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The time course of motor and cognitive decline in older adults and their associations with brain pathologies: a multicohort study

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Contributors

SO was responsible for the conception and design of the current study, performed the literature review, and wrote the first draft of the manuscript. In addition, he is one of the neurologists that adjudicates cognitive status of the participants before death in the three cohorts. TW conducted and supervised the data analysis and contributed to writing the statistical analysis section and revising the manuscript. LLB is the principal investigator of the MARS study and was involved in data collection. JAS is the director of the pathology core of Rush Alzheimer's Disease Center that collects indices of brain pathologies. She is also the director of Rush Alzheimer's Disease Research Center that oversees data collection of the ROS cohort. DAB is the principal investigator of MAP, was involved in data collection, and contributed to the revision of the manuscript. ASB oversees data collection of motor performances across all Rush Alzheimer's Disease Center cohorts and contributed to the conception and design of this study and drafting the manuscript. ASB and DAB had full access to all the data in the study, accessed and verified the data, and take responsibility for the integrity of the data and the accuracy of the data analysis. All authors had access to the data and had final responsibility for the decision to submit for publication.

Declaration of interests We declare no competing interests.

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Summary

Background—Many studies have reported that impaired gait precedes cognitive impairment in older people. We aimed to characterise the time course of cognitive and motor decline in older individuals and the association of these declines with the pathologies of Alzheimer's disease and related dementias.

Methods—This multicohort study used data from three community-based cohort studies (Religious Orders Study, Rush Memory and Aging Project, and Minority Aging Research Study, all in the USA). The inclusion criteria for all three cohorts were no clinical dementia at the time of enrolment and consent to annual clinical assessments. Eligible participants consented to post-mortem brain donation and had post-mortem pathological assessments and three or more repeated annual measures of cognition and motor functions. Clinical and post-mortem data were analysed using functional mixed-effects models. Global cognition was based on 19 neuropsychological tests, a hand strength score was based on grip and pinch strength, and a gait score was based on the number of steps and time to walk 8 feet and turn 360°. Brain pathologies of Alzheimer's disease and related dementias were assessed at autopsy.

Findings—From 1994 to 2022, there were 1570 eligible cohort participants aged 65 years or older, 1303 of whom had cognitive and motor measurements and were included in the analysis. Mean age at death was 90·3 years (SD 6·3), 905 (69%) participants were female, and 398 (31%) were male. Median follow-up time was 9 years (IQR 5–11). On average, cognition was stable from 25 to 15 years before death, when cognition began to decline. By contrast, gait function and hand strength declined during the entire study. The combinations of pathologies of Alzheimer's disease and related dementias associated with cognitive and motor decline and their onsets of associations varied; only tau tangles, Parkinson's disease pathology, and macroinfarcts were associated with decline of all three phenotypes. Tau tangles were significantly associated with cognitive decline, gait function decline, and hand function decline ($p<0·0001$ for each); however, the association with cognitive decline persisted for more than 11 years before death, but the association with hand strength only began 3·57 years before death and the association with gait began 3·49 years before death. By contrast, the association of macroinfarcts with declining gait function began 9·25 years before death ($p<0·0001$) compared with 6·65 years before death ($p=0·0005$) for cognitive decline and 2·66 years before death ($p=0·024$) for decline in hand strength.

Interpretation—Our findings suggest that average motor decline in older adults precedes cognitive decline. Macroinfarcts but not tau tangles are associated with declining gait function that precedes cognitive decline. This suggests the need for further studies to test if gait impairment is a clinical proxy for preclinical vascular cognitive impairment.

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Introduction

Brain imaging and post-mortem studies suggest that Alzheimer's disease pathology accumulates over many years and that during its earliest preclinical stage,[1] cognition is unimpaired. There has also been increasing recognition that pathologies of Alzheimer's disease and related dementias might play a role not only in cognitive impairment, but might also contribute to the impairment of non-cognitive phenotypes, including hand strength and

gait in adults aged 65 years and older.[2,3] Because many studies have reported that impaired gait precedes and predicts cognitive impairment,[4] it has been suggested that gait impairment might serve as a clinical biomarker for preclinical Alzheimer's disease,[2] either alone or in combination with memory decline (as in dual decline).[4] However, many of these studies have been based on dichotomous classifications of gait or cognitive impairment without showing that longitudinal trajectories of motor decline precede cognitive decline.

Few studies have examined the associations of pathologies of Alzheimer's disease and related dementias with cognitive and motor decline in the same individuals. Moreover, these studies have used linear mixed-effect models that summarised cognitive and motor decline using a single slope measure that describes the entire follow-up.[5,6] However, these linear models do not characterise the temporal onset and course of cognitive versus motor decline during follow-up, so it is unknown if one precedes the other. Similarly, linear models can examine if a covariate shows an association with the slope of cognitive or motor decline, but these linear models do not characterise the point in time when pathologies of Alzheimer's disease and related dementias are first associated with cognitive or motor decline and if their course over time varies. Hence, it is currently unknown at what point in time a specific pathology of Alzheimer's disease and related dementias is first associated with cognitive or motor decline or if the associations for one phenotype precede the other.

We aimed to characterise the time course of the trajectories of cognitive and motor decline in older adults and examine whether the onset and the temporal course for the associations of pathologies of Alzheimer's disease and related dementias with cognitive and motor decline vary. To address the limitations of linear mixed-effect models, we used functional mixed-effects models.[7,8] Functional mixed-effects models do not assume trajectories to be linear, but can be used to assess non-linear changes in the trajectories of cognitive and motor decline and allow the associations of pathologies of Alzheimer's disease and related dementias with the trajectories of cognitive and motor decline to vary over time.

Methods

Study design and participants

This multicohort study used data from older adults enrolled in one of three community-based cohort studies of chronic conditions of ageing. Enrolment began in January, 1994, for the Religious Orders Study (ROS),[9] in September, 1997, for the Rush Memory and Aging Project (MAP),[9] and in August, 2004, for the Minority Aging Research Study (MARS).[10] All three studies are still recruiting. The inclusion criteria for all three cohorts were no clinical dementia at the time of enrolment and consenting to annual clinical assessments. ROS and MAP required consenting to brain donation, which was optional in MARS. Eligible participants also had post-mortem pathological assessments and three or more repeated annual measures of cognition and motor functions.

Participants in ROS were volunteers who were older nuns, priests, and religious brothers recruited across the USA. Participants in MAP were volunteers living in northeastern Illinois (USA) and were recruited from personal accommodations, subsidised housing, and retirement facilities. MARS enrols only African American individuals to partially

fill the gap in recruitment of African Americans in the other two cohorts. Staff at the Rush Alzheimer's Disease Center (Chicago, IL, USA) oversaw harmonised clinical and post-mortem data collection administered by the same personnel, a strategy that facilitates joint analyses of data from these three cohorts. Additional details about each of the cohorts have been published previously.[9,10] Each of the three studies was approved separately by a Rush University Medical Center Institutional Review Board. Written informed consent was obtained from all participants.

Procedures

Annually, 19 neuropsychological tests (appendix p 6) were administered and their scores were standardised and averaged to construct a global cognition score and five cognitive abilities scores.[11] A higher score indicates better cognition. A neurologist reviewed clinical findings and neuropsychologist ratings of the neuropsychological test scores and adjudicated cognitive status of the participants before death.[12]

We chose to focus our analysis on gait function and hand strength as these are the two most commonly examined motor performances for assessment of motor function in older adults.[13] Gait function was assessed annually by requesting each participant to walk 8 feet and turn 360° twice. Based on a factor analysis, a reciprocal of time and number of steps was used to make a composite gait function score, with higher values indicating faster walking with fewer steps.[14] A summary measure of hand strength was based on annual grip and pinch strength assessments, in which the participants performed each of two tasks twice with each hand using a hand-held dynamometer (appendix p 6).

After post-mortem brain removal, one hemisphere was frozen for further studies, and the other hemisphere was fixed in a 4% paraformaldehyde solution. Indices of Alzheimer's disease and related dementias pathologies were collected from the fixed hemisphere by the staff masked to clinical data, as described previously[15] (appendix pp 6–8).

For assessment of Alzheimer's disease, immunohistochemical methods using antibodies against Aβ and tau were used for identification of Aβ and tau tangle depositions in eight brain regions. The regional Aβ and tau tangles were summarised and averaged across brain regions to measure global Aβ load and tau tangle density.

Hippocampal sclerosis was assessed as being present on the basis of severe neuronal loss and gliosis at CA1 or subiculum.

Immunohistochemical methods using antibodies against phosphorylated transactive response DNA binding protein-43 (TDP-43) were used for identification of TDP-43 inclusions that were summarised by a dichotomous variable indicating the presence of TDP-43 inclusion in the hippocampus or beyond.

For assessment of Parkinson's disease, immunohistochemical methods using antibodies against α-synuclein were used for identification of Lewy bodies. Sections of the midbrain containing substantia nigra were examined for assessment of neuronal loss. Parkinson's disease pathology was considered present when Lewy bodies and moderate to severe nigral neuronal loss were present.[16]

The hemispheres were visually searched for the presence of infarcts, which were subsequently confirmed microscopically. A dichotomous variable indicating the presence of one or more macroinfarcts was used for summarising chronic macroinfarcts. By contrast, microinfarcts are infarcts that are only identifiable under microscope. Sections of nine brain regions were examined for identification of chronic microinfarcts, which were summarised by a dichotomous variable indicating the presence of one or more microinfarcts.

Large vessels of the circle of Willis were inspected and examined for the severity of atherosclerosis, which was rated semiquantitatively from none to severe. Atherosclerosis was summarised using a dichotomous variable indicating moderate to severe atherosclerosis. Sections in the anterior basal ganglia region were examined for arteriolosclerosis (defined by vessel wall thickening and lumen narrowing in small arteries and arterioles). Arteriolosclerosis was summarised by a dichotomous variable indicating moderate to severe arteriolosclerosis.

Finally, for the assessment of cerebral amyloid angiopathy, presence of Aβ in the walls of the meningeal and parenchymal vessels was examined using antibodies against Aβ, was semiquantitatively scored, and was summarised as the presence of moderate to severe cerebral amyloid angiopathy.

Other covariates were age at death, at the last visit, and at baseline, calculated using date of visits, date of birth, and date of death. Participants identified their sex, race, and years of education through self-report questions at study entry.

Statistical analysis

The statistical analyses were done and supervised by TW at Rush Alzheimer's Disease Center (appendix pp 8–9). Functional mixed-effects models[7,8] were used to examine the associations of covariates with the longitudinal outcomes. To confirm superiority of functional mixed-effects models compared with linear mixed-effects models, we calculated model fit using the Bayesian information criterion. A lower value of Bayesian information criterion indicates a better model.

First, we examined the trajectories of cognition, gait function, and hand strength in separate functional mixed-effects models. Next, we added terms for age at death, sex, education, race, and indices of brain pathologies to examine associations of the brain pathologies with the trajectories of cognitive and motor decline. Then, we examined the associations of age at death with cognitive and motor decline using two series of models: one without and one with pathologies of Alzheimer's disease and related dementias. We used a χ^2 test to examine whether the whole curve of the association of a covariate (eg, a pathology) with the outcome (eg, cognitive decline) was statistically different from zero. Then, we used the point-wise 95% CIs to assess when this covariate started to have a significant association with the longitudinal trajectory of the outcome. We included terms for age at death, rather than age at baseline, because the trajectories of cognitive and motor decline were aligned and anchored to the time of death when pathologies of Alzheimer's disease and related dementias were collected. Finally, we examined residual cognitive and motor decline by regressing out the

associations of pathologies of Alzheimer's disease and related dementias alone or together with the associations of age at death, sex, race, and education. Because the associations of pathologies of Alzheimer's disease and related dementias with cognitive decline were stronger than with motor decline, we used different scales to illustrate curves of associations of cognitive decline compared with gait function and hand strength decline. Rejection of the null hypothesis was considered when p values were less than 0·05.

We did four sensitivity analyses to assess the robustness of the findings. First, we investigated the associations of the pathologies of Alzheimer's disease and related dementias with cognitive and motor decline separately in participants with and without dementia at death. Second, we replaced global cognition with the five cognitive abilities and examined them in relation to the pathologies of Alzheimer's disease and related dementias. Third, we examined the associations of the pathologies of Alzheimer's disease and related dementias with cognitive and motor decline in subgroups of participants, in women and men or those with short (less than median 9·9 years) or long duration of follow-up, or after exclusion of 96 participants who reported race other than non-Latino White. Fourth, we replaced Parkinson's disease pathology with cortical Lewy bodies, which is used more often as a part of the pathologies of Alzheimer's disease and related dementias, and examined the associations of the pathologies with cognitive and motor decline. All preprocessing and statistical analyses were performed using R (version 4.2.2).

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

Among 1570 participants enrolled in the three cohorts, 267 (17%) had missing cognitive or motor measurements and were excluded from the analyses. Therefore, the analytic sample comprised 1303 participants, all of whom were aged 65 years or older. Selection of participants in each of the three cohorts and comparison of included and excluded participants are in the appendix (pp 13–16).

The mean age at death was 90·3 years (SD 6·3), 905 (69%) were female, and 398 (31%) were male. Alzheimer's disease was the most common pathology, but most participants had more than one pathology (mean number of pathologies in each decedent was 3·9 [SD 1·6]; table 1). The median post-mortem interval was 6·9 h (IQR 5·1–10·2).

The functional mixed-effects model-derived trajectories of cognition, gait function, and hand strength show that the mean of all three phenotypes declined during follow-up (figure 1).

Comparison of the functional mixed-effects models with the corresponding linear mixed-effects models indicated that functional mixed-effects models had better model fit statistics. The Bayesian information criteria were as follows: for global cognition, functional mixed-effects 8152·4 versus linear mixed-effects 9321·6; for gait function, functional mixed-effects

−1241·9 versus linear mixed-effects −1143·8; and for hand strength, functional mixed-effects −2222·0 versus linear mixed-effects −2140·5.

Functional mixed-effects models showed differences in the trajectories of cognitive and motor decline. On average, cognition was roughly stable from 25 to 15 years before death. Cognitive decline began about 15 years before death and accelerated decline was observed during the last 5 years before death. By contrast, gait function and hand strength declined during the entire study (figure 1). When we replaced global cognition with the five cognitive abilities in separate models, the derived trajectories were heterogeneous: decline in working memory and visuospatial abilities started later than decline in episodic and semantic memory or processing speed (appendix p 17).

Median follow-up time was 9 years (IQR 5–11, range 3–27), and only 275 (21%) of the participants had more than 11 years of follow-up. To obtain more reliable point-wise estimates for examining the associations of pathologies of Alzheimer's disease and related dementias and demographic covariates with cognitive and motor decline, we restricted our further analyses to data obtained during the last 11 years before death.

Using three separate functional mixed-effects models controlling for age at death, sex, education, and race, we examined associations of pathologies of Alzheimer's disease and related dementias with cognitive and motor decline. Eight of the ten pathologies were associated with faster cognitive decline, although when the association between amyloid-β and cognitive decline was examined by piece-wise method to determine the onset year of the association none of the piece-wise examinations were significant. Three of the ten pathologies were associated with declining gait function, and six with declining hand strength (table 2; appendix pp 18–23). In summary, only tau tangles, Parkinson's disease pathology, and macroinfarcts were associated with decline of all three phenotypes and cerebral amyloid angiopathy was not associated with any of the three phenotypes in these models that included all the pathologies together. The associations of the pathologies with cognitive and motor decline were heterogeneous over the years of follow-up (figure 2; appendix pp 18–24). For example, the effect size of the association of tau tangles with faster cognitive decline was approximately 7 times larger in the last year of life compared with 10 years before death.

Using the point-wise estimates we compared the year of onset of a significant association for each pathology with trajectories of declining cognition, gait, or hand strength (table 2). The associations of the neurodegenerative pathologies, such as tau tangles, with cognitive decline preceded the associations with declining gait function and hand strength (figure 2; appendix pp 18–23). Tau tangles were associated with cognitive decline during all 11 years before death. However, the association of tau tangles with declining hand strength began 3·57 years before death and with declining gait function 3·49 years before death (table 2). By contrast, the association of macroinfarcts with declining gait function began 9·25 years before death and preceded its association with cognitive decline that began 6·65 years before death and decline in hand strength that began 2·66 years before death. Like tau tangles, Parkinson's disease pathology was also associated with faster cognitive, gait function, and hand strength decline. The association between Parkinson's disease pathology

and cognitive decline began earlier (7·93 years before death) than the association with gait function decline (4·60 years before death) or hand strength decline (5·80 years before death). The four sensitivity analyses did not change the main findings that the associations of neurodegenerative pathologies, including tau tangles, with cognitive decline started earlier than their associations with gait function decline in contrast to the associations of cerebrovascular disease pathologies with cognitive and gait function decline (appendix pp 25–60).

We analysed the association of age at death with non-linear cognitive and motor decline. The findings showed that the association of age with cognitive decline was attenuated to a large extent when the model was adjusted for pathologies of Alzheimer's disease and related dementias (figure 3). Moreover, the remaining association of age with cognitive decline was further attenuated and was no longer significant when the model was additionally adjusted for sex, education, and race (appendix pp 61–62). These findings suggest that most of the cognitive decline observed in older adults was due to the contribution of pathologies of Alzheimer's disease and related dementias, including hippocampal sclerosis, TDP-43, Parkinson's disease pathology, macroinfarcts, microinfarcts, and atherosclerosis. However, controlling for pathologies of Alzheimer's disease and related dementias did not change the associations of age with motor decline.

In contrast to cognition, which has underlying neural pathways that are nearly all contained within the brain, the pathways underlying motor function extend beyond the brain to the brainstem, spinal cord, peripheral nerves, and muscles.[17] Therefore, we hypothesised that motor decline, rather than cognitive decline, would not be fully explained after regressing out the associations of the brain pathologies. To test this hypothesis, we examined residual cognitive and motor decline after regressing out the associations of pathologies of Alzheimer's disease and related dementias. We found that the mean of residual cognition was not declining during the follow-ups; however, we found considerable residual gait function and hand strength decline (figure 4A–C). Further regressing out the associations of age at death, sex, education, and race mainly changed intercepts and did not substantially change the estimated trajectories of the residual cognitive and motor decline (figure 4D–F). However, there was heterogeneity in person-specific residual decline for each of the three phenotypes, including cognitive decline. Some individuals showed no residual cognitive decline whereas some others showed very fast residual decline (figure 4).

Discussion

In this study, we applied a novel non-linear modelling approach to assess the time course of cognitive and motor decline as well as the onset and time course of their respective associations with pathologies of Alzheimer's disease and related dementias in more than 1300 community-dwelling older adults who underwent brain autopsy at death. Average gait and hand strength decline preceded cognitive decline by up to a decade in many older adults. The onset and time course of the associations of different pathologies of Alzheimer's disease and related dementias varied with cognitive and motor decline. For example, macroinfarcts but not tau tangles were associated with declining gait function that preceded cognitive decline. On average, most cognitive decline was explained by brain pathologies in contrast

to motor decline that was not entirely explained by age and brain pathologies. Further work is needed to determine if gait impairment can be used as a proxy to identify older adults at risk for vascular cognitive impairment.

Two of the primary concerns of ageing adults are to not develop dementia and to maintain the ability to ambulate independently. Much work has been done to advance the understanding of the inter-relationship of cognitive and motor decline and their shared associations with pathologies of Alzheimer's disease and related dementias.[5,18] Nearly all previous studies have either examined the association of baseline levels of one phenotype with longitudinal decline in the other phenotype[19] or used modelling that did not characterise non-linear decline or the temporal course of cognitive and motor decline in the same individual.[20] The current study provides novel data and visualisation of non-linear decline and the complex temporal course of cognitive and motor decline that was not previously appreciated. In addition, the findings showed that the onset and temporal course of pathologies of Alzheimer's disease and related dementias associated with non-linear cognitive and motor decline varied.

Functional mixed-effects modelling suggested that gait function declined throughout the 25 years of follow-up in contrast to cognitive function in the same individuals, which did not begin to decline until about 15 years before death. This finding is supported by previous studies reporting that impaired gait speed precedes and predicts future cognitive impairment.[4,21] Previous studies have suggested that slower gait speed might be a clinical biomarker for preclinical Alzheimer's disease.[2] The current analyses identified differences in temporal onset of the associations of pathologies of Alzheimer's disease and related dementias with clinical phenotypes and showed that macroinfarcts rather than Alzheimer's disease pathology are associated with gait decline that precedes cognitive decline. In contrast to previous studies, these results suggest that gait impairment in older adults might rather serve as a robust clinical proxy for adults at risk for cognitive impairment related to cerebrovascular disease pathologies[22] rather than Alzheimer's disease, a suggestion that needs to be tested in future prospective studies.

These findings are not meant to suggest that gait decline alone is sufficient to predict distinct adverse health outcomes or types of Alzheimer's disease and related dementias. In fact, we found that gait declined in older adults even after regressing out the associations of age and brain pathologies. These findings indicate that in contrast to cognitive decline, brain pathologies alone do not fully account for gait decline in older adults, and additional clinical covariates such as obesity, musculoskeletal disorders including osteoarthritis of back, hip, and knee, and other comorbidities, as well as pathologies in motor pathways outside the brain, need to be examined in relation to gait decline in further studies.

Assessment of hand strength, including grip strength, is another motor performance that is commonly assessed in older adults as a marker of general health.[23] The functional mixed-effects models in our study showed that Alzheimer's disease and other neurodegenerative pathologies had stronger associations with declining hand strength compared with cerebrovascular disease pathologies, which might be due to different neural substrates underlying grip and gait function.[14] This suggests that hand strength rather than gait

function might better supplement cognitive function to improve the identification of adults at risk for accumulating Alzheimer's disease pathology. However, both hand strength and gait might decline in older adults because of age-related muscle atrophy,[24] and future studies examining muscle morphology and histology and indices of pathologies of Alzheimer's disease and related dementias within and outside the brain are needed to explicate declining strength and gait function in this population.

After regressing out the effects of the brain pathologies and demographic characteristics, on average there was no residual cognitive decline, whereas residual motor decline remained. However, there was considerable heterogeneity in the person-specific trajectories of residual cognitive and motor decline as there was much residual decline in many participants that was not accounted for by the brain pathologies and the demographic characteristics. This finding highlights the importance of work that has identified genes and proteins[25] as well as lifestyle and behavioural factors[26] that are related to cognitive and motor decline but unrelated to brain pathologies of Alzheimer's disease and related dementias.

Motoric cognitive risk syndrome, defined as dual impairment of gait speed and subjective cognitive complaints, was coined to identify older adults at risk of dementia.[4] An implication of our finding that gait function was declining before objectively measured cognitive decline supports the use of the gait component of motoric cognitive risk syndrome. However, we also found that gait decline persisted even after controlling for the associations with brain pathologies, which are the main causes of dementia. Therefore, gait might be impaired in an older individual who does not have clinically significant brain pathologies related to the risk of dementia. Consequently, we hypothesise that more elaborate methods of measurements of gait and cognitive function, rather than a cross-sectional measurement of memory decline and gait speed, might be required to improve accuracy of prediction of dementia on the basis of motoric cognitive risk syndrome and dual decline.

Several strengths underlie our study findings. Participants were community-dwelling older adults and therefore represented a wide range of the full health spectrum. The study had a high autopsy rate, and staff were masked to clinical diagnosis when collecting post-mortem indices, reducing selection and measurement biases. The statistical approach assessed non-linear trajectories of cognitive and motor decline and their associations with pathologies of Alzheimer's disease and related dementias to yield novel findings not appreciated with conventional linear modelling.

However, the study has several limitations. Although we included Black participants from MARS in the analytic cohort, White non-Latino participants of European descent with high educational years still comprised most of the analytic sample. Moreover, pathological data were obtained from deceased participants who had consented for autopsy and might be different from alive participants or deceased individuals who were not included in this study. Therefore, further studies are needed to confirm the generalisability of our findings. These studies should include more diverse participants that capture the full spectrum of race, education, and cognitive and motor function to assess the robustness of our findings.[27] Alternatively, examining the current study's analyses in population-based samples will address selection bias and serve to validate our findings. The measures of pathologies of

Alzheimer's disease and related dementias were assessed at a single timepoint after death, and their relationship with the trajectories of cognitive and motor decline was examined retrospectively. Considering the dynamic nature of the accumulation of pathologies of Alzheimer's disease and related dementias, future studies will be needed to confirm our findings using biomarkers or brain imaging during life. These methods should be used to prospectively collect repeated measures of pathologies and repeated measures of cognitive and motor function to prospectively decipher differential associations of pathologies of Alzheimer's disease and related dementias with cognitive and motor decline. Moreover, collection of indices of pathologies of Alzheimer's disease and related dementias has been ongoing for more than 20 years. Although all the pathological examinations were done in one centre, immunohistochemical methods have advanced with the development of new antibodies over time that might have affected measured levels of pathologies of Alzheimer's disease and related dementias. However, we believe that such possible effects should be trivial following consistent patterns of associations observed between the pathological indices and clinical phenotypes over years of analyses. The analyses examined phenotypes (cognition, gait, and hand strength) in separate models, and the inferences about the relative associations of pathologies of Alzheimer's disease and related dementias with the phenotypes were made by comparing averages of timing of the associations. Future advanced statistical models that simultaneously examine in a single model non-linear changes of more than one phenotype or the methods that can retrospectively analyse multistate modelling will enable identification of subgroups of older adults and related pathologies of Alzheimer's disease and related dementias.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Data sharing

The data are available via the Rush Alzheimer's Disease Center Research Resource Sharing Hub. Qualified applicants should complete an application including study premises and a brief description of the research plan.

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Research in context

Evidence before this study

To identify literature that had examined changes of cognition, gait, and hand strength in older adults, we searched PubMed with no language restrictions for publications from database inception to Aug 30, 2023, with the following terms: cognition AND (gait OR hand strength) AND (longitudinal OR trend OR cohort) AND (older OR elder). The query retrieved 887 articles. Most of the relevant articles had examined baseline levels of one of cognition, gait, or hand strength, with longitudinal changes of the other phenotype or other adverse health outcomes. Few studies had examined longitudinal changes of two or all three phenotypes in the same adults. Studies that had examined gait speed and cognitive decline had used linear modelling that cannot differentiate heterogeneous trajectories of the phenotypes over time. Then, we added "pathology" to the search terms and found 65 articles, only one of which examined associations of brain pathologies with longitudinal changes of the phenotypes using linear models. Previous studies suggest that impaired gait might serve as a clinical biomarker of preclinical Alzheimer's disease. However, these studies did not examine the temporal course of cognitive versus motor decline in the same adults or the onset of the associations of pathologies of Alzheimer's disease and related dementias with cognitive and motor decline.

Added value of this study

We found that the mean of global cognition, gait function, and hand strength were declining in older adults, consistent with previous studies that reported correlated cognitive and motor decline in older adults. However, by using a statistical model that allows non-linear changes in the trajectories of motor and cognitive decline we found that cognition was stable from 25 to 15 years before death, when cognition began to decline. By contrast, gait function and hand strength declined during the entire study. Therefore, gait and hand strength decline preceded cognitive decline by up to a decade in many older adults. Macroinfarcts but not tau tangles were associated with declining gait function that preceded cognitive decline. In addition, most cognitive decline was explained by brain pathologies in contrast to motor decline that was not entirely explained by age and brain pathologies.

Implications of all the available evidence

This study's findings suggest that linear models cannot deconvolute the complexity of the trajectories of cognitive and motor decline in older adults. Gait decline alone is insufficient to predict types of Alzheimer's disease and related dementias because gait declined in older adults even after regressing out the associations of age and brain pathologies. Hand strength might improve the identification of adults at risk for accumulating Alzheimer's disease pathology. Gait impairment occurring before cognitive impairment might be a marker of incipient vascular cognitive impairment, not a preclinical marker of Alzheimer's disease.

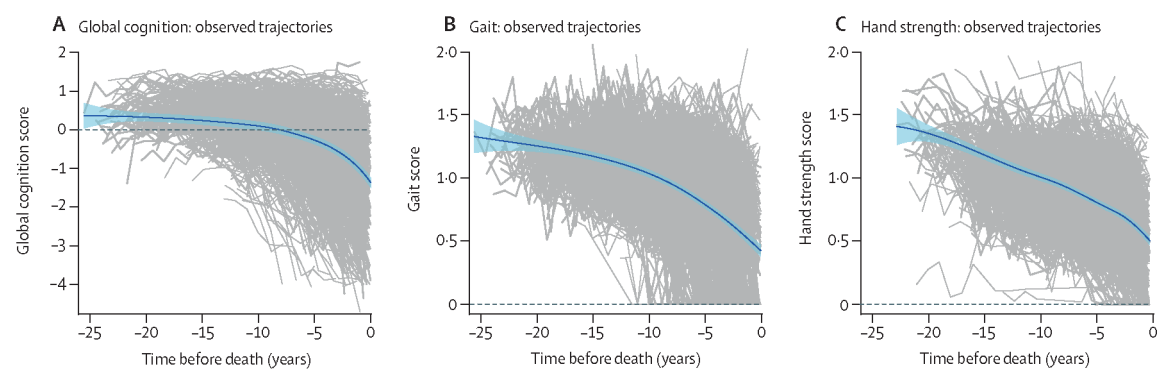

Figure 1: Trajectories of cognitive and motor decline

The blurred grey lines illustrate the trajectories of participants' repeated measures of cognition (A), gait function (B), and hand strength (C). The superimposed blue curves show the mean functional mixed-effects model-derived trajectories of the three functions, and the shaded blue areas surrounding the blue curves indicate 95% CIs.

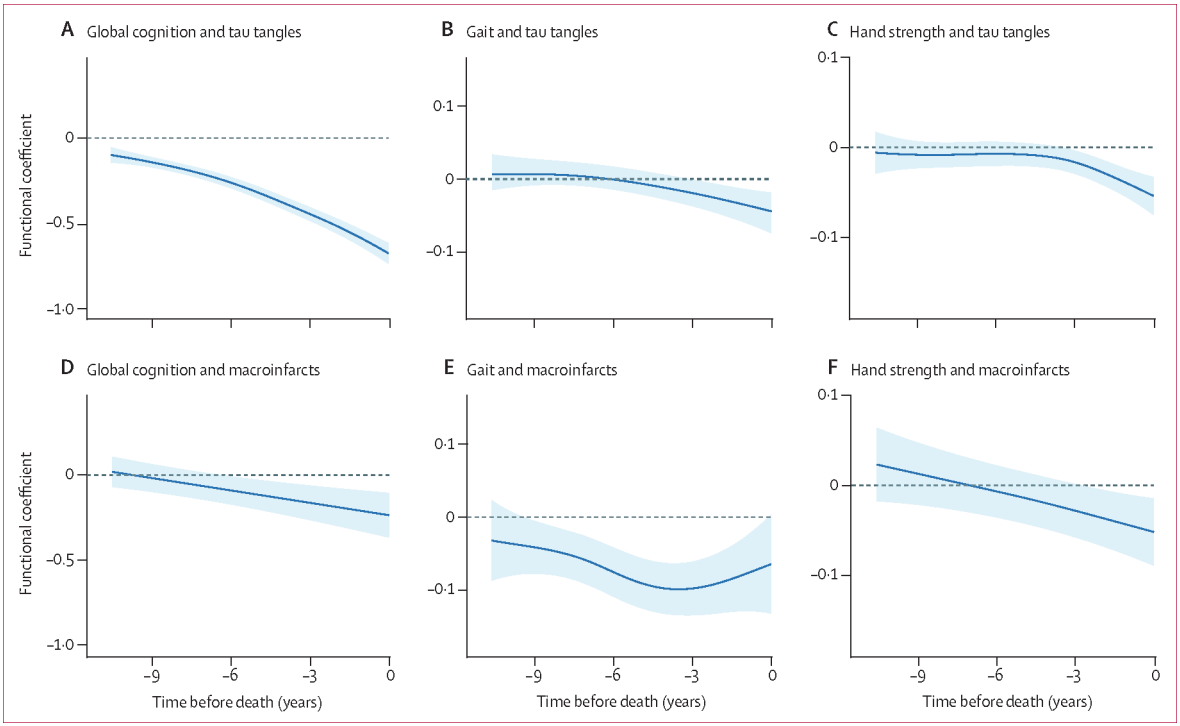

Figure 2: Associations of tau tangles and macroinfarcts with cognitive and motor decline

(A) Association of tau tangle with cognitive decline. (B) Association of tau tangles with gait function decline. (C) Association of tau tangles with hand strength decline. (D) Association of macroinfarcts with cognitive decline. (E) Association of macroinfarcts with gait function decline. (F) Association of macroinfarcts with hand strength decline. The solid blue lines indicate the associations and the shaded blue areas indicate 95% point-wise CI. The dashed line represents zero, and by comparing its course with the blue line and shaded blue area an association between a brain pathology and cognitive or motor decline can be inferred. Only trajectories below the dashed line indicate a significant association. Please note that the y-axis scale is different in the panels showing the associations with cognitive decline *vs* motor decline because of the stronger associations between pathologies of Alzheimer's disease and related dementias and cognitive decline. This figure includes only the associations of tau tangles and macroinfarcts to illustrate the differences in association of a neurodegenerative and a cerebrovascular brain pathology with cognitive and motor decline. Associations of all the pathologies with cognitive and motor decline are in the appendix (pp 18–23).

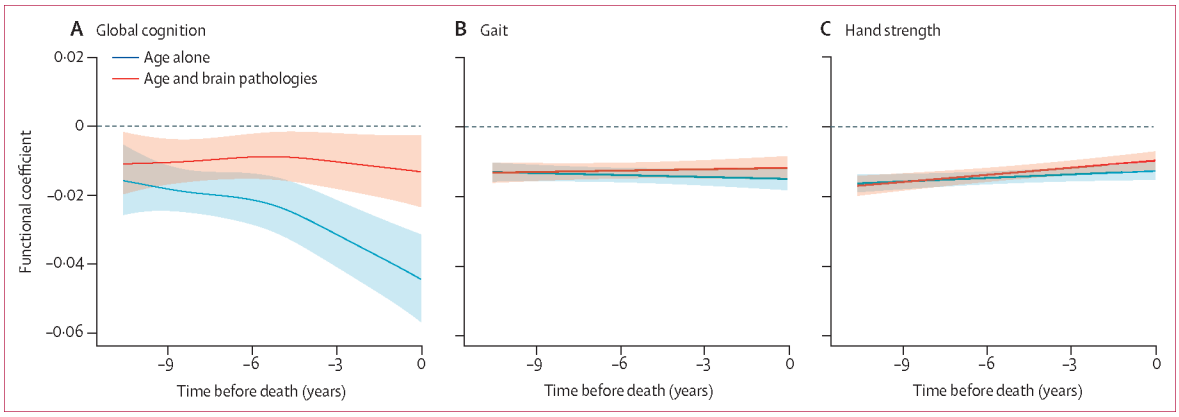

Figure 3: Association between age at death and cognitive and motor decline

(A) Association of age with cognition. (B) Association of age with gait function. (C) Association of age with hand strength. Each chart shows the results from two functional mixed-effects models: one model included age alone and one included brain pathologies and age. Blue and red lines indicate the associations and the shaded blue and red areas indicate 95% point-wise CI. The dashed line represents zero, and by comparing its course with the blue and red lines and shaded blue and red areas, an association between age at death and cognitive or motor decline can be inferred. Only trajectories below the dashed line indicate a significant association.

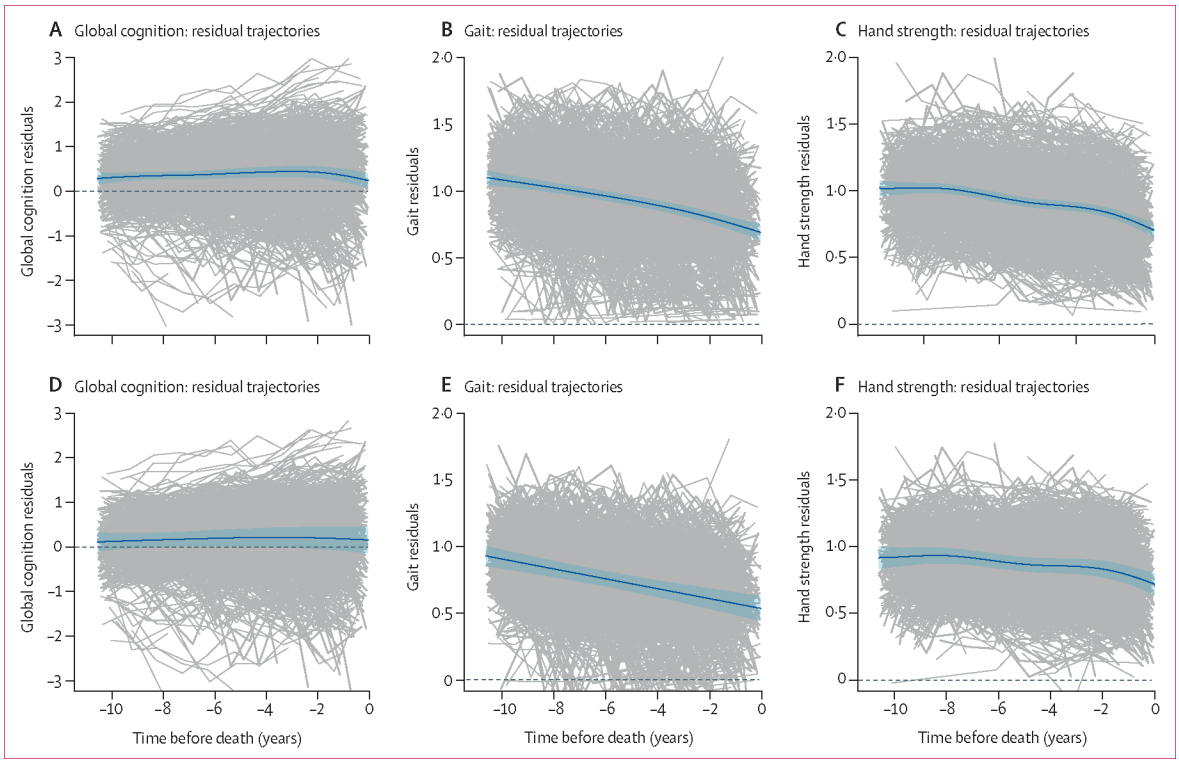

Figure 4:

Residual cognitive and motor decline after regressing out the associations of the brain pathologies of Alzheimer's disease and related dementias without and with demographics The charts show the residual cognitive function decline (A), gait function decline (B), and hand strength decline (C) after regressing out the associations of the brain pathologies, and the residual cognitive function decline (D), gait function decline (E), and hand strength decline (F) after regressing out the associations of the brain pathologies together with age at death, sex, education, and race using functional mixed-effects models. The grey lines show person-specific residual decline, the superimposed blue curves show the mean residual decline derived from the same models, and the shaded blue area around the curves shows the 95% CIs.

Table 1:

Characteristics of study participants

	Religious Orders Study (n=651)	Rush Memory and Aging Project (n=628)	Minority Aging Research Study (n=24)	All (n=1303)
Demographics				
Female	438 (67%)	448 (71%)	19 (79%)	905 (69%)
Male	213 (33%)	180 (29%)	5 (21%)	398 (31%)
Race				
Non-Latino White	600 (92%)	607 (97%)	0	1207 (93%)
Non-Latino Black	23 (4%)	10 (2%)	24 (100%)	57 (4%)
Latino	26 (4%)	10 (2%)	0	36 (3%)
Other	2 (<1%)	1 (<1%)	0	3 (<1%)
Education, years	18·0 (3·5)	14·8 (2·9)	13·8 (2·3)	16·4 (3·6)
Clinical characteristics at baseline				
Age at baseline, years	76·9 (6·8)	82·3 (5·7)	76·9 (7·0)	79·5 (6·8)
Cognitive status				
Normal cognition	446 (69%)	435 (69%)	17 (71%)	898 (69%)
Mild cognitive impairment	164 (25%)	173 (28%)	4 (17%)	341 (26%)
Dementia	41 (6%)	20 (3%)	3 (13%)	64 (5%)
Probable Alzheimer's disease	38 (6%)	18 (3%)	2 (8%)	58 (4%)
Possible Alzheimer's disease	1 (<1%)	2 (<1%)	0	3 (<1%)
Other dementia	2 (<1%)	0	1 (4%)	3 (<1%)
Mini-Mental State Examination score	28·1 (2·2)	27·7 (2·4)	27·3 (2·5)	27·9 (2·4)
Global cognition score	0·01 (0·60)	−0·04 (0·58)	−0·40 (0·56)	−0·02 (0·59)
Gait function score	1·1 (0·28)	1·0 (0·27)	0·99 (0·25)	1·0 (0·28)
Hand strength score	1·2 (0·31)	0·90 (0·26)	1·2 (0·29)	0·93 (0·28)
Clinical characteristics at the last visit				
Age at death, years	89·3 (6·5)	91·4 (5·8)	86·1 (7·4)	90·3 (6·3)
Age at the last visit, years	88·0 (6·0)	89·8 (6·0)	84·3 (7·4)	88·8 (6·4)
Cognitive status				
Normal cognition	181 (28%)	213 (34%)	13 (54%)	407 (31%)
Mild cognitive impairment	135 (21%)	141 (22%)	4 (17%)	280 (22%)

	Religious Orders Study (n=651)	Rush Memory and Aging Project (n=628)	Minority Aging Research Study (n=24)	All (n=1303)
Dementia	335 (51%)	274 (44%)	7 (29%)	616 (47%)
Probable Alzheimer's disease	282 (43%)	239 (38%)	5 (21%)	526 (40%)
Possible Alzheimer's disease	41 (6%)	27 (4%)	1 (4%)	69 (5%)
Other dementia	12 (2%)	8 (1%)	1 (4%)	21 (2%)
Mini-Mental State Examination score	20·8 (8·9)	22·1 (8·2)	25·6 (4·7)	21·5 (8·6)
Global cognition score	−0·95 (1·2)	−0·84 (1·1)	−0·62 (0·98)	−0·89 (1·17)
Gait function score	0·55 (0·37)	0·71 (0·24)	0·72 (0·26)	0·63 (0·32)
Hand strength score	0·61 (0·31)	0·64 (0·29)	0·95 (0·28)	0·63 (0·30)
Post-mortem indices of brain pathologies				
Alzheimer's disease	441/650 (68%)	414/628 (66%)	14/24 (58%)	869/1302 (67%)
Square root of amyloid-β *	1·5 (1·0)	1·8 (1·2)	0·97 (0·98)	1·61 (1·12)
Square root of tau tangles †	1·7 (1·3)	1·7 (1·3)	1·5 (1·1)	1·69 (1·33)
Hippocampal sclerosis	56/649 (9%)	65/628 (10%)	2/24 (8%)	123/1301 (9%)
TDP-43	207/629 (33%)	237/626 (38%)	7/24 (29%)	451/1279 (35%)
Parkinson's disease	61/624 (10%)	44/603 (7%)	0	105/1250 (8%)
Lewy bodies	172/650 (26%)	171/628 (27%)	3/24 (13%)	346/1302 (27%)
Moderate to severe nigral neuronal loss	84/649 (13%)	56/628 (9%)	0	140/1301 (11%)
One or more macroinfarcts	222 (34%)	247 (39%)	6 (25%)	475 (36%)
One or more microinfarcts	200 (31%)	220 (35%)	7 (29%)	427 (33%)
Moderate to severe atherosclerosis	229/649 (35%)	188/627 (30%)	1/24 (4%)	418/1300 (32%)
Moderate to severe arteriolosclerosis	185/648 (29%)	205/627 (33%)	5/24 (21%)	395/1299 (30%)
Moderate to severe cerebral amyloid angiopathy	252/639 (39%)	219/627 (35%)	7/24 (29%)	478/1290 (37%)

Data are n (%), mean (SD), or n/N (%). TDP-43=transactive response DNA binding protein-43.

* Religious Orders Study N=594; Rush Memory and Aging Project N=549; Minority Aging Research Study N=11.

† Religious Orders Study N=623; Rush Memory and Aging Project N=607; Minority Aging Research Study N=18.

Table 2:

Associations of brain pathologies with cognitive and motor decline, including the earliest year before death when an association began

	Cognitive decline		Gait function decline		Hand strength decline	
	Association p value	**Onset of the association (years before death)**	**Association p value**	**Onset of the association (years before death)**	**Association p value**	**Onset of the association (years before death)**
Amyloid-β	0·0052 *	..	>0·99	..	0·13	..
Tau tangles	<0·0001	<−11	<0·0001	−3·49	<0·0001	−3·57
Hippocampal sclerosis	<0·0001	<−11	>0·99	..	0·014	−4·42
TDP-43	0·0002	−4·00	0·36	..	0·046	−1·39
Parkinson's disease	<0·0001	−7·93	0·0032	−4·60	0·030	−5·80
Macroinfarcts	0·0005	−6·65	<0·0001	−9·25	0·024	−2·66
Microinfarcts	0·028	−6·60	0·054	..	0·96	..
Atherosclerosis	0·0008	<−11	0·98	..	0·15	..
Arteriolosclerosis	>0·99	..	0·91	..	0·032	−4·5
Cerebral amyloid angiopathy	0·077	..	>0·99	..	0·93	..

TDP-43=transactive response DNA binding protein-43.

*Although the association between amyloid-β and cognitive decline was significant, when we examined the association by piece-wise method to determine the onset year of the association, none of the piece-wise examinations were significant.