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PHYSICAL FRAILTY AND WHITE MATTER ABNORMALITIES: THE ARIC STUDY

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ABSTRACT

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Emma L. Ducca

Physical frailty is associated with increased risk for dementia and other neurologic sequelae. However, the neurobiological changes underlying frailty and frailty risk remain unknown. The association of cerebral white matter structure with current and future frailty was examined. 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 non-frail at baseline. 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 history of stroke or dementia. Among participants non-frail 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. 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 frail to non-frail status.

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Introduction

Frailty is a complex health condition in older adults that results in diminished physiologic reserve due to the decline in functioning across multiple physiologic systems (Fried et al., 2001). Estimates of frailty and prefrailty prevalence among community-dwelling older adults (i.e., aged 65 and older) varies widely from 4.9-27.3% to 34.6-50.9% (Choi et al., 2015). Frailty is associated with increased vulnerability to health sequelae including falls, disability, chronic illness, increased health care utilization, and premature death (X. Chen et al., 2014; Kanapuru & Ershler, 2009). Increased healthcare utilization and disability among frail individuals are associated with increased healthcare costs and represent significant economic burden for these individuals and our greater society (Bock et al., 2016). Large population studies have found that frailty is associated with subjective measures of poor health (i.e., depressive symptoms, self-reported poor health, low medication adherence) in addition to elevated biomarkers of inflammation and hyperglycemia (i.e., hemoglobin A1c, white blood cell count, and C-reactive protein) and poorer cardiovascular health (i.e., hemoglobin, total cholesterol) (Kucharska-Newton et al., 2017).

Frailty is characterized by individuals experiencing maladaptive responses to physiological stressors, often resulting in declines in overall health and reduced functional independence (X. Chen et al., 2014). The existing literature suggests chronic systemic inflammation, as measured by blood inflammatory markers, may be a key factor in frailty pathogenesis independent of medical comorbidities (Soysal et al., 2016; Walker et al., 2019). However, the precise mechanisms driving this relationship remain unclear and multiple physiologic pathways may be involved. One hypothesis is that chronic, sustained inflammation may result in excessive “wear and tear” which over time

increases vulnerability to stressors, while others suggest that inflammation is a biproduct of underlying disease processes (Franceschi & Campisi, 2014).

Frailty frequently coexists with neurologic disease including cerebrovascular disease and dementia (Kulmala et al., 2014; Palmer et al., 2019). Furthermore, there is evidence to suggest that frailty may contribute to cognitive decline and development of neurodegenerative brain changes (Buchman et al., 2007; Wallace et al., 2020). There is some conflicting evidence regarding the etiopathogenesis of these conditions. To elaborate, frailty appears to increase risk for overall cognitive and functional decline as well as Alzheimer's disease (AD) and vascular neurocognitive disorders (Boyle et al., 2010; Gray et al., 2013; Solfrizzi et al., 2013; Kojima et al., 2016). Contrastingly, other studies suggest that cognitive impairment may increase risk for developing frailty (Doba et al., 2012; Gross et al., 2016; Raji et al., 2010). Taken together, these results suggest that frailty and neurodegenerative conditions may be bidirectional or have shared etiologies.

Neuroimaging studies provide insight into the underlying neural correlates of frailty. Although there is considerable evidence suggesting that frailty and pathological aging are connected, there is some conflicting evidence regarding the etiological origins of these conditions. As noted above, physical frailty prevalence has been linked to development of several neurodegenerative diseases. However, there is evidence suggesting that brain changes implicated the development of neurodegenerative diseases may also promote physical frailty (Dobryakova et al., 2013; Wennberg et al., 2017). That is, patients with age-related pathology in subcortical gray matter structures and frontal

cortex often demonstrate many of the physical frailty criteria including slowed gait speed, fatigue, and exhaustion as well as cognitive fatigue.

Cerebral white matter abnormalities are associated with cognitive decline and dementia (Hahn et al., 2013; Knopman et al., 2015) as well as frailty (Chung et al., 2016; Avila-Funes et al., 2017; Del Brutto et al., 2017; Siejka et al., 2018). However, results have been somewhat inconsistent. A 2018 review of neuroimaging studies examining frailty and its components found only 17 studies (n = 979 records identified) which examined neuroimaging correlates of frailty among an older adult population. Results consistently showed associations between frailty and its components (gait speed and grip strength) and measures of white matter disease (López-Sanz et al., 2018). The existing literature suggests that there is a relationship between physical frailty and cerebrovascular abnormalities including increased presence of infarcts, WMH, and other measures of cerebral small vessel disease (Kant et al., 2018, 2019).

Although a number of studies have demonstrated that frailty is associated with increased levels of cerebral white matter abnormalities, the existing evidence on the relationship between white matter abnormalities and frailty progression is limited, with only three studies identified to date (Avila-Funes et al., 2017; X. Chen et al., 2014; Choi et al., 2015; Fried et al., 2001; Kant et al., 2019; López-Sanz et al., 2018; Newman et al., 2001; Siejka et al., 2018; Tian et al., 2020). Two such investigations found that baseline WMH volume was associated with progression of frailty symptoms, but not frailty incidence (Maltais et al., 2019; Siejka et al., 2020). One other study has examined white matter microstructural integrity and frailty incidence (Maltais et al., 2020). Results of this investigation suggested that progression of frailty symptoms was associated with

increased diffusivity among specific white matter tracts. However, this relationship did not extend to other indicators of white matter integrity (i.e., fractional anisotropy [FA]). Thus, while frailty and white matter disease appear to be related, it remains unclear whether white matter abnormalities are associated with 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 association of WMH volume and white matter microstructural integrity with current frailty status and future frailty status across a 7-year follow-up period. The following hypotheses were proposed:

(1) Participants who were frail at baseline would have increased evidence of white matter disease on neuroimaging as compared to non-frail participants.

(2) Participants with greater white matter disease on neuroimaging at baseline would be more likely to convert to frailty as compared to participants with lower white matter disease.

Given the potential influence of neurodegenerative disease on the white matter - frailty relationship, the effect of cognitive status was examined 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 (Nyquist et al., 2014). We predicted that the effect of white matter disease on frailty would be moderated by self-identifying as Black and female sex.

Methods

Study design and participants

The ARIC study is an ongoing, community based prospective cohort study. For the initial visit (1987-89) 15,792 participants ages 45-65 were recruited from four communities within the Washington County, MD; Forsyth County, NC; northwestern suburbs of Minneapolis, Minnesota; and Jackson, Mississippi. Of the 6,528 participants who attended ARIC Visit 5, 1,978 participants completed 3T brain MRI. Participant selection criteria are outlined below and are outlined in Knopman (2015). Briefly, participants with known MRI contraindications were excluded. MRI selection criteria included if they completed a brain MRI as part of the ARIC Brain MRI Ancillary Study in 2004-2006 or, demonstrated cognitive impairment. Cognitive impairment was defined as either a low Mini Mental Status Exam (MMSE) score (<21 for White participants and <19 for Black participants), or impairment on two or more cognitive domain scores at Visit 5 (<-1.5 standard deviations) and decline on the Delayed Word Recall test, Digit Symbol Substitution test, or Word Fluency test (Visit 5 score minus highest previous score <10th percentile on 1 or more tests or <20th percentile on 2 or more tests). An additional sample of cognitively intact participants with an age distribution that approximated that of the cognitively impaired participants were also selected. A flowchart of exclusion criteria and study timeline is provided in **Figure 1**. Participants missing essential covariates (i.e., demographic variables, APOEε4 status, and cardiovascular risk factors) were excluded from the analysis. A subset of participants (N = 6) who completed MRI but did not have complete DTI data were excluded from this portion of analysis.

Frailty assessment

Participants who attended Visits 5, 6, and 7 of the ARIC Neurocognitive Study (NCS) were categorized as frail, pre-frail, or robust based on the frailty phenotype definition operationalized by the Cardiovascular Health Study (CHS) (Fried et al., 2001) and validated within this population (Kucharska-Newton et al., 2017). This definition of frailty is based on 5 components: exhaustion, low physical activity, slowness, unintended weight loss, and weakness.

At Visit 5, exhaustion was defined as responses to two questions from the Center for Epidemiological Study's-Depression (CES-D) scale (Radloff, 1977); as the lowest quintile of level of sport activity in leisure time from the Baecke physical activity questionnaire; slowness as 4m walking speed within the lowest 20^{th} percentile, adjusted for sex and height; weight loss as >10% lb decrease from Visit 4 (occurred in midlife) to Visit 5, a body mass index (BMI) at Visit 5 less than 18.5kg/m^2 (Visit 5); and weakness as grip strength in the lowest 20^{th} 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 two questions from the Center for Epidemiological Study's-Depression (CES-D) scale (Radloff, 1977); 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 Visit 5 to 6 or 6 to 7 or BMI at Visit 6 or 7 less than 18.5 kg/m^2; and grip strength as the lowest 20^{th} percentile adjusted for sex and BMI. To reflect the changing age demographic of participants from Visit 5 (midlife) to Visits 6 and 7 (older adulthood), the weight loss

component of the frailty assessment was adjusted from >10% at Visit 5 to >5% at Visits 6 and 7. Participants were categorized as frail if they met 3 or more of the criteria listed above. Otherwise, participants were classified as non-frail.

Dementia classification

Cognitive classification was conducted by expert adjudications based on National Institute on Aging-Alzheimer's Association (NIA-AA) and Diagnostic and Statistical Manual for Mental Disorders, 5th Edition criteria (American Psychiatric Association, 2013). More specifically, mild cognitive impairment (MCI) and dementia at Visit 5 were classified by an expert panel of adjudicators according to National Institute on Aging-Alzheimer's Association (NIA-AA) workgroup and Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5) criteria (Albert et al., 2011; American Psychiatric Association, 2013; McKhann et al., 2011). Assessment included a comprehensive battery of cognitive tests administered at ARIC visits, 2, 4, and 5, informant interview conducted at Visit 5 which included the Clinical Dementia Rating Scale (CDR) and Functional Activities Questionnaire (FAQ). MCI was defined as one or more cognitive domain score 1.5 SD below normative mean, CDR score between >0.5 and ≤3, FAQ score ≤5, and decline on the ARIC repeated cognitive battery below 10th percentile on one test or 20th percentile on two tests (Knopman et al., 2016). Dementia was defined as two or more cognitive domain scores 1.5 SD below normative mean, CDR score >3 or FAQ >5, and decline on the ARIC repeated cognitive battery below 10th percentile on one test or 20th percentile on two tests (McKhann et al., 2011). Participants who did not meet criteria for MCI or dementia were classified as cognitively normal.

Brain MRI

Brain MRIs were conducted with a 3T MRI scanner. Acquisition details have been described previously (Knopman et al., 2015). All images were analyzed with a common set of sequences: MP-RAGE, Axial T2*GRE, Axial T2 FLAIR, and Axial diffusion tensor imaging (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 (Raz et al., 2013). WMH volumes were log transformed due to skewness.

White matter fractional anisotropy (FA) and mean diffusivity (MD) were measured using DTI, as described previously (Power et al., 2017). Lower FA and higher MD values are an indicator of poorer white matter microstructural integrity. For primary analyses, composite FA and MD values were generated 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 (Avila-Funes et al., 2017; Maltais et al., 2020). 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 as summarized in **Table 1**.

Covariate and clinical assessment

Participant demographic (i.e., age, race, education, sex, center) data were obtained at ARIC Visit 1 based on self-report. All other covariates were defined at Visit 5. BMI kg/m^2 was defined by participant measured height and weight. Participants were classified as hypertensive if their mean of the second and third of three blood pressure

measurements were ≥140 for systolic blood pressure, ≥ 90 mm diastolic blood pressure, or used antihypertensive medications. Diabetes was defined as presence of hemoglobin A1C levels ≥6.5%, use of medication for diabetes, or self-reported history of diabetes. History of coronary artery disease was defined as self-report at Visit 1 or adjudicated events between Visits 1 and 5. Smoking status was defined based on self-reported current tobacco use. The TaqMan assay (Applied Biosystems, Foster City, California) was used to measure *APOE* genotype (0 vs. ≥1 *APOE*ε4 alleles). Given the uneven sampling distribution of race groups across sites and potential influence of geographic regions on participant characteristics, a combined race-center variable a combined race-center variable was used as a covariate in analyses. There were five race-center groups included in analyses: 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. Categorical variables were dummy coded. Separate multivariable linear regression models to examine the cross-sectional associations between measures of white matter integrity (i.e., WMH volume, gFA, and gMD) and frailty status in order to derive beta estimates for neuroimaging variables and to be consistent with the existing literature. Three models were assessed: an unadjusted model (Model 1), a model adjusting for potentially confounding demographic variables (i.e., age, education, sex, race-center, and *APOE*e4 status) (Model 2), and a third model which additionally adjusted for the effects

of cardiovascular risk factors (i.e., BMI, hypertension, diabetes, coronary heart disease, and smoking status) (Model 3). Analyses examining WMH also adjusted for intracranial volume. Given that follow-up neuroimaging data were not available for review and in order to be consistent with the existing literature, separate multivariable logistic regression models were used to examine the cross-temporal association of WMH volume, gFA, and gMD with incident frailty. Analyses were adjusted for demographic and clinical characteristics as described in Models 1-3.

Several secondary/sensitivity analyses were conducted. First, analyses were conducted without participants with known history of stroke, dementia, or MCI confirmed by the end of Visit 5. Second, sampling weights were incorporated to account for the ARIC Visit 5 MRI sampling strategy as has been previously described in the literature (Gottesman et al., 2014). Third, DTI analyses were repeated including WMH volume and estimated intracranial volume as covariates. Fourth, effect moderation by race and sex was examined using multiplicative interaction terms followed by stratified analyses. Lastly, as part of a post-hoc exploratory analyses, DTI analyses were repeated examining many individual white matter tracts associated with frailty in the existing literature. The false discovery rate correction was applied to account for multiple comparisons.

Results

A total of 1,754 participants were included in the analysis (mean age = 76.2 years, SD = 5.2 years; 59.4% female, 29.1% Black) with 1,625 (92.6%) classified as non-frail and 129 (7.4%) as frail at Visit 5. Compared to non-frail participants, those classified as frail were older, had less education, and greater prevalence of diabetes and coronary artery disease. Full sample characteristics are summarized in **Table 2**. Relative to those included in the cross-temporal analysis, participants who did not return for follow-up frailty assessment at either Visit 6 or 7 were younger, more likely to be White, less educated, and less likely to have one or more APOEε4 allele **(Table 3)**. Incident frailty analyses were limited to 1,379 participants non-frail at baseline with available MRI data and frailty follow-up assessments at either Visit 6 or Visit 7.

Cross-sectional association of frailty and white matter structure

Compared to non-frail participants, individuals with frailty demonstrated greater WMH volume in an unadjusted model, after adjusting for demographic characteristics (**Table 4**), and after additionally adjusting for cardiovascular risk factors (**Table 4**). In the fully adjusted model, frailty was associated with a 0.29 SD greater WMH volume (95% CI: 0.13, 0.45; p <0.001). This relationship was maintained when excluding participants with history of stroke and dementia. However, this relationship did not persist when analyses were restricted to cognitively normal participants (i.e., the group of participants without MCI or dementia; **Table 5**).

Examination of DTI measures of white matter microstructural integrity yielded similar results. Frailty status, compared to non-frail, was associated with lower gFA and greater gMD in an unadjusted model, after adjusting for demographic characteristics, and

after additionally adjusting for cardiovascular risk factors (**Table 5**). 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 5**). Given the robust association between frailty status and WMH volume, analyses of DTI measures with WMH volume as a covariate were performed. Results are summarized in **Table 6**. gFA was associated with physical frailty in all groups, with the exception of the cognitively normal subgroup. The relationship between physical frailty and gMD remained statistically significant across groups when adjusting for WMH volume.

Cross-temporal association of white matter structure and frailty risk

Among the 1,379 non-frail participants with available brain MRI data at ARIC visit 5, 270 developed incident frailty at either Visit 6 or 7. Median follow-up time from Visit 5 to Visit 6 was 4.9 years, and 6.6 years from Visit 5 to Visit 7. Non-frail 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 (**Table 3**). Presence of cognitive impairment (i.e., MCI/dementia) did not differ between participants who completed follow-up frailty assessment as compared to those who did not (**Table 3**).

WMH volume at Visit 5 alone was not associated with future frailty (**Table 7, Model 1**). However, when demographic covariates were included, there was an apparent relationship between increased WMH volume and future frailty (**Table 7, Model 2**). In the fully adjusted model, greater WMH volume at Visit 5 was associated with increased odds of frailty at a future visit (either 6 or 7; OR = 1.47 per SD increase in WMH volume; 95% CI: 1.12, 1.86; $p = 0.002$) **(Table 8)**. The relationship between greater

WMH volume and incident frailty was similar when participants with baseline stroke and dementia were excluded. Among cognitively normal participants, each SD higher WMH volume was associated with nearly 80% increased odds of incident frailty (OR = 1.77; 95% CI: 1.24, 2.399; $p = 0.001$).

Although gFA and gMD were associated with incident frailty in the unadjusted model, this association was attenuated and non-significant with the addition of demographic covariates (**Table 7, Models 1 and 2**). There was no significant association between either gFA or gMD and frailty incidence in the fully adjusted model. Surprisingly, after adjusting for WMH volume, lower gMD was associated with greater odds of incident frailty across participant groups **(Table 9)**. Inclusion of WMH volume in gFA models did not change these results.

Secondary and post-hoc analyses

Across analyses there was no evidence of effect modification by race and sex. Primary results were similar when incorporating sampling weights to account for inclusion into the MRI study (**Table 10**). The association between FA and MD values was examined with the individual tracts used to generate factor scores which are summarized in **Figure 2**. In cross-sectional analyses, frailty was associated with lower FA of the corpus callosum and higher MD of the body of the corpus callosum, as well as the right and left posterior limb of the internal capsule and superior longitudinal fasiculus. Interestingly, frailty prevalence was associated with lower MD in the splenium and genu of the corpus callosum. However, these associations were not significant in cross-temporal analyses.

As part of an exploratory hypothesis-generating analysis, we examined the association between frailty and a broader selection of white matter tracts which have been implicated in frailty in the existing literature: the uncinate fasiculus, external capsule, superior fronto-occipital fasiculus, hippocampal cingulate, cingulate, posterior corona radiata, superior corona radiate, posterior thalamic radiation, and anterior limb of the internal capsule. There was a similar pattern of results observed in the main findings **(Figure 3)**. Briefly, frailty prevalence was associated with lower FA of the left uncinate fasiculus and cingulum hippocampus, as well as the external capsule, superior fronto-occipital fasiculus, cingulum cingulate, posterior thalamic radiation, and anterior limb of the internal capsule bilaterally **(Figure 3, Part A)**. Additionally, frailty was associated with higher MD across all tracts, apart from the aforementioned splenium and genu. Cross-temporally, results were generally nonsignificant **(Figure 3, Part B)**. MD values of the tracts examined was not associated with frailty incidence. However, lower FA values of the bilateral posterior and superior corona radiata, as well as the anterior limb of the internal capsule, were associated with future frailty.

Discussion

Using a community-based study of older adults, the current study demonstrates that individuals with physical frailty have greater WMH volume and white matter structural abnormalities than do non-frail individuals. Importantly, this relationship was observed in participants without history of stroke or dementia, but did not persist when analyses were restricted to cognitively normal individuals. Furthermore, among non-frail individuals, WMH volume was significantly associated with 4-7-year frailty risk, 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 risk of future frailty.

There is growing evidence to suggest a relationship between frailty, as well as it's individual components, and white matter changes cross-sectionally (Kant et al., 2019; López-Sanz et al., 2018; Siejka et al., 2018). White matter abnormalities have also been associated with progression of frailty components over time (Maltais et al., 2020; Siejka et al., 2020; Sullivan et al., 2021).). 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.

By comparison, the present study assessed the cross-sectional and cross-temporal link between macrostructural and microstructural white matter integrity in a multiracial community-based cohort and found that macrostructural abnormalities in white matter are more severe in those older adults who will go on to develop frailty. This link between WMH and incident frailty, which was especially strong even among cognitively normal older adults, suggests that declining cerebrovascular health may be a risk factor for the

decline of multiple physiologic systems (i.e., frailty) even outside the context of clinically significant cognitive impairment or dementia.

Few studies have examined white matter microstructural integrity and physical frailty, particularly with regard to frailty incidence. Cross-sectional studies have demonstrated associations between poorer white matter microstructural integrity of specific white matter tracts (i.e., internal capsule, external capsule, posterior thalamic radiation, and corpus callosum) and frailty (Avila-Funes et al., 2017; Tian et al., 2020). To date, one study has examined the relationship between white matter microstructural integrity and progression of frailty symptoms. After adjustment for multiple comparison, this investigation demonstrated a relationship between higher baseline MD values of specific tracts (i.e., internal capsule, external capsule, posterior and superior corona radiata, posterior thalamic radiation, superior fronto-occipital fasiculus, and superior longitudinal fasiculus) and progression of frailty symptoms (Maltais et al., 2020). However, there was no association between FA values and frailty progression.

Results from the present analyses, which suggests a link between WMH volume, but not overall measures of FA/MD, and future frailty, support the notion that WMHs are an indicator of more severe white matter damage, compared to DTI microstructural measures. In general, there is evidence supporting the idea that WM microstructural integrity is less predictive of potential negative health outcomes among older adults relative to more severe structural abnormalities (Power et al., 2019; Scott et al., 2020). Although WM microstructural integrity is associated with cognition, including cognitive domain scores, MCI and dementia status, in older adults cross-sectionally, these relationships appear to generally attenuate over time. While both general and tract-

specific DTI measures were not consistently or strongly associated with incident frailty in these analyses, 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 non-frail to frail status. However, these findings did not extend to measures of MD, or to other white matter 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 (i.e., 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. Although white matter microstructural properties are associated with cognitive outcomes in older adults, these relationships appear to attenuate over time (Power et al., 2019; Scott et al., 2020). Physical frailty and cognitive decline can occur independent of one another, however, there is often overlap between these syndromes which suggests some common underlying neurobiological

pathways. 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.

Our investigation found no effect moderation by race or sex. Although physical frailty is generally more prevalent among Black identifying individuals and women, we did not observe an interaction between self-identified race and frailty (Hirsch et al., 2006). There are some characteristics of our sample which may explain the lack of observed association in the current analyses. Frailty prevalence at Visit 5 did not differ significantly among Black and White participants within our study sample. However, there were group differences in other characteristics which have been implicated in frailty pathogenesis, namely age, cardiovascular disease, and cognitive status. These other factors appear to have had a greater relative contribution to frailty prevalence and incidence than race alone. Although prevalence rates of frailty may vary across racial ethnic groups, this observed difference may not necessarily be associated with effect moderation. To elaborate, frailty prevalence may be increased among Black as opposed to White populations. However, the underlying mechanisms associated with frailty are likely governed by white matter pathology as opposed to racial/ethnic identity in and of itself. Furthermore, the existing literature suggests that the increased prevalence of frailty among racial/ethnic minorities may be better explained by psychosocial and medical stressors frequently associated with health disparities.

The observational nature of this study prohibits causal inferences. However, one possible mechanism for these changes is shared or overlapping causes of physical frailty and cerebral white matter changes. The present findings suggest that volume of WMH may be an important marker of frailty risk. One possible mechanism for these changes is

inflammation. Although there has been conflicting results regarding frailty and inflammation, there is compelling evidence to suggest that chronic inflammation sustained during midlife is associated with frailty incidence. Furthermore, midlife inflammation may precipitate changes in cerebral white matter, which could suggest that WMH volume mediates the relationship between inflammation and frailty (Soysal et al., 2016; Walker et al., 2018, 2019). Another potential contribution is caridiovascular disease and impaired hemostasis are associated with frailty incidence (Afilalo et al., 2009; Kanapuru & Ershler, 2009; Walker et al., 2019). Each of these factors, that is systemic inflammation, cardiovascular disease and impaired hemostatsis have also been consistently associated with WMH volume and white matter structural integrity (Markus et al., 2005; Power et al., 2017; Soysal et al., 2016; Walker et al., 2018).

Physical frailty may clinically represent the early stages of a neurodegenerative process affecting white matter structure. Indeed, frailty is conceptualized as a syndrome representing decline across multiple physiologic systems, including neurologic functioning and there is increasing evidence that frailty is an early indication of cognitive and functional decline (Borges et al., 2019; Fried et al., 2001). Frailty has been established as a risk factor for cognitive decline and specifically Vascular dementia (VaD) (Avila-Funes et al., 2012; Solfrizzi et al., 2013). Although white matter disease is frequently associated with VaD, changes to the cerebrovasculature and white matter properties are prevalent across neurodegenerative conditions (Sweeney et al., 2018). Our findings suggest that WMH volume and microstructural integrity of specific afferent projection fibers contribute to future frailty, even among individuals who do not demonstrate cognitive decline. Previous studies have noted changes in grey matter among

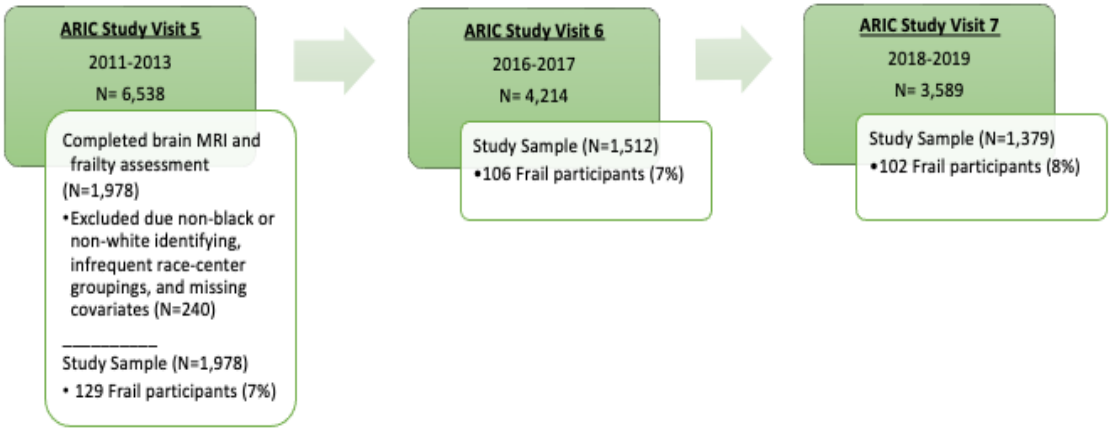
individuals with physical frailty, as well as individual frailty components (W.-T. Chen et al., 2015; Nishita et al., 2019). However, the relationship between grey and white matter changes in the development of frailty remains unclear.

There are several notable strengths of the current analysis including a large community-based cohort, a racially and geographically diverse sample, the prospective study design, and investigation of frailty incidence, as opposed to progression of symptoms. However, there are several limitations which warrant further discussion. First, risk factors for sensitivity groups (i.e., individuals with history of stroke, dementia, or MCI) were assessed only at baseline. Although the cross-sectional associations between frailty and WMH volume were largely statistically significant, it is possible that development of stroke or cognitive impairment may explain the observed relationship between WMH and incident frailty. Second, follow-up MRI data for participants was not available concurrently with follow-up frailty status. Therefore, it was not possible to examine the frailty – WMH volume relationship bidirectionally. While the results from the present analysis suggest a strong relationship between frailty incidence and WMH volume, it is unclear from the current results if physical frailty is associated with progression of white matter abnormalities. Due to the observational nature of this study, determination of whether the link between frailty and white matter changes are due to frailty itself, or its associated comorbidities is not possible. Despite adjustment for several baseline cardiovascular risk factors and physiological measures, the possibility that the observed effects are driven by separate clinical or subclinical variables which have not been accounted for cannot be excluded based on the present analysis. Lastly, 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 cyclical relationship between frailty and associated health comorbidities 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. Based on the results of the current analyses, frail individuals could be considered at risk for white matter pathology. As such, development of physical frailty may serve as an early indication of dementia or cognitive deterioration, such as depression or decline in functional abilities. Implementation of frailty assessment in healthcare settings may be helpful in identifying individuals at risk for cognitive and functional decline.

Figure 1. Study Design



Abbreviations: ARIC, Atherosclerosis Risk in Communities; MRI, Magnetic Resonance Imaging.

Table 1. Principal component analysis (PCA) for white matter tracts included in general FA (gFA) and MD (gMD) composite scores.

White matter tract	PC1 (gFA)	PC1 (gMD)
Superior Longitudinal Fasciculus, Left	0.76	0.86
Superior Longitudinal Fasciculus, Right	0.77	0.88
Posterior Limb of Internal Capsule, Left	0.66	0.79
Posterior Limb of Internal Capsule, Right	0.61	0.81
Genu of the Corpus Callosum	0.59	0.74
Body of the Corpus Callosum	0.56	0.78
Splenium of the Corpus Callosum	0.49	0.83
Eigenvalue	2.88	4.64
Proportion of variance	41.19%	66.30%

Factor scores for gFA and gMD are derived from these principal component analyses capture the shared variance in white matter integrity across multiple white matter tracts. Abbreviations: gFA. general fractional anisotropy; gMD, general mean diffusivity.

Table 2. Baseline demographic and clinical characteristics stratified by frailty status.

Characteristics	Total (N =1,754)	Non-frail (N = 1,625)	Frail (N = 129)
Age [a]	76.2 (5.2)	76.0 (4.7)	78.5 (5.5)
Female Sex (n%) [b]	1,041 (59.4)	954 (58.7)	87 (67.4)
Black (n%)	510 (29.1)	473 (29.1)	37 (28.7)
White (n%)	1,244 (70.9)	1,152 (70.9)	92 (71.3)
Level of education (n%) [a]			
Less than high school	247 (14.1)	217 (13.4)	30 (25.6)
High school/ GED/vocational	713 (40.6)	657 (40.4)	56 (43.4)
College/graduate/ professional	794 (45.3)	751 (46.2)	43 (33.3)
APOE e4 alleles (n%)			
0 e4 alleles	1,248 (70.8)	524 (32.2)	87 (67.4)
1 e4 alleles	460 (26.2)	188 (11.6)	33 (25.6)
2 e4 alleles	46 (2.6)	21 (1.3)	4 (3.1)
BMI	28.4 (5.6)	28.4 (5.2)	28.8 (6.8)
Hypertension (n%) [b]	1,314 (74.9)	1,209 (74.4)	105 (81.4)
Coronary Artery Disease (n%) [a]	184 (10.5)	163 (10.0)	21 (16.3)
Diabetes (n%) [a]	540 (30.8)	488 (30.0)	52 (9.6)
Current Smoking (n%)	90 (5.1)	81 (5.0)	9 (7.0)
Stroke (n%)	59 (3.4)	18 (1.1)	7 (5.4)
Cognitive Status (n%) [a]			
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)

Values are represented as mean (standard deviation) for continuous variables and frequency (percentage of sample) for categorical variables. One way analysis of variance were used for continuous variables and chi-square for categorical variables.

Abbreviations: BMI, body mass index; MCI, Mild Cognitive Impairment.

[a] $P \leq 0.05$ Difference between frail and non-frail participants.

[b] $P < 0.10$ Difference between frail and non-frail participants.

Table 3. Participant characteristics stratified by inclusion in cross-temporal analyses, excluding participants classified as frail at Visit 5.

Characteristics	Total Baseline MRI (N = 1,737)	Non Cross-temporal Sample (N = 258)	Cross-temporal MRI Sample (N = 1,379)
Age [a]	76.1 (5.2)	75.2 (5.2)	76.1 (5.2)
Female Sex	1,019 (58.7)	163 (63.2)	803 (58.2)
Black [a]	503 (29.0)	3 (0.<1)	473 (34.3)
White [a]	1,230 (70.8)	252 (99.9)	906 (65.7)
Level of education [a]			
Less than high school	235 (13.5)	37 (14.3)	183 (13.3)
High school/GED/vocational	700 (40.3)	142 (55.0)	523 (37.9)
College/graduate/professional	800 (46.1)	79 (30.6)	673 (48.8)
APOE e4 alleles [a]			
0 e4 alleles	1,189 (68.5)	187 (72.5)	973 (70.6)
1 e4 alleles	445 (25.6)	60 (23.3)	368 (26.7)
2 e4 alleles	43 (2.5)	4 (< 0.1)	38 (2.8)
BMI	28.5 (5.5)	28.9 (5.7)	28.3 (5.5)
Hypertension	1,281 (73.7)	184 (71.3)	1,030 (74.7)
Coronary Artery Disease	177 (1.1)	25 (9.7)	136 (9.9)
Diabetes	523 (30.1)	85 (32.9)	404 (29.3)
Current Smoking	90 (5.2)	11 (4.3)	71 (5.1)
Stroke	53 (3.1)	5 (< 0.1)	46 (3.3)
Cognitive Status			
Normal	1,083 (62.3)	153 (59.3)	875 (63.5)
MCI	567 (32.6)	93 (36.0)	434 (31.5)
Dementia	85 (4.9)	12 (< 0.1)	68 (4.9)

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.

Abbreviations: BMI, body mass index; MCI, Mild Cognitive Impairment.

[a] P $\leq$0.05 Difference between cross-temporal and non-cross-temporal participants.

Table 4. Cross-sectional study sample associations between frailty status and white matter structure using alternative models.

MRI Characteristics	Model 1 N = 1,870		Model 2 N = 1,791	
	ß (95% CI)	*P*	ß (95% CI)	*P*
WMH volume	0.52 (0.36, 0.69)	<0.001	0.31 (0.15, 0.47)	<0.001
gFA	-0.49 (-0.65, -0.32)	<0.001	-0.35 (-0.52, -0.19)	<0.001
gMD	0.59 (0.43, 0.75)	<0.001	0.46 (0.31, 0.60)	<0.001

Model 1 is adjusted for intracranial volume. Model 2 is additionally adjusted for age, center, race, sex, education, and *APOE* ε4 status. Seventy-nine participants included in model 1 were excluded from model 2 due to missing one or more model 2 covariate. Values represent the adjusted difference in standardized WMH volume, gFA, and gMD between the frail and non-frail group. Abbreviations: ß, standardized beta coefficient, BMI, body mass index; gFA. general fractional anisotropy; gMD, general mean diffusivity; OR, odds ratio; WMH, white matter hyperintensity. Characteristic

Table 5. Cross-sectional associations between frailty status and white matter structure.

MRI Characteristics	Total N = 1,748	No prior stroke N = 1,689	Non-demented N = 1,653	Cognitively normal N = 1,076
	ß (95% CI)	ß (95% CI)	ß (95% CI)	ß (95% CI)
WMH volume	0.29 (0.13, 0.45) [a]	0.26 (0.10, 0.43) [b]	0.28 (0.11, 0.45) [a]	0.05 (-0.19, 0.29)
gFA	-0.31 (-0.47, -0.14) [a]	-0.27 (-0.44, -0.11) [a]	-0.33 (-0.50, -0.16) [a]	-0.20 (-0.43, 0.03)
gMD	0.43 (0.29, 0.58) [a]	0.41 (0.27, 0.56) [a]	0.40 (0.25, 0.55) [a]	0.29 (0.09, 0.49) [b]

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. Values represent the adjusted difference in standardized WMH volume, gFA, and gMD between the frail and non-frail group.

Abbreviations: ß, standardized beta coefficient; BMI, body mass index; gFA, general fractional anisotropy; gMD, general mean diffusivity; WMH, white matter hyperintensity.

[a] Results significant at the $p \leq 0.001$ level.

[b] Results significant at the $p < 0.05$ level.

Table 6. Cross-sectional associations between frailty status and white matter microstructural integrity, adjusted for white matter hyperintensity volume.

MRI Characteristics	All participants N = 1,726	No prior stroke N = 1,669	Non-demented N = 1,639	Cognitively Normal N = 1,069
	ß (95% CI)	ß (95% CI)	ß (95% CI)	ß (95% CI)
gFA	-0.26 (-0.40, -0.11) [a]	-0.23 (-0.38, -0.08) [b]	-0.26 (-0.42, -0.33) [a]	-0.20 (-0.41, 0.01)
gMD	0.32 (0.19, 0.45) [a]	0.30 (0.17, 0.43) [a]	0.31 (0.17, 0.44) [a]	0.26 (0.08, 0.44) [b]

Models are adjusted for age, sex, race-center, education, APOE, BMI, hypertension, coronary artery disease, diabetes, cigarette use, WMH volume, and estimated intracranial volume obtained at the time of neuroimaging. Values represent the adjusted difference in standardized gFA, and gMD between the frail and non-frail group.

Abbreviations: B, unstandardized beta coefficient; BMI, body mass index; gFA. general fractional anisotropy; gMD, general mean diffusivity; WMH, white matter hyperintensity.

[a] Results significant at the $P \leq 0.001$ level.

[b] Results significant at the $P < 0.05$ level.

Table 7. Associations between white matter structure and future frailty using alternative models.

MRI Characteristics	Model 1 N= 1,472		Model 2 N=1,413	
	OR (95% CI)	*P*	OR (95% CI)	*P*
WMH volume	1.08 (0.93, 1.25)	0.33	1.43 (1.13, 1.81)	≤0.01
gFA	0.58 (0.50, 0.67)	≤0.001	0.86 (0.70, 1.06)	0.15
gMD	2.47 (2.09, 2.92)	≤0.001	0.91 (0.71, 1.16)	0.43

Model 1 is adjusted for intracranial volume. Model 2 is additionally adjusted for age, center, race, sex, education, and *APOE* ε4 status. Values represent the odds of incident frailty per one unit increase in standardized WMH volume, gFA, and gMD. Fifty-nine participants included in model 1 were excluded from model 2 due to missing one or more model 2 covariate.

Abbreviations: BMI, body mass index; gFA. general fractional anisotropy; gMD, general mean diffusivity; OR, odds ratio; WMH, white matter hyperintensity.

Table 8. Associations between white matter structure and future frailty.

MRI Characteristics	All participants N = 1,379	No prior stroke N = 1,333	Non-demented N = 1,309	Cognitively Normal N = 875
	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
WMH volume	1.46 (1.15, 1.87) [b]	1.51 (1.17, 1.94) [a]	1.52 (1.21, 2,01) [a]	1.78 (1.26, 2.51) [a]
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)

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. Values represent the odds of incident frailty per one unit increase in standardized WMH volume, gFA, and gMD.

Abbreviations: BMI, body mass index; gFA, general fractional anisotropy; gMD, general mean diffusivity; OR, odds ratio.

[a] Results significant at the $p \leq 0.001$ level.

[b] Results significant at the $p < 0.05$ level.

Table 9. Cross-temporal associations between frailty status and white matter microstructural integrity, adjusted for white matter hyperintensity volume.

MRI Characteristics	All participants N = 1,360	No prior stroke N = 1,315	Non-demented N = 1,296	Cognitively Normal N = 869
	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
gFA	0.96 (0.74, 1.24)	0.99 (0.77, 1.29)	0.98 (0.75, 1.27)	1.18 (0.83, 1.68)
gMD	0.82 (0.60, 1.11)	0.76 (0.55, 1.04)	0.8 (0.58, 1.09)	0.6 (0.39, 0.92) [a]

Models are adjusted for age, sex, race-center, education, APOE, BMI, hypertension, coronary artery disease, diabetes, cigarette use, WMH volume, and estimated intracranial volume obtained at the time of neuroimaging. Values represent the odds of incident frailty per one unit change in standardized WMH volume, gFA, and gMD.

Abbreviations: BMI, body mass index; gFA. general fractional anisotropy; gMD, general mean diffusivity; OR, odds ratio; WMH, white matter hyperintensity.

[a] Results significant at the $P < 0.05$ level.

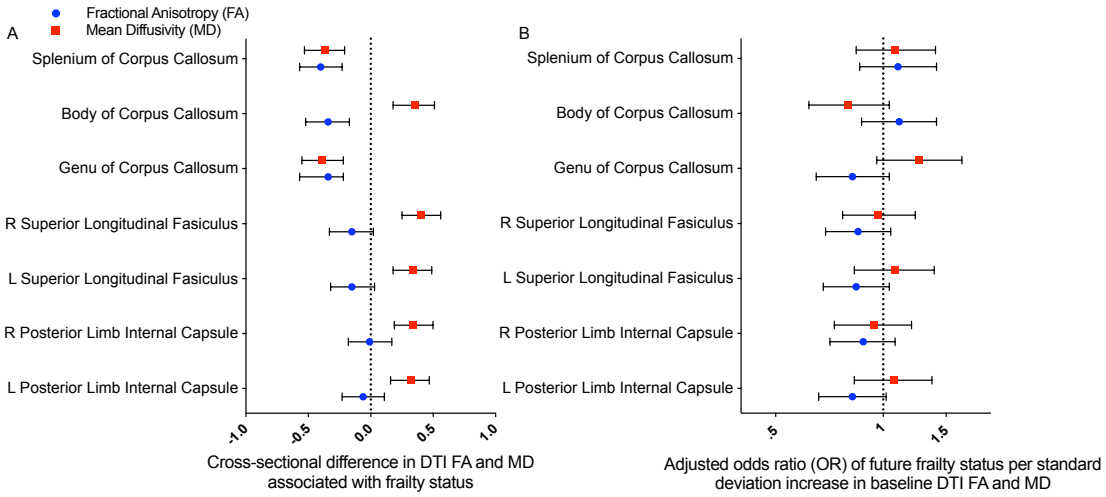
Table 10. Cross-sectional and cross-temporal associations between frailty status and white matter structure, after incorporation of ARIC sampling weights.

MRI Characteristics	Cross-sectional N = 1,748		Cross-temporal N = 1,379	
	B (95% CI)	*P*	OR (95% CI)	*P*
WMH Volume	0.22 (0.06, 0.38)	0.009	1.30 (1.01, 1.63)	0.01
gFA	-0.31 (-0.51, -0.10)	0.001	0.82 (0.59, 1.13)	0.227
gMD	0.39 (0.24, 0.54)	<0.001	0.99 (0.68, 1.44)	0.958

Models are adjusted for age, sex, race-center, education, *APOE* ε4 status, BMI, hypertension, coronary artery disease, diabetes, and cigarette use obtained at the time of neuroimaging. Cross-sectional values represent the adjusted difference in standardized WMH volume, gFA, and gMD between the frail and non-frail group. Cross-temporal values represent the odds of incident frailty per one unit increase in standardized WMH volume, gFA, and gMD.

Abbreviations: FA, fractional anisotropy; MD, general mean diffusivity; OR, odds ratio; WMH, white matter hyperintensity.

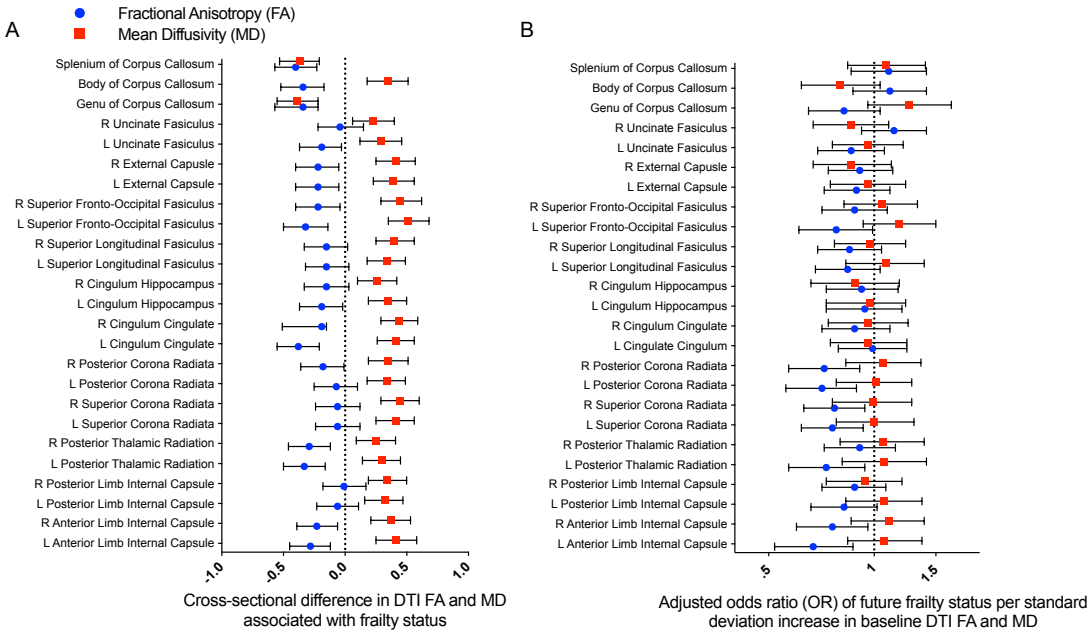
Figure 2. Cross-sectional and cross-temporal associations between frailty and tract specific measures of microstructural integrity.



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.

Abbreviations: BMI, body mass index; FA, fractional anisotropy; MD, mean diffusivity, OR, odds ratio.

Figure 3. Cross-sectional and cross-temporal associations between frailty and tract specific measures of microstructural integrity by individual tract.



Models are adjusted for age, sex, race-center, education, *APOE* ε4 status, BMI, hypertension, coronary artery disease, diabetes, and cigarette use 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 and FDR correction. Figure B. represents the adjusted OR of future frailty per standard deviation increase in FA and MD using logistic regression. Abbreviations: BMI, body mass index; FA, fractional anisotropy; FDR, false discovery rate; MD, general mean diffusivity; OR, odds ratio.

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