Older People with Dementia Have Reduced Daily-Life Activity and Impaired Daily-Life Gait When Compared to Age-Sex Matched Controls

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Abstract. Understanding the characteristics of physical activity and daily-life gait in older people with dementia may help identify those at risk of negative health outcomes and inform targeted interventions. Questionnaires are often used to assess physical activity but may be more affected by recall bias in people with dementia and provide little information about daily-life gait characteristics. The aim of the study was to assess differences in daily-life activity levels and gait characteristics between community-dwelling older people with mild to moderate dementia (n = 45; mean age 81 ± 6 years, 42% female) and age-sex matched (1:2) cognitively-healthy controls (n = 90). Participants wore a tri-axial accelerometer (DynaPort MoveMonitor, McRoberts) on their lower back for 7 days and were assessed on neuropsychological and physical performance. Compared to age-sex matched controls, participants with dementia demonstrated reduced daily-life activity (fewer steps per day, fewer and shorter walking bouts, and lower daily walk time) and walking intensity (reduced speed, stride length and cadence). Participants with dementia also had significantly increased within-walk variability (stride time) and less regular gait (higher sample entropy). Within the group of participants with dementia, higher daily-life activity levels were associated with greater self-reported physical activity and better executive function. Fallers (1+ falls past year) with dementia had significantly reduced daily-life activity and walking speed when compared to non-fallers with dementia. In conclusion, people with dementia are less active in daily-life and present with significant impairments across multiple gait domains when compared to age-sex matched controls. These findings highlight opportunities for targeted interventions and support further research to examine interventions aimed at addressing these deficits.

Keywords: Accidental falls, daily-life gait, dementia, executive function, neurocognitive disorders, physical activity, walking speed

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INTRODUCTION

Dementia is a global health challenge, in that, with population aging, the number of people with dementia and the associated cost will increase exponentially in the coming years [1]. Cognitive decline is the hallmark feature of dementia, but functional and physical impairments are also present, and these impairments have been associated with important health outcomes [2, 3]. For example, clinically assessed gait impairments (e.g., slow gait speed and increased variability) have been identified as important fall risk factors in this population [3, 4].

Quantitative gait assessments performed under standardized conditions tend to assess “best-performance” rather than “usual” gait and have low to moderate correlations with corresponding measures of daily-life gait [5, 6]. While the dual task paradigm can elucidate adverse effects of secondary cognitive and physical tasks on gait performance in the clinic setting [4], it only partially reflects the challenges to gait experienced in more complex home and community environments [7, 8]. Recent studies have highlighted differences in daily-life gait and gait assessed under standardized conditions in healthy older people, which suggests they represent different constructs of physical function [6, 9]. However, daily-life and standardized gait assessments have not been compared in people with dementia and may differ to healthy controls due to their physical and cognitive impairments [2].

Previous research has demonstrated significant relationships between poorer neuropsychological performance, particularly executive function, and impaired gait tested under standardized conditions and reduced self-reported physical activity (PA) [4, 10, 11]. However, in people with dementia, self-reported PA may suffer recall bias. Two recent studies of daily-life gait in community-dwelling participants with dementia reported significant associations between objectively measured PA or daily-life gait and cognitive performance (global cognition [8] and attention/concentration [7]), but not executive function. These studies have limitations, however, in that both enrolled small samples (i.e., 16 and 24 participants) and neither included age-sex matched controls. Therefore, further research is warranted to examine the relationship between objectively measured PA and daily-life gait patterns in this population will quantify how physical and cognitive impairments influence everyday function and activities.

The primary aim of this study was to compare daily-life gait in community-dwelling older people with dementia to age-sex matched controls (1:2 ratio; 45:90 participants). Secondary aims included investigating the relationship between daily-life gait and: 1) self-reported PA, 2) history of falls, and 3) neuropsychological function in participants with dementia. We hypothesized that participants with dementia would be less active and have impaired gait when compared to the cognitively healthy age-sex matched controls. We further hypothesized that PA measured using a questionnaire would be moderately correlated with objectively measured daily-life activity, in line with previous research [12], and this correlation would be weaker in participants with dementia compared to controls because of difficulties with recall in this group, and that previous falls and poorer cognitive performance, especially executive dysfunction, would be associated with lower daily-life activity levels and poorer daily-life gait performance (particularly increased daily-life gait variability) in participants with dementia.

METHODS

Study design

Case-control study of daily-life activity and daily-life gait in a convenience sample of participants with dementia and age-sex matched healthy controls (1:2).

Participants

Forty-five community-dwelling participants with mild to moderate dementia took part in a feasibility trial of StandingTall or a cognitive training randomized controlled trial (RCT; Australian New Zealand Clinical Trials Registry [ANZCTR] 12617000364370). For these studies, participants were recruited from health services, e.g., Cognitive Disorders/Memory/Aged Care Clinics or had previously participated in research projects and agreed to be contacted for future studies. Mild to moderate dementia was defined as a specialist clinician diagnosis of dementia, Mini-Mental State Examination (MMSE) <24 (sensitivity 85%, specificity 90% for dementia) [13] and/or Addenbrooke’s Cognitive Examination (ACE)-III <83 (sensitivity 93%, speci-
criteria for the in residential aged care facility. Additional exclusion ity to speak English, blindness, delirium and living dementia, acute/severe psychiatric conditions, inabil-

Exclusion criteria included: severe dementia (MMSE <11), progressive neurological conditions other than dementia, acute/severe psychiatric conditions, inabil-

ficity 100% for dementia) [14]. Inclusion criteria were: aged ≥60 years, living in the community, on a stable dose of dementia medication for 3 months and an available person responsible/caregiver who had a minimum of 3.5 h face-to-face contact each week. Exclusion criteria included: severe dementia (MMSE <11), progressive neurological conditions other than dementia, acute/severe psychiatric conditions, inability to speak English, blindness, delirium and living in residential aged care facility. Additional exclusion criteria for the StandingTall trial were indoor walking aid use and unstable medical conditions precluding exercise participation. Ethical approval was obtained from the South Eastern Sydney Local Health District Human Research Ethics Committee and all participants and their person responsible/caregivers consented to participation prior to baseline assessment.

The comparison group of 90 cognitively healthy community-dwelling participants were drawn from the StandingTall balance exercise RCT (ACTRN 1261500138583) [15]. These participants were recruited from advertisements in community services newsletters, notice boards, local newspapers, social media, retirement villages and community centers. Inclusion criteria were: ≥70 years, community-dwelling, English-speaking and able to walk in their home without the use of a walking aid. Exclusion criteria included: unstable or acute medical condition that precluded exercise participation, progressive neurological conditions, cognitive impairment (Short Portable Mental Status Questionnaire score <8 [sensitivity 100%, specificity 97–100% for dementia]) [13], and/or current participation in a fall prevention program. Ethical approval for the cognitively healthy cohort was obtained from UNSW Ethics Committee and all participants consented to participation prior to baseline assessment.

Assessment

Assessments were conducted at participants’ homes and/or at Neuroscience Research Australia. For participants of RCTs, the baseline assessments were completed prior to randomization. Baseline data were used for all participants. Demographic characteristics, falls in the past year, and medical history were collected through interview. For participants with dementia, their person responsible/caregiver was also present for the interview and contributed to question responses. A fall was defined as ‘an event that involves the person unintentionally coming to rest on the ground or lower level’ [16]. Self-reported PA was assessed with caregiver assistance using the Incidental and Planned Exercise Questionnaire (IPEQ) and expressed as hours/week of walking as well as incidental, planned and total activity [17].

Daily-life activity and daily-life gait

Participants wore a tri-axial accelerometer (DynaPort MoveMonitor, McRoberts, The Hague, The Netherlands) housed in a small (107 × 58 × 11.5 mm), light (55 grams) case for seven consecutive days. The accelerometer was worn using an elastic belt around the trunk, with the accelerometer positioned dorsally over the lumbar spine region. Acceleration data were recorded with a sample frequency of 100 Hz and with a range of ±6 gravitational acceleration. Participants were instructed to wear the accelerometer during waking hours except during activities involving water (such as showering). The MoveMonitor can detect and classify walking with a sensitivity of 86–94% and specificity of 72–99% and ‘not worn’ periods with a sensitivity of 89% and specificity of 100%, as well as extract total walking time, number of steps, number of walking bouts, and walking bout durations [18, 19]. Using a minimum wear time criterion of six hours per day for at least two days, we used the McRoberts algorithm to determine daily-life activity/gait quantity (macro gait characteristics), including mean steps per day, mean number of walking bouts per day and mean daily walk time (minutes) as our measures of daily-life activity. Mean steps per day was selected as our PA questionnaire comparison measure of physical activity because it is easy to understand, accurate, commonly used to measure physical activity and has been associated with health outcomes [20]. Daily-life gait duration was calculated from all walks ≥3 steps (Fig. 1). Gait duration (%) was assessed by summing all walk durations of ≥60 s (as a measure of capacity to complete long walks without pausing), then dividing by total walking time and multiplying by 100 [21].

Daily-life gait characteristics related to quality of gait (micro gait characteristics) were determined from all walks greater than 8-steps [22] or 10 s [23, 24], depending on the measure and in line with published methods (a minimum of 50 walking bouts was required from each participant). Gait intensity was assessed by estimating median walking speed [25, 26], stride length [24, 25] and cadence [22]. Within-walk variability (Fig. 2A, B) was estimated as the mode of stride time variability (ms; Fig. 2B).
Between-walk adaptability, capacity to walk at different gait velocities cadences and/or stride lengths, was measured using vigor interquartile range (IQR; cm/s; Fig. 2C) [21, 22]. Gait regularity was assessed as median sample entropy (mediolateral and anteroposterior) [26, 27] with embedding dimension 5 and tolerance 0.3. A glossary with further details of these gait measures is provided in Supplementary Table 1.

**Physical assessment**

Gait speed was assessed at usual pace over distances of 3.66 m to 14 m, dependent on available space. To omit the acceleration and deceleration phases, gait speed was computed from the middle-sections of the walks (2.4–10 m). For test distances less than 10 m, two trials were completed, and the average walking speed was computed. Functional mobility was assessed with the Timed-Up-and-Go test (TUG) which involves standing from a standard chair (height 45 cm), walking 3 m at usual pace, turning and returning to the chair and sitting down [28].

**Neuropsychological assessment**

Global cognition was assessed with the Montreal Cognitive Assessment (MoCA) in the age-sex matched controls and 12 participants with dementia, and with the mini-Addenbrooke’s Cognitive Examination (M-ACE) derived from the ACE-III in the remaining 33 participants with dementia [14, 29, 30]. The Trail Making Tests (TMT) A and B were administered to assess visual search and processing speed [31]. The TMT B also assesses divided attention, mental flexibility and executive function [31], and the subtraction of TMT A times from TMT B times provided a measure of executive function less dependent on processing speed [31]. Tests of phonemic fluency, number of words beginning with either ‘P’ or ‘F’ in 60 s, were used to assess language and executive function. Depressive symptoms were assessed with the 15-item Geriatric Depression Scale (GDS) in people with the dementia and with the Patient Health Questionnaire (PHQ-9) in the age-sex matched controls. The presence of significant depressive symptoms was determined using cut-points previously described in...
the literature: six or more for the GDS and nine or more for the PHQ-9 [32–34].

Statistical analysis

Data were analyzed with SPSS (SPSS Inc., Chicago, IL), version 25. Continuous data are reported as mean ± SD or mean [bias corrected accelerated bootstrap confidence intervals (BCa 95%CI)]. BCa 95% CIs were based on 2000 samples and Mersenne Twister seed of 2000000. If normality assumptions were violated, medians (IQR) are reported. Participants physically unable to perform a physical test and cognitively unable to perform a cognitive test were given 3SD above the participant group mean for that measure (TMT B\(n=13\); TUG \(n=3\)). Pearson’s \(r\) [BCa 95% CI] are reported for the correlation between daily-life activity (mean steps per day) and self-reported (IPEQ) total and walking activity. Pearson’s \(r\) effect sizes have been interpreted as: 0.1 = small, 0.3 = medium and 0.5 = large, as recommended by Cohen [35]. One-way analysis of variance (ANOVA) and Kruskal-Wallis H test were used to compare daily-life activity and daily-life gait between participants with dementia and age-sex matched controls. In participants with dementia, one-way ANOVA and Kruskal-Wallis H test were used to compare daily-life activity and daily-life gait in non-fallers (zero falls in the past year) and fallers (1+ falls in the past year). Pearson’s \(r\) [BCa 95%CI] were used to assess associations between neuropsychological, gait speed assessed under standardized conditions, TUG, and daily-life gait and activity measures in participants with dementia. The \(p\)-value threshold for significance was set at \(p<0.05\) and not adjusted for multiple comparisons because such adjustments may increase Type II errors [36].

RESULTS

Participants’ characteristics are reported in Table 1. The participants (\(N=135\)) had a mean age of 81 ± 6 years and 42% were women (Table 1). Participants with dementia reported 57 falls (fall rate 1.27 falls per person-year) in the past year. In comparison, the age-sex matched controls reported 58 falls for this period (0.64 falls per person-year). Thirty-three (73%) of the participants with dementia provided self/caregiver-reported dementia diagnoses, 11 (33%) reported Alzheimer’s disease, eight (24%) vascular, four (12%) mixed, one (3%) frontotemporal, and nine (27%) unspecified dementia. Participants physical and neuropsychological performance are also reported in Table 1.

Daily-life activity in participants with dementia and age-sex matched controls

Participants in both groups wore the activity monitors for a median of seven days (IQR 6–7). Forty-one (91%) of the participants with dementia and 87 (97%) of the age-sex matched controls wore the activity monitors for five days or more. When using the minimum wear time criterion of six hours per day for at least two days, the mean number of steps per day, mean number of walking bouts per day and mean daily walk time in participants with dementia was significantly less than their age-sex matched peers (Table 2; Fig. 1).

However, as the mean wear time per day worn was significantly less in participants with dementia (median 12.5 h (IQR 10.5–13.5) compared to the age-sex matched controls (median 14.8 h (IQR 13.3–20.3); \(H(1)=29.24, p<0.001\)), we conducted sensitivity analyses that included stricter wear time criterion—a minimum of 12 hours per day for at least three days. As shown in Supplementary Table 2, these analyses supported the results in Table 2.

There was a higher proportion of participants with significant depressive symptoms and outdoor walking aid use in the group with dementia. Sensitivity analyses revealed mean number of steps per day, mean number of walking bouts per day and mean daily walk time remained significantly reduced in participants with dementia compared to controls when data from participants with depression and participants who used outdoor walking aids were excluded from the analyses (Supplementary Table 3).

Daily-life activity and self-reported physical activity

There were strong positive correlations between mean steps per day and self-reported hours of total PA (\(r(44)=0.569, \text{BCa 95\% CI [0.287}, 0.748, p<0.001\)) and self-reported hours of walking activity (\(r(45)=0.624, \text{BCa 95\% CI [0.314}, 0.794, p<0.001\)) in the participants with dementia. For the age-sex matched controls the positive correlations were weaker, self-reported total hours of PA: (\(r(90)=0.375, \text{BCa 95\% CI [0.210}, 0.525, p<0.001\)) and self-reported hours of walking activity (\(r(90)=0.423, \text{BCa 95\% CI [0.211}, 0.620, p<0.001\)).
Daily-life gait in participants with dementia and age-sex matched controls

Participants with dementia had significantly reduced daily-life walking endurance (fewer walks 60 s or more), lower walking speed, shorter stride lengths, and lower cadence when compared to age-sex matched controls (Table 2). Participants with dementia demonstrated significantly lower between-walk adaptability as indicated by the reduced vigor IQR in this group (Table 2; Fig. 2C). They also exhibited significantly increased stride time variability (Table 2; Fig. 2A, B), and reduced gait regularity (i.e., anteroposterior sample entropy; Table 2). The difference between gait speed under standardized conditions and daily-life walking speed was significantly smaller for participants with dementia (mean difference in gait speed 0.35 m/s, BCa 95% CI [0.30, 0.39]; F(1,126) = 48.10, p < 0.001).

Daily-life activity and daily-life gait in fallers and non-fallers with dementia

There was no significant difference in mean wear time between fallers and non-fallers (median 12.4 h (IQR 10.5–15.4) versus 12.5 (IQR 10.3–13.4); H(1) = 0.04, p = 0.838) with dementia. The fallers had significantly fewer walking bouts per day (median 210 (IQR 143–278) versus 306 (IQR 200–399); H(1) = 4.57, p = 0.032), less time walking per day (median 33.6 minutes (IQR 18.5–46.3) versus 58.2 (IQR 34.3–66.3); H(1) = 3.92, p = 0.048), and slower daily-life walking speed (median 0.67 m/s (IQR 0.64–0.73) versus 0.76 (IQR 0.70–0.81); H(1) = 4.28,
The fallers and non-fallers did not significantly differ with respect to steps per day (median 2562 (IQR 1233–3868) versus 4216 (IQR 2842–5231); $H(1) = 3.40$, $p = 0.065$) or any other daily-life gait characteristic (data not shown) when compared to non-fallers with dementia.
Neuropsychological performance, daily-life activity, and daily-life gait correlates in participants with dementia

Greater daily-life activity was correlated with better executive function as measured with the TMT B-A and phonemic fluency (≥11) tests (Table 3), and faster daily-life walking speed was associated with better phonemic fluency (Table 3). No other daily-life gait characteristics were correlated with neuropsychological performance (Table 3). Faster gait speed measured under standardized conditions and quicker TUG times were correlated with better executive function (TMT B-A times and phonemic fluency scores) and quicker TUG times were moderately correlated with better global cognition (MoCA or M-ACE scores).

All daily-life activity and daily-life gait measures were correlated with gait speed under standardized conditions and TUG times with moderate to strong associations (Table 3).

DISCUSSION

This study quantified daily-life activity and daily-life gait in older people with dementia and compared these characteristics to age-sex matched healthy controls. Participants with dementia demonstrated significantly reduced daily-life activity and significant multi-domain impairments in daily-life gait (e.g., reduced cadence, stride length, and regularity) when compared to age-sex matched controls.

Our findings are consistent with more traditional gait analyses, in that participants with dementia performed worse in all gait domains [37], and reduced gait speed was associated with poor health outcomes [3, 38]. Daily-life walking speed was on average 0.11 m/s slower in participants with dementia compared to age-sex matched controls. This slower walking speed was also evident in the gait test performed under standardized conditions, which revealed a gait speed on average of 0.43 m/s slower in participants with dementia. Faster gait speeds in the timed gait assessments (instructed to be at “usual” pace) compared to daily-life walking speed, illustrates the variability of daily-life walking speed, some of which may be due to performing additional tasks, and the slower selected walking speeds used for activities of daily living. The relatively smaller difference between daily-life walking speed and gait speed under standardized conditions in the group with dementia suggests that they are either less affected by being observed or have a reduced ability to increase their gait speed under timed test conditions. The latter proposition is supported by previous findings that indicate participants with dementia have reduced walking speed reserve (preferred and fast walking speed assessed under standardized conditions) when compared to healthy controls [39]. Such an inability to increase gait speed has functional consequences, for example the minimum speed to safely cross roads vary according to location, but can require gait speeds of 1.2–1.4 m/s [39, 40].

Self-reported PA (assessed using the IPEQ) and PA measured with the activity monitor (quantified as mean steps per day) were positively correlated in the participants with dementia. In contrast with our hypothesis, this relationship was stronger in participants with dementia than controls. Caregivers assisted in providing information on activity levels, and this appears to have resulted in more accurate estimations of PA. Further, older people with dementia are less active, which may facilitate more accurate activity quantification. This finding provides confidence that questionnaire measures of PA reflect actual PA levels in people with dementia if caregivers are consulted. However, accelerometer-based PA measurements have additional benefits in that they can capture micro gait characteristics and performance in complex ‘real world’ environments.

Higher daily-life activity levels were correlated with better executive function (TMT B-A and phonemic fluency), supporting our hypothesis and prior work using a self-reported PA measure in a population based study [11]. The findings also agree with a previous study of older adults across the cognitive spectrum, where executive function partially mediated the relationship between PA and physical decline [41]. Furthermore, daily-life walking speed, TUG time, and clinical gait speed were significantly correlated with executive function (TMT B-A and/or phonemic fluency) and each other. Together, these observations suggest inter-relationships between the capacity to walk fast (both in daily-life and under standardized conditions), the desire to participate in daily-life activities, and executive function. The detrimental effects of apathy and/or the beneficial effects of exercise may offer possible explanations for these relationships.

The daily-life gait measures of stride length, stride-time variability, and vigor IQR were significantly correlated with physical (gait speed assessed under standardized conditions and the TUG) but not cognitive performance. In contrast, physical performance
was associated with cognitive performance and more specifically executive function. This suggests daily-life gait quality is more dependent on physical rather than cognitive function in people with dementia. This was unexpected and contrary to our hypothesis that executive dysfunction would be associated with poorer daily-life gait, particularly within-walk variability [4]. This hypothesis was based on research demonstrating increased gait variability under dual task conditions, the assumption that daily-life gait often involves dual tasking and previously reported associations between increased gait variability and executive dysfunction [4]. However, in daily-life participants may not experience a standardized dual task load. It is possible that the participants with dementia reduced their dual task load by spending more time in their familiar home environment that required less cognitive demand (as indicated by fewer walks ≥60 s and lower between walk adaptability). Also, individuals with dementia may have limited their daily-life walking to reduce cognitive challenge as indicated by their reduced hours of self-reported planned activity. Together these findings highlight the need for more research in this area, with longitudinal design and larger sample sizes, allowing for better examination of causal relationships and identification of weaker, but potentially clinically important associations.

With respect to wear time, our inclusion criteria of at least six hours per day for a minimum of two days are different from two previous studies of community-dwelling older people with dementia [7, 8]. Participants with dementia in the current study wore the activity monitor for a median of 12.5 hours per day and a median of seven days. In previous studies involving people with dementia, daily-life gait/activity data were collected for one day [7] and seven days [8], but wear times were not reported. In healthy older people, two days has been suggested as the minimum wear time to assess daily-life activity with good to excellent reliability (ICC >0.7) [42]. Concerning how representative our data (at least six hours per day for a minimum of two days) are of total PA, the sensitivity analysis showed little difference in recorded activity for thresholds of six and 12 hours (3,301 and 3,307 steps/day, respectively) in participants with dementia. This suggests participants were wearing the device when they were active. Future research could establish consensus on minimum wear time for people with dementia.

The main strengths of the study were the acquisition of daily-life gait over 7 days, the relatively large sample size, the age-sex matching of controls, and the comprehensive assessment. Our study, however, also has certain limitations. First, the retrospective reporting of falls most likely resulted in under-reporting, particularly in the group with dementia. Future longitudinal studies could examine associations between daily-life gait measures and neuropsychological performance and prospectively ascertained falls. Second, although participants with dementia were given the same instructions regarding the activity monitors, they wore them for shorter periods. Reassuringly, the sensitivity analyses based on longer daily wear time for more days did not alter our findings. Thirdly, the distribution of the data and the sample size limited our ability to examine the effect of potential confounders (e.g., type of dwelling, depressive symptoms, outdoor walking aid use, or medication use) on daily life gait and activity. However, sensitivity analyses, removing participants with significant depressive symptoms and outdoor walking aid use (Supplementary Table 3), suggested that the significant between group differences remained. Further research involving larger samples would help quantify daily-life gait and activity in subgroups of people with dementia (e.g., in relation to type of dwelling, depressive symptoms, centrally acting medication use, walking aid use, dementia subtypes, and dementia severity). Finally, some of the standardized gait assessments were conducted over shorter distances, which may have resulted in slower gait speeds. However, both shorter and longer standardized gait assessments included acceleration and deceleration phases that were omitted when calculating gait speed. Further, standardized gait assessments less than 10 m were repeated, and the average gait speed computed.

The current study highlights future research opportunities in people with dementia. For example, targeted interventions aimed at improving PA levels and gait quality could be examined. However, safety considerations would be required, e.g., supervision. Daily-life gait and activity measurement has some advantages over standardized assessment, e.g., it can be performed remotely, measures both macro (PA) and micro gait (gait quality) characteristics objectively, measures gait over longer timeframes, captures gait in the complex but familiar home environment, and removes the potential variation in performance associated with being observed. However, longitudinal studies examining the predictive ability and clinical utility of daily-life gait for health outcomes need further examination. Reduced gait speed assessed under standardized conditions has
been associated with prospective falls, cognitive decline, and mortality [3, 38, 43] and these relationships could be investigated using daily-life gait and activity in older people with dementia.

Conclusions

We found people with dementia were less active in daily-life and had impairments across multiple daily-life gait domains when compared to age-sex matched controls. Within the group with dementia, daily-life activity was correlated with a questionnaire measure of physical activity as well as executive function and falls during the past year. The effect of interventions targeting daily-life activity and executive functioning in people with dementia need further evaluation, particularly with respect to fall outcomes while considering activity exposure.

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SUPPLEMENTARY MATERIAL

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