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## Title

# Cross-sectional and prospective associations between cerebral cortical thickness and frailty in older adults

Short title: Cortical Thickness and Frailty

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## **ABSTRACT**

**Background:** Several neurodegenerative markers measured by magnetic resonance imaging (MRI) have shown to be related with frailty. While most studies have focused on surrogates of cerebral vascular damage such as increased white matter lesions, the associations between cortical atrophy and frailty were less often investigated.

**Objectives:** To investigate the cross-sectional and prospective associations between cortical thickness and frailty evolution in older adults.

**Methods:** We enrolled 484 community-dwelling adults aged  $\geq 70$  years, participants from the Multidomain Alzheimer Preventive Trial (MAPT), with data on cerebral cortical thickness and frailty. Cortical thickness was acquired by MRI for whole-brain and regional cortices. Two function-specific regions of interest, ie, mobility-related regions and Alzheimer's disease (AD) signature, were selected on the basis of previous studies. Frailty status was assessed by the Fried frailty phenotype (ie, weakness, slowness, involuntary weight loss, fatigue and low physical activity level) at baseline, after 6 months and every year until the end of the 5-year follow-up.

**Results:** Older adults with higher global cortical thickness were less likely to be pre-frail and frail at baseline (adjusted OR: 0.13, 95% CI: 0.03–0.65,  $p=.013$ ). In addition, higher cortical thickness in mobility-related and AD-signature regions were associated with lower likelihood of being pre-frail and frail. Similar associations were observed for having weakness and slowness. However, neither global nor region-specific cortical thickness showed prospective associations with future frailty onset.

**Conclusions:** The global and regional cortical thickness cross-sectionally associated with frailty in older adults, but no prospective associations with incident frailty were found. The longitudinal relationship between cortical thickness and frailty evolution requires further investigation.

**Keywords:** frailty, cortical thickness, Alzheimer's disease, brain aging, older adults

## 1. INTRODUCTION

Frailty is a common condition characterized by reduced physiological reserve and increased vulnerability to adverse health outcomes in older adults <sup>1,2</sup>. A growing number of studies have demonstrated that frailty is closely related to cognitive decline <sup>3</sup> and it is accompanied by structural changes in the brain <sup>4</sup>. Several neurodegenerative markers measured by magnetic resonance imaging (MRI) have shown to be related with frailty. While most studies have focused on surrogates of cerebral vascular damage such as increased white matter lesions and decreased white matter integrity <sup>5-8</sup>, the associations between cortical atrophy and frailty were less often investigated. Moreover, studies investigating cortical atrophy and frailty had a cross-sectional design <sup>9-11</sup>. Furthermore, the results of these studies were inconsistent, with Chen et al. (2015) <sup>9</sup> and Kant et al. (2018) <sup>10</sup> showing that reduced gray matter volume was associated to frailty status; while Nishita et al. (2019) <sup>11</sup> reported that only weakness and slowness components, but not frailty per se, were linked to lower volume of gray matter.

Cortical thickness, defined as the distance between gray-white matter boundary and the outer cortical surface <sup>12</sup>, is a sensitive morphometric markers reflecting the changes of gray matter volume. Cortical thinning has shown region-specific patterns during normal aging, most prominently in prefrontal cortex <sup>12,13</sup>, primary sensory and motor cortices <sup>14</sup>. On the other hand, thinner cortex of the Alzheimer's disease (AD) signature <sup>15</sup>, consisting of several frontal,

parietal, and temporal gyri, has been proposed to be a potential biomarker of neurodegeneration<sup>16</sup>. Whether cortical thickness has similar predictive ability for frailty is unclear. To the best of our knowledge, only one cross-sectional study has evaluated the relationship between cortical thickness and physical frailty<sup>10</sup>, with no significant associations being found.

The purpose of the present study was to investigate the cross-sectional and prospective associations between cortical thickness and frailty in older adults. In addition to whole-brain area, regions of interest (ROI) associated with frailty components in literature (defined as “mobility-related regions”) were explored, as also regions related to cognitive impairment (known as “AD-signature regions”), due to the potential impact of neurodegeneration on frailty development.

## **2. MATERIAL AND METHODS**

### **2.1. Study source**

This study used the magnetic resonance imaging (MRI) data of participants of the Multidomain Alzheimer's Preventive Trial (MAPT) Study<sup>17</sup>. Briefly, the MAPT study was a large multicenter, 3-year randomized controlled trial which aimed to investigate the effect of the multidomain intervention (physical activity advice, nutritional counseling, cognitive

training) and omega-3 fatty acid supplementation on the prevention of cognitive decline in community-dwelling older adults. The primary analysis showed no significant effects of interventions on cognitive function over 3 years after adjustment for multiplicity<sup>18</sup>. After the end of the 3-year intervention period, a 2-year observational follow-up without any intervention was conducted. Therefore, overall 5-year data were retrieved for this secondary analysis. The MAPT study was approved by the French Ethical Committee located in Toulouse (CPP SOOM II) and was authorized by the French Health Authority. All participants signed an informed consent.

## **2.2. Study population**

The MAPT study enrolled 1,679 community-dwelling men and women older than 70 years with spontaneous memory complaint, limitations in one instrumental activity of daily living, or slow gait speed. Among the whole MAPT participants, a total of 503 subjects performed MRI scan. After excluding 5 subjects without data on cortical thickness and 14 subjects with poor quality of imaging data (not interpretable), 484 participants were included in this study. Among them, 453 participants who were robust or pre-frail at baseline and who had at least one post-baseline frailty measurement were selected to investigate frailty incidence (frail individuals were excluded of this analysis).



### 2.3. Outcome measure

The frailty status was assessed at baseline and after 6, 12, 24, 36, 48 and 60 months of follow-up by using the Fried frailty phenotype, which considers: weakness, slowness, involuntary weight loss, fatigue and low physical activity level<sup>1,19</sup>. Weakness was defined as poor handgrip strength measured by a handheld dynamometer. Cutoffs were  $\leq 29$ ,  $\leq 30$ , and  $\leq 32$  kg in men with body mass index (BMI)  $\leq 24$ , between 24.1 and 28, and  $> 28$  kg/m<sup>2</sup>, respectively;  $\leq 17$ ,  $\leq 17.3$ ,  $\leq 18$ , and  $\leq 21$  kg in women with BMI  $\leq 23$ , between 23.1 and 26, between 26.1 and 29, and  $> 29$  kg/m<sup>2</sup>, respectively. Slowness was measured by 4-m usual walk test<sup>20</sup> applying with sex- and height-specific cutoffs ( $< 0.65$  m/s for men  $\leq 173$  cm and women  $\leq 159$  cm;  $< 0.76$  m/s for men  $> 173$  cm and women  $> 159$  cm). Physical activity level in the past 2 weeks was defined by using Minnesota Leisure Time Activity 15-item questionnaire. Subjects were assessed for fatigue according to two items of the Center for Epidemiologic Studies depression scale<sup>21</sup>, and involuntary weight loss was considered as reporting  $> 4.5$  kg of weight loss in the prior year. For each of the five components of the frailty phenotype, participants meeting the criterion were scored as 1 (global scores varying from 0 to 5, higher is worse); robust people met no criterion (score = 0), pre-frail met 1 or 2 (score = 1 or 2) criteria, and frail met  $\geq 3$  criteria (score  $\geq 3$ ). Participants who were robust or pre-frail at baseline (score  $< 3$ ; people with baseline frailty were excluded) were identified as having incident frailty if their frailty score increased to 3 or above during the follow-up

period.

## **2.4. MRI acquisition and analyses**

The acquisition protocol for brain MRI has been detailed elsewhere <sup>6,17</sup>. In brief, the MRI scan was performed within the first 12 months of MAPT study enrollment, using a standardized protocol in each of the centers (Toulouse, Bordeaux, Montpellier, Limoges, Dijon, Lyon, Foix, Tarbes and Nice). In this study, we included MRI measurement for the total intracranial volume (TICV, cm<sup>3</sup>), gray matter volume (cm<sup>3</sup>), and cortical thickness (mm). Quality of each imaging data was assessed, and measures were excluded from our analysis if presenting poor or unreliable quality. The 3D T1-weighted sequence, derived by the SPM5 toolbox ([fil.ion.ucl.ac.uk/spm](http://fil.ion.ucl.ac.uk/spm)), was used to compute the TICV and the gray matter volume.

The surface-based estimation of cortical thickness was measured by using the standard FreeSurfer software (version 5.3) (<https://surfer.nmr.mgh.harvard.edu>). The local thickness measurements were averaged across the whole brain and across the 34 regions of the Desikan-Killiany atlas in each hemisphere <sup>22</sup>. In this study, several ROIs of cortical thickness were selected and evaluated based on previous research:

- Mobility-related ROI, consisted of the aggregation of 9 brain regions <sup>11</sup>: fusiform, superior temporal, medial orbitofrontal, lateral orbitofrontal, insula, pars opercularis,

pars orbitalis, pars triangularis and postcentral.

- AD-signature ROI, composed of the aggregation of 12 brain regions<sup>15,23</sup>: entorhinal, parahippocampal, inferior temporal, temporal pole, inferior parietal, supramarginal, superior frontal, superior parietal, precuneus, pars opercularis, pars orbitalis and pars triangularis.
- Anatomic regions included frontal, parietal, temporal, occipital lobes, limbic system and insula, which were defined according to the suggestion on FreeSurfer website (**Supplementary Table S1**).
- Individual 34 brain regions in each hemisphere (Desikan-Killiany classification)<sup>22</sup>.

The average cortical thickness in mobility-related ROI, AD-signature ROI and anatomic regions were computed across both hemispheres, so each participant had single values representing the arithmetic mean cortical thickness for each ROI.

## **2.5. Timing of assessments**

Among the 484 participants, 459 participants (94.8%) underwent the MRI scan at baseline (n=223) or between baseline and the 6-month visit (n=236), while 25 (5.2%) underwent the MRI scan between 6- and 12-month visits. We considered the starting point of follow-up for each participant at the clinical evaluation closest to the MRI scan. Among 453 participants

included in the incident frailty analysis, the mean number of days between the MRI scan and final clinical assessment was  $1,325 \pm 502$  days (ranging from 91 to 2,092 days).

## **2.6. Confounders**

Confounding variables were selected on the basis of data availability and their potential associations with frailty, cortical thickness or gray matter atrophy<sup>10,11,24,25</sup>: age, sex, MAPT intervention groups, level of education (categorized as: no diploma or primary school certificate, secondary education, high-school diploma, university level), cognitive function evaluated by 30-item Mini Mental State Examination (MMSE)<sup>26</sup> and TICV. In addition, we created a single, dichotomous variable for indicating the presence of at least one of the following cardiovascular risk factors: diabetes mellitus, hypertension, hypercholesterolemia, ischemic heart disease or history of stroke. This composite cardiovascular-risk variable was further used for model adjustment in order to avoid potential multi-collinearities between each cardiovascular-risk diseases. The sensitivity analysis with adjustment for all five cardiovascular diseases was provided in the supplementary material (further described below).

## **2.7. Statistical analysis**

Baseline characteristics and cortical thickness of the study subjects were present as mean and

standard deviation (SD) or frequencies and percentages. Analysis of variance (ANOVA) was performed to compare the baseline cortical thickness of the studied population across frailty groups. Multivariable logistic regressions, adjusted for all confounders mentioned above, were performed on frailty groups and each component separately. Considering the low prevalence of frailty (n=12) at baseline, which probably lead to the very small odds ratios found, we investigated the odds of being non-robust (pre-frail and frail combined) in an additional logistic models. Cox proportional hazard models, with discrete time variable (ie, the number of the clinical visit), were run in participants without frailty at baseline and with at least one post-baseline assessment of frailty (n=453) to explore prospective associations between cortical thickness and incident frailty. Time-to-event was defined as the time interval between the starting point of follow-up (the closest visit to the MRI scan) and the first time the participant was classified as frail. Participants were censored at the last frailty evaluation if they remained robust or pre-frail. Proportional hazard assumption was checked using the Kolmogorov-type supremum test ( $p > 0.05$  was considered as non-violation of the assumption).

Several sensitivity analyses were conducted. First, we performed a subgroup analysis restricted to the placebo group to exclude potential effects of MAPT intervention on incident frailty (**Supplementary Table S4**). Second, considering that mild cognitive impairment (MCI)

might mediate the relationship between cortical atrophy and frailty evolution, we inserted into the Cox models an interaction between cortical thickness and the groups of Clinical Dementia Rating scale (CDR) <sup>27</sup> (baseline CDR score=0 vs. 0.5) (**Supplementary Table S5**). We also re-ran the Cox models without adjustment for MMSE score (**Supplementary Table S6**). Third, we performed the similar Cox models by adjusting for five cardiovascular-risk diseases instead of using a composite cardiovascular-risk variable (**Supplementary Table S7**). Fourth, in order to confirm the time sequence of cortical thickness and incident frailty, we re-defined the baseline time-point as the closest visit after MRI scan (n=432) into Cox regressions (**Supplementary Table S8**). Finally, we re-ran the Cox models with center stratification in view of the potential variation of MRI measurements among different study centers (**Supplementary Table S9**). Statistical significance was defined as  $p < 0.05$  with adjustments for multiple comparisons based on Hochberg procedure <sup>28</sup>. All data was analyzed by using SAS, version 9.4 (SAS Institute, Inc, Cary, NC).

### **3. RESULTS**

The baseline characteristics of the 484 participants are presented in **Table 1**. The average age of the participants was  $74.8 \pm 4.0$  years with a majority of women (63.8%). 56.2% participants were robust at baseline; 41.3% were pre-frail and 2.5% frail. Baseline cortical thickness across frailty groups are shown in **Table 2**. The distributions of cortical thickness

across frailty and age, and across frailty and cognitive function are presented, respectively, in **Supplementary Figure S1** and **Supplementary Figure S2**. We further examined the cross-sectional associations of cortical thickness with frailty groups by using logistic regressions (**Table 3**). Participants with higher global cortical thickness had decreased likelihood of being pre-frail or frail at baseline. In addition, people with higher cortical thickness in mobility-related and AD-signature regions were less likely to be pre-frail or frail. The additional analysis examining non-robust status (pre-frail and frail) also indicated the lower likelihood of being non-robust as cortical thickness increasing (**Table 3**). Similar patterns were found for weakness and slowness, with higher cortical thickness being associated with lower probability of meeting these frailty components (**Supplementary Table S2**).

Among 453 participants who were robust or pre-frail at baseline, 51 (11.3%) became frail during the 5-year follow-up (the average length of follow-up:  $3.6 \pm 1.4$  years). Neither global nor region-specific cortical thickness showed prospective associations with incident frailty over 5 years (**Table 4**). No significant associations between cortical thickness in each brain region and incident frailty were found (**Supplementary Table S3**). The subanalysis among MAPT placebo group (**Supplementary Table S4**) presented similar results. The interaction term between CDR and cortical thickness was not associated with incident frailty

(**Supplementary Table S5**). Similar result was found in the sensitivity analysis without adjustment for MMSE in the Cox models (**Supplementary Table S6**). The sensitivity analysis with adjustment for five cardiovascular-risk diseases in the Cox regressions provided unchanged findings (**Supplementary Table S7**). Results of sensitivity analysis taking into account only frailty assessments after the MRI scans provided similar findings (**Supplementary Table S8**). Results of Cox regressions with center stratification provided unchanged results (**Supplementary Table S9**).

#### **4. DISCUSSION**

This is the first work to investigate cross-sectional and prospective associations between brain cortical thickness and frailty among older adults. In our cross-sectional analysis, we found that cortical thickness in whole brain, mobility-related and AD-signature regions were all related to a reduced probability of being pre-frail and frail. Similar relationships were found for some of the frailty components, in particular for weakness and slowness.

Nevertheless, we did not find any prospective associations between baseline cortical thickness and incident frailty.

Neither global nor regional cortical thickness showed prospective association with frailty incidence in the present study. Among the reasons that might explain these findings, it is



possible that incident frailty is more related to the speed of cortical thinning rather than the absolute values of baseline thickness. Since our study only measured the baseline cortical thickness, we could not evaluate the association between the degree of cortical thinning over the years and frailty onset. Further studies with longitudinal measurements of cortical thickness and frailty are needed to investigate this hypothesis. Moreover, the reduction of cortical volume could be predominantly driven by surface area rather than thickness. A previous study had noted that change in intelligence among healthy older adults mainly reflected on regional cortical surface area rather than cortical thickness<sup>29</sup>. Whether brain structure alterations during frailty development are more related to declining surface area instead of cortical thickness is unclear. Further research focused on several brain cortical characteristics including both surface area and thickness should be encouraged.

Since the key cortical regions vulnerable to frailty are not yet fully established<sup>4</sup>, our study replicated the regions of interest based on previous cross-sectional analysis<sup>11</sup>, which demonstrated that mobility-type components, especially slowness, were significantly associated with reduced total and several regional gray matter volume. Our cross-sectional analysis, which focused on cortical thickness, provided similar findings. However, in contrast to their results, we also found significant associations between overall frailty status and cortical thickness. Inconsistent changes between cortical thickness and gray matter volume

had been proposed in a previous study <sup>14</sup>; sometimes reduced thickness was found in the areas that have not shown volumetric decline during normal ageing <sup>12</sup>. Although the underlying mechanisms remain unclear, it is possible that frailty-related cortical changes is similar to age-related atrophy, which impact more specifically on cortical thickness rather than on brain volume per se <sup>13,14</sup>.

Considering the specific pattern of cortical atrophy is highly dependent on dementia progression <sup>4,30</sup> and due to the high coexistence of frailty and cognitive impairment <sup>3</sup>, we also included AD vulnerable regions in our analysis. Our results showed significant cross-sectional associations between AD-signature cortical thickness and frailty even after adjusting for cognitive function, suggesting that frailty and neurodegeneration are associated even before the onset of dementia. Similar associations observed in motor-related frailty components (weakness, slowness) also support the results in previous studies, which indicated that gait speed and grip strength are the components of frailty more strongly correlated with cognitive function <sup>3</sup>. Both findings highlight the close relationship between frailty and cognitive impairment and the need to provide early cognitive prevention in old, frail adults. More studies exploring the potential mechanisms of frailty and dementia would shed light on this topic in the future.

A number of strengths should be mentioned in our study. This is the first study to examine the association between cortical thickness and frailty in a large-population, using a longitudinal study design. Moreover, we examined several ROIs of cortical thickness, including function-specific (mobility-related and AD signature) as well as anatomic classification. However, there were some limitations in our approach. This study represents a secondary analysis of a randomized controlled trial in which the majority of participants received interventions until the third year of the 5-year follow-up. Although the interventions did not show to affect the physical function <sup>18</sup> or frailty incidence <sup>19</sup>, the generalization of our findings should be cautious. It is important to highlight that our sensitivity analysis focused on the placebo group provided similar results than the main analysis, supporting the idea that MAPT interventions did not influence our findings. In addition, as usually observed in longitudinal studies, some measures of frailty status were missing during the follow-up, which might have underestimated the time of incident frailty for some individuals.

## **5. CONCLUSIONS**

To conclude, our study provides evidence that cortical thickness was cross-sectionally, but not prospectively, associated with frailty in older adults. The significant cross-sectional associations between AD-signature cortices and frailty suggest a role of cognitive impairment in the pathophysiology of frailty, and highlight the need for further observational research

with longitudinal measurements of cortical thickness and frailty in several time-points for deeper comprehension of this possible long-term relationship.

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**Conflict of interest:** The authors have no conflicts of interest.

**Author contributions:** WHL designed and conceptualized the research, performed the analyses, interpreted the data and drafted the manuscript. PSB designed and conceptualized the research, interpreted the data and revised the draft critically for intellectual content. YR,

LRM and KVG interpreted the data and revised the draft critically for intellectual content.

AB, CF and JFM managed image data, interpreted the data and revised the draft critically for intellectual content. BV conceived the MAPT study, interpreted the data, and revised the draft critically for intellectual content. All authors have read and agreed with the final version to be submitted.

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Table 1. Baseline characteristics of the study population (n=484)

Characteristics	Values
Age, mean (SD), years	74.8 (4.0)
Sex (female)	309 (63.8)
MAPT groups	
Multidomain intervention + omega-3	123 (25.4)
Omega-3	115 (23.8)
Multidomain intervention	129 (26.6)
Placebo	117 (24.2)
Education (n=481)	
No diploma or primary school certificate	81 (16.8)
Secondary education	159 (33.1)
High school diploma	69 (14.3)
University level	172 (35.8)
Cardiovascular risk factors*	334 (69.0)
Diabetes	39 (8.1)
Hypertension	239 (49.4)
Hypercholesterolemia	176 (36.4)
Ischemic heart disease	32 (6.6)
History of stroke	5 (1.0)
Fried frailty score, median (IQR)	0 (0, 1)
Robust (0/5)	272 (56.2)
Pre-frail (1-2/5)	200 (41.3)
Frail ( $\geq 3/5$ )	12 (2.5)
CDR	
Score 0	250 (51.6)
Score 0.5	234 (48.4)
MMSE, mean (SD) (n=483)	28.1 (1.6)
Total intracranial volume, mean (SD), cm <sup>3</sup> (n=480)	1374.6 (134.3)
Total gray matter volume, mean (SD), cm <sup>3</sup> (n=480)	639.1 (59.0)

\*Presence or not of at least one of cardiovascular risk factors: diabetes mellitus, hypertension, hypercholesterolemia, ischemic heart disease or history of stroke.

Note: Values presented in number (percentage) unless otherwise indicated.

Abbreviations: AD, Alzheimer's disease; CDR, clinical dementia rating scale; IQR, interquartile range; MAPT, Multidomain Alzheimer Preventive Trial; MMSE, Mini-Mental State Examination; SD, standard deviation

Table 2. Baseline cortical thickness of the study population across frailty group

Cortical thickness (mm)	Total (N=484)	Robust (N=272)	Pre-frail (N=200)	Frail (N=12)	p-value*
Whole brain	2.35 (0.13)	2.36 (0.12) <sup>a</sup>	2.32 (0.13) <sup>a</sup>	2.30 (0.20)	0.002
Mobility-related regions	2.46 (0.13)	2.48 (0.12) <sup>a,b</sup>	2.44 (0.13) <sup>a</sup>	2.38 (0.22) <sup>b</sup>	<.001
AD signature	2.61 (0.15)	2.64 (0.14) <sup>a</sup>	2.58 (0.16) <sup>a</sup>	2.54 (0.23)	<.001
By brain region					
Frontal lobe	2.42 (0.15)	2.44 (0.14) <sup>a</sup>	2.40 (0.15) <sup>a</sup>	2.37 (0.21)	0.012
Parietal lobe	2.19 (0.15)	2.21 (0.14) <sup>a</sup>	2.17 (0.15) <sup>a</sup>	2.15 (0.22)	0.028
Temporal lobe	2.75 (0.17)	2.78 (0.15) <sup>a</sup>	2.71 (0.17) <sup>a</sup>	2.67 (0.26)	<.001
Occipital lobe	1.79 (0.12)	1.80 (0.11) <sup>a</sup>	1.77 (0.12) <sup>a</sup>	1.75 (0.15)	0.015
Limbic system	2.57 (0.16)	2.59 (0.17)	2.55 (0.15)	2.55 (0.22)	0.089
Insula	2.93 (0.18)	2.95 (0.17) <sup>a,b</sup>	2.90 (0.18) <sup>a</sup>	2.81 (0.31) <sup>b</sup>	<.001

Note: Presented in mean (standard deviation); \*p-value determined using analysis of variance

Abbreviations: AD, Alzheimer's disease

Footnote a,b: same letters indicate difference between groups (p<.05)



Table 3. Logistic regressions examining the cross-sectional association between baseline frailty group and cortical thickness (n=484)

Cortical thickness (mm)	Unadjusted model				Adjusted model <sup>b</sup>			
	N	OR <sup>a</sup>	95% CI	p-value	N <sup>c</sup>	OR <sup>a</sup>	95% CI	p-value
Whole brain								
Pre-frail	200	0.084	0.019 – 0.371	0.001	196	0.148	0.028 - 0.772	0.023
Frail	12	0.020	0.001 – 1.290	0.066	11	0.007	0.001 - 1.088	0.054
Pre-frail and frail	212	0.078	0.018 – 0.334	0.001	207	0.126	0.025 - 0.646	0.013
Mobility-related regions								
Pre-frail	200	0.075	0.017 – 0.324	0.001	196	0.127	0.025 - 0.643	0.013
Frail	12	0.005	0.001 – 0.225	0.006	11	0.002	0.001 - 0.192	0.008
Pre-frail and frail	212	0.064	0.015 – 0.272	<.001	207	0.102	0.021 - 0.503	0.005
AD signature								
Pre-frail	200	0.076	0.021 – 0.275	<.001	196	0.115	0.027 - 0.493	0.004
Frail	12	0.016	0.001 – 0.458	0.016	11	0.005	0.001 - 0.338	0.014
Pre-frail and frail	212	0.069	0.019 – 0.246	<.001	207	0.098	0.023 - 0.411	0.002

Abbreviations: AD, Alzheimer's disease; CI, confidence interval; OR, odds ratio

Footnote a: odds ratio (OR) of presenting pre-frailty or frailty on per unit (mm) increase in cortical thickness, comparing to robust participants (reference group, n=272 for unadjusted model and n=269 for adjusted model)

Footnote b: adjusted for age, sex, Multidomain Alzheimer Preventive Trial (MAPT) groups, education, cardiovascular risk, baseline Mini-Mental State Examination (MMSE) score and total intracranial volume

Footnote c: excluded participants without data of education, baseline MMSE score and total intracranial volume

Table 4. Cox proportional hazard models for 5-year incident frailty <sup>a</sup> (n=453)

Cortical thickness (mm)	Unadjusted model				Adjusted model <sup>b</sup>				Adjusted model <sup>c</sup>			
	HR	95% CI	p	adjusted p <sup>d</sup>	HR	95% CI	p	adjusted p <sup>d</sup>	HR	95% CI	p	adjusted p <sup>d</sup>
Whole brain	0.56	0.06 – 5.03	0.603	-	1.03	0.10 – 10.14	0.983	-	1.18	0.12 – 11.92	0.888	-
Mobility-related regions	0.35	0.04 – 2.74	0.314	-	0.54	0.06 – 4.67	0.579	-	0.78	0.08 – 7.30	0.826	-
AD signature	0.33	0.05 – 2.05	0.236	-	0.62	0.09 – 4.24	0.626	-	0.74	0.10 – 5.52	0.771	-
By brain region												
Frontal lobe	2.08	0.29 – 14.81	0.463	0.613	2.02	0.30 – 13.70	0.473	0.651	2.61	0.35 – 19.29	0.347	0.793
Parietal lobe	0.53	0.08 – 3.48	0.511	0.613	1.01	0.14 – 7.54	0.991	0.991	1.06	0.14 – 7.89	0.953	0.953
Temporal lobe	0.12	0.03 – 0.59	0.009	0.051	0.24	0.04 – 1.38	0.110	0.651	0.34	0.06 – 2.14	0.252	0.793
Occipital lobe	0.21	0.02 – 2.48	0.215	0.430	0.45	0.04 – 5.82	0.543	0.651	0.70	0.06 – 8.93	0.782	0.939
Limbic system	0.72	0.12 – 4.42	0.722	0.722	0.43	0.07 – 2.72	0.371	0.651	0.45	0.06 – 3.38	0.440	0.793
Insula	0.30	0.06 – 1.47	0.138	0.415	0.42	0.10 – 1.82	0.244	0.651	0.62	0.14 – 2.75	0.529	0.793

Abbreviations: AD, Alzheimer's disease; CI, confidence interval; HR, hazard ratio; p, p-value

Footnote a: 51 of 453 participants became frail over the 5-year follow-up.

Footnote b: adjusted for age and sex

Footnote c: adjusted for age, sex, Multidomain Alzheimer Preventive Trial (MAPT) groups, education, cardiovascular risk, Mini-Mental State Examination (MMSE) score, baseline frailty score and total intracranial volume; excluding participants without data of education, MMSE score and total intracranial volume (n=447)

Footnote d: p-value adjusted for multiple comparison using the Hochberg procedure