siu, 1990). The inability to perform the activities of the Rosow-Breslau questionnaire falls within the concept of disability of the International Classification of Impairments, Disabilities and Handicaps (WHO, 1980). This measure has also been related to functional disability and mortality in older populations (Brock, Lemke, Branch, Evans, & Berkman, 1994; Thomas & Lichtenstein, 1986).

In this survey, trained interviewers asked the participants "*How many hours do you dedicate daily to.....*" (a) sedentary lifestyle (i.e., only minimal house chores or short walks at home); (b) slight physical activity (i.e., regular house chores, walks independently at home); (c) moderate physical activity (i.e., regular house chores, walks up to one kilometer per day); (d) high activity (i.e., performs heavy housework, walks more than one kilometer or practices any sport regularly). Therefore, PA was classified into four groups (sedentary, light, moderate, and high PA). These groups were formed with the aim of grading PA under a dose-effect hypothesis (Laurin, Verreault, Lindsay, MacPherson, & Rockwood, 2001; Liu, LaCroix, White, Kittner, & Wolf, 1990).

Statistical Analysis

Statistical analyses were performed with the SAS software (9.3 version, SAS Institute Inc, 2011). Baseline characteristics of the groups were compared using analysis of variance (ANOVA) tests for numerical variables and χ^2 tests for categorical variables. Moreover, we calculated the effect sizes with Cohen's *d* index for continuous variables and Phi coefficient for categorical ones. Cox regression models were used to test the association between PA and the risk of dementia 3 years later, controlling for different covariates. A value of $p < .10$ was conservatively chosen to select different sources of confusion from the univariate analyses. Person-years for subjects who did not develop dementia were calculated as the time between the screening test for the baseline survey and the screening test for the follow-up survey or death. On the other hand, person-years for those subjects who developed dementia were calculated as the time between the screening test of the first wave and the reported dementia onset. When onset was unknown, person-years were calculated as the midpoint between the first wave screening test and the second wave screening test or death (Bermejo-Pareja et al., 2008). To test the dose-effect hypothesis, the number of hours was weighted, multiplying the sedentary category by 1; the slight PA by 1.2; the moderate PA by1.4; and the high PA by 1.8. Next, different cutoff points were calculated based on the quartile distribution to classify the subjects as follows: ≤15.6 hr (sedentary group), ≤17.6 hr (light PA group), ≤19.4 hr (moderate PA group), and >19.4 hr (high PA group). The presence of a dose-effect was tested using the incremental coding procedure (Rothman, Greenland, Greenland, & Lash, 2008).

RESULTS

Of the 5278 participants screened for neurological disorders at baseline (1994–1995), 306 prevalent dementia cases (5.8%) were excluded from further analyses. Therefore, 4972 participants were classified as non-demented at baseline. Of 3891 participants with available information at follow-up (1997 to 1998), 3891 participants were followed from baseline (1994–1995) for an interval of 3.2 years (range = 0.03–6.6). In this cohort, 3105 individuals (134 incident dementia cases [70.9% with AD subtype] *vs.* 2971 without dementia) had available information about PA. No significant differences were found between the final sample and participants ($N = 786$) without PA assessment in terms of age ($p = .40$) or sex ($p = .18$), but the educational level (years) was lower in individuals without PA information (3.88 ± 4.21 *vs.* 7.02 ± 5.27, $p < .001$). The flow chart of this survey is shown in Figure 1.

Table 1 compares the baseline characteristics of the groups with and without dementia at baseline. The findings show that higher age, lower educational level, hypertension, and history of stroke were associated with the incidence of dementia, whereas alcohol consumption was less frequent in those who progressed to dementia. Statistical trends were found between the development of dementia and health indicators (Charlson index and self-reported heath).

According to the level of PA, 790 individuals were classified as "sedentary lifestyle," 865 as "light PA," 681 as "moderate PA," and 769 as "high PA" (see Table 2). As shown, the sedentary group was significantly older and had more men than the PA groups. Moreover, the sedentary group also showed a lower educational level, more of them were smokers, and more had a history of prior stroke than the other PA groups. Light and moderate PA were associated with better health in terms of morbidity and subjective health.

The Cox regression model showed that the light, moderate, and high PA groups have a lower risk for dementia at 3 years compared with the sedentary lifestyle group (see Table 3). Even when the Cox model was adjusted by controlling for significant covariates of the univariate analyses (age, sex, education, current alcohol consumption, previous stroke, hypertension, and comorbidity index), PA at any level *versus* sedentary lifestyle remained as a protective factor against dementia. Likewise, when self-rated health was introduced in the model in instead of the Charlson index, the hazard ratios (HRs) for PA remained significant as follows: light PA (HR = 0.54; 95% confidence interval {CI} [0.35, 0.83]; $p < .01$), moderate PA (HR = 0.47; 95% CI [0.28, 0.78]; $p < .0.01$), and high PA (0.30, 95% CI [0.17, 0.54]; $p < .001$). Finally, after the exclusion of subjects with doubtful dementia at baseline ($n = 61$), all PA groups remained as a significant predictor of lower dementia risk.

DISCUSSION

This research shows that PA (*vs.* sedentary lifestyle) is associated with a lower risk of dementia after controlling for the effect of several covariates. These findings confirm

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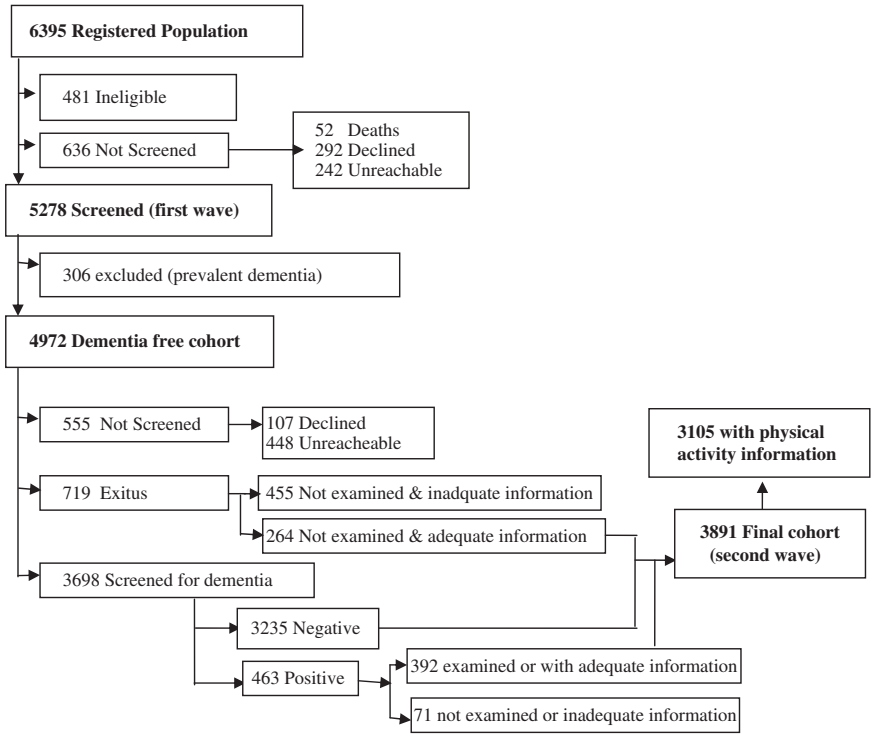

Fig. 1. Flow chart of the survey.

previous epidemiological evidence about PA as a protective factor for dementia (Hamer & Chida, 2009; Smith et al., 2011; Sofi et al., 2010). Our study did not yield a significant dose-effect according to PA intensity, but there was a tendency indicating that higher levels of PA are associated with lower risk of dementia. Similarly, some prospective cohort studies have shown a gradual reduction of risk for persons with higher levels of PA (Laurin et al., 2001; Scarmeas et al., 2009). It should be noted that other studies did not find this association (Wilson et al., 2002; Yamada et al., 2003), but methodological differences in terms of PA measures, duration of follow-ups, and covariates could explain the divergent results.

Considering that late life PA sustains cerebral perfusion and cognition (Rogers, Meyer, & Mortel, 1990; Smith et al., 2011), knowledge of PA as a protective, modifiable factor of dementia in late life periods is of special interest for preventive strategies. It is well known that age is possibly the major risk factor for dementia (Bermejo-Pareja et al., 2008), with prevalence doubling every 5.5–6.3 years (Prince et al., 2013). However, it is important to determine whether PA is a late life protective factor after controlling for the effects of confirmed risk factors such as age and CR proxies, such as education (Contador, Bermejo-Pareja, Del Ser, & Benito-León, 2015). In fact, people with high educational or socioeconomic status may be more aware of the importance of PA, whereas the pattern of PA is not

Table 1. Characteristics of participants at baseline: statistical comparisons

Characteristics	Incident dementia (N = 134)	Without dementia (N = 2971)	*p*	Effect sizes
Age (years)	79.04 ± 6.8	72.88 ± 6.1	<0.001	−1.00
Female	85 (64.0%)	1675 (56.3%) Educational	0.10	0.02
	49 (3.6%)	1296 (96.3%)		
Education (years)	4.84 ± 4.39	7.11 ± 5.28	<0.001	0.43
Illiterates/read-write (%)	90 (68.1%)	1562 (52.5%)		
Primary school/higher (%)	44 (32.8%)	1409 (47.4%)		
Current alcohol (% yes) 5	29 (21.6%)	1060 (35.7%)	<0.001	−0.06
Previous stroke (%yes)	18 (13.4%)	108 (3.6%)	<0.001	0.10
Hypertension (%yes)	80 (59.7%)	1056 (50.7%)	0.05	0.06
Charlson Index	0.80 ± 0.71	0.69 ± 0.68	0.08	−0.16
Self-reported health			0.08	−0.03
Poor or very poor	20 (14.9%)	309 (10.4%)		

Note: Data are given as Mean ± SD and frequency (%).
Effect sizes were calculated using Cohen's d index (continuous variables) and Phi coefficient (categorical variables).

https://doi.org/10.1017/S1355617715000831 Published online by Cambridge University Press

Table 2. Characteristics of participants stratified by the intensity of physical activity

Characteristic	Sedentary (N = 790)	Light PA (N = 865)	Moderate PA (N = 681)	High PA (N = 769)	*p*
Age (years)	74.60 ± 6.87	72.90 ± 6.17	72.48 ± 5.83	72.52 ± 5.84	<0.001
Sex (% female)	393 (49.7%)	498 (57.5%)	372 (54.6%)	497 (64.6%)	<0.001
Education (years)	6.18 ± 5.10	7.34 ± 5.02	7.42 ± 5.32	7.12 ± 5.56	< 0.001
Illiterates/read-write (%)	480 (60.7%)	425 (49.1%)	345 (50.6%)	402 (52.2%)	
Primary school/higher (%)	310 (39.2%)	440 (50.8%)	336 (49.3%)	367 (47.7%)	
Current drinking	255 (32.3%)	298 (34.5%)	246 (36.1%)	290 (37.71%)	0.15
Current smoking	106 (13.4%)	103 (11.9%)	89 (13.0%)	67 (8.71%)	0.01
Previous stroke	53 (6.7%)	37 (4.2%)	18 (2.6%)	18 (2.3%)	<0.001
Charlson Index	2.48 ± 0.90	2.39 ± 0.82	2.37 ± 0.84	2.47 ± 0.89	<0.05
Self-related health					<0.05
Poor or very poor (%)	95 (12.1%)	73 (8.4%)	67 (9.8%)	94 (12.6%)	

Note: Data are given as mean ± standard deviation or frequencies (%).

the same in older adults compared to middle-aged people. For instance, Matthews et al. (2008) described that the most sedentary groups in the United States were older adolescents and adults over 60. In addition, Mace et al. (2015) showed that 65% of adults aged 65 or older did not meet the guidelines for regular PA (at least 150 min of PA per week). At this point, our study indicates that, even after controlling for the effect of important covariates such as age or education, regular PA is associated with a lower risk of dementia at a 3-year follow-up.

There are several hypotheses about the physiological mechanism underlying the effect of PA as a preventive factor of cognitive decline and dementia. Evidence from animal and human research suggests that PA moderates the stress cascade, promotes angiogenesis and neurogenesis, reduces amyloid load, inflammatory markers, insulin resistance, and oxidative stress, while it may increase brain-derived neurotrophic factor (BDNF) and serotonin function (Tortosa-Martínez & Clow, 2012). Moreover, Radack et al. (2010) showed that PA enhances the endurance of cells and tissues to oxidative stress, vascularization, energy metabolism, and neurotrophin synthesis. Finally, PA influences cardiovascular risk factors linked to cognitive decline such as hypertension, diabetes, and cholesterol (Hayes, Alosco, & Forman, 2014; Murtagh et al., 2015).

Table 3. Cox regression models: risk of dementia and physical activity level.

General model (without adjustment for covariates)			
PA groups	HRs	95% HR CI	p
Light	0.40	0.26–0.62	<0.001
Moderate	0.32	0.20–0.54	<0.001
High	0.23	0.13–0.40	<0.001
Model adjusted by covariates*			
PA groups	HRs	95% HR CI	p
Light PA	0.53	0.34–0.82	<0.01
Moderate PA	0.45	0.27–0.76	<0.01
High PA	0.29	0.16–0.52	<0.001

PA = Physical activity; HRs = Hazard ratios
*age, sex, education, alcohol consumption, stroke, hypertension and Charlson Index.

Focusing on neuroimaging studies, a randomized controlled trial with 120 older adults showed that aerobic exercise training increased the size of the anterior hippocampus, leading to improvements in spatial memory (Erickson et al., 2011). Likewise, Smith et al. (2014), demonstrated a protective effect of PA on hippocampal volume, but this effect was specific for persons at genetic risk for AD over a relatively brief period (18-month follow-up). Moreover, Yuki et al. (2012) showed that a high level of PA and total energy expenditure suppressed the frontal lobe atrophy progression associated with aging. Finally, Lamont, Mortby, Anstey, Sachdev, and Cherbuin (2014) suggest that sulcal width provides additional information and may be a more sensitive marker than cortical volume.

This study has several limitations. First, information about PA was collected by a self-report questionnaire more weighted toward functionality at home and walking abilities, whereas other studies have used a daytime actigraphy to measure PA objectively (Buchman et al., 2012). Second, non-exercise PA in daily life was not measured, which may play an important role on the benefits of total activity. Third, individuals who developed dementia may have experienced a higher decline in PA, but our findings did not change after adjusting for subjects under suspicious of dementia (CDR 0.5). Fourth, although an important group of covariates were controlled, others such as apolipoprotein E genotype were not available for the study. Fifth, the follow-up was relatively short compared to other studies, but it was long enough to find a significant effect of PA on dementia incidence. Finally, the NEDICES study showed an attrition rate of 28.1% at follow-up, which is similar to other longitudinal studies on aging (Chatfield, Brayne, & Matthews, 2005; Vega et al., 2010). In this study, the presence of a possible bias should not be ignored, due to the fact that 20% of the subjects who were reachable at follow-up did not have any PA information. The group without PA information showed a lower educational level, which limits generalization. However, we highlight that the final sample is mainly composed by people with a low educational level but the results remained stable after controlling for its effect.

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In this research, several strengths should be highlighted. All participants were selected from a prospective population-based study. In this regard, a broad spectrum of older Spanish individuals was analyzed. Moreover, dementia incidence was diagnosed by expert neurologists based on a uniform clinical evaluation, which reduces the likelihood of misclassification.

To sum up, regular PA in older people (aged 65 and older) seems to be a protective factor against dementia and AD in later life. These findings have relevant implications for preventive health care. Therefore, active lifestyle in aged people may increase late life physical and cognitive health. Future studies should focus on how various types, intensities, and frequencies of PA could influence the risk of dementia and prevent late life cognitive decline.

ACKNOWLEDGMENTS

Sara Llamas is supported by the Instituto de Salud Carlos III (ISCIII; Spanish Biomedical Research Institute) through a "Río Hortega" contract. The Spanish Health Research Agency and the Spanish Office of Science and Technology have supported NEDICES and details about funding are listed on www.ciberned.es/estudio-nedices. The authors thank all collaborators for their involvement in the NEDICES study. The authors report no conflict of interest.

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