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Research Article

Physical Frailty and Brain White Matter Abnormalities: The Atherosclerosis Risk in Communities Study

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Abstract

Background: Physical frailty is associated with increased risk for dementia and other neurologic sequelae. However, the neurobiological changes underlying frailty and frailty risk remain unknown. We examined the association of cerebral white matter structure with current and future frailty.

Methods: Atherosclerosis Risk in Communities Study Neurocognitive Study participants who underwent 3T brain MRI were included. Frailty status was classified according to the Fried criteria. Cerebral white matter integrity was defined using white matter hyperintensity (WMH) volume and microstructure, measured using diffusion tensor imaging fractional anisotropy (FA) and mean diffusivity (MD). Multivariable linear regression was used to relate baseline frailty to white matter structure; multivariable logistic regression was used to relate baseline white matter to frailty risk among participants nonfrail at baseline.

Results: In the cross-sectional analysis (N = 1 754; mean age: 76 years), frailty was associated with greater WMH volume, lower FA, and greater MD. These associations remained consistent after excluding participants with a history of stroke or dementia. Among participants nonfrail at baseline who completed follow-up frailty assessment (N = 1 379; 6.6-year follow-up period), each standard deviation increase in WMH volume was associated with 1.46 higher odds of frailty at follow-up. Composite FA and MD measures were not associated with future frailty; however, secondary analyses found several significant white matter tract-specific associations with frailty risk.

Conclusion: The current study demonstrates a robust association of WMH volume with current and future frailty. Although measures of white matter microstructure were altered in frail individuals, these measures were not generally associated with progression from nonfrail to frail status.

Keywords: Aging, Diffusion tensor imaging, MRI

Frailty is a prevalent health condition among older adults resulting in a decline of multiple physiologic systems. Frailty is characterized by increased vulnerability to poor health outcomes, functional impairment, and elevated risk of morbidity and mortality (1,2). Estimates of frailty prevalence among community-dwelling older adults (ie, aged 65 and older) vary widely, from 5% to 27% (3).

Frailty frequently co-occurs with neurologic disease including cerebrovascular disease and dementia (4,5), and there is evidence to suggest that frailty may contribute to cognitive decline and the development of neurodegenerative brain changes (6,7).

Although a number of studies have demonstrated that frailty is associated with increased levels of cerebral white matter abnormalities (1,3,8–12), the existing evidence on the relationship between white matter abnormalities and frailty risk or progression of frailty is limited, with only three studies identified to date (13–15). Two such investigations found that baseline white matter hyperintensity (WMH) volume was associated with progression of frailty components, but not the incidence of frailty (13,15). An additional study examining white matter microstructural properties and frailty incidence (14) suggested that greater tract-specific diffusivity among specific white matter tracts is associated with progression of frailty components. However, this study was limited by small sample size, a brief follow-up, and the effect of cognitive status (eg, co-occurring dementia and mild cognitive impairment [MCI]) was not examined. Thus, while frailty and white matter disease appear to be related, it remains unclear whether white matter abnormalities are associated with the risk of future frailty and whether these associations differ across the spectrum of cognitive impairment.

Using a large community-based sample of Black and White older adults, the present study examined the cross-sectional association of WMH volume and white matter microstructural alterations with current frailty status and the risk of frailty across a 7-year follow-up period. We hypothesized that (1) baseline frailty would be associated with poorer white matter structure, and that (2) poorer white matter structure at baseline in nonfrail participants would be associated with the development of future frailty. Given the potential influence of neurodegenerative disease on the white matter–frailty relationship, we also examined the effect of cognitive status using stratified analyses. Race and sex were examined as effect modifiers given the existing literature demonstrating racial and sex disparities in cardiovascular health, and the increased prevalence of cerebrovascular disease among Black participants (16).

Method

Study Design and Participants

The Atherosclerosis Risk in Communities (ARIC) Study is an ongoing, community-based prospective cohort study. For the baseline Visit (1987–1989), 15 792 participants aged 45–65 years were recruited from 4 communities within Washington County, MD; Forsyth County, NC; northwestern suburbs of Minneapolis, MN; and Jackson, MS. A total of 6 538 participants returned for ARIC Visit 5 (2011–2013), among which 1 978 participants received a brain 3T magnetic resonance imaging (MRI) scan (participant selection detailed in Supplementary Material). The study design and exclusion criteria are provided in Figure 1. Participants missing essential covariates (ie, demographic variables, *APOE*ε4 status, and cardiovascular risk factors) were excluded from the analysis. A subset of participants ($N = 6$) who completed MRI but did not have complete diffusion tensor imaging (DTI) data were excluded from the DTI analyses.

Frailty Assessment

Participants who attended Visits 5, 6, and 7 of the ARIC Neurocognitive Study (NCS) were categorized as frail, prefrail, or robust based on the frailty phenotype definition operationalized by the Cardiovascular Health Study (2) and validated within ARIC (17). As previously described, this definition of frailty is based on 5 components: exhaustion, low physical activity, slowness, weight loss, and weakness (2,17). At Visit 5, exhaustion was defined as responses to 2 questions from the Center for Epidemiological Study's-Depression (CES-D) scale (18); low physical activity as the lowest quintile of level of sport activity in leisure time from the Baecke physical activity questionnaire; slowness as 4 m walking speed within the lowest 20th percentile, adjusted for sex and height; weight loss as >10% weight loss from Visit 4 (which occurred in midlife) to Visit 5, or a body mass index (BMI) at Visit 5 less than 18.5 kg/m^2; and weakness as grip strength in the lowest 20th percentile, adjusting for sex and BMI. Follow-up frailty assessment was obtained at Visit 6 and/or Visit 7. In the event that participants had complete frailty assessment data for both Visits 6 and 7, Visit 7 data were used. At Visits 6 and 7, exhaustion was defined as responses to 2 questions from the CES-D scale (18); low physical activity as the lowest quintile of level of sport activity in leisure time from the Baecke physical activity questionnaire; weight loss as >5% weight loss from Visits 5 to 6 or Visits 6 to 7 or BMI at Visit 6 or 7 less than 18.5 kg/m^2; and grip strength as the lowest 20th percentile adjusted for sex and BMI. The change in weight loss component from Visits 4–5 (>10%) to Visits 5–6 and 6–7 (>5%) reflects the change in follow-up time and participant age. Participants were categorized as frail if they met three or more of the criteria listed previously. Otherwise, participants were classified as nonfrail.

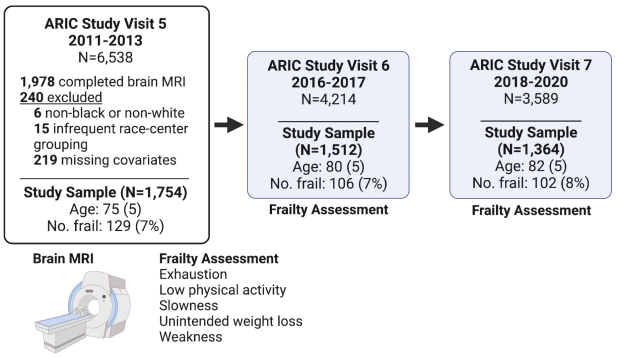

Figure 1. Study inclusion and exclusion criteria. Note: Details of missing covariates: 69 participants were missing *APOE* data, 94 missing frailty status, 2 missing education, 53 missing cardiovascular risk factors (ie, BMI, smoking status, hypertension, diabetes, and coronary artery disease). *APOE* = Apolipoprotein e4; BMI = body mass index; MRI = magnetic resonance imaging.

Brain MRI

Brain MRIs were conducted with a 3T MRI scanner. Acquisition details have been described previously (19). All images were analyzed with a common set of sequences: MP-RAGE, Axial T2*GRE, Axial T2 FLAIR, and Axial DTI. WMH volume (mm^3) was derived from T2 FLAIR images using a computer-aided segmentation program (FLAIR-histoseg) to measure the total volumetric burden (20). WMH volumes were log-transformed to due to skewness.

White matter fractional anisotropy (FA) and mean diffusivity (MD) were measured using DTI, as described previously (21). Lower FA and higher MD values are an indicator of poorer white matter microstructural integrity. For our primary analyses, we generated composite FA and MD values from a representative sample of projection, commissural, and association tracts implicated in frailty in

existing literature: the superior longitudinal fasiculus, posterior limb of the internal capsule, as well as the genu, body, and splenium of the corpus callosum (8,14). General factors for FA (gFA) and MD (gMD) were derived from the first unrotated principal component of the standardized FA and MD values from the aforementioned white matter tracts (Supplementary Table 1).

Covariate and Clinical Assessment

Participant demographics (age, race, education, and sex) were obtained at ARIC Visit 1 based on self-report. All other covariates were defined at Visit 5. BMI in kg/m^2 was defined by participant height and measured weight. Participants were classified as having hypertension if the mean systolic blood pressure of the second and third of 3 blood pressure measurements ≥140 mm Hg, diastolic blood pressure ≥90 mm Hg, or use of antihypertensive medications. Diabetes was defined as presence of hemoglobin A1C levels ≥6.5%, use of medication for diabetes, self-reported history of diabetes as diagnosed by a physician. History of coronary heart disease was defined based on self-report at Visit 1 or adjudicated events between Visits 1 and 5. Smoking status was defined based on self-reported current tobacco use history. Cognitive classification was conducted by expert adjudications based on National Institute on Aging-Alzheimer's Association and Diagnostic and Statistical Manual for Mental Disorders, fifth Edition criteria (22). See the Supplementary Material for a detailed description of MCI and dementia classification. The TaqMan assay (Applied Biosystems, Foster City, CA) was used to measure *APOE* genotype (0 vs ≥1 *APOE*ε4 alleles). To account for race-geographic aliasing of participants, a combined race-center variable was created. Race-center groups were Black from Jackson, MS; Black from Forsyth County, NC; White from Washington County, MD; White from Forsyth County, NC; and White from Minneapolis, MN.

Data Analysis

Chi-square and independent-sample *t* tests were used to compare participant demographic and clinical characteristics for categorical and continuous variables, respectively. We used separate multivariable linear regression models to examine the cross-sectional associations between frailty status and measures of white matter structure (ie, WMH volume, gFA, and gMD) which were standardized to the sample mean and standard deviation. Here, white matter structure was used as a dependent variable to capture the extent of white matter abnormalities associated with frailty status, consistent with the methods of existing literature (8,9,11). We examined three models: an unadjusted model (Model 1), a model adjusting for potentially confounding demographic variables (ie, age, education, sex, race-center, and *APOE*ε4 status; Model 2), and a third model which additionally adjusted for the effects of cardiovascular risk factors (ie, BMI, hypertension, diabetes, coronary heart disease, and smoking status; Model 3). We used separate multivariable logistic regression models to examine the prospective association of WMH volume, gFA, and gMD with future frailty among nonfrail participants at Visit 5. Analyses examining WMH were also adjusted for intracranial volume.

We conducted several secondary/sensitivity analyses. First, we examined in separate models the effect of excluding participants with known history of stroke, dementia, or MCI/dementia confirmed by the end of Visit 5. Second, we determined the impact of incorporating sampling weights to account for the MRI sampling strategy. Third, effect moderation by race and sex was examined using multiplicative interaction terms. Finally, as part of a post hoc exploratory analyses we examined the relationship between frailty and specific DTI-defined white matter tracts associated with frailty in the existing literature.

Results

A total of 1 754 participants were included in the cross-sectional analysis (mean age = 76.2, standard deviation [*SD*] = 5.2, 59.4% female, 29.1% Black) with 1 625 (92.6%) classified as nonfrail and 129 (7.4%) as frail at Visit 5. Compared to nonfrail participants, those classified as frail were older, had less education, and demonstrated a greater prevalence of diabetes and coronary heart disease. Full sample characteristics are summarized in Table 1. Incident frailty analyses were limited to 1 379 participants nonfrail at baseline with available MRI data and frailty follow-up assessments at either Visit 6 or 7.

Cross-sectional Association of Frailty and White Matter Structure

Compared to nonfrail participants, individuals with frailty demonstrated greater WMH volume in unadjusted and demographically-adjusted models (Supplementary Table 3), and after additionally adjusting for cardiovascular risk factors (Table 2). In the fully-adjusted model, frailty was associated with a 0.29 *SD* greater WMH volume (95% confidence interval [CI]: 0.13, 0.45; $p < .001$). This relationship was maintained when participants with history of stroke and dementia were excluded. However, this relationship did not persist when analyses were restricted to cognitively normal participants, that is, the group of participants without MCI or dementia (Table 2).

Examination of DTI measures of white matter microstructural properties yielded similar results. Frailty status, compared to nonfrail, was associated with lower gFA and greater gMD in unadjusted and demographically-adjusted models (Supplementary Table 3), and after additionally adjusting for cardiovascular risk factors (Table 2). Results were similar when participants with confirmed history of stroke or dementia were excluded. Among cognitively normal participants, only gMD was associated with frailty status (Table 2).

Cross-temporal Association of White Matter Structure and Frailty Risk

Among the 1 379 participants nonfrail at baseline who were included in this analysis, 270 developed incident frailty at either Visit 6 or 7. Median follow-up time from Visit 5 was 4.9 years to Visit 6 and 6.6 years to Visit 7. Nonfrail participants who dropped out before the first follow-up visit were more likely to be White and less educated; however, groups did not differ in terms of health or cognitive characteristics (Supplementary Table 2).

Greater WMH volume at Visit 5 was associated with increased odds of frailty at a future visit in unadjusted, demographically-adjusted, and fully-adjusted models (odds ratio [OR] = 1.46 per *SD* increase in WMH volume; 95% CI: 1.15, 1.87; $p = .002$; Table 3 and Supplementary Table 4). The relationship between greater WMH volume and incident frailty was similar when participants with baseline stroke and dementia were excluded. Among cognitively normal participants, that is, excluding participants with baseline MCI and dementia, each *SD* higher WMH was associated with a nearly 80% higher odds of incident frailty (OR = 1.77; 95% CI: 1.24, 2.40; $p = .001$). After exclusion of the 858 participants who were prefrail

Table 1. Study Sample Baseline (Visit 5) Demographic and Clinical Characteristics Stratified by Frailty Status

Characteristics	Total (*N* = 1 754)	Nonfrail (*N* = 1 625)	Frail (*N* = 129)
Age*	76.2 (5.2)	76.0 (4.7)	78.5 (5.5)
Female sex†	1 041 (59.4)	954 (58.7)	87 (67.4)
Black	510 (29.1)	473 (29.1)	37 (28.7)
White	1 244 (70.9)	1 152 (70.9)	92 (71.3)
Level of education*			
Less than high school	247 (14.1)	217 (13.4)	30 (23.3)
High school/GED/vocational	713 (40.6)	657 (42.9)	56 (43.4)
College/graduate/professional	794 (45.3)	751 (46.2)	43 (33.3)
APOE e4 alleles			
0 e4 alleles	1 248 (70.8)	1 149 (70.7)	87 (67.4)
1 e4 alleles	460 (26.2)	426 (26.2)	33 (25.6)
2 e4 alleles	46 (2.6)	42 (2.3)	4 (3.1)
BMI	28.4 (5.6)	28.4 (5.2)	28.8 (6.8)
Hypertension†	1 314 (74.9)	1 209 (74.4)	105 (81.4)
Coronary artery disease*	184 (10.5)	163 (10.0)	21 (16.3)
Diabetes*	540 (30.8)	488 (30.0)	52 (40.3)
Current smoking	90 (5.1)	81 (5.0)	9 (7.0)
Stroke	59 (3.4)	18 (1.1)	7 (5.4)
Cognitive status*			
Normal	1 079 (61.6)	1 023 (63.0)	56 (43.4)
MCI	581 (33.2)	523 (32.2)	58 (45.0)
Dementia	92 (5.3)	77 (4.7)	15 (11.6)

Notes: Values are represented as mean (standard deviation) for continuous variables and frequency (percentage of sample) for categorical variables. Independent sample *t* tests were used for continuous variables and chi-square for categorical variables. *APOE* = Apolipoprotein e4; BMI = body mass index; MCI = mild cognitive impairment.

*$p < .05$ difference between frail and nonfrail participants.

†$p < .10$ difference between frail and nonfrail participants.

Table 2. Cross-sectional Association of Frail Versus Nonfrail Status With White Matter Structure

	All Participants *N* = 1 748	No Prior Stroke *N* = 1 689	Nondemented *N* = 1 653	Cognitively Normal *N* = 1 076
MRI Characteristics	ß (95% CI)	ß (95% CI)	ß (95% CI)	ß (95% CI)
WMH volume	0.29 (0.13, 0.45)*	0.26 (0.10, 0.43)†	0.28 (0.11, 0.45)*	0.05 (–0.19, 0.29)
gFA	–0.31 (–0.47, –0.14)*	–0.27 (–0.44, –0.11)*	–0.33 (–0.50, –0.16)*	–0.20 (–0.43, 0.03)
gMD	0.43 (0.29, 0.58)*	0.41 (0.27, 0.56)*	0.40 (0.25, 0.55)*	0.29 (0.09, 0.49)†

Notes: Linear regression models are adjusted for age, sex, race-center, education, *APOE* ε4 status, BMI, hypertension, coronary artery disease, diabetes, and cigarette use status obtained at the time of neuroimaging. WMH analyses are additionally adjusted for intracranial volume. Values represent the adjusted difference in standardized WMH volume, gFA, and gMD between the frail and nonfrail group. *APOE* = Apolipoprotein e4; ß = standardized beta coefficient; BMI = body mass index; CI = confidence interval; gFA = general fractional anisotropy; gMD = general mean diffusivity; MRI = magnetic resonance imaging; WMH = white matter hyperintensity.

*$p < .001$.

†$p < .05$.

at baseline, the relationship between WMH and frailty risk was increased further (OR = 2.00; 95% CI: 1.28, 3.11; $p < .001$). There was no significant association of gFA or gMD with frailty incidence.

Secondary and Post Hoc Analyses

Across analyses, we found no evidence of effect modification by race and sex. Additionally, primary results were similar when incorporating sampling weights (Supplementary Table 5), suggesting the generalizability of results to the full ARIC Visit 5 sample. As part of a secondary exploratory analysis, we examined the association between frailty and DTI measures of individual white matter tracts used to generate the gFA and gMD factor scores (Figure 2). For descriptive purposes, we additionally present data on a broader set of white matter tracts that have been implicated in frailty previously (Supplementary Figure 1). These results suggest that the microstructure (FA) of specific white matter tracts, including the anterior limb of the internal capsule, superior corona radiata, and posterior corona radiata, may indeed be associated with incident frailty.

Discussion

In a large community-based study of older adults, we found that individuals with physical frailty have greater WMH volume and white matter microstructural abnormalities than do nonfrail individuals. Importantly, this relationship was observed in participants without a history of stroke or dementia but did not persist when analyses were

Table 3. Associations Between White Matter Structure and Future Frailty

	All Participants *N* = 1 379	No Prior Stroke *N* = 1 333	Nondemented *N* = 1 309	Cognitively Normal *N* = 875
MRI Characteristics	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
WMH volume	1.46 (1.15, 1.87)*	1.51 (1.17, 1.94)†	1.52 (1.21, 2,01)†	1.78 (1.26, 2.51)†
gFA	0.84 (0.67, 1.04)	0.83 (0.66, 1.05)	0.84 (0.66, 1.04)	0.95 (0.68, 1.3)
gMD	0.93 (0.72, 1.20)	0.89 (0.68, 1.18)	0.92 (0.71, 1.20)	0.78 (0.53, 1.14)

Notes: Logistic regression models are adjusted for age, sex, race-center, education, *APOE* ε4 status, BMI, hypertension, coronary artery disease, diabetes, cigarette use, stroke, and cognitive status obtained at the time of neuroimaging. WMH analyses are additionally adjusted for intracranial volume. Values represent the odds of incident frailty per one unit increase in standardized WMH volume, gFA, and gMD. *APOE* = Apolipoprotein e4; BMI = body mass index; CI = confidence interval; gFA = general fractional anisotropy; gMD = general mean diffusivity; MRI = magnetic resonance imaging; OR = odds ratio; WMH = white matter hyperintensity.

*$p < .05$.

†$p < .001$.

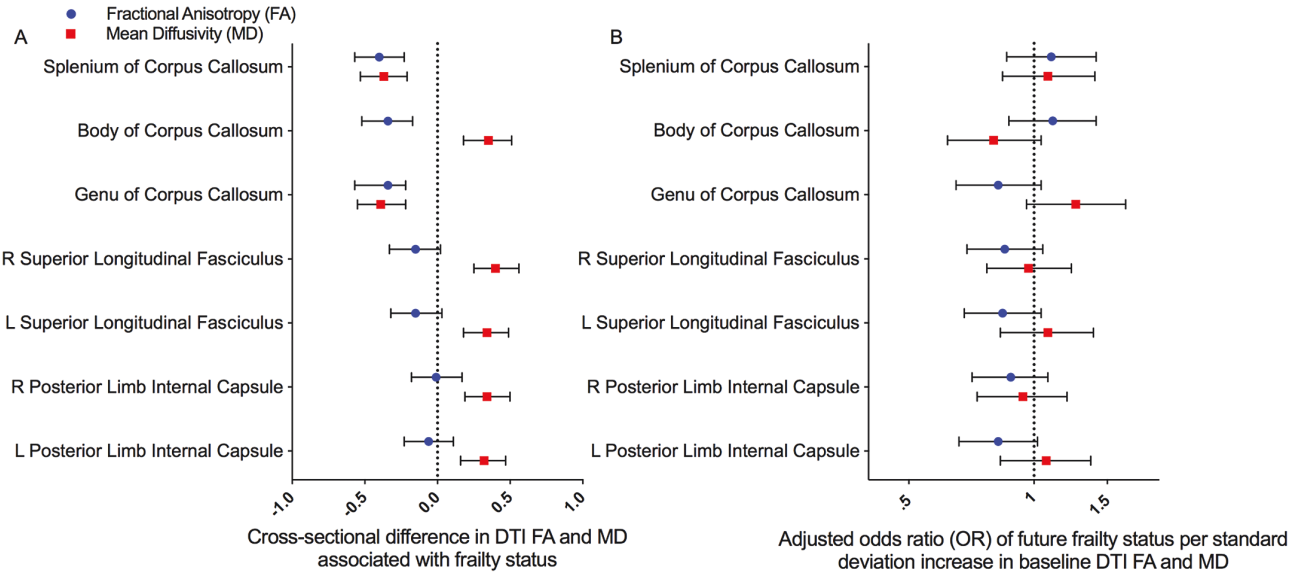

Figure 2. Cross-sectional and cross-temporal associations between frailty and tract-specific measures of microstructural integrity. All models are adjusted for age, sex, race-center, education, *APOE* ε4 status, BMI, hypertension, coronary artery disease, diabetes, and cigarette use status obtained at the time of neuroimaging. Figure A represents the adjusted standardized ß coefficient and 95% confidence interval of frailty and FA and MD using linear regression. Figure B represents the adjusted OR of future frailty per standard deviation increase in FA and MD using logistic regression. *APOE* = Apolipoprotein e4; BMI = body mass index; FA = fractional anisotropy; MD = mean diffusivity; OR = odds ratio.

restricted to cognitively normal individuals. Furthermore, WMH volume was significantly associated with new-onset frailty over a 7-year follow-up period, even among cognitively normal adults. These results were consistent in Black and White participants, and in men and women. Unlike WMH volume, general measures of white matter microstructural integrity were not associated with the risk of future frailty. However, secondary analyses did find that the microstructural integrity of specific white matter tracts was associated with future frailty.

The existing literature suggests modest positive relationships between individual frailty components and alterations to white matter structure cross-sectionally (9,10,12). White matter abnormalities have also been associated with progression of frailty components over time (13,15,23). However, the literature that has examined the relationship between structural indicators of neurological health and frailty risk to date has been largely limited by modest sample sizes, a lack of inclusion of participants across the robust-to-frailty spectrum, and a lack of racial diversity. In addition to replicating the association between prevalent frailty and white matter abnormalities, the present study assessed the cross-temporal link between WMH, white matter microstructure, and risk of future frailty over nearly a decade of follow-up. We show that WMHs are more severe in older adults at risk for frailty, including cognitively normal older adults. This link between WMH volume and incident frailty suggests that declining cerebrovascular health may be an indicator of, or a risk factor for, the decline of multiple physiologic systems (ie, frailty), even outside the context of clinically significant cognitive impairment or dementia.

The observational nature of this study prohibits causal inferences. However, we believe it is unlikely that frailty as a syndrome causes white matter disease. One possible explanation for the robust relationship between frailty and the health of cerebral white matter is the existence of one or more shared etiologies. That is, the same systemic conditions or health factors that increase one's risk for frailty may also promote the development of cerebral white

matter abnormalities. For example, there is evidence that cardiovascular disease, systemic inflammation, and impaired hemostasis are associated with frailty incidence (24–26). Each of these factors has also been consistently associated with WMH volume, white matter microstructural properties, and dementia risk (21,27–29). Thus, physical frailty may serve as an indicator of one or more of these physiological processes that also adversely affect brain health. Though frailty itself is an unlikely cause of brain changes, it is possible that structural damage to cerebral white matter promotes the development of frailty. For example, frailty features can result from damage to brain projection or commissural fibers involved in motor function, whereas white matter dysfunction in prefrontal or subcortical brain regions can result in fatigue, feelings of exhaustion, or even mood changes (23,30). The temporal ordering of our own findings also supports the mechanistic relationship between white matter disease and frailty.

Few studies have examined the relationship between white matter microstructural integrity and physical frailty, particularly with regard to frailty incidence. Cross-sectional studies have demonstrated associations between alterations to microstructural properties of specific white matter tracts (ie, internal capsule, external capsule, posterior thalamic radiation, and corpus callosum) and frailty (8,11). To the best of our knowledge, only one study has examined the relationship between white matter microstructural properties and progression of frailty components. This study demonstrated that higher tract-specific MD was associated with progression of frailty components (14). However, there was no association between FA values and progression of these same frailty components. While both general and tract-specific DTI measures were not consistently or strongly associated with incident frailty in the present study, the few statistically significant tract-specific findings derived from secondary analyses may contribute to our understanding of frailty risk. Specifically, we found that the FA of multiple tracts, including the anterior limb of the internal capsule, superior corona radiata, and posterior corona radiata, was associated with progression from nonfrail to frail status. However, these findings did not extend to measures of MD, or to other WM tracts that have been associated with prevalent frailty previously. These varying tract-specific associations with incident frailty suggest a differential contribution of specific white matter tracts—in this case, afferent projection fibers—to frailty development. However, these findings may also be explained by white matter tract-specific associations with motor control components of frailty (ie, grip strength and gait speed), rather than frailty as a syndrome.

Taken together, our primary results suggest that for white matter structural abnormalities to increase frailty risk, alterations must be severe enough to manifest as macroscopic changes visible on FLAIR MRI. Thus, relative to macrostructural changes, white matter altered at the microstructural level does not appear to be a robust frailty risk factor. In general, there is evidence supporting the idea that white matter microstructural alterations are less predictive of potential negative health outcomes among older adults relative to more severe structural abnormalities. The degree to which such attenuation can be explained by limited follow-up for a less severe manifestation of a pathological change merits further study.

Based on the results of the current analyses, frail individuals could be considered at risk for white matter pathology, even those frail individuals without dementia. As such, physical frailty may serve as a clinical indicator of cerebral small vessel disease and perhaps as a sign that one is at increased risk for future dementia or cognitive deterioration. Implementation of frailty assessment in health care settings may be helpful in identifying individuals at risk for cognitive and functional decline. Importantly, the association between frailty and white matter structure was not apparent among individuals who were cognitively normal, suggesting that frailty and WMHs do not necessarily co-occur outside the context of clinically significant cognitive impairment. Accordingly, the robust association between WMH volume and incident frailty among cognitively normal individuals may be due, in part, to the increased risk of progression to MCI/dementia among individuals with greater WMH volume (31).

Although prevalence rates of frailty may vary across racial ethnic groups, our work suggests that this observed difference may not necessarily translate to effect modification (moderation) by race. Rather, our findings indicate that the factors linking frailty to white matter disease operate similarly among Black and White individuals living in the United States. Through the lens of the shared etiology hypothesis: if the risk for WMHs and frailty is enhanced by, for example, cardiovascular disease, our findings suggest that the magnitude of the joint effect of cardiovascular disease on frailty and WMHs does not differ between Black and White individuals. However, a greater prevalence of cardiovascular disease among Black individuals may still translate to a greater burden of frailty and WMHs in this group.

There are several notable strengths of the current analysis including a large community-based cohort, a racially and geographically diverse sample, and the prospective study design. However, there are several limitations that warrant further discussion. First, we assessed risk factors, including stroke, dementia, and MCI, only at baseline. Although the cross-sectional associations between frailty and WMH volume that accounted for these risk factors were largely statistically significant, it is possible that development of stroke or cognitive impairment after the index exam may explain the observed relationship between WMH and incident frailty. Second, follow-up MRI data for participants were not available concurrently with follow-up frailty assessments. Therefore, we were unable to examine the frailty-WMH volume relationship bidirectionally. Third, despite adjustment for several baseline cardiovascular risk factors and physiological measures, we cannot exclude the possibility that the observed effects are driven by separate clinical or subclinical variables for which we have not accounted. Finally, differential attrition of participants after the baseline visit may have biased our analysis of frailty risk. However, we found minimal difference between participants who did and did not attend follow-up on the characteristics most strongly associated with frailty risk. Future research is needed to further examine the potential bidirectional relationship between frailty and biomarkers of brain health in order to establish whether frailty in and of itself contributes to neurobiological changes, which may in turn reinforce negative health outcomes.

In summary, the current study suggests that individuals who are physically frail tend to have greater white matter structural abnormalities, even among those without dementia. Moreover, WMH, but not white matter microstructural integrity, may be an important marker of frailty risk, particularly among cognitively normal individuals.

Supplementary Material

Supplementary data are available at *The Journals of Gerontology, Series A: Biological Sciences and Medical Sciences* online.

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Conflict of Interest

C.R.J. serves on an independent data monitoring board for Roche, has served as a speaker for Eisai, and consulted for Biogen, but he receives no personal compensation from any commercial entity. He receives research support from NIH, the GHR Foundation and the Alexander Family Alzheimer's Disease Research Professorship of the Mayo Clinic. D.S.K. serves on a Data Safety Monitoring Board for the DIAN study. He serves on a Data Safety Monitoring Board for a tau therapeutic for Biogen but receives no personal compensation. He is an investigator in clinical trials sponsored by Biogen, Lilly Pharmaceuticals and the University of Southern California. He has served as a consultant for Roche, Samus Therapeutics, Magellan Health and Alzeca Biosciences but receives no personal compensation. He receives funding from the NIH. R.F.G. is a former Associate Editor for the journal *Neurology*. The other authors declare no conflict.

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Author Contributions

Conceptualization (E.L.D., J.W., and K.A.W.); formal analysis (E.L.D.); methodology (E.L.D., G.T.G., P.P., K.J.S., C.R.J., D.S.K., R.F.G., B.G.W., and K.A.W.); original draft (E.L.D. and K.A.W.); reviewing and editing (E.L.D., G.T.G., P.P., K.J.S., C.R.J., D.S.K., R.F.G., J.W., B.G.W., and K.A.W.); data curation (P.P., C.R.J., D.S.K., R.F.G., and B.G.W.); project administration (C.R.J., D.S.K., R.F.G., and B.G.W.); resources (C.R.J.); funding acquisition (R.F.G.).

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