Physical Activity Prevents Progression for Cognitive Impairment and Vascular Dementia
Results From the LADIS (Leukoaraiosis and Disability) Study

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Background and Purpose—We aimed to study if physical activity could interfere with progression for cognitive impairment and dementia in older people with white matter changes living independently.

Methods—The LADIS (Leukoaraiosis and Disability) prospective multinational European study evaluates the impact of white matter changes on the transition of independent elderly subjects into disability. Subjects were evaluated yearly during 3 years with a comprehensive clinical protocol and cognitive assessment with classification of cognitive impairment and dementia according to usual clinical criteria. Physical activity was recorded during the clinical interview. MRI was performed at entry and at the end of the study.

Results—Six hundred thirty-nine subjects were included (74.1±5 years old, 55% women, 9.6±3.8 years of schooling, 64% physically active). At the end of follow-up, 90 patients had dementia (vascular dementia, 54; Alzheimer disease with vascular component, 34; frontotemporal dementia, 2), and 147 had cognitive impairment not dementia. Using Cox regression analysis, physical activity reduced the risk of cognitive impairment (dementia and not dementia: β=−0.45, P=0.002; hazard ratio, 0.64; 95% CI, 0.48–0.85), dementia (β=−0.49, P=0.043; hazard ratio, 0.61; 95% CI, 0.38–0.98), and vascular dementia (β=−0.86, P=0.008; hazard ratio, 0.42; 95% CI, 0.22–0.80), independent of age, education, white matter change severity, medial temporal atrophy, previous and incident stroke, and diabetes.

Conclusions—Physical activity reduces the risk of cognitive impairment, mainly vascular dementia, in older people living independently. (Stroke. 2012;43:00–00.)

Key Words: cognition ■ cognitive impairment ■ dementia ■ magnetic resonance ■ physical activity ■ white matter disease

Physical activity can prevent functional decline associated with age and promote global health status. Recent reports suggested that physical activity can prevent cognitive decline and progression for dementia, including Alzheimer disease,1–6 and the explanation for this relation remains a matter of debate.7 Several reasons can explain the protective effect of physical activity on the evolution for cognitive impairment. Beneficial effects of physical exercise can be observed in mental and social stimulation and can be integrated in a healthier life status to explain the association.8

More biological explanations have been proposed: physical activity can improve cerebral blood flow, reduce vascular risk factors, decrease secretion of stress hormones, and stimulate plasticity.9 Recently physical activity has been associated with enhancement of endothelial function, counteracting the loss of vasodilatory function associated with aging.10,11 Some data support a decreased progression of intima-media thickness associated with physical activity.12

In this study we aimed to study the impact of physical activity on the evolution for cognitive impairment and dementia.
in a cohort of old people with white matter changes (WMC) living independently who were followed prospectively during 3 years with comprehensive cognitive evaluation and careful control of concomitant factors implicated in disability.

Materials and Methods

The LADIS (Leukoaraiosis and Disability) study is a prospective multinational European project investigating the independent impact of WMC on the transition to disability in the elderly. The rationale, methodology, and baseline assessment have been described previously.13,14 Inclusion criteria for the study were: (1) 65 to 84 years of age; (2) changes in WMC on MRI of any degree, according to the scale of Fazekas;15 and (3) no disability, as determined by the Instrumental Activities of Daily Living scale.16 Patients were enrolled because of minor neurological, cognitive, mood, or motor complaints or incidental findings on cranial imaging caused by non-specific events, without impact on daily living activities, as detailed elsewhere.17 Subjects were evaluated at baseline and yearly during 3 years with a comprehensive clinical and functional protocol that included registry of demographic factors, vascular risk factors including stroke and diabetes, comorbidities, depression, quality of life, and neuropsychological evaluation.12 During the interview physical activity was assessed and defined according to the American Heart Association Scientific Position (at least 30 minutes of activity on at least 3 days per week).11 Patients were classified as physically active or inactive according to this definition. For those patients who could not attend the clinical visit, a phone interview was performed.14 Investigators were provided with a specifically developed handbook with guidelines for applying criteria and tools and trained medical personnel used a structured and comprehensive questionnaire together with review of the available records.13

Neuropsychological Evaluation and Cognitive Criteria

The LADIS neuropsychological battery has been described in detail elsewhere.18 References from the battery neuropsychological tests are given in Supplemental Appendix I. In short, the neuropsychological battery included the Mini-Mental State Examination as a global measure of cognitive function; the Vascular Dementia Assessment Scale cognitive subscale (VADAS-Cog) as a comprehensive instrument to assess orientation, language, ideational and constructional praxis, immediate memory and delayed recall, attention and speed of mental processing; and the Stroop and Trail Making tests as measures of executive function. Additionally, in the follow-up clinical visits, patient cognitive status was classified into the following groups: (1) dementia; (2) cognitive impairment no dementia; or (3) no cognitive impairment. For this purpose, we used the following criteria and definitions (references are given in Supplemental Appendix I). We considered 2 types of cognitive impairment not dementia: (1) amnestic mild cognitive impairment, according to Petersen RC, Doody R, Kurz A, Mohs RC, Morris JC, Rabins PV, et al. Current concepts in mild cognitive impairment. Arch Neurol. 2001;58:1985–1992. (defined as memory complaint, preferably corroborated by an informant; impaired memory function for age and education, preserved general cognitive function, intact activities of daily living and no dementia); or (2) vascular cognitive impairment without dementia (defined as evidence of cognitive impairment and clinical consensus to identify significantly related vascular features, exclusion of dementia when impairments were not sufficiently severe to interfere with social or occupational functioning or when impairments were more focal than the global requirement for a diagnosis of dementia). We considered the following clinical criteria for subtypes of dementia: Alzheimer disease according to the National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer’s Disease and Related Disorders Association (NINCDS-ADRDA) Work Group, vascular dementia according to National Institute of Neurological Disorders and Stroke (NINDS) criteria, frontotemporal dementia according to the Recherche et l’Enseignement en Neurosciences (AIREN) criteria, subtype of subcortical vascular dementia according to Erkinjuntti T, Iniizari D, Pantoni L, Wallin A, Scheltens P, Rockwood K, et al. Research criteria for subcortical vascular dementia in clinical trials. J Neural Transm Suppl. 2000;59:23–30, and frontotemporal dementia according to McKhann GM, Albert MS, Grossman M, Miller B, Dickson D, Trojanowski JQ; Work Group on Frontotemporal Dementia and Pick’s Disease. Clinical and pathological diagnosis of frontotemporal dementia: report of the Work Group on Frontotemporal Dementia and Pick’s Disease. Arch Neurol. 2001;58:1803–1809. The criteria for Alzheimer disease with vascular component were considered when the investigator judgment considered that the clinical picture was due simultaneously to Alzheimer disease and vascular dementia.

Progression for cognitive impairment (or cognitive decline) during the study was defined clinically as a change in the clinical cognitive diagnosis in the different times of follow-up. That is, decline was determined by: (1) transition from no cognitive impairment to cognitive impairment no dementia; or (2) transition from cognitive impairment no dementia to dementia; or (3) transition from no cognitive impairment to dementia.

MRI Study

MRI was performed at entry and at the end of the study following a protocol previously described.13 The degree of WMC severity was rated on fluid-attenuated inversion recovery sequences by central readers blind to the clinical data using the 3 classes (mild, moderate, and severe) in the revised version of the visual scale of Fazekas and colleagues.19 Medial temporal lobe atrophy was assessed on coronal T1-weighted sequences using the medial temporal atrophy scale.18

Statistical Analysis

The influence of physical activity (recorded at baseline) on the cognitive status during follow-up was assessed using Cox proportional hazard models that relied on a noninformative censoring process. We considered as a dependent variable the last cognitive evaluation as described in the Methods section, and progression for cognitive impairment was considered as described in Methods section, with a change between baseline and last follow-up. We performed different models considering the cognitive diagnosis at the end of follow-up: any cognitive impairment (dementia and cognitive impairment not dementia); or diagnosis of dementia, Alzheimer disease, and vascular dementia. We considered the following independent variables: age, education, medial temporal atrophy, and WMC severity. Age and educational level were considered continuous variables. Medial temporal atrophy and WMC severity were considered categorical variables. We controlled analysis for the variables found relevant in predicting cognitive impairment in previous publications (diabetes and previous stroke)19 and for global cognitive status at baseline using Mini-Mental State Examination because it was found in our sample to be sensitive to the evolution for cognitive impairment and dementia.20 Data were analyzed using SPSS 16.0 software.

Results

Six hundred thirty-eight subjects were included (74.1 years, SD 5; 55% women; 9.6 years of educational level, SD 3.8). Baseline characteristics, including vascular risk factors of the study population, were already described;19 in short, concerning relevant risk factors for the present study, 29.6% of the study population had previous stroke and 14.6% were diabetic at baseline (Table 1). WMC severity at baseline was as follows: mild, 44%; moderate, 31%; and severe, 25%. At entry, 63.8% of subjects performed physical activity. At the end of follow-up, vital status or Instrumental Activities of Daily Living scale was possible to ascertain in 633 patients (99.1% of initial sample). Fifty-one patients missed complete cognitive evaluation in any follow-up clinical visit; for those 51 patients, no cognitive diagnosis was attributed.

Considering the cognitive diagnosis ascertained in the last clinical visit, dementia was diagnosed in 90 patients
(vascular dementia, 54; Alzheimer disease with vascular component, 34; frontotemporal dementia, 2), and 147 patients had cognitive impairment not dementia (vascular cognitive impairment without dementia, 86; mild cognitive impairment, 61).

Using Cox regression analysis we found that physical activity measured at baseline was an independent protective factor for cognitive impairment over time (dementia and cognitive impairment not dementia; Table 2). The preventive effect of physical activity for the progression for cognitive impairment was unchanged when controlling for diabetes (β=−0.35, P=0.021; hazard ratio, 0.71; 95% CI, 0.524–0.949).

Because the impact of physical activity over time could be due to cognitive differences already at baseline, we repeated the analysis considering Mini-Mental State Examination at baseline. Even so, physical activity at baseline remained an independent predictor of vascular dementia, reducing in half the risk for vascular dementia (Table 5), even controlling for incident stroke (β=−0.80, P=0.015; hazard ratio, 0.45; 95% CI, 0.236–0.858).

Considering patients with criteria for vascular dementia (N=54) we found that physical activity reduced in more than half the risk for vascular dementia (Table 5), even controlling for incident stroke (β=−0.80, P=0.015; hazard ratio, 0.45; 95% CI, 0.236–0.858).
Table 5. Cox Proportional Hazards Model

<table>
<thead>
<tr>
<th></th>
<th>β</th>
<th>HR</th>
<th>P Value</th>
<th>95% CI</th>
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</thead>
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<td>Age</td>
<td>0.029</td>
<td>1.029</td>
<td>0.352</td>
<td>0.969</td>
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<td>Educational level</td>
<td>0.008</td>
<td>1.008</td>
<td>0.835</td>
<td>0.937</td>
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<td>Sex</td>
<td>0.320</td>
<td>1.377</td>
<td>0.300</td>
<td>0.752</td>
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<tr>
<td>WMC severity</td>
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<tr>
<td>WMC severity (moderate vs mild)</td>
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<td>1.867</td>
<td>0.156</td>
<td>0.787</td>
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<tr>
<td>WMC severity (severe vs mild)</td>
<td>1.029</td>
<td>2.798</td>
<td>0.012</td>
<td>1.255</td>
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<tr>
<td>MTA</td>
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<td></td>
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<td>MTA (1 vs 0)</td>
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<td>7.102</td>
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<td>MTA (2 vs 0)</td>
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<td>14.208</td>
<td>0.011</td>
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<td>MTA (3 vs 0)</td>
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<td>22.751</td>
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<td>MTA (4 vs 0)</td>
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<td>0.001</td>
<td>5.297</td>
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<td>Physical activity</td>
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<td>0.421</td>
<td>0.008</td>
<td>0.223</td>
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</tbody>
</table>

Dependent variable: vascular dementia in last clinical evaluation (54 subjects).
CI indicates confidence interval; HR, hazard ratio; MTA, medial temporal atrophy; WMC, white matter changes.

Discussion

Our results showed that among nondisabled old people with WMC, physical activity reduced the risk for cognitive impairment and vascular dementia, independently of the severity of WMC even controlling for educational level, age, and temporal atrophy and for risk factors found to be predictive of dementia.

Previous studies suggested a beneficial impact of physical activity on the progression for cognitive impairment and dementia, even for subjects with Alzheimer disease and a reduced amount of exercise.\(^1\)\textsuperscript{-6} Recently, a panel reviewed evidence on the prevention for Alzheimer disease; although globally physical activity (particularly high levels) have been associated with decreased risk of Alzheimer disease, associations were not always significant after adjusting for confounding factors risk and in some studies the risk estimates were in the direction indicating increased risk of Alzheimer disease.\(^2\)\textsuperscript{1}

A recent meta-analysis addressed the preventive effect of physical activity for vascular dementia, but among the 5 studies included, only 1 showed a significant association between physical activity and risk for vascular dementia. Several studies reported no association between physical activity and all dementias or vascular dementia.\(^2\)\textsuperscript{2} Moreover, those studies, with 1 exception,\(^2\)\textsuperscript{3} did not control for imaging data, namely WMC or medial temporal atrophy, and stroke was a prognostic factor for vascular dementia. For this reason we controlled our findings for both diseases, and the protective effect of physical activity remained unchanged. Our data support the conviction that older subjects with vascular risk factors and evidence for vascular cerebral damage benefit from regular physical activity. We think that relation between physical activity and cognitive impairment should be further studied by interventional studies.

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Disclosures

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References


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