HHS Public Access

Author manuscript

Alzheimer Dis Assoc Disord. Author manuscript; available in PMC 2017 January 01.

Published in final edited form as:

Alzheimer Dis Assoc Disord. 2016 ; 30(1): 60–66. doi:10.1097/WAD.0000000000000091.

Trajectory of mobility decline by type of dementia

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Abstract

Cognitive and physical aspects of functionality are closely related. However, whether physical decline differs by dementia type and progression rate is debatable. To address these issues, we conducted a longitudinal study of 766 older adults whose physical performance and cognitive status were assessed annually with standard assessment tools (e.g. Physical Performance Test, Clinical Dementia Rate-CDR) for =8yrs. Compared to participants who remained cognitively-normal, those progressing to later-stage dementia (CDR=1) declined in their mobility by a factor of 2.82 ($p<0.001$), followed by those who maintained a later-stage diagnosis (slope=−1.84, $p<0.001$), those progressing from early-to-later (CDR=0.5 to CDR=1) stage dementia (slope=−1.20, $p<0.001$), and those who progressed to early-stage dementia (slope=−0.39, $p=0.038$) suggesting a steeper physical decline with dementia progression, particularly in those with the fastest disease progression. Although all types of dementia experienced mobility decline, those progressing to non-AD dementias, especially vascular dementia declined faster than those who remained normal (slope=−2.70, $p<0.001$) or progressed to AD (slope=−2.18, $p<0.001$). These associations were better captured by the gait/balance component of physical functionality. Our findings suggest that rapidly progressing dementia patients particularly those with non-AD subtypes should be targeted for interventions to maintain or improve gait/balance and prevent functional decline and disability although AD patients may also benefit.

Keywords

Alzheimer's disease; Dementia with Lewy bodies; Frontotemporal dementia; vascular dementia; mobility; physical functional decline

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Conflict of interest disclosures: Drs. Tolea, Morris, and Galvin report no personal, financial or potential conflicts of interest.

Author Contributions: All authors had full access to all the data in the study, gave final approval of the current version to be published, and take responsibility for the conduct of the research. The authors take responsibility for the integrity of the data and accuracy of the data analysis, has the right to publish any and all data, separate and apart from the guidance of any sponsor.
MIT: study concept and design, analysis and interpretation of data, drafting of manuscript, critical revision of manuscript for important intellectual content.
JCM: data acquisition, critical revision of manuscript for important intellectual content, obtained funding
JEG: data acquisition, study concept and design, analysis and interpretation of data, critical revision of the manuscript for important intellectual content, obtained funding, provided study supervision.

Introduction

The ability to move about one's environment is one of the requisites for independent living and a significant determinant of quality of life in old age. Mobility often measured by performance on physical tests such as walking for 4 feet at usual pace, may represent a very early marker of a generalized decline in physical functionality and future adverse outcomes associated with aging[1]. Mobility impairment in older adults likely results from impairment in multiple physiological and neurological domains, each contributing to further age-related decline in functionality and vitality. When coupled with physiological changes in muscle bulk and strength, peripheral neuropathies, and osteoarthritic changes, cognitive impairment may negatively impact mobility [1]. Impairments in cognition and mobility often go hand-in-hand, and impairment in one is often seen accompanying impairment in the other. Compared to cognitively-normal individuals, older adults with cognitive impairment[2] tend to perform poorly on mobility tests[3] and to report higher levels of disability [4]. Global measures of cognition [5] as well as specific domains including working memory[6] and executive function[7] have been linked to changes in physical performance in older adults. Moreover, likelihood of disability increases with worsening severity of cognitive impairment[2] and the rate of progression to disability is exacerbated by presence of impaired cognitive function[8]. There is also evidence to suggest that decline in cognition is associated with decline in mobility regardless of whether the physical task requires a great cognitive input or not[9].

Further support for a relationship between cognitive and physical performance is provided by evidence that dementia represents a major cause of functional dependence likely surpassing the effect of other risk-factors[10]. Although AD is the leading cause of dementia and has been the most studied cognitive disorder when assessing the cognitive-physical functional relationship, non-AD dementias, which comprise 30% of all dementia cases[11], may pose an even higher risk than AD because prominent non-cognitive symptoms (e.g., extrapyramidal signs, weakness, motor-neuron disease, apathy) may negatively impact mobility and increase ADL impediments. Therefore, to test this hypothesis, the current study was designed to investigate whether mobility decline patterns differ by baseline level of cognition and rate of progression to dementia (research question 1) or dementia type (research question 2) with the expectation that higher levels of cognitive impairment, faster rates of cognitive decline, and development of non-AD phenotypes would be associated with steeper mobility decline.

Methods

Study Participants

Study participants were older adults enrolled in a 30-year longitudinal study of memory and aging at the Knight Alzheimer's Disease Research Center (ADRC) at Washington University in St. Louis. The Physical Performance Test (PPT), measuring the mobility aspect of physical functionality, was administered between January 1998 and December 2007. A subset of the participants in the longitudinal study who were administered and completed the PPT, were at least 50 years of age or older, were able to ambulate, and had at least 1 follow-up assessment was obtained. A total of 766 individuals, both cognitively

normal and cognitively impaired, fulfilled study requirements and were included in the study for a total of 3,090 observations. Participants were followed annually for up to 8 years with a mean follow-up of 2.6±1.6 years. At baseline, participants had a mean age of 76.8±8.5 years with 14.1±3.1 years of education. The sample was mostly Caucasian (90.2%) and 57.6% were female. The mean baseline CDR-SB was 1.8±2.4 and baseline total PPT scores were 26.1± 6.2. Physically impaired individuals (total baseline PPT<28) were older (81.2±8.7 vs. 75.2±7.1 years, p<0.001), less educated (13.9±3.1 vs. 14.8±2.9 years of education, p<0.001), more likely to be female (63.8 vs. 51.2%, p<0.001), non-White (12.9 vs. 6.4%, p=0.003) and have greater dementia severity (mean CDR-SB: 3.0±3.7 vs. 1.3±2.2, p<0.001) compared to functionally-normal individuals (total PPT=28). Compared to participants who remained cognitively normal, those who progressed to either AD or non-AD phenotypes were on average older, less educated, had lower baseline PPT scores and worse baseline cognition (as captured by CDR-SB) (Table 1).

Signed informed consents were obtained from all study participants and the study protocol was approved by the Institutional Review Board at Washington University.

Cognitive Assessments

At baseline and each annual follow-up, all participants underwent identical clinical, cognitive, and physical assessments. During the clinical evaluation social, medical, and family history were obtained from a reliable informant and a detailed neurological examination and neuropsychological testing [12] were administered. A composite factor score (z-score) was created for each person using weights obtained from a previous principal components analysis of all individuals without dementia in our study and used as a global measure of cognition in data analysis[13]. Diagnoses of AD and non-AD dementia were made using standard criteria[14–17].

Staging of dementia-severity was determined using the Clinical Dementia Rating (CDR)[18] based on information obtained from the clinical assessment without reference to the participant's psychometric performance and with input from the informant regarding changes in participant's cognitive ability to function in each of following 6 domains: Memory, Orientation, Judgment, Community Affairs, Home and Hobbies, and Personal Care. For the purpose of this study, we used the global CDR score to categorize participants as having normal cognition (CDR=0), MCI/early stage dementia (CDR=0.5), or later stages of dementia (CDR=1). The global CDR score is derived from scores obtained on the 6 domains using an algorithm that is available at http://www.biostat.wustl.edu/~adrc/cdrpgm/index.html. A quantitative expansion of the global CDR (CDR-SB) was obtained by summing the six individual domain scores with a range of 0–18[19], with a higher CDR-SB score indicating greater dementia severity.

Physical Assessment

The physical assessment consisted of a modified 9-item Physical Performance Test (PPT) administered by a trained research nurse, which added a repeated chair rise (participants were asked to stand up and sit down for 5 times) and a progressive Romberg balance (side-by-side, semi-tandem, and tandem positions)[20] to the original 7-item PPT test [21] to measure

lower extremity muscle strength and balance - known risk factors for falls [22, 23], institutionalization[24], and mortality[25]. Each task was scored on a 5-point scale (range: 0–4) with higher scores indicating better performance and summed-up to obtain a total PPT score (range 0–36)[26].

Statistical Analyses

Data were analyzed with SAS (SAS Institute Inc., Cary, NC). P values were derived from 2-tailed T tests for continuous variables and Chi-square tests for categorical variables. Change in diagnosis from baseline to the last follow-up was measured in each participant. To answer research question 1, the following categories were created to measure change in diagnosis: remained cognitively (CDR 0) normal (1035 observations); remained early stage (CDR 0.5) dementia (366 observations); remained later stage (CDR 1) dementia (394 observations); progressed from normal to early stage (CDR 0 to CDR 0.5) dementia (753 observations); progressed from early to later stage (CDR 0.5 to CDR 1) dementia (456 observations); and progressed from normal to late stage (CDR 0 to CDR 1) dementia (39 observations). This categorization allowed us to compare groups based on a combination of cognitive status at baseline and rate of cognitive decline (type of dementia not considered here).

To answer the research question 2, we restricted the analysis to individuals with CDR=0 at baseline (normal cognition; n=386 for a total of 1,827 observations), and the following categories of change in diagnosis were computed: remained cognitively normal (1035 observations); progressed to AD diagnosis (666 observations); and progressed to non-AD diagnosis (126 observations; 13 FTD, 29 LBD, and 22 VaD. There were 62 other forms of cognitive impairment (35 cases of non-AD other primary; 18 uncertain, possible non-AD; and 9 incipient, non-AD) that were not sufficiently characterized to be assigned a specific diagnosis and were thus excluded from further analysis. For this analysis, severity of dementia was not taken into account, therefore the groups that progressed to AD or non-AD dementia included individuals who progressed to any stage of dementia. To get a sense of whether specific types of non-AD dementia may be associated with faster mobility decline, we conducted a sub-analysis in which the 3 different non-AD phenotypes were on rates of mobility decline against those who remained cognitively normal and AD participants.

Across all analyses, decline in mobility (outcome) was modeled with mixed effects regression techniques using an interaction term of change in diagnosis (predictor) with time as measuring the effect of change in diagnosis on rate of mobility decline. A sequence of models were tested including an unadjusted model, a model adjusted for socio-demographic variables found to correlate with the outcome, and a model further adjusted for baseline cognition using the z-score variable (full model). To rule out a potential floor effect, the full model was tested in a subsample that excluded the bottom 5% on baseline total PPT-score. A $p<0.05$ was used to indicate statistical significance. Also to test whether the effects would be influenced by the modified PPT scale's tendency to be weighted more toward gait/posture, we broke down the PPT scale into 2 components: gait/balance (i.e. lifting a book, picking up penny, turning in a complete circle, walking for 50ft, chair raises, and the Romberg balance test) and non-gait/balance (i.e. writing a sentence, simulating eating, and simulating dressing) and ran all analyses separately for these components.

Results

Rate of Mobility Decline by Cognitive Status

All participants declined in mobility over the study duration (Figure 1). However, the rate of decline in individuals who progressed from normal cognition to later stage dementia (CDR of 0 at baseline to CDR 1 at last visit) was 2.8-fold greater than that observed in individuals who remained cognitively normal (Slope=−2.823, SE=0.657; p<0.001). The next fast declining group was that consisting of individuals who maintained their diagnosis of later stage dementia, which declined 2-fold faster than the group that remained cognitively normal (Slope=−1.838; SE= 0.297; p<0.001). Finally, the slope of decline in mobility was also increased in participants who progressed from early to later stage dementia (CDR of 0.5 at baseline to CDR 1 at last visit) and those who progressed from normal cognition to early stage dementia (CDR of 0 at baseline to CDR 0.5 at last visit). In contrast, those who maintained their early stage dementia status were similar to the group that remained normal in terms of rate of mobility decline (Slope=−0.555; SE=0.304; p=0.068). In addition, we found no evidence of additive effects for progressing through the different severity stages of dementia. Combining the effects of progression from CDR 0 to CDR 0.5 with progression from CDR 0.5 to CDR 1 was associated with a smaller effect (Slope=−0.65, p<0.001) than progressing from CDR 0 to CDR 1 (Slope=−2.81, p<0.001).

Rate of Mobility Decline by Dementia Type

Table 2 presents baseline and longitudinal effects of progression to different types of dementia on mobility among initially cognitively normal participants. As expected, those who progressed to any stage of dementia (CDR =0.5) started at baseline with lower levels of mobility compared to their normal counterparts. The unadjusted rate of mobility decline was slightly higher in the group progressing to non-AD dementia compared to the group progressing to AD, though significance was reached only in the AD group. After adjustment for age, gender, education, race, and baseline cognitive level, rates of mobility decline became significantly steeper in both AD and non-AD groups compared with participants who remained cognitively normal. Excluding participants with the lowest performance (bottom 5%) on baseline PPT (1712 observations) further demonstrates the effect in the non-AD dementia group, which had a double rate of decline than that seen in the AD group (Slope=−0.827, SE=0.261, p=0.002 vs. Slope=−0.354, SE=0.138, p=0.011, Figure 2).

To further explore the impact of different dementias on physical performance, we compared decline rates among subtypes of non-AD individuals against those who remained cognitively normal or progressed to AD. Although all groups declined over the follow-up period (Figure 3), the greatest rate of decline was observed in the group progressing from normal cognition to VaD. The VaD group declined by a factor of 2.7 (Slope=−2.704, SE=0.623, p<0.001) compared to the group who remained normal and by a factor of 2.2 (Slope=−2.182, SE=0.628; p<0.001) compared to the group progressing to AD. The AD group declined significantly more than those who remained cognitively normal (Slope=−0.521, SE=0.169, p=0.002). Interestingly, participants who progressed to FTD scored higher on PPT throughout the study. Although not statistically different due to small sample size, FTD was slightly younger at baseline than the groups progressing to AD and VaD (77.6 yrs. vs. 78.6

yrs. and 81.3 yrs. for AD and VaD, respectively), which may provide a partial explanation of the observed differences in PPT.

The same pattern of faster decline in mobility with greater progression rate to dementia, higher baseline cognitive impairment, and with progression to vascular dementia was observed regardless of functional component. The rate of decline remained highest in those who progressed from normal cognition to dementia (Est.= −2.04, $p<0.001$ and −0.78, $p<0.001$ for gait and non-gait items, respectively), followed by those who maintained their dementia diagnosis (Est.=−1.07, $p<0.001$ for gait items and Est.=−0.76, $p<0.001$ for non-gait items), those who progressed from early to later stage dementia (Est. gait=−0.71, $p<0.001$ and Est. non-gait=−0.41, $p<0.001$), and those who progressed to vascular dementia (Est. gait=−2.052, $p<0.001$ and Est. non-gait=−0.700, $p<0.001$), although in each case the estimates are higher for the gait items.

Discussion

Although physical impairment may play a role in the development of dementia, our results suggest that cognitive impairment may also be involved in the process that leads to greater physical impairment than expected for age alone and development of subsequent functional disability. We found that although most individuals experience decline in physical functionality over time, individuals progressing to CDR 1 or greater from either CDR 0 or CDR 0.5 have the greatest risk of physical decline based on baseline cognitive status and rate of progression. Moreover, the specific etiology of dementia may play an important role in how rapidly one progresses to disability. Non-AD dementia disorders in general, and VaD in particular, may be associated with a faster decline in physical functionality compared to both AD and normal cognition.

Our findings of an association between change in cognitive status and physical functional decline extend findings from previous investigations. For example, in a large multicenter prospective study of 2405 middle-aged women followed over a period of 4 years, greater change in cognitive abilities predicted faster mobility decline adjusted for the effect of age, race, and study site[27]. Our finding of sharp mobility decline in individuals experiencing rapid progression through the different dementia stages suggests that continued efforts should be focused on identifying individuals at risk for cognitive decline and understanding what specific features in their disease process predispose them to increased functional decline.

As hypothesized, baseline severity of disease (measured by CDR) was a significant predictor of how fast participants declined in mobility. In our study, participants in later stages of dementia (CDR 1 or greater) declined more compared to those in earlier stages (CDR 0.5) and those with normal cognition (CDR 0). Interestingly, the group that started out as demented at baseline was not the most rapid declining group, instead being surpassed by those who progressed from normal cognition to a diagnosis of dementia. This suggests that a floor effect is quickly reached once an individual reaches the CDR 1 stage or greater, however this hypothesis needs further validation.

A role for dementia in the development of functional dependence has been previously reported[10] with earlier stages of disease conferring an increased likelihood of limitations in both basic and instrumental ADLs compared to normal cognition though of a lesser magnitude than later stages[2]. Taken together these findings suggest that decline in mobility may have a cognitive component and that interventions to maintain functionality and prevent future disability are likely more successful at earlier stages in the disease process. There is increasing evidence that exercise-based interventions are well received by cognitively impaired individuals and may also help improve functionality and prevent disability[28]. For example, a twice per week 45 minute exercise regimen in individuals with MCI improved gait parameters such as speed and stride length[29] which would likely reduce risk of developing mobility-related disability. In addition, such interventions may help maintain global cognitive function[30] and reduce brain atrophy[31] which may further reduce risk of functional decline and disability. Whether or not cognitive interventions that do not include a physical component may be efficacious in reducing the risk of functional decline is unclear at this time[32]. Techniques such as mental imagery in which participants imagine performing certain motor tasks[33] may provide benefits by decreasing the attentional demands to control these tasks[34]. However, whether the effectiveness of such cognitive interventions translates into better performance needs to be further investigated.

Our results indicate that type of dementia should also be considered when discussing prognosis for functional decline with patients and their caregivers. Although functional disability is mostly a feature of later stage AD, mobility disturbances (e.g. postural instability), which precede and lead to disability can occur much earlier in the disease process in non-AD dementias and can serve as targets for disability prevention interventions. While the mechanisms linking physical impairment and dementia of the Alzheimer's type the two are still unclear, pathways including behavioral symptoms (e.g. apathy) and executive dysfunction have been proposed[35, 36]. For example, a recent review of higher-level gait disturbances in mild dementia suggests that postural instability in early AD may be the result of neurodegeneration in brain areas (e.g. the superior longitudinal fasciculus, the uncinate fasciculus, and the fronto-cerebellar connections) involved in motor imagery, spatial navigation, and coordination of limb movement all required ingredients for gait steadiness[37]. Our findings of a sharp decline in mobility in individuals progressing to AD compared to those who remained cognitively normal support these previous reports. This effect was robust retaining its statistical significance even after important risk factors (e.g., age, gender, education, race, and baseline cognitive status) for functional decline were accounted for.

However, while progression to AD was associated with greater decline in mobility compared to remaining cognitively normal, our study suggests that non-AD dementia may lead to an even greater decline. Compared to those who remained cognitively normal, participants who progressed to non-AD diagnoses (covering different stages of dementia) declined in mobility at a rate that was twice that observed in AD individuals. This finding supports previous reports of faster functional decline in non-AD variants compared to AD. For example, in an autopsy-confirmed dementia study, FTD patients became dependent in basic ADLs in the subsequent year at a rate that exceeded that of AD patients[38]. However not all forms of FTD are equal in terms of their impact on functionality. The behavioral

variant has been associated with the greatest ADL burden exceeding that seen in AD patients, possibly due to (a) an increased social withdrawal and apathy leading to an inactive lifestyle and functional decline[39], (b) a greater risk of motor neuron disease, or (c) degeneration of neural networks involved in motor inhibition and head and trunk stabilization[37]. The semantic and progressive non-fluent aphasia subtypes have been associated with the least ADL burden[40] suggesting behavioral deficits coming from frontal lobe degeneration as potential mediation mechanisms[38].

Other types of non-AD dementia have also been associated with higher ADL burden compared to AD. VaD, for example, has been associated with accumulation of subcortical white matter lesions which may cause weakness, sensory disturbances, executive dysfunction, imbalance and gait alteration[41]. In addition, neurodegeneration of the uncinate fasciculus, the fronto-cerebellar and fronto-striatal connections, and the cingulum – all brain networks involved in spatially guided limb movement sequencing and coordination may also lead to postural instability, freezing, and gait apraxia commonly seen in VaD[37]. Our findings of a steeper decline in mobility among VaD participants compared to both AD and those who remained cognitively normal supports the idea that compared to AD, specific non-AD variants may have a more dramatic impact on functionality particularly basic ADL.

Our results should be interpreted in light of limitations specific to our study. Generalizability of results may be limited by the nature of our sampling strategy of recruiting from the pool of participants in cognitive and functional aging studies conducted at the Knight ADRC. Individuals who participated in our study may differ from the general population in relevant ways including higher educational levels. Most of the sample was Caucasian so it is unclear how these findings translate to other racial/ethnic groups.

Follow-up time also differed slightly between groups defined by rate of progression to dementia and baseline cognition with potential effects on the observed differences in mobility decline trajectories. However, the group found to decline most (i.e. participants who progressed from CDR 0 at baseline to CDR 1 at last follow-up) was not different from those who remained cognitively normal throughout the study (Est. follow-up difference= −0.08, p=0.784). The other groups found to decline faster than those who remained cognitively normal were followed for shorter periods (i.e. those who remained dementia and those progressing from MCI to dementia), suggesting potential underestimation of effects in these groups. However, the finding of a steeper decline in mobility observed in the group progressing from CDR 0 to 0.5 should be interpreted with caution as this group may have had a better chance to experience mobility decline compared to participants who remained cognitively normal throughout the study, due to a slightly longer follow-up time (Estimate=0.19, p=0.023).

Clinical diagnoses were made using standardized criteria; however, it is likely that most cases of dementia (especially AD, LBD, and VaD) would have mixed pathologies at autopsy. While we sought to distinguish the effect of progression of disease on functional decline from that of other significant risk factors, potentially important risk factors may have been left unaccounted for in this analysis. Finally, our physical functional instrument may have been weighted more heavily toward gait/balance and may therefore have mostly

captured these aspects of physical functionality. To investigate this possibility, we tested whether the observed effects differed by type of functional measure and found that although the results held regardless of functionality component, the association between cognitive decline and physical decline appears to be captured better by the gait/balance component. Further investigation of these differential effects on various components of physical functionality is warranted. On the positive side, strengths of our study include the large sample size, the long follow-up period, and the use of both participants and informants to obtain information on cognitive change and functional loss.

Conclusion

This study highlights the importance of cognitive impairment in the process that leads to development of functional impairment and disability. By finding an association with performance-based functional decline, we linked progression to cognitive impairment to earlier stages in the disablement process when early intervention to maintain functionality and prevent future decline may be more successful. Given the success reported with exercise interventions designed to increase muscle strength and other functional components (e.g. balance) in individuals with MCI and early stages of dementia, our findings suggest the need to target individuals at-risk with interventions to prevent functional decline. Our findings suggest that non-AD dementia patients, particularly those with diagnoses of VaD, experience the greatest decline in mobility suggesting them as the group likely to benefit most from an intervention. However, the effectiveness of preventive interventions in VaD could be negatively impacted by factors such as a greater mortality rate than in cognitively normal and AD patients[43]. As many older adults experience declines in physical functionality and mobility, a broad approach towards improving physical functioning (aerobic exercise, resistance training, and flexibility) could be recommended to all patients with a more tailored intervention designed to address the specific components of disease (e.g. cognitive, behavioral, motor dysfunction) that are linked to functional decline based on their specific type of dementia (i.e. executive function in VaD). Taking steps to maintain mobility in these at-risk individuals may lead to improved quality of life, delayed institutionalization, and possible additional free-of-disability years with a positive impact not only on the affected person but also on their caregivers and the health care system.

Acknowledgments

Study funding: Data collection was supported by grants from NIH (P01 AG03991 and P50 AG05681) to JCM. Data Analysis was supported by grants from the NIH (R01 AG040211 and P30 AG008051), Morris and Alma Schapiro Fund, and the New York State Department of Health (DOH-2011-1004010353) to JEG.

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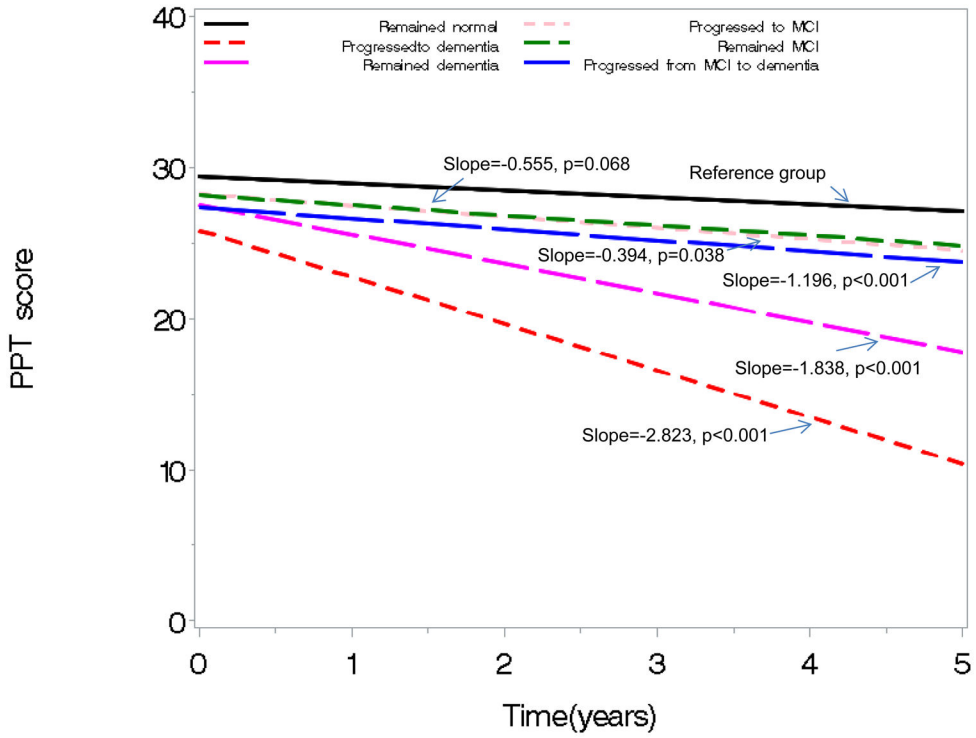

Figure 1. Rate of mobility decline according to initial cognitive status and progression to dementia rate of cognitive decline

Y-axis represents total PPT (=physical performance test) score. Slopes with their respective p-value were derived from mixed effects regression models adjusted for age, gender, race, education, and baseline cognition measured using a composite factor z-score. MCI=mild cognitive dementia; Dementia includes both AD and non-AD types

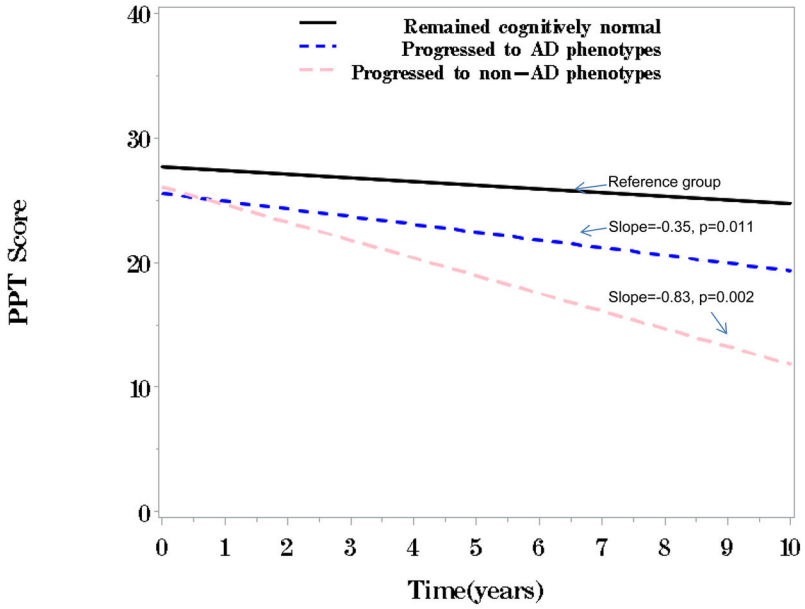

Figure 2. Rate of mobility decline among initially cognitively normal participants

Trajectories of decline in total PPT score based on change in cognitive status were derived from mixed effects regression models adjusted for age, gender, race, education, and baseline global cognition measured using a composite factor z-score. PPT=physical performance test; AD=Alzheimer's disease; bottom 5% on baseline PPT score excluded to account for potential floor effect.

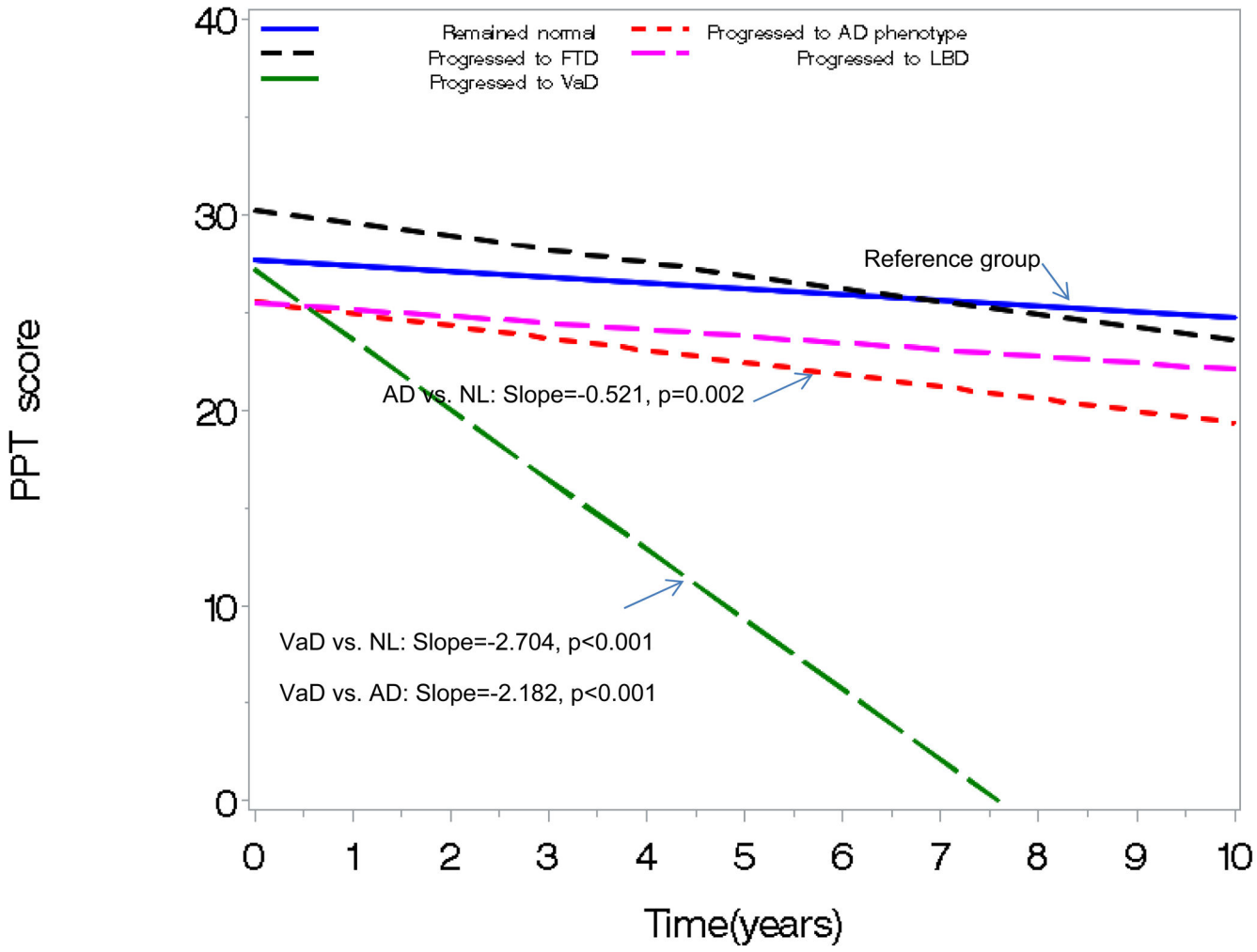

Figure 3. Slope of decline in mobility based on type of dementia developed over the study period

Slopes with their respective p-value were derived from mixed effects regression models adjusted for age, gender, race, education, and baseline cognition measured using a composite factor z-score. PPT=physical performance test; AD=Alzheimer's disease; FTD=frontotemporal dementia; LBD=Lewy body dementia; VaD=vascular dementia.

Table 1

Baseline characteristics by type of dementia developed among initially cognitively normal participants.

	Remained Normal	Progressed to AD	Progressed to LBD	Progressed to FTD	Progressed to VaD	Progressed to other non-AD	P value
Age, years	75.1±0.3	78.6±0.3	75.7±1.6	77.6±2.3	81.3±1.8	75.5±1.1	<0.001
Education, years	15.0±0.1	14.3±0.1	16.7±0.5	13.1±0.8	16.4±0.6	14.3±0.3	<0.001
Baseline PPT	28.1±0.2	26.6±0.2	26.5±1.0	31.8±1.5	25.5±1.1	20.7±0.7	<0.001
Baseline CDR-SB	0.03±0.01	0.06±0.01	0.10±0.03	0.00±0.04	0.00±0.03	0.28±0.02	<0.001

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Table 2

Baseline and longitudinal effects of change in cognitive status on mobility decline among initially normal participants

	Unadjusted model		Adjusted for socio- demographics[1]		Adjusted for socio- demographics and baseline cognition	
	Estimate	**p**	**Estimate**	**p**	**Estimate**	**p**
Intercept	27.831	<.001	58.248	<.001	57.055	<.001
Baseline effects						
Remained normal	Ref		Ref		Ref	
Progressed to AD	−1.972	0.005	−0.399	0.500	0.027	0.963
Progressed to non-AD	−2.328	0.121	−2.527	0.039	−1.587	0.185
Longitudinal effects						
Remained normal*Time	Ref		Ref		Ref	
Progressed to AD*Time	−0.336	0.021	−0.460	0.001	−0.442	0.002
Progressed to non-AD*Time	−0.470	0.060	−0.717	0.003	−0.666	0.007
Time	−0.600	<.001	−0.119	0.198	−0.207	0.028
Age	-	-	−0.436	<.001	−0.376	<.001
Female	-	-	−1.709	<0.001	−1.568	0.001
Education	-	-	0.212	0.011	0.059	0.488
White race	-	-	2.454	0.008	0.665	0.488
General cognitive score	-	-	-	-	1.478	<.001

Notes: Estimates and p-values were derived from mixed-effects regression models.

[1] Adjusted socio-demographics: age, gender, education, and race.