Physical frailty in older persons is associated with Alzheimer disease pathology

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ABSTRACT

Objective: We examined the extent to which physical frailty in older persons is associated with common age-related brain pathology, including cerebral infarcts, Lewy body pathology, and Alzheimer disease (AD) pathology.

Methods: We studied brain autopsies from 165 deceased participants from the Rush Memory and Aging Project, a longitudinal clinical-pathologic study of aging. Physical frailty, based on four components, including grip strength, time to walk 8 feet, body composition, and fatigue, was assessed at annual clinical evaluations. Multiple regression analyses were used to examine the relation of postmortem neuropathologic findings to frailty proximate to death, controlling for age, sex, and education.

Results: The mean age at death was 88.1 years (SD = 5.7 years). The level of AD pathology was associated with frailty proximate to death ($\hat{\beta} = 0.252$, SE = 0.077, $p = 0.001$), accounting for 4% of the variance of physical frailty. Neither cerebral infarcts ($\hat{\beta} = -0.121$, SE = 0.115, $p = 0.294$) nor Lewy body disease pathology ($\hat{\beta} = 0.07$, SE = 0.156, $p = 0.678$) was associated with frailty. These associations were unchanged after controlling for the time interval from last clinical evaluation to autopsy. The association of AD pathology with frailty did not differ by the presence of dementia, and this association was unchanged even after considering potential confounders, including physical activity; parkinsonian signs; pulmonary function; or history of chronic diseases, including vascular risk factors, vascular disease burden, falls, joint pain, or use of antipsychotic or antihypertensive medications.

Conclusion: Physical frailty in old age is associated with Alzheimer disease pathology in older persons with and without dementia. *Neurology*® 2008;71:499–504

GLOSSARY

AD = Alzheimer disease; BMI = body mass index; FEV₁ = forced expiratory volume in 1 second; PEF = peak expiratory flow; VC = vital capacity.

Physical frailty is common in the elderly and associated with adverse health outcomes, but its underlying biology is poorly understood. Although frailty is a heterogeneous syndrome, a number of features, including strength, gait, body composition, and fatigue, are generally accepted as core components of physical frailty.^{1,2} Cerebral infarcts and Lewy body disease are known to be associated with impaired physical performance.^{3,4} Furthermore, recent work by several groups suggests that several core components of frailty, including impaired grip strength, slowed gait, and low body mass index (BMI), predict subsequent development of dementia.^{5–7} These reports suggest that common brain pathology may contribute to physical frailty in the elderly.

We used data from the Rush Memory and Aging Project,⁸ a longitudinal epidemiologic clinical-pathologic study of chronic conditions of aging, to examine to what extent common

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age-related brain pathologies, including cerebral infarcts, Lewy body pathology, and Alzheimer disease (AD) pathology, are related to physical frailty before death in older persons with and without dementia.

METHODS Subjects. Subjects were deceased and autopsied participants in the Rush Memory and Aging Project, a longitudinal clinical-pathologic study of aging and AD.⁸ Subjects enroll without known dementia and consent to annual follow-up and organ donation at death. The study was approved by the institutional review board of Rush University Medical Center, and participants signed an informed consent and an Anatomic Gift Act. Since 1997, more than 1,100 persons have enrolled and completed their baseline clinical evaluation. Participation in the annual follow-up evaluations exceeds 95% of survivors, and the autopsy rate exceeds 80%. At the time of this study, 209 brains were collected, final neuropathologic examination was still pending for 44 brains, and the analyses were restricted to the first 165 consecutive brains with completed neuropathologic assessment.

Clinical evaluation. The Memory and Aging Project performs a uniform structured clinical evaluation each year that includes medical history, neurologic examination, and neuropsychological performance tests.⁸ At the time of death, all clinical data from all years were reviewed by a neurologist, blinded to all postmortem data, and a diagnostic opinion was rendered regarding the most likely clinical diagnoses at the time of death.⁹

Physical frailty. Frailty is an evolving concept with numerous definitions proposed, and the categorical measure proposed by Fried et al. is a widely used construct.^{1,2} Rather than using a categorical measure, we used a continuous composite measure of frailty. Composite measures have been used effectively in other areas of aging research,¹⁰⁻¹² offer considerably more power to detect associations when working with postmortem indices, and can be used to document change over time.¹³ As described previously, composite frailty is highly correlated with the categorical measure used by other investigators.^{13,14} Furthermore, composite frailty was associated with mortality, incident disability, cognitive decline, and incident AD and has been used to document change in the rate of frailty.^{13,14}

Frailty was based on grip strength, timed walk, body composition, and fatigue.¹² Strength was based on grip strength measured with the Jamar hydraulic hand dynamometer (Lafayette Instruments, Lafayette, IN). Gait was based on the time to walk 8 feet. Body composition was based on BMI. Fatigue was assessed with two questions from a modified version of the Center for Epidemiologic Studies–Depression Scale. Composite frailty was constructed by converting the raw score from each of the four component measures to z scores using the mean and SD from all participants at baseline, as described previously.^{13,14} Higher frailty values indicate poorer performance, and lower frailty values indicate better performance.

Comorbidities and other covariates. Sex, race, and years of education were recorded at the baseline interview and cognitive testing. Age in years was computed from self-reported date of birth and date of the clinical examination at which the frailty measures were collected. Physical activity was assessed using questions adapted from the 1985 National Health Interview Survey.¹⁵ Activities included walking for exercise, gardening or yard work, calisthenics or general exercise, bicycle riding, and swimming or water exercise and were expressed as hours of activ-

ity per week (mean = 1.8 h/wk, SD = 2.8 h/wk), as previously described.¹⁶ Parkinsonian signs were based on a modified version of the motor portion of the Unified Parkinson's Disease Rating Scale.¹⁷ Spirometry, including forced expiratory volume in 1 second (FEV₁), vital capacity (VC), and peak expiratory flow (PEF), were measured (MicroPlus Spirometer MS03, Micro-Medical Ltd.) as described.¹⁶ The sum of the number of vascular risk factors (i.e., the sum of hypertension, diabetes mellitus, and smoking; mean = 1.19, SD = 0.78) and vascular disease burden (myocardial infarction, congestive heart failure, claudication, and stroke; mean = 0.77, SD = 0.97) were used as covariates as previously described.¹⁷ Joint pain and falls were based on participant report. Antihypertensive and psychoactive (antipsychotic, sedative, or anxiolytic) medications were inspected and coded using the Medi-Span system (Medi-Span, Inc.).¹⁶

Measures of AD pathology. Bielschowsky silver stain was used to visualize neuritic plaques, diffuse plaques, and neurofibrillary tangles in the frontal, temporal, parietal, and entorhinal cortex and the hippocampus, as previously described.¹⁸⁻²⁰ Briefly, the operator used a graticule to project a grid to count numbers of each pathologic marker in a 1-mm² area (magnification ×100) under the microscope. Counts were performed by a board-certified neuropathologist or trained technician blinded to all clinical data. Plaques and tangle counts had different ranges and were not normally distributed; therefore, we created standardized scores for each plaque and tangle count in each cortical area as previously described.¹⁸⁻²⁰ These scaled scores for each region were then averaged across the five regions (midfrontal, superior temporal, inferior parietal, entorhinal, and hippocampal cortex) to develop summary scores for diffuse plaques, neuritic plaques, and neurofibrillary tangles for each subject. We then averaged the summary scores of the three AD markers to yield the global measure of AD pathology for each subject used in the analyses described below.

Measures of cerebral infarcts. For each brain, we identified the age, volume (in mm³), side, and location of all cerebral infarcts visible to the naked eye as previously reported.¹⁹ For these analyses, we included all old cortical and subcortical gray and white matter cerebral, cerebellar, and brainstem infarcts. Infarct age was estimated by degree of excavation and microscopic features. Acute and subacute infarcts, defined as age less than 3 to 6 months, were not included in the analyses. Ischemic lesions with small amounts of hemorrhage were included in analyses. We dichotomized the number of infarcts as present or absent.

Measures of Lewy bodies. Lewy bodies were identified with antibodies to α -synuclein using alkaline phosphatase as the chromogen as previously described.²¹ The presence of Lewy bodies in the frontal, temporal, parietal, or entorhinal gyrus cortices, cingulate gyrus cortices, or substantia nigra was considered evidence for Lewy body disease.

Statistical analyses. Spearman correlations were used to compare the relationship between physical frailty and demographic variables and brain pathologies; a *t* test was used to compare physical frailty between men and women. We used a series of linear regression models to document the association of common brain pathologies with physical frailty proximate to death, controlling for age, sex, and education in all models. In secondary analyses, we repeated these models, adding an additional term for the time interval from the last clinical evaluation to autopsy. We tested for both a linear and a nonlinear (quadratic) association between AD pathology and frailty. In a final model, we added an interaction term to examine whether the association of

AD pathology and frailty was modified by the presence of dementia. We then repeated a series of regression models that controlled for age, sex, and education, while adding terms for potential confounding variables to examine their influence on the association of AD pathology with physical frailty. Finally, we used regression analyses to examine the association of AD pathology with each of the four components used to construct composite frailty. Linear regressions as described above were used with grip strength and BMI. Because the distributions of timed walk and fatigue were not normal, we dichotomized these measures as frail and not frail, as done previously by other investigators, and used logistic regression analyses.¹ Model assumptions of linearity, normality, independence of errors, and homoscedasticity of errors were examined graphically and analytically and were adequately met.²² We also determined that residual SDs were similar in participants with and without dementia. For the sample size of 165 for the core model and demographic variables accounting for 18% of the variability in physical frailty, for a type I error rate of 0.05 and a two-sided test, we had 80% power to detect an increase in R^2 of four percent. All analyses were performed using SAS/STAT software version 8 on a Sun UltraSparc workstation (Palo Alto, CA).²³

RESULTS Summary of physical frailty and neuro-pathologic findings. There were 165 deceased participants included in these analyses, 56.4% female, with a mean age at baseline of 84.6 years (SD = 5.6 years), mean years of education of 14.5 years (SD = 2.8 years), mean BMI of 25.7 kg/m² (SD = 4.8 kg/m²), and mean Mini-Mental State Examination score of 25.6 (SD = 4.9). The mean age at death was 88.1 (SD = 5.7), and the mean postmortem interval was 6.6 hours (SD = 12.3 hours).

The last frailty assessment occurred approximately 6 months before death (mean = 6.4 months, SD = 4.2 months). The last frailty assessment was related to age ($\rho = -0.20$, $p = 0.008$), was higher in female participants ($t = 3.99$, $df = 163$ from Satterthwaite adjustment, $p < 0.001$), and unrelated to education ($\rho = -0.10$, $p = 0.197$). Fifty-nine participants (35.8%) had a clinical diagnosis of dementia at the time of death.

The summary measure of AD pathology ranged from a low of 0, indicating no pathology, to a high of 3.2; all but 3 participants had a nonzero AD pathology score (mean = 0.7, SD = 0.66). Twenty-four subjects (14.3%) had Lewy body pathology, and 57 subjects (34.6%) had macroscopic cerebral infarcts. AD pathology was not related to the presence of chronic macroscopic infarcts ($\rho = -0.02$, $p = 0.822$) or Lewy body pathology ($\rho = 0.06$, $p = 0.448$), and macroscopic infarcts were not related to the presence of Lewy body pathology ($\chi^2 = 2.6$, $p = 0.106$).

Association of AD pathology, cerebral infarcts, and Lewy body disease with physical frailty. We first examined the association of AD pathology with frailty, controlling for age, sex, and education. As shown in

the figure, a higher level of AD pathology was associated with higher frailty, i.e., poorer performance ($\hat{\beta} = 0.252$, SE = 0.077, $p = 0.001$). In this model, age, sex, and education explained 18% of the variance of frailty, and AD pathology accounted for an additional 4% of the variance of frailty. The level of frailty was approximately two times higher in a person with 1.6 units of global AD pathology (90th percentile) compared with a person with 0.2 units of global AD (10th percentile). We repeated this model, adding a quadratic term (AD pathology²), which did not show a nonlinear association between AD pathology and frailty ($\hat{\beta} = -0.047$, SE = 0.086, $p = 0.584$). Next, we examined the association of other common brain pathologies with frailty. Neither cerebral infarcts nor Lewy body pathology ($\hat{\beta} = 0.065$, SE = 0.156, $p = 0.678$) were associated with frailty. We also repeated the analyses, including all three brain pathologies in a single model. Only AD pathology was associated with frailty ($\hat{\beta} = 0.285$, SE = 0.080, $p < 0.001$), whereas cerebral infarcts and Lewy body disease pathology were unrelated to frailty (results not shown). These associations were unchanged after including terms to adjust for the time interval from the last clinical examination to the time of death (results not shown).

Association of AD pathology with physical frailty and dementia. Increasing frailty has been shown to be associated with an increased risk of AD.¹⁴ The dementia group is more frail (dementia 0.9 [SD = 0.64] vs no dementia 0.5 [SD = 0.60]; $t = 3.92$, $p < 0.001$) and has more AD pathology (dementia 1.0 [SD = 0.60] vs no dementia 0.5 [SD = 0.49]; $t = 4.88$, $p < 0.001$). Therefore, we next examined whether there was an interaction between AD pathology and dementia status by adding a term for an interaction between dementia status and AD pathology with frailty. There was no interaction between dementia and AD pathology ($\hat{\beta} = -0.005$ for the interaction, SE = 0.172, $p = 0.976$). The fact that the interaction term is not significant suggests that the increase in frailty per increase in unit AD pathology was similar in persons with and without dementia before death.

Association of AD pathology with physical frailty and other covariates. Because chronic conditions or different levels of physical activity might cause increased or decreased frailty, which would enhance or suppress the association of interest, we repeated a series of regression models that controlled for age, sex, and education, while adding terms for potential confounding variables to examine their influence on the association of AD pathology with frailty. These included physical activity, parkinsonian signs, pulmo-

The x-axis shows the summary measure of global Alzheimer disease (AD) pathology (quantified standard units), and the y-axis shows composite physical frailty (z score) proximate to death. The scatterplot shows the individual values for physical frailty and AD pathology for participants with dementia (solid circle) and without dementia (triangle) before death. Superimposed are the regression line and 95% CI showing the estimated physical frailty against global AD pathology, from a linear regression model adjusting for age, sex, education, and AD pathology. This model accounts for approximately 22% of the variation in the physical frailty.

nary function (FEV₁, VC, and PEF), vascular risk factors, vascular disease burden, history of joint pain or falls, and use of antipsychotic or antihypertensive medications. In each case, the association of AD pathology with frailty remained significant (results not shown).

Association of AD pathology with the components of composite physical frailty. Because frailty is a multidimensional construct, it is possible that postmortem indices may vary in their association with the individual operational components of frailty. We conducted regression analyses to examine the association of AD pathology with each of the four individual components used to construct composite frailty. AD pathology was associated with grip strength ($\hat{\beta} = 0.229$, SE = 0.097, $p = 0.019$) and with BMI ($\hat{\beta} = 0.231$, SE = 0.106, $p = 0.030$). There was a trend for an association between AD pathology and gait (estimate = 0.510, SE = 0.282, $p = 0.071$). There was no association between AD pathology and fatigue (estimate = 0.122, SE = 0.252, $p = 0.627$).

DISCUSSION In this clinical-pathologic study of 165 older persons in the community setting, we found that physical frailty proximate to death was

related to level of AD pathology on postmortem examination but was not related to the presence of cerebral infarcts or Lewy body disease. This association was similar in persons with and without dementia and was unchanged even after considering level of physical activity, various physical performance measures, and chronic diseases. These findings raise the possibility that AD pathology may contribute to frailty or that frailty and AD pathology share a common etiopathogenesis.

Physical frailty is common in the elderly, with cross-sectional studies suggesting that approximately 7% of persons older than 65 years are frail, and that the occurrence of frailty increases with age and may exceed 45% after age 85 years.² Frailty is conceptualized to represent an age-related reduction in physiologic reserve and resistance to stressors and is associated with adverse health outcomes.^{1,2} While features used to operationalize frailty may be shared by other chronic conditions of aging (i.e., loss of muscle or strength), frailty is common in elders, even after controlling for common chronic health conditions and traditional measures of disability.^{1,2} The biologic basis of frailty is poorly understood and is thought to be multifactorial and may reflect a subclinical accumulation of common chronic diseases (e.g., cardiovascular and pulmonary disease, diabetes) and their interaction with nonspecific indices (e.g., inflammatory markers) as well as endocrine or metabolic changes, mitochondrial dysfunction, and reduced physical activity.²⁴

In an effort to better understand the biology of frailty, this study examined the extent to which frailty is related to the accumulation of the common age-related brain pathologies, including cerebral infarcts, AD pathology, and Lewy body pathology. In the current study, only AD pathology was related to frailty proximate to death such that a higher level of AD pathology is associated with higher level of frailty (figure). The association between AD pathology with frailty persisted even after we controlled for other possible factors, such as cardiovascular risk factors and a range of chronic diseases as well as postmortem evidence of infarcts that may contribute to increasing frailty in older persons.²⁵ This study extends findings from a previous clinical study in this same cohort which showed that baseline frailty and rate of increasing frailty were associated an increased risk of subsequent AD and cognitive decline.¹⁴ The current postmortem study in those participants, who died, shows that of the three most common age-related neuropathologies, only AD pathology was related to frailty before death. Interestingly, further analyses found that the association of AD pathology

with frailty did not differ for persons with and without dementia. Prior work in this²⁶ and other cohorts^{27,28} found that AD pathology is related to level of cognition among persons without dementia. The results of this current study suggest that one possible explanation for the previously reported clinical association of frailty and incident AD is that frailty may be a noncognitive manifestation of AD pathology that can manifest before dementia. These results should not be surprising. Several indices of motor structure and function, grip strength, gait speed, parkinsonian gait, BMI, and physical activity predict incident AD,^{5-7,29-31} and some of these measures have been reported to be related to AD pathology.^{30,32} We speculate that accumulation of AD pathology in brain regions that subserve cognition could affect components of frailty by impairing neural systems involved in the planning, and monitoring of even simple movements. This is suggested by the terminal cognitive decline observed in the elderly without dementia years before death.³³⁻³⁵ Alternatively, AD pathology in cognitive regions might serve as a proxy for AD pathology in other brain regions that regulate components of frailty (e.g., primary motor cortex). Last, frailty and AD pathology may share an underlying etiopathogenesis (e.g., vascular pathology, energy production, stress).^{36,37} These different mechanisms are not mutually exclusive and underscore the need for further studies of the relationship between AD and frailty.

Our study also has some limitations. Although we were able to control for common neuropathology indices and clinical confounders, postmortem assessment did not directly assess motor brain regions and thus might underestimate the association of frailty with brain pathology. It is possible that a larger study might have shown an association between cerebral infarcts and Lewy body pathology and frailty. The study's main limitation is that the findings are based on a selected cohort that differs in important ways from older persons in the general population in regard to education, socioeconomic status, and lifestyle. It will be important to investigate these findings in more diverse cohorts.

Confidence in these findings is enhanced by several factors. Participants underwent detailed annual structured clinical examinations for up to 10 years, with more than 95% follow-up participation in survivors and a high autopsy rate. Uniform structured procedures were followed with masking of examiners to previously collected data, as well as to postmortem data, reducing the potential for bias. The association of AD pathology and frailty was derived from the same larger cohort in whom we have previously demonstrated a clinical association of frailty and incident

AD. Furthermore, analyses controlled for a wide range of potentially confounding variables.

AUTHOR CONTRIBUTIONS

Statistical analysis was performed by A.S.B. in consultation with S.L., Senior Statistician at the Rush Alzheimer's Disease Center.

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