Performance-Based Physical Function and Future Dementia in Older People

Li Wang, MS; Eric B. Larson, MD, MPH; James D. Bowen, MD; Gerald van Belle, PhD

Background: The association of physical function with progression to dementia has not been well investigated. We aimed to determine whether physical function is associated with incident dementia and Alzheimer disease (AD).

Methods: We performed a prospective cohort study of 2288 persons 65 years and older without dementia. Patients were enrolled from 1994 to 1996 and followed up through October 2003. Main outcome measures included incident dementia and AD.

Results: During follow-up 319 participants developed dementia (221 had AD). The age-specific incidence rate of dementia was 53.1 per 1000 person-years for participants who scored lower on a performance-based physical function test at baseline (≥10 points) compared with 17.4 per 1000 person-years for those who scored higher (>10 points). A 1-point lower performance-based physical function score was associated with an increased risk of dementia (hazard ratio, 1.08; 95% confidence interval, 1.03-1.13; P<.001), an increased risk of AD (hazard ratio, 1.06; 95% confidence interval, 1.01-1.12; P=.01), and an increased rate of decline in the Cognitive Ability Screening Instrument scores (0.11 point per year; 95% confidence interval, 0.08-0.14; P<.001) after adjusting for age, sex, years of education, baseline cognitive function, APOE ε4 allele, family history of AD, depression, coronary heart disease, and cerebrovascular disease.

Conclusions: Lower levels of physical performance were associated with an increased risk of dementia and AD. The study suggests that poor physical function may precede the onset of dementia and AD and higher levels of physical function may be associated with a delayed onset.

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to dementia at a certain stage during disease development by examining the relationship of physical function with incident dementia in persons without cognitive impairment (an earlier stage) and in persons who might have mild cognitive impairment (a later stage).

METHODS

STUDY SAMPLE

Participants were enrolled in the Adult Changes in Thought (ACT) study, a population-based longitudinal study of aging and dementia. The ACT study was designed to determine the incidence of AD, other types of dementia, and cognitive impairment and to determine risk factors for these conditions. A random sample of 6782 individuals was initially drawn from Seattle-area members of Group Health Cooperative, a consumer-governed health maintenance organization. Participants were 65 years or older at enrollment from 1994 to 1996. Persons who were ineligible (n=1360) were those who had an existing diagnosis of dementia, were current residents of a nursing home, or were participating in other studies. Of 5422 eligible individuals, 2581 remained and 2841 declined participation. Refusal was more common among the oldest group (>85 years), women, and African American or minority groups. Dementia and AD incidence rates from the ACT study have previously been published and are consistent with rates reported in US and European cohort studies.

Participants received the Cognitive Ability Screening Instrument (CASI) as initial screening for cognitive function and were interviewed with structured questionnaires for baseline data, including demographics, medical history, memory, and general functioning, and potential epidemiologic risk factors. Persons who scored 86 or higher on the CASI were entered directly into the ACT cohort. (A CASI score of 86 corresponds to a Mini-Mental State Examination score of 25 to 26.) We conducted a standardized clinical and neuropsychological evaluation for dementia in persons with a CASI score lower than 86. Those who did not meet established criteria for dementia or were included in the ACT cohort. In this study, we excluded persons with invalid measurements on either the cognitive performance test or physical performance tests at baseline (n=53) and persons without a follow-up examination (n=238), leaving 2288 persons for analysis.

INCIDENT DEMENTIA

Follow-up examinations were conducted biennially to identify incident dementia and AD. Participants were rescreened with the CASI. Those who scored 86 or higher on the CASI remained in the ACT cohort as dementia free. Those who scored lower than 86 on the CASI underwent a standardized clinical examination. The results of rescreening by the CASI and the clinical examinations were reviewed at a consensus diagnosis conference. Those who met Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) criteria for dementia were considered incident dementia cases. Dementia type was determined by the National Institute of Neurological and Communicative Diseases and Stroke-Alzheimer’s Disease and Related Disorders Association criteria for AD and DSM-IV criteria for other types of dementias.

PHYSICAL PERFORMANCE TESTS

Physical function was assessed by 4 physical performance tests: 10-ft timed walk, chair-stand time (time to stand from a seated position in a chair to a standing position, repeated 5 times), standing balance, and grip strength (in kilograms) in the dominant hand. Each test was scored from 0 to 4 points. Sex-specific quartiles from the study population were used as cut-off points for scoring 10-ft timed walk, chair-stand time, and grip strength. Standing balance was scored by ability to maintain each position: side by side for 10 seconds, semitandem for 10 seconds, full tandem for 1 to 9 seconds, and full tandem for 10 seconds. A performance-based physical function (PPF) score was the total score from the 4 physical tests and ranged from 0 to 16, with higher scores indicating better physical performance. The PPF test had adequate scale reliability with a Cronbach α coefficient of 0.74.

COGNITIVE PERFORMANCE TEST

The CASI provides quantitative assessment of attention, concentration, orientation, short-term memory, long-term memory, language ability, visual construction, list-generating fluency, abstraction, and judgment. The CASI has a potential range of 0 to 100, with higher scores indicating better cognitive performance. The CASI scores of 90 or lower might indicate possible mild cognitive impairment.

OTHER BASELINE VARIABLES

Other baseline variables include age, sex, years of education, family history of AD, APOE ε4 genotype, depression, physical exercise, and reports of coronary heart disease (CHD) and cerebrovascular disease (CVD). Family history of AD was defined as reporting a first-degree relative with AD. Depression was measured by the 11-item Center for Epidemiologic Studies Depression Scale. Physical exercise was assessed by asking participants the number of days per week they did each of the following activities for at least 15 minutes at a time during the past year: walking, hiking, bicycling, aerobics or calisthenics, swimming, water aerobics, weight training, or stretching and other exercise. Participants who exercised at least 3 times per week were classified as exercising regularly in this study. Coronary heart disease included congestive heart failure, myocardial infarction, angina pectoris, and coronary artery bypass surgery. Cerebrovascular disease included stroke, cerebral hemorrhage, and small strokes or transient ischemic attacks.

STATISTICAL ANALYSIS

The relationship between cognitive performance and physical performance at baseline was examined by linear regression models. The CASI score was the dependent variable. The PPF score and each physical test score, as independent variables, were individually fitted into a model adjusting for other baseline variables.

The temporal relationship of physical performance with incident dementia was evaluated by Cox proportional hazards regression models. We used age during the study as the time scale, with left truncation at age of entering the study, and kept age at baseline as a covariate in the Cox models. Therefore, analyses were completely adjusted for age. The event time for dementia was the halfway point between the diagnosis date and the previous examination date. Persons who dropped out of the study before developing dementia were censored at the last examination date. Persons who remained dementia free during follow-up were censored at the most recent follow-up date. We examined results of the PPF test and each physical test individually. The Schoenfeld residual test was used to check the proportional hazards assumption.

To explore whether the association of physical function with incident dementia changes at varying stages of progression, we performed analyses separately in persons without apparent cogn...
RESULTS

During the 5.9 years of follow-up, 1422 participants remained dementia free, 319 developed dementia (221 had AD, 55 had vascular dementia, and 43 had other types of dementia), 362 died, and 185 withdrew from the study. Table 1 lists the baseline characteristics of study participants who remained dementia free, developed dementia, died, or withdrew from the study. Figure 1 displays distributions of baseline PPF scores by those who remained dementia free and those who developed dementia. The PPF score distributions significantly differ in the 2 groups (Wilcoxon rank sum test; P < .001). The mean (SD) and the median baseline PPF scores were 12.5 (2.7) and 13 for the dementia-free group and 10.8 (3.3) and 12 for the dementia group.

At baseline, physical performance was associated with cognitive performance. All of the physical test scores were associated with the CASI score, except the chair-stand score, after adjusting for age, sex, years of education, and other baseline variables.

Sensitivity analyses were conducted to evaluate whether a potential bias could be introduced by the censoring mechanism for persons who died or withdrew. Persons with a low CASI score at the time they left the study might be more likely to develop dementia, and random censoring for those persons might not be appropriate. We examined the last CASI score for those who died or withdrew from the study. If a person had a last CASI score lower than 86 before he or she left the study, we assumed that the person would develop dementia 1 year after the last examination, so we repeated analyses to determine whether the association of physical function with incident dementia was changed. Statistical analyses were conducted using Stata statistical software, version 7 (Stata Corp, College Station, Tex).

Table 1. Baseline Characteristics by Follow-up Status

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Dementia Free (n = 1422)</th>
<th>Dementia (n = 319)</th>
<th>Died (n = 362)</th>
<th>Withdrew (n = 185)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at baseline, mean (SD), y</td>
<td>73.5 (5.2)</td>
<td>78.7 (6.1)</td>
<td>77.4 (6.8)</td>
<td>75.8 (6.1)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Female, No. (%)</td>
<td>868 (61)</td>
<td>192 (60)</td>
<td>186 (51)</td>
<td>119 (64)</td>
<td>.004</td>
</tr>
<tr>
<td>Race, No. (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>1297 (91)</td>
<td>296 (93)</td>
<td>332 (92)</td>
<td>164 (89)</td>
<td>.14</td>
</tr>
<tr>
<td>Black</td>
<td>49 (3)</td>
<td>16 (5)</td>
<td>15 (4)</td>
<td>11 (6)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>75 (5)</td>
<td>7 (2)</td>
<td>15 (4)</td>
<td>10 (5)</td>
<td></td>
</tr>
<tr>
<td>Education, mean (SD), y</td>
<td>14.1 (2.8)</td>
<td>13.1 (3.1)</td>
<td>13.6 (3.1)</td>
<td>13.0 (2.8)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>CASI score, mean (SD)*</td>
<td>94.1 (4.1)</td>
<td>89.6 (6.0)</td>
<td>92.6 (4.7)</td>
<td>91.8 (5.1)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Physical performance, mean (SD)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Timed-walk score†</td>
<td>3.3 (0.9)</td>
<td>2.6 (1.2)</td>
<td>2.7 (1.1)</td>
<td>2.9 (1.0)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Balance test score†</td>
<td>3.7 (0.7)</td>
<td>3.3 (1.1)</td>
<td>3.3 (1.1)</td>
<td>3.6 (0.8)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Grip test score†</td>
<td>3.0 (0.9)</td>
<td>2.5 (1.0)</td>
<td>2.6 (1.0)</td>
<td>2.8 (1.0)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Chair-stand score†</td>
<td>2.9 (1.1)</td>
<td>2.5 (1.3)</td>
<td>2.4 (1.3)</td>
<td>2.7 (1.2)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>PPF score‡</td>
<td>12.9 (2.4)</td>
<td>10.8 (3.3)</td>
<td>11.1 (3.4)</td>
<td>11.9 (2.8)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>CES-D score§</td>
<td>3.8 (4.0)</td>
<td>5.4 (4.8)</td>
<td>5.2 (4.9)</td>
<td>4.2 (4.6)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Any APOE ε4 allele, No. (%)</td>
<td>296 (21)</td>
<td>111 (35)</td>
<td>67 (19)</td>
<td>50 (27)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Family history of AD, No. (%)</td>
<td>92 (6)</td>
<td>26 (8)</td>
<td>15 (4)</td>
<td>16 (9)</td>
<td>.10</td>
</tr>
<tr>
<td>Exercise ≥3 times per week, No. (%)</td>
<td>1079 (76)</td>
<td>212 (66)</td>
<td>237 (65)</td>
<td>143 (77)</td>
<td>.001</td>
</tr>
<tr>
<td>Coronary heart disease, No. (%)</td>
<td>225 (16)</td>
<td>83 (26)</td>
<td>117 (32)</td>
<td>37 (20)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Cerebrovascular disease, No. (%)</td>
<td>88 (6)</td>
<td>45 (14)</td>
<td>53 (15)</td>
<td>25 (14)</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

Abbreviation: AD, Alzheimer disease; CASI, Cognitive Ability Screening Instrument; CES-D, Center for Epidemiologic Studies Depression Scale; PPF, performance-based physical function.

*Range, 0-100.
†Range, 0-4.
‡Range, 0-16.
§Range, 0-33.

We tested the interaction terms of each physical test and the PPF test with the initial cognitive status (baseline CASI score >90) and persons with possible mild cognitive impairment (baseline CASI score ≤90). The mean (SD) and the median baseline PPF scores were 12.5 (2.7) and 13 for the dementia-free group and 10.8 (3.3) and 12 for the dementia group.

To examine whether baseline physical performance is associated with the rate of change in cognitive function, linear regressions with the generalized estimating equation were conducted on the repeated measurements of CASI scores. We examined interaction terms of years of follow-up by baseline physical performance, adjusting for other baseline variables.

Sensitivity analyses were conducted to evaluate whether a potential bias could be introduced by the censoring mechanism for persons who died or withdrew. Persons with a low CASI score at the time they left the study might be more likely to develop dementia, and random censoring for those persons might not be appropriate. We examined the last CASI score for those who died or withdrew from the study. If a person had a last CASI score lower than 86 before he or she left the study, we assumed that the person would develop dementia 1 year after the last examination, so we repeated analyses to determine whether the association of physical function with incident dementia was changed. Statistical analyses were conducted using Stata statistical software, version 7 (Stata Corp, College Station, Tex).

Figure 1. Baseline performance-based physical function (PPF) score distributions by participants who remained dementia free and participants who developed dementia during 6 years of follow-up. Participants who developed dementia during follow-up were more likely to be at lower levels of physical performance at baseline compared with those who remained dementia free.
tion, exercise, depression, APOE ε4 allele, family history of AD, CHD, and CVD.

The age-specific incidence rate of dementia was 53.1 per 1000 person-years for participants with a baseline PPF score of 10 or lower (below the 25th percentile) compared with 7.4 per 1000 person-years for those with a baseline PPF score higher than 10. In Figure 2, Kaplan-Meier survival estimates show that participants at lower levels of physical performance at baseline were less likely to remain dementia free than those at higher levels.

Table 2 lists estimated hazard ratios of dementia and AD by physical performance. Better performance on the PPF, timed-walk, and grip tests was associated with a lower risk of dementia and a lower risk of AD.

At baseline, participants with a CASI score higher than 90 had better performance on the PPF test and the 4 specific physical tests compared with those with a CASI score of 90 or lower. The age-specific incidence rates of dementia were 14.6 per 1000 person-years for participants with a baseline CASI score higher than 90 and 58.3 per 1000 person-years for those with a baseline CASI score of 90 or lower. Table 2 lists the estimated hazard ratios of dementia by physical tests stratified by baseline CASI scores. Better performance on the balance test was associated with a lower risk of dementia in those with CASI scores higher than 90. Better performance on the grip test was associated with a lower risk of dementia in those with CASI scores of 90 or lower. Better performance on the PPF and timed-walk tests was associated with a lower risk of dementia in both groups. The interaction between the balance test and the initial cognitive function (CASI score >90 or CASI score ≤90) approached statistical significance (P = .04).

Baseline physical performance was associated with the rate of decline in CASI scores. A 1-point decrease in score on the timed-walk test, balance test, grip test, chair-stand test, and PPF test was associated with an increase in the rate of decline in CASI score by 0.30 (95% confidence interval [CI], 0.21-0.38; P < .001) point per year, 0.24 (95% CI, 0.14-0.34; P < .001) point per year, 0.19 (95% CI, 0.12-0.26; P < .001) point per year, 0.14 (95% CI, 0.08-0.20; P < .001) point per year, and 0.11 (95% CI, 0.08-0.14; P < .001) point per year, respectively, after adjusting for age, sex, years of education, APOE ε4 allele, CHD, CVD, baseline Center for Epidemiologic Studies Depression Scale score, and baseline CASI score.

Of 547 participants who died or withdrew from the study, 99 (18%) had a last CASI score lower than 86 and were assumed as incident dementia cases 1 year after they left the study. In repeated analyses, the adjusted hazard ratios of dementia by 1 point higher on each test score were 0.74 (95% CI, 0.67-0.82; P < .001) for the timed-walk test, 0.84 (95% CI, 0.76-0.92; P < .001) for the balance test, 0.86 (95% CI, 0.77-0.96; P = .008) for the grip test, 0.93 (95% CI, 0.86-1.01; P = .11) for the chair-stand test, and 0.91 (95% CI, 0.88-0.95; P < .001) for the PPF test. The results remained robust.

In this cohort of 2288 participants older than 65 years and dementia free initially, persons with poor physical function were at an increased risk for developing dementia and AD and had an increased rate of cognitive decline during the 6 years of follow-up. Poor standing balance was associated with an increased risk of dementia among persons without apparent cognitive impairment. Poor handgrip was associated with an increased risk of dementia among persons with possible mild cognitive impairment. The associations of overall physical performance and gait speed with future dementia were observed in persons with and without mild cognitive impairment.

Gait disorders are a well-known feature of non-AD dementia, such as vascular and parkinsonian dementias. A previous study20 reported that gait abnormality may precede and predict non-AD dementia. Although motor slowing and gait disorders were also observed in patients with AD,21-23 whether and to what extent gait slowing may precede AD is unknown. A recent report from the Sydney Older Persons Study24 shows that participants with cognitive impairment and gait slowing were most likely to progress to dementia during a 6-year period. In this study we found that gait slowing was associated with an increased risk of both dementia and AD during the 6-year follow-up in persons with and without mild cognitive impairment. The results from the Sydney Older Persons Study were obtained from 394 participants older than 75 years without dementia at baseline. Our results were obtained from a larger dementia-free population (n = 2288) older than 65 years.

Changes in specific physical functions could occur at different stages during the course of dementia. We observed that among participants without apparent cognitive impairment, those with gait slowing and poor balance were more likely to develop dementia, and among participants with possible mild cognitive impairment, those with poor handgrip were more likely to develop dementia. These findings suggest that gait slowing and poor balance might relate to dementia and may occur during an earlier stage before cognitive impairment is apparent, and that poor handgrip might relate to dementia during a later stage when cognitive impairment has occurred. The Hispanic Established Population for the Epi-
Alzheimer Disease

Table 2. Hazard Ratios (95% CIs) for Incident Dementia and Alzheimer Disease by 1-Point Increase in the Scores of Each Physical Test*

<table>
<thead>
<tr>
<th>Physical Test</th>
<th>Age and Sex Adjusted</th>
<th>Adjusted for Multiple Factors†</th>
<th>Age and Sex Adjusted</th>
<th>Adjusted for Multiple Factors†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Timed walk</td>
<td>0.68 (0.62-0.76)‡</td>
<td>0.79 (0.70-0.89)§</td>
<td>0.70 (0.62-0.79)‡</td>
<td>0.81 (0.71-0.94)§</td>
</tr>
<tr>
<td>Balance</td>
<td>0.80 (0.72-0.89)‡</td>
<td>0.87 (0.78-0.96)‖</td>
<td>0.86 (0.75-0.97)‖</td>
<td>0.93 (0.82-1.06)</td>
</tr>
<tr>
<td>Grip strength</td>
<td>0.85 (0.75-0.96)§</td>
<td>0.87 (0.77-0.99)‖</td>
<td>0.84 (0.73-0.98)‖</td>
<td>0.86 (0.74-1.00)¶</td>
</tr>
<tr>
<td>Chair stand</td>
<td>0.86 (0.79-0.94)§</td>
<td>0.95 (0.86-1.05)</td>
<td>0.87 (0.79-0.97)‖</td>
<td>0.96 (0.86-1.08)</td>
</tr>
<tr>
<td>PPF</td>
<td>0.88 (0.85-0.92)‡</td>
<td>0.93 (0.89-0.97)†</td>
<td>0.90 (0.86-0.94)†</td>
<td>0.94 (0.90-0.99)¶</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; PPF, performance-based physical function.
*Higher scores in the physical tests indicate better physical function.
†Multiple factors, in addition to age and sex, include years of education, APOE ε4 allele, family history of Alzheimer disease, baseline Cognitive Ability Screening Instrument score, Center for Epidemiologic Studies Depression Scale score, coronary heart disease, and cardiovascular disease.
‡P<.001.
§P<.01.
¶P<.05.

Table 3. Hazard Ratios (95% CIs) for Incident Dementia by 1-Point Increase in the Score of Each Physical Test Among Participants Without Cognitive Impairment and Participants With Mild Cognitive Impairment

<table>
<thead>
<tr>
<th>Physical Test</th>
<th>No Cognitive Impairment (Baseline CASI Score &gt;90) (n = 1740)</th>
<th>Mild Cognitive Impairment (Baseline CASI Score &lt;90) (n = 548)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age and Sex Adjusted</td>
<td>Adjusted for Multiple Factors*</td>
<td>Age and Sex Adjusted</td>
</tr>
<tr>
<td>Timed walk</td>
<td>0.75 (0.64-0.87)†</td>
<td>0.82 (0.69-0.96)‡</td>
</tr>
<tr>
<td>Balance</td>
<td>0.76 (0.66-0.89)†</td>
<td>0.81 (0.69-0.94)‡</td>
</tr>
<tr>
<td>Grip strength</td>
<td>0.96 (0.81-1.13)¶</td>
<td>1.01 (0.86-1.19)</td>
</tr>
<tr>
<td>Chair stand</td>
<td>0.93 (0.81-1.07)†</td>
<td>0.98 (0.85-1.12)</td>
</tr>
<tr>
<td>PPF</td>
<td>0.91 (0.86-0.96)§</td>
<td>0.94 (0.89-0.99)‡</td>
</tr>
</tbody>
</table>

Abbreviations: CASI, Cognitive Ability Screening Instrument; CI, confidence interval; PPF, performance-based physical function.
*Multiple factors, in addition to age and sex, include years of education, APOE ε4 allele, family history of Alzheimer disease, baseline CASI score, Center for Epidemiologic Studies Depression Scale score, coronary heart disease, and cardiovascular disease.
†P<.001.
‡P<.05.
§P<.01.

Physical function and cognitive function are likely connected, especially in aging. Cognitive ability is essential for conducting physical tasks; performing physical tasks, in return, may enhance or maintain cognitive ability. Recent studies have shown that physical exercise is associated with a lower rate of cognitive decline and a reduced risk of dementia. The cognitive benefits from physical exercise may result from the connection between physical function and cognitive function, especially at advanced old age, when cognitive decline is more likely.

This study has several limitations. The ACT cohort is likely healthier than a general population because of healthy volunteer effect. Persons with existing dementia were excluded at the beginning of the study, and the ACT participants were dementia-free survivors. Although we have adjusted for many possible confounding factors (age, sex, years of education, depression, APOE ε4 allele, family history of AD, baseline cognitive function, CHD, and CVD), other confounding factors could exist. We did not make a formal diagnosis of mild cognitive impairment and used only a CASI score greater than 90 to differentiate persons who were more likely to be cognitively intact from persons who might have mild cognitive impairment. Even though this study demonstrated a temporal relationship between physical func-

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tion and future dementia, we do not know the causal pathway of functional decline and the development of dementia. We speculate that physical decline and cognitive decline may be inseparable during the development of dementia.

In conclusion, this study demonstrated an association of lower levels of physical function with an increased risk of future dementia and AD. The findings suggest that poor physical function may precede the onset of dementia and AD and higher levels of physical function may be associated with a delayed onset; slow gait might be an earlier sign and poor handgrip a later sign of development of dementia in older people. If confirmed, this study might also help explain the association of physical exercise with a reduced risk of dementia, suggesting that exercise, by improving and maintaining physical function, might benefit cognitive function through a connection between the two.

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REFERENCES