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**Association between middle- to late-life physical performance and incident Alzheimer's disease: Recent findings and potential mechanisms**

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**Abstract**  Dementia is recognized as one of the major formidable public health challenges in modern aging societies. Among the several subtypes of dementia, Alzheimer’s disease (AD) is the most frequent, probably accounting for 40-50% of total dementia cases. Recent findings from prospective cohort studies suggest that impairment, found in certain physical performance measures, precedes the clinical diagnosis of AD. The main aim of this review paper is to provide a brief summary of recent findings regarding the associations between middle- to late-life physical performance measures and incident AD and total dementia including AD. This paper also aims to discuss the potential mechanisms underlying the prospective associations between physical performance and incident AD. The reviewed findings suggest that poor baseline status in physical performance measures, including gait performance, muscle strength, balance, aerobic performance, and composite physical performance, is associated with greater risk for the subsequent incidence of AD. Preclinical pathologies leading to AD and physical fitness are named as part of plausible factors underlying the prospective association between physical performance and incident AD. It is also speculated that the prospective association is mostly non-causal, where physical performance measures probably serve as “early markers” of the future incidence of AD. Further studies are expected to establish solid evidence of the prospective association, to clarify the whole picture of the mechanisms underlying the association, and to explore the practical application of physical performance measures in attempts to identify individuals at a higher risk of AD before or early in the disease.

**Keywords**: dementia, primary prevention, exercise epidemiology, physical activity

**Introduction**

Dementia has been recognized as one of the major formidable public health challenges in modern aging societies. A recent report by the Japanese Ministry of Health, Labour and Welfare estimated that in 2012 the number of Japanese people aged 65 or older suffering from dementia was 4.62 million and it will sharply increase to 7 million (about one-fifth of the total older population) by 20251). The economic and social burdens due to dementia are easy to comprehend given the severity of the disease and also because it is the second largest reason for long-term care among Japanese older people2). Of the several subtypes of dementia, Alzheimer’s disease (AD) is the most prevalent and probably accounts for 40-50% of total dementia cases in Japan3).

Although the etiology of AD is still not thoroughly understood, accumulating evidence indicates that it has a long preclinical phase (Fig. 1). The pathophysiological processes leading to AD may begin many years before its clinical diagnosis4,5). This preclinical phase of AD sounds important as it may allow earlier detection of individuals at high risk and the implementation of subsequent interventions to prevent or delay the onset of AD. At this stage, clinical tools including neuroimaging and cerebrospinal fluid assays are often used in an attempt to detect the preclinical phase of AD6). However, these tools are expensive and cannot be readily used in primary care settings. Along with such clinical efforts, non-clinical investigations have explored sociodemographic and lifestyle related factors7-8). These may be useful for the early detection of symptomatic events typically observed in preclinical AD, as well as the risk of incident AD.
In line with these challenges, recent evidence from population-based studies suggests that impairment in a variety of physical performance tests precedes the clinical diagnosis of AD. Thereby, these measures may have utility as predictive factors of the future risk of incident AD. This review paper aims to provide a brief summary of recent findings regarding the association between middle-to late-life physical performance measures and incident AD and total dementia including AD. This paper will also discuss the potential mechanisms underlying the prospective associations between physical performance and incident AD.

Recent findings regarding the association

To date, a number of studies have addressed the aforementioned associations with various populations (e.g., different age or cognitive status at baseline), time frames (e.g., cross-sectional or longitudinal), and cognitive outcome measures (e.g., incidence of cognitive impairment, cognitive decline, or some cognitive disorders). Of those, in order to yield a direct and clear summary of the topic, this review focuses on prospective cohort studies with the following features: 1) cognitively intact individuals without dementia were intended to be recruited as participants of interest at baseline, 2) exposure variables were defined using some types of physical performance score, and 3) AD, total dementia including AD, or both were considered as outcome measures. Meta-analysis studies of such prospective cohort studies were also included.

After a literature search conducted in a quasi-systematic manner, 15 papers, including 14 prospective cohort studies9-20,22,23) and one meta-analysis study21), were identified and are summarized in Table 1. Overall, most studies examined participants older than 70 years of age at baseline except two studies recruiting middle-aged participants17,18). Baseline cognitive status was reported in 13 studies9-16,19-23). In these studies, participants were non-demented at baseline, but two studies included individuals with mild cognitive impairment (MCI) at baseline as a small part of the participants11,21). Another two studies didn’t examine baseline cognitive status while their participants were relatively young at baseline (average ages: 43.5 and 49.8 years) and probably unlikely to be demented17,18). Regarding the cognitive outcome measures in the studies identified, three used the incidence of AD12,14,19), two used the incidence of total dementia which includes AD18,20), seven included both incidences9,11,13,16,21,22), and one used the combined incidence of AD and MCI15). Another two studies didn’t directly address the incidence of AD and/or total dementia, but that of related events: mortalities due to AD/total dementia17) and “disabling dementia” based on an evaluation for older people with dementia administered in the Japanese long-term care insurance system23). Finally, in these studies, a variety of physical performance measures, including gait performance9,13,16,21-23), muscle...
strength\textsuperscript{12,14,15}, balance\textsuperscript{15,20}, aerobic performance\textsuperscript{17,18}, and composite physical performance\textsuperscript{10,11,19}, were found to be used as exposure variables. A brief summary of these recent findings will be discussed with respect to each of these exposure variables.

Gait performance. In five of the prospective cohort studies identified, gait performance was quantified as a main exposure variable through neurologic examination\textsuperscript{9}, laboratory-based evaluation\textsuperscript{13}, or field-based timed walk tests\textsuperscript{16,22,23}. Despite the difference in exposure variables investigated, all of the studies reported a significant association between late-life gait performance and the incidence of total dementia or a related event. A relative risk (RR) including hazard ratio (HR) and odds ratio (OR) for poorer gait performance ranged from 1.37 (95\% confidence interval [95\%CI]: 1.05-1.78)\textsuperscript{13} to 3.46 (95\%CI: 1.88-6.40)\textsuperscript{20}. The same association was also found in one study that examined a timed walk score as a supplementary exposure variable\textsuperscript{1} and in a meta-analysis study\textsuperscript{23}. This meta-analysis included pooled samples of 23,512 non-demented participants aged 60 years or older and found that those with poorer gait performance at baseline had an approximately 53\% increased risk for incident total dementia when compared to their normal counterparts (HR: 1.53, 95\%CI: 1.42-1.65)\textsuperscript{3}.

In contrast, findings regarding the association of late-life gait performance with incident AD were inconsistent. For example, one study conducted by Abellan van Kan\textsuperscript{60} reported that a unit decrease in baseline usual gait speed was associated with an increased risk for incident AD independent of demographics, self-reported physical activity, self-reported disabilities, comorbidities, and dual-energy X-ray absorptiometry (DXA)-derived body composition among 647 older women (OR: 3.38, 95\%CI: 1.80-6.33). A similar result was also reported in a French study examining the association in 3,663 community-dwelling older people\textsuperscript{22}. In this study, each 1-standard deviation (SD) decrease in usual gait speed was associated with an increased risk for incident AD (HR: 1.47, 95\%CI: 1.27-1.71) in an age/sex-adjusted model. This trend was preserved after excluding AD cases observed in the first four years of follow-up\textsuperscript{22}. However, two other prospective cohort studies, including AD diagnosis, reported no statistically significant association between late-life gait performance and incident AD\textsuperscript{11,13}. The aforementioned meta-analysis reported a significant association of gait performance with incident AD (HR: 1.03, 95\%CI: 1.01-1.05) while the pooled effect was weaker than that for non-AD dementia (HR: 1.89, 95\%CI: 1.60-2.22) and vascular dementia (VaD) (HR: 1.79, 95\%CI: 1.51-2.12)\textsuperscript{21}. One possible interpretation might be that the association observed between gait performance and total dementia was driven more by non-AD dementia including VaD.

Muscle strength. Four prospective cohort studies were found to examine muscle strength as a main exposure variable\textsuperscript{12,14,15} or a supplementary exposure variable\textsuperscript{11}. Of these, one study performed by Boyle and his colleague investigated an association between whole-body muscle strength and incident AD among 970 community-dwelling older adults\textsuperscript{41}. In this study, a comprehensive muscle strength score was derived from nine strength tests for muscles in upper and lower extremities and axial muscles at baseline. They found that a unit increase in the baseline comprehensive score was associated with about a 43\% decrease in the risk for incident AD (HR: 0.57, 95\%CI: 0.41-0.79); this association persisted after full adjustments of potential covariates including body mass index (BMI), self-reported physical activity, pulmonary function, vascular risk factors, vascular diseases, and apolipoprotein E4 (APOE4) status. In addition, they found that grip strength and axial muscle strength were associated with the risk of AD, independent of the other components of muscle strength (HR: 0.61, 95\%CI: 0.47-0.80 and HR: 0.68, 95\%CI: 0.53-0.87, respectively)\textsuperscript{40}. Another three studies examined the association between grip strength and incident AD and the results were inconsistent; two studies found a significant association\textsuperscript{11,22}, but one did not\textsuperscript{19}.

Balance. Three cohort studies addressed balance as a main exposure variable\textsuperscript{15,20} or a supplementary exposure variable\textsuperscript{11}. One German study reported that cognitively unimpaired participants who were successful in the one-foot balance test at the first examination had a reduced risk for incident AD/MCI at the third examination conducted 12 years later, compared to participants who failed the balance test (OR: 0.35, 95\%CI: 0.19-0.66)\textsuperscript{11}. A similar trend was also found in another study in which balance was treated as a supplementary exposure variable\textsuperscript{11}. In this study, standing balance was scored (0-4 points) by ability for each task: side by side for 10 seconds, semi-tandem for 10 seconds, full tandem for 1 to 9 seconds, and full tandem for 10 seconds. A significant association was found between the balance score and incident AD after adjusting for age and sex among 2,288 participants who were non-demented, but included 548 individuals with MCI at baseline (HR: 0.86, 95\%CI: 0.75-0.97). The association didn’t persist after additional adjustments for education, APOE4 status, family history of AD, baseline cognitive and depressive status, and comorbidities\textsuperscript{11}. Another short communication paper also reported that dementia-free participants having poor balance in the one-foot balance test at baseline had a greater risk for incident total dementia six years later when compared to those with normal balance at baseline (OR: 2.27, 95\%CI: 1.53-3.37)\textsuperscript{20}.

Aerobic performance. Although baseline cognitive status was unclear, two prospective cohort studies addressing middle-aged participants in relatively longer follow-up periods reported somewhat indirect but intriguing find-
Table 1. Summary of papers addressing associations of physical performance with incident Alzheimer’s disease and dementia.

| References    | Country, Study name or design, Participants (n, % of men, age* [year old] at baseline) | Physical performance measures | Follow-up duration (years) | Incident case of dementia | Main results |
|---------------|----------------------------------------------------------------------------------------|-------------------------------|---------------------------|--------------------------|--------------|
| Verghese (2002) | US, BAS, n=422, 35.8%, 79.1±3.1                                                        | Gait : normal vs. abnormal in neurologic status | 6.6 (median)              | DM: n=125                | Those with abnormal gait (n=85) had a greater incident risk for DM (HR: 1.96, 95%CI: 1.30-2.96) and non-AD (HR: 3.51, 95%CI: 1.98-6.24), but not for AD (HR: 1.07, 95%CI: 0.57-2.02). |
| Larson (2006)  | US, ACT, n=1,740, 39.8%, 74.4±5.7                                                     | Comprehensive : PPF including 10-ft timed walk, chair-stand time, standing balance, and grip strength (0-16: higher is better) | 6.2±2.0                   | DM: n=158                | Unit PPF increase was associated with a reduced incident risk for DM among those exercised <x3/week (HR: 0.89, 95%CI: 0.82-0.96), but not those ≥x3/week (HR: 1.01, 95%CI: 0.93-1.09). There was an interaction of exercise with PPF in relation to AD (p=0.021). |
| Wang (2006)    | US, ACT, n=2,288, 40.3%, 75.0±6.0                                                      | Comprehensive : PPF including 10-ft timed walk, chair-stand time, standing balance, and grip strength (0-16: higher is better) | 5.9 (mean)                | DM: n=319                | Unit PPF increase was associated with a reduced incident risk for DM (HR: 0.93, 95%CI: 0.89-0.97) and AD (HR: 0.94, 95%CI: 0.90-0.99) after full adjustments. Better timed walk and grip strength were also associated with a reduced incident risk for AD after full adjustments (HR: 0.81, 95%CI: 0.71-0.94 and HR: 0.86, 95%CI: 0.74-1.00, respectively). |
| Buchman (2007) | US, ROS, n=877, 30.7%, 74.4±6.9                                                        | Grip strength (higher is better) | 5.7±2.6                   | AD: n=132                | Unit increase of grip strength and that of annual increase of grip strength were associated with a reduced incident risk for AD (HR: 0.986, 95%CI: 0.973-0.998 and HR: 0.915, 95%CI: 0.884-0.948, respectively). |
| Verghese (2007) | US, EAS, n=399, 43.6%, 79.2±4.9                                                        | Gait: continuous variables for pace, rhythm, and variability (higher is worse) | 2.0 (median)              | DM: n=33                 | Unit increases of rhythm and variability factors were associated with an increased incident risk for DM (HR: 1.48, 95%CI: 1.03-2.14 and HR: 1.37, 95%CI: 1.05-1.78, respectively). No association was found for incident AD. |
| Boyle (2009)   | US, RMA, n=970, 24.8%, 80.3±7.5                                                         | Muscle strength: composite measure of testing 11 muscle groups (higher is better) | 3.6±1.5                   | AD: n=138                | Unit increase of muscle strength was associated with a decreased incident risk for AD (HR: 0.57, 95%CI: 0.41-0.79). Grip strength and axial muscle strength were associated with the risk of AD independent of the other indices (HR: 0.61, 95%CI: 0.47-0.80 and HR: 0.68, 95%CI: 0.53-0.87, respectively). |
| Sattler (2011) | Germany, ILSE, n=300, 50.7%, 74.3±1.1**                                                | Balance: success vs. fail in one foot balance | 12 (1st to 3rd waves)     | AD: n=24 MCI: n=102      | Those with successful balance at 1st wave had a reduced incident risk for AD and MCI at 3rd wave (OR: 0.35, 95%CI: 0.19-0.66). Grip strength was not associated with incident AD and MCI (OR: 1.00, 95%CI: 0.99-1.01). |
### Incident case

| Study                  | Country, Study, n | Gait: usual speed (higher is better) | Aerobic: MET to maximal aerobic power in GXT (higher is better) | Aerobic: maximal time in GXT that highly correlated with VO2max (r=.92) (higher is better) | Balance: poor performance defined by standardized tests of walking | Comprehensive: PPT including 9 life-related tasks (0-36: higher is better) | Gait: speed and decline in speed (higher is better) | Gait: speed and step length at usual and maximal paces; high, middle, and low in each index (higher is better) |
|-----------------------|------------------|-------------------------------------|---------------------------------------------------------------|---------------------------------------------------------------------------------|-----------------------------------------------------------------|----------------------------------------------------------|----------------------------------------------------------|---------------------------------------------------------------------------------|
| Abellan van Kan (2012) | France, EPI-DOS, n=647, 0%, 75 or older | 7 (baseline to follow-up) | DM: n=145 AD: n=71 non-AD: n=74 MCI: n=53 | DM: n=164 AD: n=92 VaD: n=72 (mortality) | | Unit decrease in gait speed was associated with an increased incident risk for DM (OR: 2.28, 95%CI: 1.32-3.94) and AD (OR: 3.38, 95%CI: 1.80-6.33). |
| Liu (2012)            | US, ACLS, n=59,889, 75.3%, 43.5±10.0 | 17 (mean) | DM: n=53 AD: n=75 | DM: n=164 AD: n=92 VaD: n=72 (mortality) | Longer maximal time in GXT was associated with a reduced incident risk for DM, 1.03 (95%CI: 1.01-1.05) for AD, 1.89 (95%CI: 1.60-2.22) for non-AD, and 1.79 (95%CI: 1.51-2.12) for VaD. |
| DeFina (2013)         | US, CCLS, n=19,458, 78.9%, 49.8±8.7 | 24.0±8.3 | DM: n=1,659 | DM: n=1,659 | Longer maximal time in GXT was associated with a reduced incident risk for DM (HR: 0.64, 95%CI: 0.54-0.77 when comparing the highest vs. lowest quintiles and HR: 0.93, 95%CI: 0.90-0.95 for unit increase of maximal time). |
| Wilkins (2013)        | US, KADRC, n=435, 39.1%, 75.9±8.8 | 5 (mean) | DM: n=81 | DM: n=136 | Those with poor balance had a greater incident risk for DM (OR: 2.27, 95%CI: 1.53-3.37). |
| Lee (2015)            | Hong Kong, prospective cohort, n=1,775, 37.5%, 73-75 (median) | 6 (baseline to follow-up) | DM: n=136 | DM: n=136 | Those with poor balance had a greater incident risk for DM (OR: 2.27, 95%CI: 1.53-3.37). |
| Beauchet (2016)       | Multicountry, meta-analysis, n=23,512, % unclear, ≥60 to ≥75 | 3-9 (range) | (Not clearly reported) | (Not clearly reported) | Pooled HRs for those with poor gait were 1.53 (95%CI: 1.42-1.65) for DM, 1.03 (95%CI: 1.01-1.05) for AD, 1.89 (95%CI: 1.60-2.22) for non-AD, and 1.79 (95%CI: 1.51-2.12) for VaD. |
| Dumurgier (2016)      | France, 3CS, n=3,663, 38.1%, 73.5±4.7 | 7.8 (median) | DM: n=296 AD: n=226 VaD: n=20 Other: n=50 | DM: n=296 AD: n=226 VaD: n=20 Other: n=50 | 1-SD decrease in gait speed was associated with an increased incident risk for DM (HR: 1.59, 95%CI: 1.39-1.81) and AD (HR: 1.47, 95%CI: 1.27-1.71). Those with a steeper decline of gait speed had a greater incident risk of DM (HR for 1-SD annual decline of gait speed: 3.39, 95%CI: 1.37-8.43). |
| Taniguchi (2017)      | Japan, KTS, n=1,686, 43.7%, 71.2±5.6 | 6.7±3.8 | DM: n=196 | DM: n=196 | Those in low group (vs. high) for gait speed and step length at usual and maximal paces had a greater incident risk for disabling DM (HR: 3.46, 95%CI: 1.88-6.40 and HR: 2.12, 95%CI: 1.29-3.49 at usual pace and HR: 2.05, 95%CI: 1.02-4.14 and HR: 2.80, 95%CI: 1.48-5.28 at maximal pace, respectively). |

**US:** United States, **BAS:** Bronx Aging Study, **ACT:** Adult Changes in Thought Study, **EAS:** Einstein Aging Study, **ROS:** Religious Orders Study, **ACLS:** Aerobics Center Longitudinal Study, **CCLS:** Cooper Center Longitudinal Study, **KADRC:** Knight Alzheimer’s Disease Research Center Study, **3CS:** Three-City Study, **KTS:** Kusatsu Town Study, **PPF:** Performance-based physical function test, **MET:** Metabolic equivalent, **GXT:** Graded exercise test, **VO2max:** Maximal oxygen consumption, **PPT:** Physical Performance Test, **DM:** total dementia, **AD:** Alzheimer’s disease, **MCI:** mild cognitive impairment, **VaD:** vascular dementia, **HR:** hazard ratio, **95%CI:** 95% confidence interval, **OR:** odds ratio. *In most cases, the mean and standard deviation of age for total group were estimated based on those reported for multiple stratified groups (e.g., men and women) in each paper. **Mean and standard deviation of age at the third examination waves. #Incident case of mortality due to total dementia, AD, VaD, respectively. #Incident case of “disabling dementia” defined in the Japanese long-term care insurance system.
ings regarding an association between baseline aerobic performance and incident AD\(^7,18\). One study performed maximal graded exercise testing (GXT) on a treadmill at baseline on 59,889 middle-aged participants. They determined metabolic equivalents (METs) corresponding to maximal aerobic power and examined its association with mortality due to AD in an average period of 17 years of follow-up\(^7\). This study found that each 1-MET increase in aerobic performance was associated with a reduced risk for incident mortality due to AD after controlling for potential confounders including demographics, BMI, abnormal exercise electrocardiogram, and health status (HR: 0.87, 95%CI: 0.76-0.99). This HR was comparable to that for VaD (HR: 0.82, 95%CI: 0.71-0.96) and total dementia (HR: 0.86, 95%CI: 0.78-0.94). Another study examined maximal time on a treadmill test, which was highly correlated with maximal oxygen consumption, in 19,458 middle-aged participants at baseline\(^8\). This study reported that longer maximal times were associated with a reduced risk for incident total dementia when comparing the highest and lowest quintiles with multivariate adjustment over an average of 24 years of follow-up (HR: 0.64, 95%CI: 0.54-0.77). They also found that a unit increase in maximal time was associated with a reduced risk of total dementia (HR: 0.93, 95%CI: 0.90-0.95).

**Composite physical performance.** Two US research groups measured composite physical performance as an exposure variable\(^10,11,19\). Larson and his colleague used a composite test called the performance-based physical function (PPF) test, which consisted of four performance tests: timed walk, repeated chair-stand time, standing balance, and grip strength. The PPF score was calculated as the sum of the scores for the four tests and ranged 0 to 16\(^9,10,11\). One prospective cohort study from this research group showed that each 1-point increase in the PPF score was associated with a reduced risk for incident total dementia and AD in 2,288 non-demented participants after adjusting for potential confounding factors (HR: 0.93, 95%CI: 0.89-0.97 and HR: 0.94, 95%CI: 0.90-0.99, respectively)\(^19\). A different study from the same group also reported a supplementary finding that each 1-point increase in PPF score was associated with a reduced risk for incident total dementia in those who exercised less than three times a week (HR: 0.89, 95%CI: 0.82-0.96), but not among those who exercised equal to or more than three times a week\(^9\). They also found a similar interaction between exercise and PPF scores in relation to AD (p=0.021).

Another US research group used a modified version of a conventional test, the physical performance test (PPT), consisting of nine life-related tasks: writing a sentence, spooning beans into a container, lifting a book, putting on and taking off a jacket, picking up a penny from the floor, turning in a complete circle, walking 50 feet, sitting in and rising from a chair five times, and standing with feet in tandem, semi-tandem, and side-by-side positions\(^5\). The PPT score was then determined as the total of the scores for the nine tests with a highest possible score of 36. This study reported that a unit increase in baseline PPT score was associated with a decreased risk for incident AD after controlling for age, sex, education, and APOE4 status in 435 participants with normal cognition at baseline (HR: 0.94, 95%CI: 0.89-0.99).

**Overview.** In this section, poor aerobic performance in midlife and poor gait performance, muscle strength, balance, and composite physical performance in late-life are suggested to be associated with a greater risk for the future incidence of AD and/or total dementia in cognitively healthy individuals. Despite the limited number of studies and some inconsistency of the results for several measures, these findings show some promise that impairments in these physical performance measures precede incident AD. If this is the case, these measures are expected to have good potential as predictive factors facilitating the early identification of people at a higher risk of AD. However, further prospective cohort studies are needed to rule out potential publication bias for the current findings, as well as to validate the generalizability of the findings to people living in various regions, such as Japan.

**Potential mechanisms underlying the association**

In addition to studies establishing consistent and concrete evidence for the prospective association between physical performance and the future incidence of AD, further studies are also needed to have clearer insights into the potential physiological and sociobehavioral mechanisms underlying the association. Although it is possible, the prospective associations discussed so far may not simply mean that these physical performance measures are “causal risk/protective factors” or “determinants” of the future incidence of AD. Rather, mechanisms underlying the associations are probably much more complicated and still remain to be clarified. Despite the current circumstances, this section will attempt to discuss not all, but several plausible mechanisms underlying the association in accordance with a hypothetical framework shown in Fig. 2.

**Preclinical AD pathologies may underlie the association**

Many types of physical performance, such as the exertion of muscle force, walking, and balancing in given environmental constraints, require complex interactions of motor, sensory, and cognitive functions regulated by motor control systems located throughout the central and peripheral nervous systems\(^5\). In recent investigations, preclinical AD pathologies, such as amyloidosis and neurodegeneration including cortical thinning, brain atrophy, and dysregulation of tau protein (Fig. 1), have been observed not only in the brain regions responsible for
cognitive function, but also in motor-related regions of the brain. For example, one magnetic resonance imaging (MRI) study demonstrated significant longitudinal tissue loss in overall brain structures including cognitive- and motor-related regions even in very healthy older adults. This study suggests that overall brain atrophy could have commenced in individuals who remained medically and cognitively healthy. In addition, other studies demonstrated that AD pathologies may also accumulate in brain regions involved in the initiation and regulation of motor function, such as the motor cortices, striatum, and substantia nigra.

As these pathological processes, found in the hippocampus and other cognitive regions, are reported to frequently deteriorate cognitive function, those in motor-related brain regions could also lead to declines in physical performance. In fact, several studies found an association between AD pathologies and motor decline. For example, one case-control study using MRI indicates that subcortical white matter lesions are associated with a decline in gait and balance performance, where white matter lesions are known to be related to hippocampal atrophy, a typical preclinical AD pathology. Another study also suggests that neurofibrillary tangles found in the substantia nigra are associated with gait disturbance in individuals without dementia. In line with the above findings, a low score in a challenging cognitive test (Montreal Cognitive Assessment or MoCA), another signature of preclinical AD, was associated with poor scores in five physical performance tests in community-dwelling older people free from dementia.

Taken together, these findings raise the possibility that preclinical AD pathologies underlie the association between impairment in several physical performances requiring regulation of the motor control systems and the subsequent incidence of AD as a common pathogenesis.

**Potential mechanisms underlying association of physical performance with incident Alzheimer’s disease.**

This figure depicts a hypothetical framework of multiple and intricately intertwined mechanisms underlying the association. Here, the associations between physical performance measures and incident AD are shown to mostly be non-causal, but prospective, where physical performance measures serve as “early markers” of future incidence of AD. Please note that presumably there exist many other mechanisms not included in this framework. That is, this framework is not comprehensive but is a summary of several possible, evidence-based mechanisms. The term “fitness” denotes “the state of being physically sound and healthy, especially as the result of exercise and nutrition” here. AD: Alzheimer’s disease, MVPA: moderate-to-vigorous physical activity.

**Physical fitness may underlie the association.** Fitness generally denotes “the state of being physically sound and healthy, especially as the result of exercise and nutrition” and may include not only a visible, but also invisible biophysiological “sound state” in our body. It is widely accepted that optimal modes of exercise (e.g., resistance and aerobic training) and physical activity (e.g.,
moderate-to-vigorous physical activity or MVPA) improve physical fitness, including muscular and cardiovascular fitness; and inversely, lack of regular exercise and a sedentary/inactive lifestyle results in the deterioration of such fitness. Whereas other factors also affect physical fitness, physical performance measures, including those discussed in the last section, are considered to reflect the causal association of exercise and physical activity with such physical fitness components (Fig. 2).

Previous findings suggest that muscular and cardiovascular fitness play roles in preserving the integrity of the brain in late-life through various physiological mechanisms, and probably lower the risk of incident AD. For example, one case-control study reported that reduced lean mass was associated with brain atrophy and poor cognitive performance in older individuals\(^{34}\). Other studies have also demonstrated that high cardiovascular fitness, evaluated by aerobic performance measures, was associated with reduced brain atrophy in older people with normal cognitive status\(^{35}\) or in early AD\(^{36}\). These studies indicate that physical fitness may moderate brain atrophy and probably slow or prevent the incidence of AD. Another recent study reported that a higher level of peripheral brain-derived neurotropic factor (BDNF) was associated with a lower risk of incident AD\(^{37}\). Because the peripheral BDNF was associated with age-related decline of hippocampal volume in non-demented older adults\(^{38}\), and was shown to increase after chronic exercise training\(^{39}\), it sounds plausible that BDNF partly mediates the protective and preventive effects of physical fitness. Other potential mechanisms for this may include reductions of oxidative stress, inflammation, and insulin resistance by the expression of peroxisome proliferators-activated receptor-\(\gamma\) co-activator-1\(\alpha\) (PGC-1\(\alpha\))\(^{40,41}\), and preserved cerebral blood flow and oxygen delivery\(^{42}\).

Although many other mechanisms may also mediate the protective and preventive effects, the above findings indicate that physical fitness has a causal association with incident AD, and underlies the association between physical performance measures and the incidence of AD (Fig. 2). In this case, physical performance measures are considered to be early markers of incident AD reflecting the status of physical fitness.

**Physical performance may dictate exercise and physical activity.** Despite the lack of evidence, another potential mechanism might be that physical performance dictates the levels of daily-life physical activity and exercise in older people, and therefore, serves as an indirect risk/pro-\(\text{tective factor for incident AD (Fig. 2). One recent study discussed this hypothesis}\(^{43}\) by explaining the previous findings that older people with a decline in physical performance were likely to have lower functional mobility with an increased risk of falls, and therefore, tended to avoid activities due to a fear of falling\(^{44,45}\). Another study also indicates that community-dwelling older people with lower gait speeds have a greater risk for the cessation of habitual leisure-time physical activity\(^{46}\). Although these findings appear to be plausible, further sociobehavioral studies are needed to add support for the above hypothesis.

**Overview.** This section discussed several potential mechanisms underlying the associations between physical performance measures and incident AD. Here, the associations are speculated to be mostly non-causal, but prospective, where the physical performance measures may serve as early markers of future incidence of AD. It is also speculated that preclinical AD and non-AD pathologies and physical fitness status may underlie the associations. However, it is reasonable to say that the entire picture of these mechanisms is largely unknown and still to be clarified.

**Summary.**

This review paper has briefly summarized recent findings regarding the associations between middle- to late-life physical performance measures and incident AD, and discussed several potential mechanisms underlying the associations. Recent findings suggest that poor baseline status in physical performance measures, such as gait performance, muscle strength, balance, aerobic performance, and composite physical performance, is associated with greater risk for the subsequent incidence of AD. Such associations may suggest that declines in these physical performance measures precede incident AD. Although the underlying mechanisms are largely unknown, it is suggested that the prospective associations appear to be mostly non-causal, where physical performance measures probably serve as early markers of the future incidence of AD. Future studies are expected to establish solid evidence of the prospective association between physical performance and incident AD, to clarify the whole picture of the mechanisms underlying the association, and also to explore the practical application of such physical performance measures in clinical and non-clinical attempts to identify individuals at a higher risk of AD as early as possible.

**Conflict of Interests**

The authors declare that there is no conflict of interests regarding the publication of this article.

**References**

1) Japanese Ministry of Health, Labour and Welfare. Long-term care insurance system of Japan. [internet]. [cited 2017 April 1]. Available from: http://www.mhlw.go.jp/english/policy/care-welfare/care-welfare-elderly/dl/ltcisj_e.pdf

2) Japanese Ministry of Health, Labour and Welfare. Comprehensive survey of living conditions 2010. [internet]. [cited
12) Buchman AS, Wilson RS, Boyle PA, Bienias JL and Bennett DA. 2009. Incidence and survival of dementia in a general population of Japanese elderly: the Hisayama study. J Neurol Neurosurg Psychiatry 80: 366-370.

11) Wang L, Larson EB, Bowen JD and van Belle G. 2006. Lifestyle-related factors in predementia and dementia syndromes. Expert Rev Neurother 8: 133-158.

7) Barnes DE and Yaffe K. 2009. Predicting dementia: role of dementia risk indices. Future Neurol 4: 555-560.

8) Anstey KJ, Cherbuin N, Herath PM, Qiu C, Kuller LH, Lopez OL, Wilson RS and Fratiglioni L. 2014. A self-report risk index to predict occurrence of dementia in three independent cohorts of older adults: the ANU-ADRI. PLoS One 9: e86141.

9) Verghese J, Lipton RB, Hall CB, Kuslansky G, Katz MJ and Buschke H. 2002. Abnormality of gait as a predictor of non-Alzheimer’s dementia. N Engl J Med 347: 1761-1768.

10) Larson EB, Wang L, Bowen JD, McCormick WC, Teri L, Crane P and Kukull W. 2006. Exercise is associated with reduced risk for incident dementia among persons 65 years of age and older. Ann Intern Med 144: 73-81.

11) Wang L, Larson EB, Bowen JD and van Belle G. 2006. Performance-based physical function and future dementia in older people. Arch Intern Med 166: 1115-1120.

12) Buchman AS, Wilson RS, Boyle PA, Bienias JL and Bennett DA. 2007. Grip strength and the risk of incident Alzheimer’s disease. Neuroepidemiology 29: 66-73.

13) Verghese J, Wang C, Lipton RB, Holtzer R and Xue X. 2007. Quantitative gait dysfunction and risk of cognitive decline and dementia. J Neurol Neurosurg Psychiatry 78: 929-935.

14) Boyle PA, Buchman AS, Wilson RS, Leurgans SE and Bennett DA. 2009. Association of muscle strength with the risk of Alzheimer disease and the rate of cognitive decline in community-dwelling older persons. Arch Neurol 66: 1339-1344.

15) Sattler C, Erickson KL, Toro P and Schröder J. 2011. Physical fitness as a protective factor for cognitive impairment in a prospective population-based study in Germany. J Alzheimer Dis 26: 709-718.

16) Abellan van Kan G, Rolland Y, Gillette-Guyonnet S, Gardette V, Annweiler C, Beauchet O, Andrieu S and Vellas B. 2012. Gait speed, body composition, and dementia. The EPIDOS-Toulouse cohort. J Gerontol A Biol Sci Med Sci 67: 425-432.

17) Liu R, Sui X, Laditka JN, Church TS, Colabianchi N, Hussey J and Blair SN. 2012. Cardiorespiratory fitness as a predictor of dementia mortality in men and women. Med Sci Sports Exerc 44: 253-259.

18) Defina LF, Willis BL, Radford NB, Gao A, Leonard D, Haskell WL, Weiner MF and Berry JD. 2013. The association between midlife cardiorespiratory fitness levels and later-life dementia: a cohort study. Ann Intern Med 158: 162-168.

19) Wilkins CH, Roe CM, Morris JC and Galvin JE. 2013. Mild physical impairment predicts future diagnosis of dementia of the Alzheimer’s type. J Am Geriatr Soc 61: 1055-1059.

20) Lee AT, Richards M, Chan WC, Chiu HF, Lee RS and Lam LC. 2015. Poor balance as a noncognitive predictor of incident dementia. J Am Geriatr Soc 63: 1701-1702.

21) Beauchet O, Annweiler C, Callisaya ML, De Cock AM, Hellbostad JL, Kressig RW, Srikanth V, Steinmetz JP, Blumen HM, Verghese J and Allali G. 2016. Poor gait performance and prediction of dementia: results from a meta-analysis. J Am Med Dir Assoc 17: 482-490.

22) Dumurgier J, Artaud F, Touraine C, Rouaud O, Tavernier B, Dufouil C, Singh-Manoux A, Tzourio C and Elbaz A. 2017. Gait speed and decline in gait speed as predictors of incident dementia. J Gerontol A Biol Sci Med Sci 72: 655-661.

23) Taniguchi Y, Kitamura A, Seino S, Murayama H, Amano H, Nofuji Y, Nishi M, Yokoyama Y, Shinozaki T, Yokota I, Matsuyama Y, Fujiwara Y and Shinkai S. 2017. Gait performance trajectories and incident disabling dementia among community-dwelling older Japanese. J Am Med Dir Assoc 18: 192.e13-192.e20.

24) Resnick SM, Pham DL, Kraut MA, Zonderman AB and Davatzikos C. 2003. Longitudinal magnetic resonance imaging studies of older adults: a shrinking brain. J Neurosci 23: 3295-3301.

25) Suva D, Favre I, Kraftsik R, Esteban M, Lobrinius A and Miklosy J. 1999. Primary motor cortex involvement in Alzheimer disease. J Neuropathol Exp Neurol 58: 1125-1134.

26) Gearing M, Levey AI and Mirra SS. 1997. Diffuse plaques in the striatum in Alzheimer disease (AD): relationship to the striatal mosaic and selected neuropeptide markers. J Neuropathol Exp Neurol 56: 1363-1370.

27) Burns JM, Galvin JE, Roe CM, Morris JC and McKeel DW. 2005. The pathology of the substantia nigra in Alzheimer disease with extrapyramidal signs. Neurology 64: 1397-1403.

28) Schneider JA, Li JL, Li Y, Wilson RS, Kordower JH and Bennett DA. 2006. Substantia nigra tangles are related to gait impairment in older persons. Ann Neurol 59: 166-173.

29) Baloh RW, Yue Q, Socotom-T and Jacobson KM. 1995. White matter lesions and disequilibrium in older people. I. Case-control comparison. Arch Neurol 52: 970-974.

30) de Leeuw FE, Barkhof F and Scheltens P. 2004. White matter lesions and hippocampal atrophy in Alzheimer’s disease. Neurology 62: 310-312.

31) Schneider JA, Li JL, Li Y, Wilson RS, Kordower JH and Bennett DA. 2006. Substantia nigra tangles are related to gait impairment in older persons. Ann Neurol 59: 166-173.

32) Narazaki K, Matsuo E, Honda T, Nofuji Y, Yonemoto K and Kumagai S. 2014. Physical fitness measures as potential markers of low cognitive function in Japanese community-dwelling older adults without apparent cognitive problems. J Sports Sci Med 13: 590-596.

33) Compact American Medical Dictionary. Edited by American Heritage Dictionaries. New York: Houghton Mifflin Company, 1998. ISBN 0-395-88409-8.

34) Burns JM, Johnson DK, Watts A, Swerdlow RH and Brooks
WM. 2010. Reduced lean mass in early Alzheimer disease and its association with brain atrophy. *Arch Neurol* 67: 428-433.

35) Colcombe SJ, Erickson KI, Raz N, Webb AG, Cohen NJ, McAuley E and Kramer AF. 2003. Aerobic fitness reduces brain tissue loss in aging humans. *J Gerontol A Biol Sci Med Sci* 58: 176-180.

36) Burns JM, Cronk BB, Anderson HS, Donnelly JE, Thomas GP, Harsha A, Brooks WM and Swerdlow RH. Cardiorespiratory fitness and brain atrophy in early Alzheimer disease. *Neurology* 71: 210-216.

37) Weinstein G, Beiser AS, Choi SH, Preis SR, Chen TC, Vorgas D, Au R, Pikula A, Wolf PA, DeStefano AL, Vasan RS and Seshadri S. 2014. Serum brain-derived neurotrophic factor and the risk for dementia: the Framingham Heart Study. *JAMA Neurol* 71: 55-61.

38) Erickson KI, Prakash RS, Voss MW, Chaddock L, Heo S, McLaren M, Pence BD, Martin SA, Vieira VJ, Woods JA, McAuley E and Kramer AF. 2010. Brain-derived neurotrophic factor is associated with age-related decline in hippocampal volume. *J Neurosci* 30: 5368-5375.

39) Dinoff A, Herrmann N, Swaidfliger W, Liu CS, Sherman C, Chan S and Lancêtö KL. 2016. The effect of exercise training on resting concentrations of peripheral brain-derived neurotrophic factor (BDNF): a meta-analysis. *PLoS One* 11: e0163037.

40) Handschin C and Spiegelman BM. 2008. The role of exercise and PGC1α in inflammation and chronic disease. *Nature* 454: 463-469.

41) Sweeney G and Song J. 2016. The association between PGC-1α and Alzheimer’s disease. *Anat Cell Biol* 49: 1-6.

42) Thomas BP, Yezhuvath US, Tseng BY, Liu P, Levine BD, Zhang R and Lu H. 2013. Life-long aerobic exercise preserved baseline cerebral blood flow but reduced vascular reactivity to CO2. *J Magn Reson Imaging* 38: 1177-1183.

43) Veronese N, Stubbs B, Trevisan C, Bolzetta F, De Rui M, Solmi M, Sartori L, Musacchio E, Zambon S, Perissinotto E, Crepaldi G, Manzato E and Sergi G. 2016. What physical performance measures predict incident cognitive decline among intact older adults? A 4.4 year follow up study. *Exp Gerontol* 81: 110-118.

44) Stubbs B, Schofield P and Patchay S. 2016. Mobility limitations and fall-related factors contribute to the reduced health-related quality of life in older adults with chronic musculoskeletal pain. *Pain Pract* 16: 80-89.

45) Stubbs B, Schofield P, Patchay S and Leveille S. 2016. Musculoskeletal pain characteristics associated with lower balance confidence in community-dwelling older adults. *Physiotherapy* 102: 152-158.

46) Shimada H, Lord SR, Yoshida H, Kim H and Suzuki T. 2007. Predictors of cessation of regular leisure-time physical activity in community-dwelling elderly people. *Gerontology* 53: 293-297.