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Differential brain volume between obese and underweight cognitively normal older adults with frailty in the JPSC-AD

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Frailty is common in older adults; however, the central nervous system mechanisms underlying the differences between obesity and underweight remain unclear. This study investigated brain volume in frail, cognitively normal, community-dwelling older adults across three body mass index (BMI) groups: low (< 18.5), intermediate (18.5–24.9), and high (≥ 25.0). Whole and regional brain volumes were measured and analyzed. Among 3,627 participants, those in the high BMI group ($n = 1,134$) had significantly lower multivariate-adjusted total brain volume (66.8% vs. 67.3%, $p < 0.001$) and gray matter volume (36.1% vs. 36.6%, $p < 0.001$) than participants in the intermediate BMI group ($n = 2,274$). Volume differences were observed in the frontal, parietal, temporal, and cingulate cortices, as well as the hippocampal gyrus; amygdala; superior, middle, and inferior temporal gyri; temporal pole; parahippocampal gyrus; and cuneus. Compared with the intermediate BMI group, the low BMI group ($n = 219$) presented a significantly lower volume in the middle temporal gyrus (1.91% vs. 1.95%, $p = 0.008$). These findings indicate that older adults with frailty experience differences in brain volume, with atrophy patterns differing based on BMI. Therefore, the central nervous system dysfunction may play a role in the mechanisms underlying frailty.

Keywords Frailty, Obesity, Underweight, Older adult, Brain volume, Community-dwelling

Frailty is a multidimensional geriatric syndrome that is characterized by progressive declines in physiological, physical, and cognitive functioning[1–3]. This syndrome represents a transitional state between healthy aging and overt disability or dependence, and it is associated with adverse outcomes such as falls, hospitalization, institutionalization, and mortality[4–9]. In recognition of its global relevance, the World Health Organization has

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emphasized the importance of frailty as a clinical and public health priority (https://iris.who.int/handle/10665/272437).

Frailty frequently coexists with sarcopenia, which is defined as age-related losses in muscle mass and strength. Frailty and sarcopenia share some diagnostic criteria, such as reduced grip strength and slow gait speed; furthermore, these syndromes often reflect underlying deficits in musculoskeletal and metabolic resilience[10–12]. Historically, frailty has been strongly associated with low body mass index (BMI), reflecting undernutrition and diminished energy reserves[13]. However, recent evidence has suggested that obesity may also be a risk factor for frailty both in Western populations and in countries such as Japan[14–16]. These findings have led to the identification of sarcopenic obesity, a condition that combines increased adiposity with reduced muscle function, as a distinct and particularly disabling frailty phenotype among older individuals[17–19].

Epidemiological studies have consistently reported a U-shaped association between BMI and frailty, suggesting that both underweight and obesity are independent risk factors for the development of frailty[16,20,21]. These phenotypes also differ with respect to their associated clinical and demographic profiles. For example, undernutrition-related frailty has been shown to be associated with older age and lower energy intake[22,23], whereas obesity-related frailty has been shown to be associated with metabolic comorbidities such as hypertension and diabetes mellitus[24,25]. These findings underscore the heterogeneity of frailty and raise important questions regarding the biological mechanisms that distinguish these phenotypes. Furthermore, distinct frailty phenotypes, such as sarcopenic obesity and undernutrition-related frailty, may also differ in terms of central nervous system involvement.

Cognitive function and brain structure may offer important insights into the pathophysiology of frailty subtypes. Frailty has been shown to be associated with cognitive decline, and neuroimaging studies have linked frailty to atrophic changes in brain regions, including the hippocampus, cerebellum, and frontal gyri[26,27]. Similarly, both low and high BMI have been associated with structural brain alterations in older adults[28,29]. In particular, some studies have described an "obesity paradox," where higher BMI appears to confer protection against dementia in late life[30]. Although this paradox may be partly attributable to reverse causation, since unintentional weight loss can precede dementia onset[31], it nonetheless highlights the complex and possibly bidirectional relationships among body composition, cognitive health, and brain structure.

Despite these findings, few studies have examined how frailty and BMI are related to neuroanatomical changes in older adults. It remains unclear whether undernutrition-related frailty and obesity-related frailty are associated with distinct patterns of brain atrophy. Addressing this knowledge gap could enhance our understanding of the neural correlates of BMI-related frailty and inform strategies to preserve cognitive and physical functioning in older populations. Therefore, this cross-sectional study aimed to investigate differences in whole and regional brain volumes among older adults with frailty across various BMI categories to identify potential neuroanatomical signatures underlying distinct frailty phenotypes.

Results

Sample characteristics

This cross-sectional study applied the revised Japanese Cardiovascular Health Study (J-CHS) criteria[32] to a total of 7,783 participants. Ultimately, a cohort of 3,627 eligible participants was derived and classified into low, intermediate, and high BMI groups (Fig. 1). Among the 7,783 older adults, the mean age was 72.6 ± 5.9 years, and there were 4,469 females (57.4%). A total of 2,101 (27.0%) participants had ≤ 9 years of formal education. A review of the medical information revealed that 5,613 (72.1%) participants had hypertension, and 1,265 (16.3%) had diabetes mellitus (DM). A total of 368 (4.7%) and 733 (9.4%) participants reported a history of cerebrovascular and heart disease, respectively. The mean Mini-Mental State Examination (MMSE) score was 27.5 ± 2.4. The characteristics of the 7,783 older adults are not shown in the table, as these were preliminarily analyses.

Risk of frailty stratified by BMI

Both the low and high BMI groups presented significantly greater odds of frailty than did the intermediate BMI group, indicating a U-shaped association (Fig. 2). The 7,783 participants were classified into a low BMI group (n = 412, 5.3%), an intermediate BMI group (n = 5,193, 66.7%), and a high BMI group (n = 2,178, 28.0%). The prevalence of prefrailty or frailty was 53.2% (n = 219) in the low BMI group, 43.8% (n = 2,274) in the intermediate BMI group, and 52.1% (n = 1,134) in the high BMI group. Binomial logistic regression was used to analyze the association between BMI and frailty. The low and high BMI groups presented significantly higher ORs for frailty than did the intermediate BMI group. The ORs for the low and high BMI groups were 1.41 (95% confidence intervals (CI): 1.15–1.73) and 1.43 (95% CI: 1.29–1.59), respectively, in the age- and sex-adjusted model and 1.46 (95% CI: 1.19–1.80) and 1.30 (95% CI: 1.17–1.44), respectively, in the multivariate-adjusted model (adjusted for age, sex, institution, ≤ 9 years of formal education, hypertension, DM, history of cerebrovascular disease, and history of heart disease).

Demographic and clinical characteristics of older adults living with frailty across BMI groups

We compared the following demographic and clinical characteristics of participants across BMI groups: age, sex, education, hypertension status, DM status, history of stroke, history of heart disease, and apolipoprotein E (APOE) ε4 status. We selected these variables due to their potential confounding effect on the relationship between frailty and brain volume. Analysis of variance (ANOVA) was used to compare continuous variables, and the chi-square test was used to compare categorical variables.

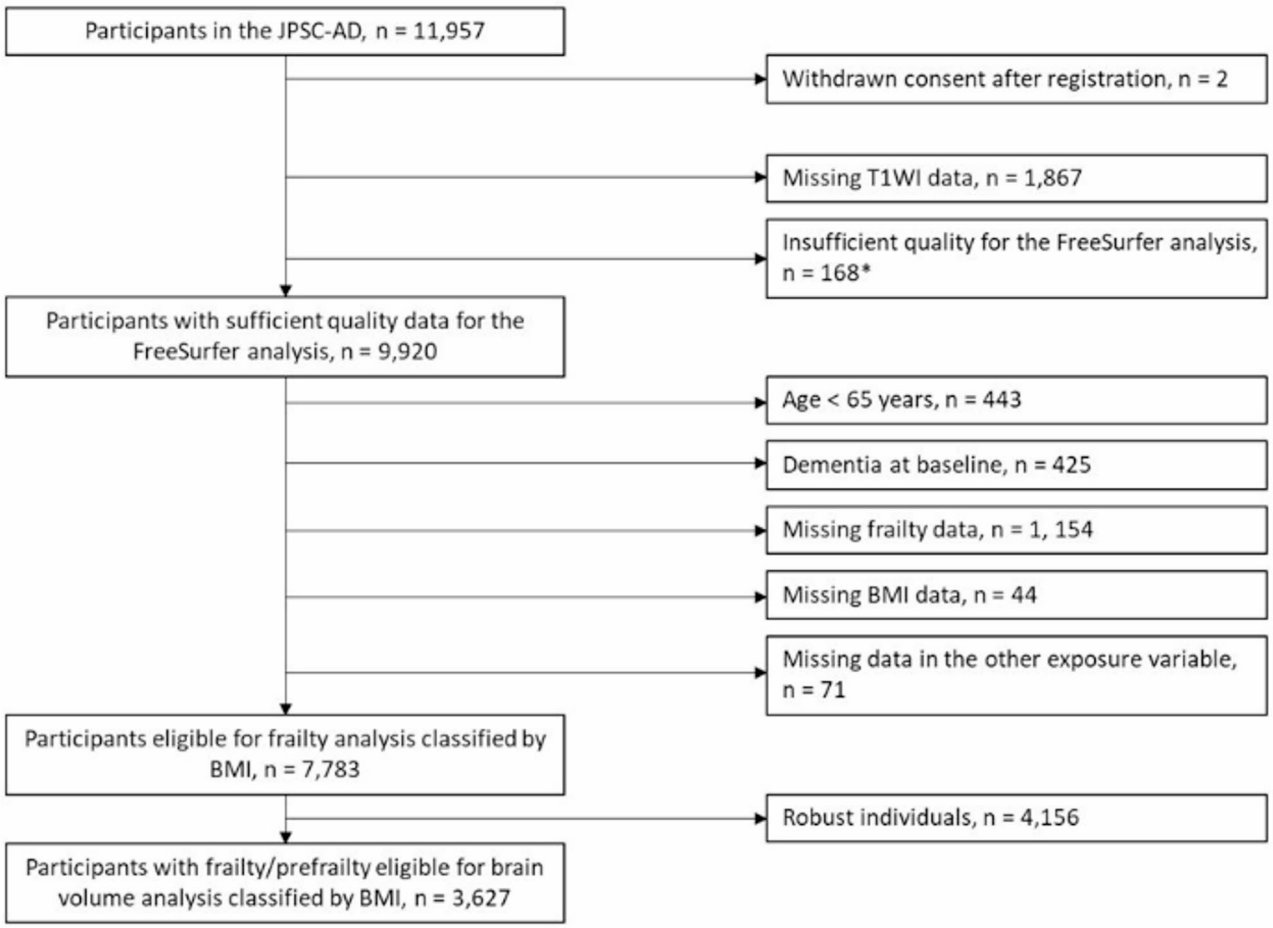

Fig. 1. Process for selecting participants for this study. Eligible participants were recruited, stratified by body mass index, and subjected to frailty and brain volume analyses. *Participants with insufficient data quality for FreeSurfer analysis, including 17 individuals in whom an error occurred during the automated analysis process, 29 with extreme outliers in the estimated total intracranial volume, and 122 with extreme outliers in the volumes of at least five brain regions. BMI, body mass index; JPSC-AD, Japan Prospective Studies Collaboration for Aging and Dementia; n, number; T1WI, T1-weighted image.

Among the 3,627 older adults living with frailty, 219 (6.0%) were classified into the low BMI group, 2,274 (62.7%) were classified into the intermediate BMI group, and 1,134 (31.3%) were classified into the high BMI group (Table 1).

Age differed significantly among the three groups ($p = 0.001$), with the high BMI group being significantly younger than the low BMI group ($p = 0.002$). There were also significant between-group differences in the proportion of females, formal education level, prevalence of hypertension, prevalence of DM, and proportion of APOE ε4 carriers ($p = 0.017$, $p < 0.001$, $p < 0.001$, and $p = 0.029$, respectively).

No statistically significant differences were found in the prevalence of cerebrovascular disease or heart disease across BMI groups. Furthermore, there was no significant association between BMI and MMSE scores.

The proportion of females was significantly higher in the low BMI group than in both the intermediate BMI ($p = 0.022$) and high BMI groups ($p = 0.008$). The formal education level and prevalence of hypertension increased with BMI; the p values for multiple comparisons (low vs. intermediate, intermediate vs. high, and low vs. high) were 0.025 and < 0.01, 0.023 and < 0.001, and < 0.001 and < 0.001, respectively.

The prevalence of DM was significantly higher in the high BMI group than in both the low ($p < 0.001$) and intermediate BMI groups ($p < 0.001$). The prevalence of APOE ε4 carriers was significantly higher in the low BMI group than in the intermediate BMI group ($p = 0.029$). The results of further subgroup analyses of frailty-related items across BMI groups are provided in Supplementary Table 1.

Brain volumes among older adults living with frailty across BMI groups

We analyzed whole and regional brain volumes among 3,627 participants with frailty or prefrailty) across BMI groups (Table 2). Brain volumes were examined via analysis of covariance (ANCOVA) after controlling for age, sex, institution, formal education ≤ 9 years, hypertension, DM, history of stroke and heart disease.

Compared with the intermediate BMI group, the high BMI group presented significantly lower total brain volume (TBV) ($p < 0.001$) and gray matter volume (GMV) ($p < 0.001$). Furthermore, compared with the

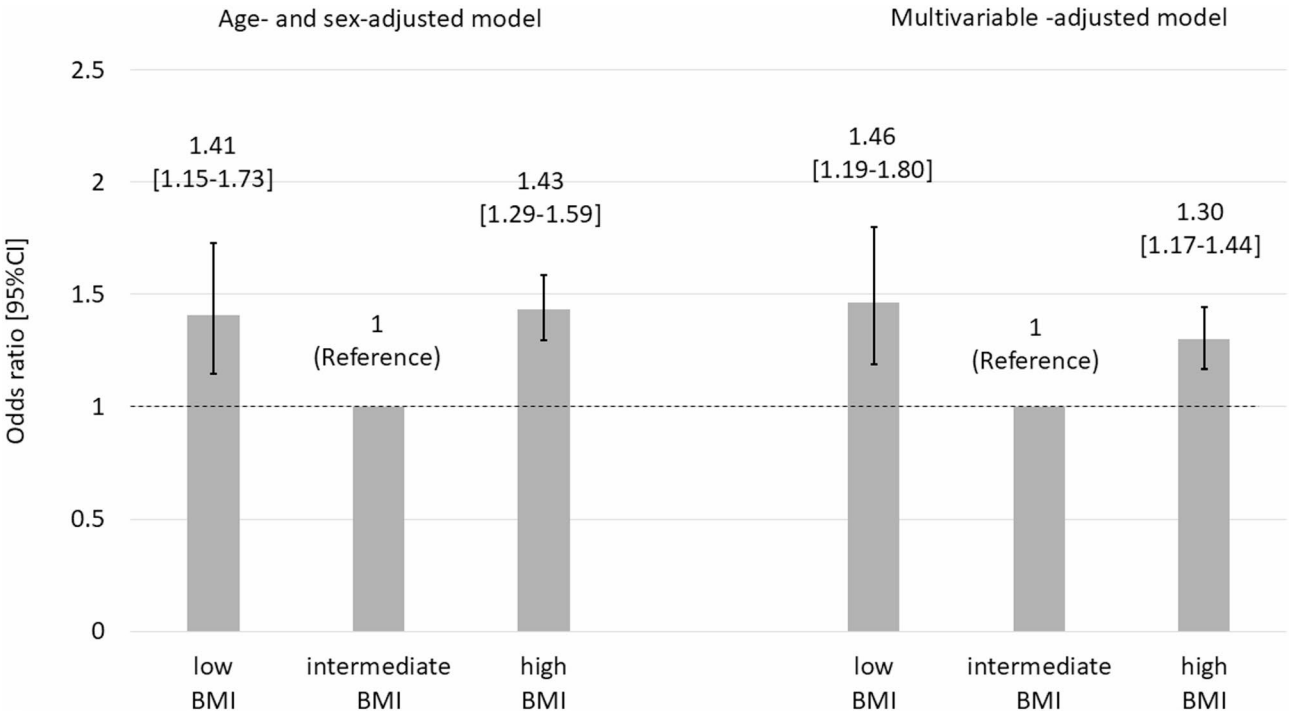

Fig. 2. Estimated odds ratios of frailty: comparison of the low and high body mass index (BMI) groups with the reference group (intermediate BMI) in 7,783 participants eligible for frailty analysis. BMI, body mass index. The values are odds ratios (95% CIs, p values). *Adjusted for age, sex, institution, ≤ 9 years of formal education, hypertension, diabetes mellitus, history of cerebrovascular disease, and history of heart disease.

	Low BMI group	Intermediate BMI group	High BMI group	*p*-value
Number	219	2,274	1,134	-
Age, years, mean ± SD	74.1 ± 6.8	74.0 ± 6.5	73.2 ± 6.4	0.001
Female sex, n (%)	150 (68.5)	1,346 (59.2)	653 (57.6)	0.017
Formal education ≤ 9 years, n (%)	52 (23.7)	738 (32.5)	420 (37.0)	< 0.001
Hypertension, n (%)	127 (58.0)	1,612 (70.9)	949 (83.7)	< 0.001
Diabetes mellitus, n (%)	23 (10.5)	359 (15.8)	286 (25.2)	< 0.001
History of stroke, n (%)	5 (2.3)	142 (6.2)	68 (6.0)	0.268
History of heart disease, n (%)	16 (7.3)	265 (11.7)	140 (12.3)	0.097
MMSE, mean ± SD	27.3 ± 2.6	27.3 ± 2.5	27.2 ± 2.4	0.348
APOE ε4 carrier, n (%)	52 (24.4)	386 (17.3)	198 (17.7)	0.034

Table 1. Characteristics of 3,627 older adults living with frailty stratified by body mass index. *BMI* body mass index, *n* number, *SD* standard deviation, *MMSE* Mini-Mental State Examination, *APOE* apolipoprotein E.

intermediate BMI group, the high BMI group exhibited widespread reductions in regional volumes, including the frontal cortex ($p = 0.032$), parietal cortex ($p = 0.032$), temporal cortex ($p < 0.001$), cingulate cortex ($p = 0.003$), hippocampal gyrus ($p = 0.016$), superior gyrus ($p = 0.002$), middle gyrus ($p = 0.001$), inferior temporal gyrus ($p < 0.001$), fusiform gyrus ($p = 0.037$), temporal pole ($p < 0.001$), parahippocampal gyrus ($p = 0.008$), and cuneus gyrus ($p = 0.027$). In contrast, compared with the intermediate BMI group, the low BMI group exhibited significantly reductions in brain volume only in the middle temporal gyrus ($p = 0.001$). No significant differences were observed between the low and high BMI groups in any brain region. A heatmap of p values for post hoc multiple comparisons of whole and regional brain volumes across BMI groups is shown in Fig. 3. These findings suggest that distinct neuroanatomical patterns are associated with lower and higher BMIs among older adults.

Owing to the small sample size in the low BMI group, Levene's test was applied to test the equality across the three groups. The results confirmed that the differences in group sizes did not significantly affect the findings except for the findings related to the hippocampus and amygdala (Supplementary Table 2).

We examined the interaction between BMI and frailty across the 7,783 frail and nonfrail participants using two-way ANOVA (Supplementary Table 3). This interaction only had a significant effect on three of the 25 regions examined: the insular cortex, fusiform gyrus and parahippocampal gyrus.

Segments	Estimated volume ratio (95%CI) of BMI group			Main effect of BMI group			Post-hoc test					
							p-value (LSD)			*p*-value (Bonferroni)		
	Low (L)	Intermediate (I)	High (H)	F	*p*-value	η_p^2	(L) vs. (I)	(L) vs. (H)	(I) vs. (H)	(L) vs. (I)	(L) vs. (H)	(I) vs. (H)
Total Brain Volume	67.2 (66.7–67.6)	67.3 (67.2–67.5)	66.8 (66.6–67.0)	9.07	< 0.001	0.005	0.462	0.160	0.000	> 0.999	0.479	< 0.001
Gray Matter Volume[a]	36.4 (36.1–36.7)	36.6 (36.5–36.7)	36.1 (36.0–36.3)	17.12	< 0.001	0.009	0.156	0.126	0.000	0.468	0.377	< 0.001
White Matter Volume[a]	29.0 (28.8–29.3)	28.9 (28.8–29.0)	28.9 (28.8–29.0)	0.24	0.784	< 0.001	0.515	0.489	0.880	> 0.999	> 0.999	> 0.999
White Matter T1-Hypointensity[a]	0.410 (0.358–0.463)	0.409 (0.392–0.425)	0.422 (0.399–0.446)	0.45	0.639	< 0.001	0.950	0.684	0.346	> 0.999	> 0.999	> 0.999
Frontal Lobe Cortex[b]	14.3 (14.1–14.4)	14.3 (14.3–14.3)	14.2 (14.2–14.3)	3.46	0.032	0.002	0.335	0.726	0.010	> 0.999	> 0.999	0.031
Parietal Lobe Cortex[b]	9.55 (9.47–9.63)	9.62 (9.59–9.65)	9.56 (9.52–9.60)	4.13	0.016	0.002	0.118	0.851	0.009	0.353	> 0.999	0.027
Temporal Lobe Cortex[b]	9.40 (9.33–9.48)	9.49 (9.47–9.52)	9.39 (9.36–9.42)	14.26	< 0.001	0.008	0.021	0.745	0.000	0.062	> 0.999	< 0.001
Occipital Lobe Cortex[b]	3.82 (3.78–3.87)	3.83 (3.82–3.85)	3.81 (3.80–3.83)	1.31	0.270	0.001	0.628	0.742	0.110	> 0.999	> 0.999	0.330
Insula Cortex[b]	1.26 (1.25–1.28)	1.27 (1.26–1.27)	1.26 (1.25–1.27)	1.74	0.176	0.001	0.424	0.901	0.074	> 0.999	> 0.999	0.222
Cingulate Cortex[b]	1.76 (1.74–1.78)	1.76 (1.75–1.77)	1.74 (1.73–1.75)	5.94	0.003	0.003	0.896	0.117	0.001	> 0.999	0.350	0.002
Hippocampal Gyrus[b]	0.740 (0.730–0.750)	0.748 (0.745–0.752)	0.741 (0.737–0.746)	4.12	0.016	0.002	0.107	0.805	0.010	0.321	> 0.999	0.029
Amygdala[b]	0.269 (0.263–0.275)	0.275 (0.273–0.276)	0.271 (0.268–0.273)	3.68	0.025	0.002	0.089	0.652	0.019	0.268	> 0.999	0.029
Subcortical Gray Matter[b]	5.12 (5.07–5.17)	5.14 (5.13–5.16)	5.11 (5.09–5.13)	2.82	0.060	0.002	0.322	0.850	0.022	0.966	> 0.999	0.067
Superior Temporal Gyrus[b]	2.01 (1.99–2.04)	2.02 (2.02–2.03)	2.00 (1.99–2.02)	3.83	0.022	0.002	0.417	0.559	0.006	> 0.999	> 0.999	0.019
Middle Temporal Gyrus[b]	1.91 (1.89–1.94)	1.95 (1.94–1.96)	1.93 (1.92–1.94)	6.70	0.001	0.004	0.003	0.114	0.011	0.008	0.341	0.034
Inferior Temporal Gyrus[b]	1.93 (1.90–1.95)	1.95 (1.94–1.95)	1.91 (1.90–1.92)	14.27	< 0.001	0.008	0.119	0.258	0.000	0.356	0.774	< 0.001
Fusiform Gyrus[b]	1.71 (1.69–1.74)	1.74 (1.73–1.74)	1.72 (1.71–1.73)	3.29	0.037	0.002	0.072	0.496	0.038	0.215	> 0.999	0.113
Transverse Temporal Gyrus[b]	0.179 (0.175–0.182)	0.181 (0.180–0.182)	0.181 (0.179–0.182)	0.54	0.584	< 0.001	0.307	0.328	0.982	0.922	0.984	> 0.999
Temporal Pole[b]	0.488 (0.479–0.497)	0.489 (0.486–0.492)	0.478 (0.474–0.482)	10.45	< 0.001	0.006	0.875	0.037	0.000	> 0.999	0.110	< 0.001
Entorhinal Cortex	0.347 (0.340–0.355)	0.354 (0.352–0.356)	0.354 (0.350–0.357)	1.44	0.236	0.001	0.091	0.118	0.943	0.274	0.353	> 0.999
Parahippocampal Gyrus	0.364 (0.357–0.370)	0.369 (0.367–0.372)	0.364 (0.361–0.367)	4.82	0.008	0.003	0.103	0.893	0.004	0.308	> 0.999	0.013
Superior Frontal Gyrus	3.63 (3.60–3.67)	3.66 (3.65–3.67)	3.66 (3.64–3.67)	1.05	0.349	0.001	0.148	0.222	0.763	0.443	0.665	> 0.999
Cuneus Gyrus	0.487 (0.479–0.495)	0.494 (0.491–0.496)	0.488 (0.484–0.492)	3.63	0.027	0.002	0.138	0.840	0.015	0.413	> 0.999	0.044
Paracentral Gyrus	0.621 (0.611–0.632)	0.620 (0.617–0.622)	0.617 (0.613–0.622)	0.51	0.599	< 0.001	0.752	0.456	0.366	> 0.999	> 0.999	> 0.999
Supramarginal Gyrus	1.806 (1.782–1.830)	1.812 (1.804–1.819)	1.798 (1.787–1.808)	2.27	0.104	0.001	0.651	0.535	0.034	> 0.999	> 0.999	0.101

Table 2. Multivariate-adjusted mean brain volumes of 3,627 older adults living with frailty stratified by body mass index. The total brain volume, gray matter volume, white matter volume, and white matter T1-hypointensity volume are presented as percentages of the intracranial volume, and the volumes of the other segments are presented as percentages of the total brain volume. The 95% CIs are in parentheses. *BMI* body mass index, *vs.* versus, *L* low BMI, *I* intermediate BMI, *H* high BMI, *F* F statistic, ηp^2 partial eta squared, *LSD* least significant difference. [a]% of intracranial volume; [b]% of total brain volume.

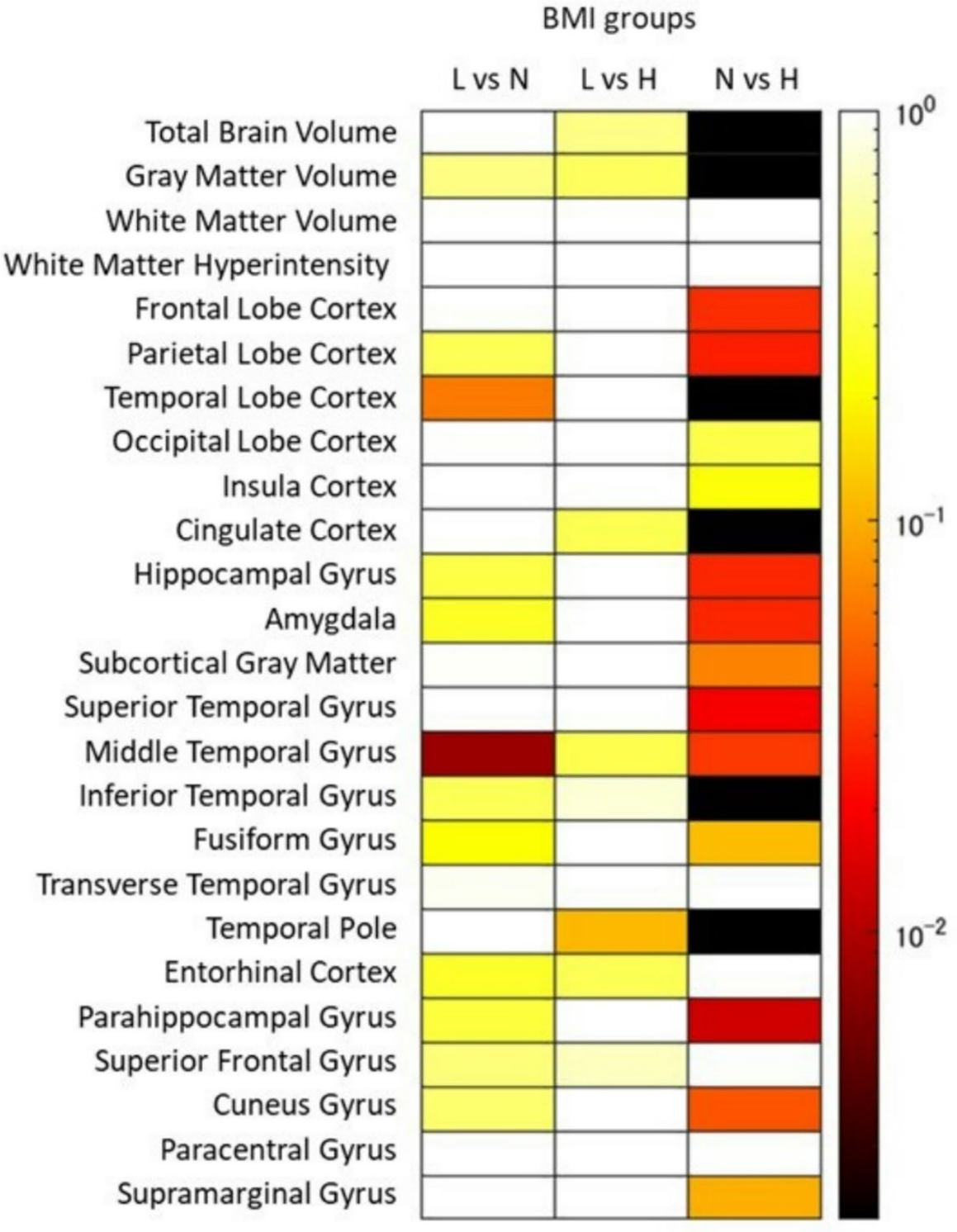

Fig. 3. Brain volume differences in 3,627 older adults living with frailty stratified by body mass index (BMI). The color intensity on the heatmap indicates the magnitude of the p value, i.e., the level of statistical significance. Significant differences in volume were apparent between the older adults living with frailty in the low and high BMI groups and those in the intermediate BMI group. *BMI* body mass index, *H* high, *L* lower, *N* normal, *vs.* versus.

Discussion

This study investigated structural brain differences among older adults living with frailty across BMI categories. The aim of this study was to identify neuroanatomical signatures underlying distinct frailty phenotypes. Our results demonstrated that, compared with the intermediate BMI group, both the low and high BMI groups presented differences in whole and regional brain volumes. Importantly, the patterns of these structural differences varied between the two groups, suggesting that the mechanisms of frailty may differ based on the BMI.

In the high BMI group, reductions in TBV, GMV, and regional volumes (e.g., the frontal, temporal, and parietal cortices) were observed. Within the temporal lobe, volume reductions were observed in the hippocampus, parahippocampal gyrus, fusiform gyrus, superior and middle temporal gyri, amygdala, and temporal pole. Additional volume reductions were observed in the cingulate and cuneus cortices compared with the intermediate BMI group. These regions collectively support a broad range of cognitive and affective functions. The frontal[33], temporal[34], and parietal cortices[35] are crucial for executive function, memory and attention; the hippocampus is pivotal for memory formation and consolidation[36]; and the amygdala regulates emotional processing[37]. These structural changes may collectively contribute to cognitive and emotional dysregulation in older adults. Differences in the cingulate[38] and cuneus cortices[39] could affect emotional processing and sensory integration. Alterations in these regions may lead to mood disturbances and sensory deficits, further exacerbating frailty symptoms. Our findings support previous reports linking higher BMI values to brain atrophy[40,41] and suggest a potential link between neuroanatomical alterations and the development or progression of frailty in older adults.

In contrast, the low BMI group presented more focal differences, with structural reduction only observed in the middle temporal gyrus. This region is involved in cognitive, sensory, and emotional functions. While mesial temporal atrophy has been reported in underweight older adults and patients with Alzheimer's disease[42,43], our participants had preserved cognitive function. These results suggest that subtle neuroanatomical changes may occur even in the absence of overt cognitive decline, possibly indicating early vulnerability related to undernutrition or systemic health conditions.

Overall, these findings indicate that frailty is not a singular condition but may represent a spectrum of phenotypes with differing etiologies. Importantly, we observed a U-shaped association between frailty and BMI, with both underweight and obese individuals exhibiting an elevated risk of frailty. This finding is consistent with the U-shaped relationship between BMI and frailty reported in previous Japanese[16] and international studies[20,21]. Furthermore, this finding is consistent with the concept that sarcopenic obesity – which is characterized by the coexistence of adiposity and muscle wasting – is a key contributor to frailty in older adults[17–19]. Although some associations between frailty and cortical thinning or hippocampal volume have been reported[44,45] and white matter hyperintensities have been implicated in longitudinal frailty progression[46], few studies have examined region-specific brain volume differences across BMI groups in frail older populations.

Previous evidence regarding the relationship between BMI and brain structure has been inconsistent. Reduced white matter volume (WMV) has been reported in individuals with obesity[39], whereas cortical thinning has been observed in underweight men, particularly in the frontal and temporal cortices[28]. Some studies reported no relationship between BMI and hippocampal volume[47], whereas others reported a negative or inverse association[41,48]. These discrepancies highlight the need for stratified analysis on the basis of frailty status and body composition, which our findings contribute to by delineating distinct brain volume signatures across BMI-based frailty phenotypes.

In addition to neuroimaging findings, frailty in the low BMI group was more strongly associated with female sex and APOE ε4 allele positivity, potentially reflecting preclinical vulnerability before the manifestation of cognitive impairment. Frailty in the high BMI group was more frequently linked to less formal education, hypertension, and diabetes mellitus. These findings suggest that clinical heterogeneity in structural brain changes, demographic characteristics, vascular parameters, and genetic factors contribute to frailty across BMI categories. This divergence in associated features reflects the multifactorial nature of frailty in older adults.

This study has several limitations. The cross-sectional design precludes causal inference regarding the relationships among BMI, brain structure, and frailty. Moreover, BMI does not accurately reflect body composition and may not capture the complex interplay between fat and muscle mass[49,50]. It is also possible that frailty itself, through mechanisms such as physical inactivity or systemic inflammation, contributes to changes in both BMI and brain volume[5,51]. The relatively small sample size of the low BMI group may have limited statistical power and increased the risk of type I error, particularly with respect to findings in the hippocampus and amygdala. Nonetheless, the equality test confirmed that, with the exception of these regions, differences in the sample size between BMI groups did not significantly bias the results. Furthermore, the generalizability of our findings may be limited by the relatively homogeneous ethnic composition and age range of the study cohort. Replication in more diverse populations, including younger cohorts and individuals from different ethnic backgrounds, will be important to validate and extend these findings.

In conclusion, compared with the intermediate BMI group, older adults with frailty who have a high or low BMI presented distinct patterns of whole and regional brain volume differences. These findings support the notion that different neurobiological mechanisms may underlie both the underweight-related frailty phenotype and the obesity-related frailty phenotype. Maintaining an Appropriate body weight may therefore be essential not only for preserving physical health but also for supporting brain integrity and mitigating frailty-related cognitive and affective impairments. Our results underscore the importance of tailored interventions and preventive strategies that address both undernutrition and obesity and highlight the need for integrated public health and clinical efforts to preserve brain health and functional independence in aging populations.

Methods

Ethics statement

This study was approved by the Medical Ethics Review Committee of Kyushu University (approval number: 686 – 10) and the Medical Ethics Review Committee of each institute participating in the JPSC-AD, including our institution (approval numbers: HGH28-12, HG2020-017, MH2022-165). This study was performed in accordance with relevant guidelines and regulations and the Declaration of Helsinki. All participants provided written informed consent.

Participants and design

We recruited participants from the JPSC-AD, a comprehensive eight-site population-based prospective cohort study conducted across Japan. The JPSC-AD aimed to identify both environmental and genetic risk factors for dementia and depression as well as to elucidate the interactions between these risk factors[52]. The JPSC-AD prospectively monitored a cohort of 11,957 community-dwelling older adults (aged ≥ 65 years) through extensive cross-sectional surveys carried out from 2016 to 2018. Details on the study protocol and the data collected at baseline are provided elsewhere[52].

Among the 11,957 participants in the JPSC-AD, two participants were excluded because they withdrew their consent after enrollment. A total of 10,090 participants underwent three-dimensional T1-weighted magnetic resonance imaging. After 168 participants who did not meet the quality control criteria for FreeSurfer analysis were excluded, 9,920 participants were ultimately included in our analysis. A total of 443 participants aged < 65 years, 425 participants with dementia at baseline, 1,154 participants with missing frailty data, 44 participants with missing BMI data, and 71 participants with missing data for the exposure variable were excluded, thus leaving 7,783 participants. Based on the revised J-CHS criteria, nonfrail participants were excluded. Thus, the remaining 3,627 participants were eligible for this cross-sectional study.

BMI measurements

Body height and weight were measured with participants wearing light clothing and no shoes. BMI was calculated as weight in kilograms divided by the square of height in meters. The participants were classified into three groups on the basis of their BMI: low (BMI ≤ 18.5 kg/m2), intermediate (18.5 < BMI < 25.0 kg/m2), and high (BMI ≥ 25.0 kg/m2). The BMI range of 18.6–24.9 is considered appropriate for the general Japanese population according to the Ministry of Health, Labour and Welfare of Japan (https://www.mhlw.go.jp/www1/topics/kenko21_11/t2a.html).

Frailty assessment

Frailty phenotypes were defined according to the revised J-CHS criteria[32]. These criteria were investigated using questions related to unintentional weight loss, low physical activity levels, and feelings of exhaustion, as well as through handgrip strength and gait speed measurements. Feelings of exhaustion were assessed on the basis of the criteria of Chen and colleagues[53]. Handgrip strength and gait speed were measured using a standardized method for all participants. Handgrip strength was measured twice for each hand using four types of digital dynamometers (T.K.K.5001 and 5401: Takei Scientific Instruments Co., Ltd., Niigata, Japan; YS: Tsutsumi, Tokyo, Japan; and 261-006-05YX: Muranaka Medical Instruments, Osaka, Japan; T-2177: TOEI, Saitama, Japan), and the maximum value was used in the analysis. Participants with pain in their upper limbs were excluded. Gait speed was also tested twice and measured as the time required to walk 5 m on a specified course. The participants were asked to walk at their usual speed, and the fastest speed was used in the analysis. Participants who had difficulty walking or who were at risk of falling were excluded from the examination. We recruited individuals who were classified as frail (met three or more criteria) or prefrail (met one or two criteria).

Brain volumetry

The magnetic resonance imaging (MRI) equipment was set up in accordance with the JPSC-AD procedure, and brain volumetry was performed using parameters for three-dimensional T1-weighted imaging and a cross-domain convolutional neural network[54,55]. Briefly, segmentation and volumetric measurements of cortical and subcortical brain structures were performed automatically using FreeSurfer (version 5.3). The TBV was calculated from segmented brain volumes excluding ventricles. The volumes of the following brain regions were used as outcomes: TBV, GMV, WMV, white matter T1-hypointensity volume, cerebral cortical volumes (frontal, parietal, temporal, and occipital lobes), insula cortex, cingulate cortex, hippocampal gyrus, amygdala, subcortical gray matter (total volume of the thalamus, caudate, putamen, accumbens, and globus pallidus), superior temporal gyrus, middle temporal gyrus, inferior temporal gyrus, fusiform gyrus, transverse temporal gyrus, temporal pole, entorhinal cortex, parahippocampal gyrus, superior frontal gyrus, cuneus gyrus, paracentral gyrus, and supramarginal gyrus. To adjust for head size, the TBV, GMV, WMV, and white matter T1-hypointensity volume were calculated as percentages of the intracranial volume, whereas values in the other segments were calculated as percentages of the TBV. All regional brain volumes were calculated as the sum of the left- and right-side volumes.

Other measurements

We collected data on sociodemographic characteristics, including sex, age, education, physical activities, activities of daily living, and functional capacity (instrumental activities of daily living, intellectual activity, social roles), as well as medical history, including cerebrovascular and heart disease. Additionally, we assessed APOE ε4 carrier status. Furthermore, we performed physical evaluations in addition to the anthropometric measurements essential for assessing BMI and frailty. Waist circumference was measured at the umbilical level with participants in a standing position. Blood pressure was recorded as the mean value of three measurements

taken using an automated sphygmomanometer with participants in a seated position after at least 5 min of rest. Hypertension was defined as blood pressure ≥ 140/90 mmHg[56], along with the current use of antihypertensive agents. DM was defined based on a previously published description[57].

Statistical analysis

ANOVA was used to compare continuous variables between the BMI groups, and the chi-square test was used to compare categorical variables. The Bonferroni post hoc test was used to correct for multiple comparisons. Binomial logistic regression analysis was used to analyze the association between BMI and frailty and to estimate ORs and 95% CIs. An age- and sex-adjusted model and a multivariate-adjusted model were constructed. In the multivariable-adjusted model, age, sex, institution, ≤ 9 years of formal education, hypertension, DM, history of cerebrovascular disease, and history of heart disease were included as covariates. ANCOVA was used to evaluate brain volume after controlling for age, sex, institution, ≤ 9 years of formal education, hypertension, DM, history of cerebrovascular disease, and history of heart disease. The differences in group means were analyzed using the F statistic. The effect size was measured using ηp^2. Levene's test was used to examine the equality of the three BMI groups. The interaction between BMI and frailty was examined via two-way ANOVA. To analyze the association between BMI and frailty, binominal logistic regression analysis was used for the eligible participants without frailty and those with prefrailty or frailty. The adjusted ORs and 95% CIs for prefrailty or frailty in the low and high BMI groups were calculated, with the intermediate BMI group as the reference. An age- and sex-adjusted model and a multivariate-adjusted model were constructed. In the multivariable-adjusted model, age, sex, institution, ≤ 9 years of formal education, hypertension, DM, history of cerebrovascular disease, and history of heart disease were included as covariates. ANOVA was used to compare demographic and clinical characteristics of individuals with prefrailty or frailty between the three BMI groups, while the chi-square test was used to compare categorical variables. The Bonferroni test was used to correct for multiple comparisons. To evaluate the brain-to-volume ratio, ANCOVA was performed after controlling for age, sex, institution, ≤ 9 years of formal education, hypertension, DM, history of cerebrovascular disease, and history of heart disease. The differences in group means were analyzed using the F statistic. The effect size was measured using ηp^2. Additionally, Levene's test was used to examine the equality of the three BMI groups. Two-way ANOVA was used to examine the effects of BMI, frailty, and their interaction on the brain-to-volume ratio. All the statistical analyses were performed using IBM SPSS Statistics, version 25 (IBM Corp., Armonk, NY, USA). A two-tailed p value < 0.05 indicated statistical significance.

Data availability

All the processed data generated during this study are provided in the main article. In order to protect the confidentiality of the participants and to comply with the terms of participant consent, the raw data are not openly available. Requests related to the raw data should be addressed to the principal investigator, Toshiharu Ninomiya (Department of Epidemiology and Public Health, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan) [t.ninomiya.a47@m.kyushu-u.ac.jp], and the Japan Agency for Medical Research and Development.

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Declarations

Competing interests

The authors declare no competing interests.

Additional information

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The Japan Prospective Studies Collaboration for Aging and Dementia (JPSC-AD) study group

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