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Muscle Health Patterns and Brain MRI Indices: A Cluster Analysis

Shou-En Wu, MD[1] and Wei-Liang Chen, MD, PhD[2,3,*]

[1]Department of Dermatology, Tri-Service General Hospital; and School of Medicine, National Defense Medical Center, Taipei, Taiwan, Republic of China.
[2]Division of Family Medicine, Department of Family and Community Medicine, Tri-Service General Hospital; and School of Medicine, National Defense Medical Center, Taipei, Taiwan, Republic of China.
[3]Division of Geriatric Medicine, Department of Family and Community Medicine, Tri-Service General Hospital; and School of Medicine, National Defense Medical Center, Taipei, Taiwan, Republic of China.

*Address correspondence to: Wei-Liang Chen, MD, PhD, Division of Geriatric Medicine, Department of Family Medicine, Tri-Service General Hospital, National Defense Medical Center, Number 325, Section 2, Chang-gong Road, Nei-Hu District, 114, Taipei, Taiwan, Republic of China.
E-mail: weiliang0508@gmail.com

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Abstract

Background and Objectives: The interplay between muscle and brain lacks a holistic approach to assess the combined effect of multiple factors. This study utilizes clustering analysis to identify muscle health patterns and their relationships with various brain magnetic resonance imaging (MRI) indices.

Research Design and Methods: Two hundred and seventy-five cognitively intact participants who completed brain MRI from the Health, Aging, and Body Composition Study were enrolled. Muscle health-related markers that showed significant relationship with total gray matter volume entered the cluster analysis. Subsequently, macrostructural and microstructural MRI indices were examined with analysis of variance and multiple linear regression analysis to determine significant associations with muscle health clusters. The muscle health cluster included 6 variables: age, skeletal muscle mass index, gait speed, handgrip strength, change of total body fat, and serum leptin level. Clustering method produced 3 clusters which had characteristics of obese, leptin-resistant, and sarcopenia, respectively.

Results: Brain MRI indices that revealed significant associations with the clusters included gray matter volume (GMV) in cerebellum ($p < .001$), superior frontal gyrus ($p = .019$), inferior frontal gyrus ($p = .003$), posterior cingulum ($p = .021$), vermis ($p = .045$), and gray matter density (GMD) in gyrus rectus ($p < .001$) and temporal pole ($p < .001$). The leptin-resistant group had most degree of reduction in GMV, whereas the sarcopenia group had most degree of reduction in GMD.

Discussion and Implications: The leptin-resistant and sarcopenia populations had higher risk of neuroimaging alterations. Clinicians should raise awareness on the brain MRI findings in clinical settings. Because these patients mostly had central nervous system conditions or other critical illnesses, the risk of sarcopenia as a comorbidity will substantially affect the prognosis and medical care.

Keywords: Brain, Cluster analysis, Cognition, Leptin, Muscle, Sarcopenia

Translational Significance: Distinct muscle health patterns are associated with alterations in different brain magnetic resonance imaging (MRI) indices. This study revealed that the leptin-resistant and sarcopenia patterns show frequent neuroimaging changes. Early findings in neuroimaging help identify individuals who are at higher risk of muscle health problems.

Background

Healthy aging refers to the concept of developing and maintaining the functional ability in older population (Organization, 2020). Main determinants are physical and mental health, which in other words point toward muscle and brain function. Age-related muscle changes can be discussed from various aspects, and many of them are to some degree associated with cognitive decline. For instance, sarcopenia is characterized by gradual loss of muscle mass and function with increasing age, and its association with cognitive impairment has been supported in previous literature (Chang et al., 2016). Likewise, obesity in midlife affects volumetric reductions in brain structure, and accelerates cognitive decline in later life (Bischof & Park, 2015). Apparently, muscle and cognitive decline affects one another remarkably. Considering that both are progressive processes, recognizing risk indicators in preclinical disease stages facilitates timely intervention and permits effective prevention strategies.

Substantial studies have demonstrated the correlation between physical activity and cognitive function. However, most of the evidence showed significance in patients like Alzheimer's disease rather than general healthy older adults

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(Drago et al., 2011), and stressed single element (e.g., gait speed or muscle strength) rather than overall muscle health (Alfaro-Acha et al., 2006; Duff et al., 2008). The interplay between muscle and brain has not been investigated from a comprehensive and holistic perspective.

In view of this, our study performs cluster analysis on cognitively intact participants from Health, Aging, and Body Composition (Health ABC) Study. We identified muscle health-related markers in the overall group, classified clusters which present similar features, and eventually examined their correlations with brain magnetic resonance imaging (MRI). We are interested in the variables that are distinct among clusters, and how they contribute to alterations in brain MRI indices. We look forward to determining muscle patterns that relate to higher risk of cognitive impairment, which may provide clinicians with clinical clues to detect at-risk patients.

Method

Study Population and Data Set

We utilized the data set of Healthy Brain Project from Health ABC Study, a longitudinal cohort started from 1997 to 1998 which aimed at investigating the association between change in body composition and strength in old age and health conditions. It enrolled 3,075 older adults (aged 70–79) who were generally healthy at baseline from Memphis, TN or Pittsburgh, PA. Healthy Brain Project was one of its substudies which provided two records of brain MRI exam, and we used the baseline data due to better data integrity. All participants provided written informed consent. This study was approved by the University of Tennessee, Memphis and the University of Pittsburgh Institutional Review Board. There were 314 participants who were eligible to undergo MRI exam. Considering the purpose of the present study is to figure out specific muscle patterns in the general population, we excluded participants who scored <77 (n = 14) in the Modified Mini-Mental State Examination. The cutoff point referred to previous literature which defined mild cognitive impairment and dementia (Bland & Newman, 2001; Ip et al., 2021). Subsequently, we excluded those with missing information of sarcopenia measurements, or serum profiles, or incomplete MRI data (n = 25), leaving 275 eligible participants to enter the analysis.

Study Design and Analytic Methods

To determine which variables enter the cluster analysis, we screened variables that are commonly mentioned pertaining to muscle health, which included body mass index (BMI), sarcopenia criteria (skeletal muscle mass index [SMI], handgrip strength, and gait speed), change of total body fat from Year 1 to 10, and serum markers (total cholesterol, fasting blood glucose, C-reactive protein [CRP], interleukin-6 [IL-6], and leptin). Participants were grouped into four according to total gray matter volume (GMV), a global neuroimaging marker (Anderson et al., 2012), which was chosen according to its importance in physical fitness (Erickson et al., 2014), cognition (Arvanitakis et al., 2016), and several neurovascular diseases (Hulshoff Pol et al., 2002; Rusinek et al., 1991). The lowest 25% named quartile (Q1), and the highest 25% named Q4 (Table 1). One-way analysis of variance (ANOVA) test was conducted, and variables which showed significant differences among quartiles of GMV were chosen. In addition, we decided to include the three main diagnostic criteria for sarcopenia irrespective of statistical significance in consideration of their non-negligible roles in age-related muscle health (Cruz-Jentoft et al., 2019). The flowchart of the study design is provided in Figure 1.

The Two-Step Cluster Analysis

For the present study, a two-step cluster analysis was used in consideration of its strength in handling large data sets and dealing with both continuous and categorical variables (Norušis, 2011). Two stages were involved. In the first step, the original raw data were grouped into preclusters based on a log-likelihood distance measure, forming a cluster feature tree. In the second step, the preclusters were divided into final clusters via a standard agglomerative hierarchical clustering algorithm. Determining the best number of clusters takes advantage of Schwarz's Bayesian inference criterion (BIC; Schwarz, 1978), which is an objective selection criteria that prevents arbitrariness of traditional clustering techniques. The one with the lowest BIC was considered the most appropriate. The validation of consistency of clustering used the Silhouette measure, with a value >0.00 suggesting goodness of the analysis.

To accentuate the differences among clusters, we performed the Z-normalization in each variable of interest. With this method, a raw × score is converted into a standard score which reveals its relationship to the mean value. Formula of calculating a z-score is as follows:

$$z = \frac{x - \mu}{\sigma}$$

where μ is the mean of the population, and σ is the standard deviation (SD) of the population. As a result, all variables of interest were rescaled to having a mean of zero and an SD of one.

Brain MRI Acquisition

MRI scanning was performed with a Siemens 12-channel head coil on a 3-Tesla Siemens Tim Trio MR scanner at the MR Research Center of the University of Pittsburgh. Details on processing protocols have been previously published (Rosano et al., 2012; Venkatraman et al., 2011). Two main parts of measurements were included: (1) macrostructural MRI markers (GMV, white matter hyperintensities volume [WMH], and cerebrospinal fluid volume) and (2) microstructural MRI global indices including gray matter integrity (relative peak-height MT ratio, and mean diffusivity) and white matter integrity (relative peak-height magnetisation transfer ratio and mean fractional anisotropy).

Results of MRI measurements were converted into standardized z-scores as mentioned in the previous section, and indices with scores significantly biased from zero were identified.

Covariates

Demographic data of Health ABC Study are collected annually since 1997–1998. Since the brain MRI data in the present study were obtained from Year 10 (2006–2007), the following variables adopted data from the same year to ensure

Table 1. Characteristic of Participants in Total Population, and in Quartile Group Based on GMV Analyzed by Analysis of Variance

Variable	Total population (N = 275)	Q1 total GMV (n = 67)	Q2 total GMV (n = 71)	Q3 total GMV (n = 67)	Q4 total GMV (n = 70)	p Value
Age (years)	82.84 ± 2.67	81.81 ± 1.94[a]	82.58 ± 2.47	82.93 ± 2.70	84.03 ± 3.01[a]	<.001
Gender						<.001
Male	42.9%	23.9%	38.0%	56.7%	52.9%	
Female	57.1%	76.1%	62.0%	43.3%	47.1%	
Body max index (kg/m^2)	27.27 ± 4.41	27.39 ± 4.52	27.46 ± 5.04	26.74 ± 3.75	27.47 ± 4.25	.732
Skeletal muscle mass index (kg/m^2)	7.31 ± 1.22	7.16 ± 1.12	7.34 ± 1.34	7.28 ± 1.05	7.51 ± 1.38	.503
Handgrip strength (kg)	30.73 ± 9.94	28.50 ± 7.92	32.04 ± 11.19	32.08 ± 9.35	30.26 ± 10.66	.117
Gait speed (m/s)	1.10 ± 0.23	1.14 ± 0.24[a]	1.09 ± 0.23	1.16 ± 0.20[b]	1.02 ± 0.24[a,b]	.004
Change of total body fat (g)	−1,030.58 ± 4,114.47	−1,063.99 ± 4,338.79	−813.19 ± 4,240.67	−1,629.11 ± 3,143.11[a]	−663.43 ± 4,552.65[a]	.046
Total cholesterol (mmol/L)	209.49 ± 36.86	209.86 ± 37.23	201.64 ± 3.45	212.26 ± 35.26	214.37 ± 40.56	.189
Serum fasting glucose (mg/dL)	101.05 ± 27.14	96.35 ± 23.61	97.45 ± 20.84	102.16 ± 25.46	108.34 ± 35.39	.062
Serum interleukin-6 (pg/mL)	2.15 ± 2.19	2.16 ± 2.38	2.26 ± 2.20	2.17 ± 2.04	1.98 ± 2.17	.901
Serum C-reactive protein (mg/L)	2.39 ± 4.24	3.38 ± 7.55	2.33 ± 2.67	1.93 ± 2.01	1.96 ± 2.09	.167
Serum leptin (ng/mL)	13.63 ± 10.51	16.17 ± 11.25[a]	14.99 ± 11.64	11.29 ± 8.87[a]	12.10 ± 9.45	.021
Neuroimaging markers						
Total brain volume (cm^3)	1,382.50 ± 142.83	1,343.50 ± 132.96[a]	1,362.44 ± 156.38	1,412.34 ± 127.89[a]	1,411.63 ± 141.51	.006
GMV (cm^3)	527.81 ± 54.05	507.17 ± 54.19[a]	525.46 ± 54.90[b]	534.33 ± 47.52	545.34 ± 52.83[a,b]	<.001
White matter volume (cm^3)	450.46 ± 58.46	447.49 ± 60.17	444.81 ± 65.11	454.73 ± 46.98	454.96 ± 62.28	.660
Intracranial volume (cm^3)	1,887.63 ± 199.81	1,853.85 ± 188.13	1,885.32 ± 228.56	1,906.07 ± 165.27	1,905.12 ± 209.30	.391

Notes: GMV = gray matter volume; Q = quartile. Different superscript letters indicate statistically significant differences between quartile groups in the same horizontal row using post hoc comparisons (Tukey test). For instance, in the "gait speed" variable, the superscript "a" represents there is a significant difference between Q1 and Q4, while the superscript "b" represents there is a significant difference between Q3 and Q4. Superscript letters in other rows stand for the same comparisons in that certain variable.

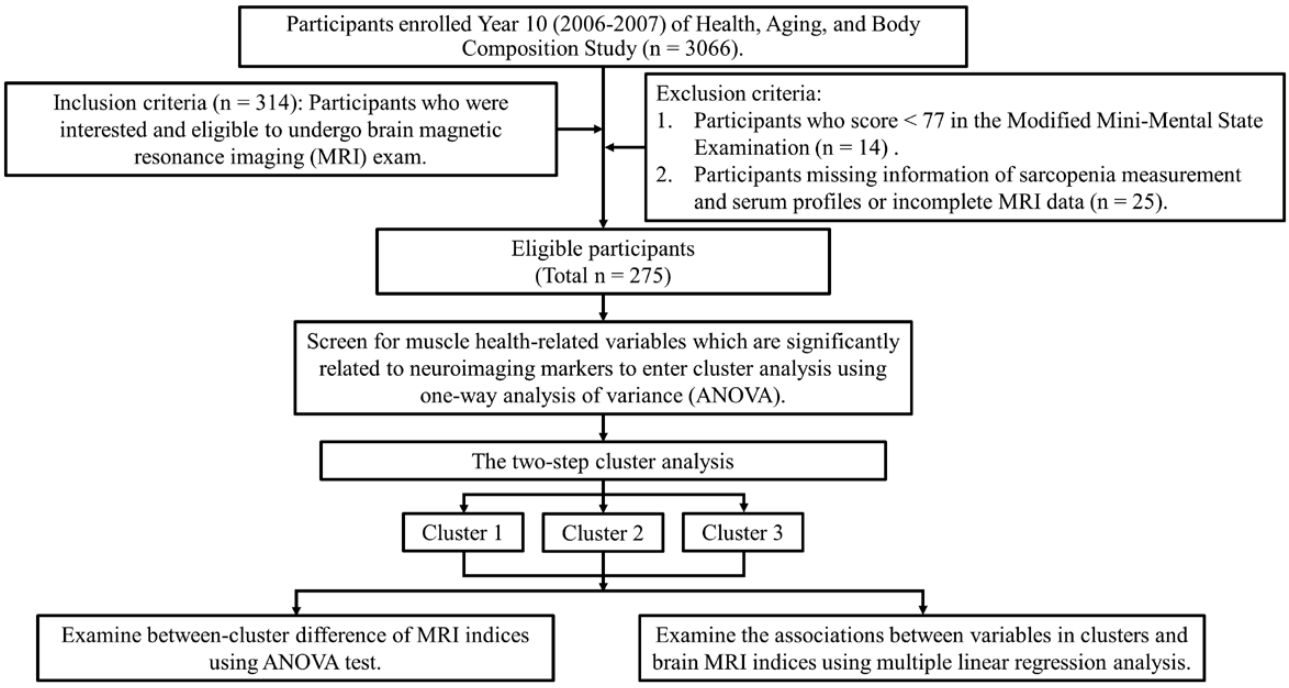


Figure 1. Flow chart of the study population and study design.

consistency. Formula of BMI is weight in kilograms divided by height in meters squared. SMI is calculated by dividing the limb skeletal muscle mass (kg) by the square of the height (m^2), where the limb skeletal muscle mass is the sum of fat-free mass of both arms and legs measured by whole-body dual-energy X-ray absorptiometry (DXA; Hologic QDR 4500A, software version 8.21, Hologic, Waltham, MA). Handgrip strength was measured using an isometric dynamometer (Jaymar; JLW Instruments, Chicago, Illinois). Gait speed (m/s) was determined by the time duration in 3-, 4-, or 6-m walk test. Change of total body fat (g) subtracts total body fat (assessed by the same DXA mentioned in the above content) of Year 10 from Year 1 to present the alteration between the observed year and baseline. Total serum cholesterol was measured using an enzymatic method described previously (Allain et al., 1974) with Olympus AU400 analyzer (Hamburg, Germany). Serum fasting glucose was measured by automated glucose oxidase reaction (YSI 2300 Glucose Analyzer; Yellow Springs, OH). IL-6 was analyzed with commercial enzyme-linked immunosorbent assay (ELISA) kits (R&D Systems, Minneapolis, MN). Serum CRP levels were also measured using ELISA on the basis of purified protein and polyclonal anti-CRP antibodies (Calbiochem, San Diego, CA). Serum leptin level was measured using the Linco Sensitive Human Kit (catalog no. SHL-81K; St Charles, MO).

Statistical Analysis

ANOVA test was used to (1) determine variables that were significantly associated brain MRI indices to enter the cluster analysis and (2) examine between-cluster difference of MRI indices. We also performed the post hoc comparison tests using the Tukey method to examine which pair of means differ significantly. Multiple linear regression analysis was used to explain the relationship between a cluster (as well as the variables within) and brain MRI indices. For all analyses, a p value < .05 was considered statistically significant. Data were processed with SPSS (IBM SPSS Statistics for Windows, Version 22.0; IBM Corp., Armonk, NY).

Results

Characteristics of the Population

The average age of the total population was 82.84 ± 2.67 years old (Table 1). Male accounted for 42.9% of the participants. According to the revised consensus on sarcopenia diagnosis proposed by European Working Group on Sarcopenia in Older People in 2019 (Cruz-Jentoft et al., 2019), the average value of SMI, handgrip strength, and gait speed did not meet the criteria of sarcopenia. The mean value of SMI was 7.31 ± 1.22 kg/m^2, which was higher than either the cutoff point of male (<7 kg/m^2) or female (<5.5 kg/m^2); the mean value of handgrip strength was 30.73 ± 9.94 kg, which was also higher than either the cutoff point of male (<27 kg) or female (<16 kg); the mean value of gait speed was 1.10 ± 0.23 m/s, which was higher than the cutoff point (<0.8 m/s). These suggest that the study population represents general healthy old adults that have not developed sarcopenia. Other serum markers were also within normal limits: mean value of total cholesterol was 209.49 ± 36.86 mmol/L, fasting glucose was 101.05 ± 27.14 mg/dL, IL-6 was 2.15 ± 2.19 pg/mL, CRP was 2.39 ± 4.24 mg/L, and leptin was 13.63 ± 10.51 ng/mL.

Selection of Muscle Health-Related Variables for Cluster Analysis

Before entering cluster analysis, we first determined several muscle health-related markers that were significantly related to total GMV. Variables that showed significant difference between quartile groups were age (p < .001), gait speed (p = .004), change of total body fat (p = .046), and serum leptin level (p = .021). In addition, SMI and handgrip strength were included despite nonsignificant p values due to their nonnegligible roles in sarcopenia diagnosis (Cruz-Jentoft et al., 2019).

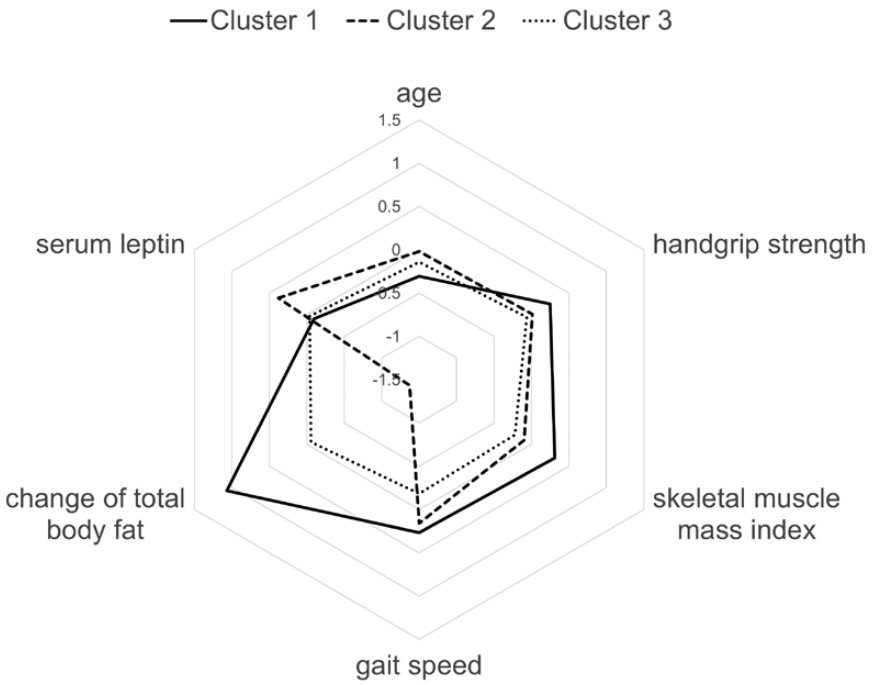


Figure 2. A radar graph displaying muscle health characteristics of the three clusters. Each spike represented one of the six muscle health-related markers. The mean *z*-scores of the six variables were presented by the data length of a spike.

Characteristics of Each Cluster

Three clusters were produced using the two-step clustering method, and their characteristics were shown in Figure 2. The mean *z*-scores of the six variables were presented by the data length of a spike. Cluster 1 was characterized by the highest value of change of total body fat from Year 1 to 10; Cluster 2 was characterized by the highest value of serum leptin level; and Cluster 3 was characterized by the lowest value of the three diagnostic criteria of sarcopenia, namely handgrip strength, SMI, and gait speed. According to the features of the three clusters, we distinguished them in brief as follows: Cluster 1 was the relative obese group, Cluster 2 was the leptin-resistant group, and Cluster 3 was the sarcopenia group.

Association Between Cluster and Brain MRI Indices

All global and regional MRI indices in the Healthy Brain Project and their relationship with muscle health-related clusters were examined using multiple linear regression analysis. As shown in Table 2, seven MRI indices revealed significant associations with clusters. Cerebellum GMV (total significance $p < .001$) was correlated with handgrip strength (standardized β-coefficient = 0.203, $p = .025$). Superior frontal gyrus GMV (total significance $p = .019$) was positively correlated with gait speed (standardized β-coefficient = 0.128, $p = .045$) and inversely with serum leptin level (standardized β-coefficient = −0.181, $p = .013$). Inferior frontal gyrus GMV (total significance $p = .003$) and posterior cingulum GMV (total significance $p = .021$) were both inversly correlated with serum leptin level (standardized β-coefficient = −0.174 and −0.147, $p = .016$ and .042, respectively). Vermis GMV (total significance $p = .045$) was positively correlated with age (standardized β-coefficient = 0.169, $p = .011$) and inversely correlated with change of body fat (standardized β-coefficient = 0.112, $p = .044$). Gyrus rectus gray matter density (GMD; total significance $p < .001$) and temporal pole GMD (total significance $p < .001$) were both positively correlated with age (standardized β-coefficient = 0.211 and 0.205, $p = .002$ and .003, respectively) and inversely with gait speed (standardized β-coefficient = −0.146 and −0.164, $p = .042$ and .021, respectively). Gyrus rectus GMD also had inverse relationship with serum leptin level (standardized β-coefficient = −0.148, $p = .047$), and temporal pole GMD also had positive relationship with handgrip strength (standardized β-coefficient = 0.188, $p = .046$). To sum up, serum leptin level and gait speed were the two variables that presented significant relationships with most MRI indices.

Other important brain MRI indices that were frequently mentioned in previous studies pertaining muscle health, though they did not reveal significant correlations in the present study, are listed below for reference. Anterioir thalamic radiation WMH (total significance $p = .267$), inferior fronto-occipital fasciculus WMH (total significance $p = .695$), frontal corpus callosum WMH (total significance $p = .168$), hippocampus GMV (total significance $p = .132$), and amygdala GMV (total significance $p = .804$).

Between-Cluster Difference of Brain MRI Indices

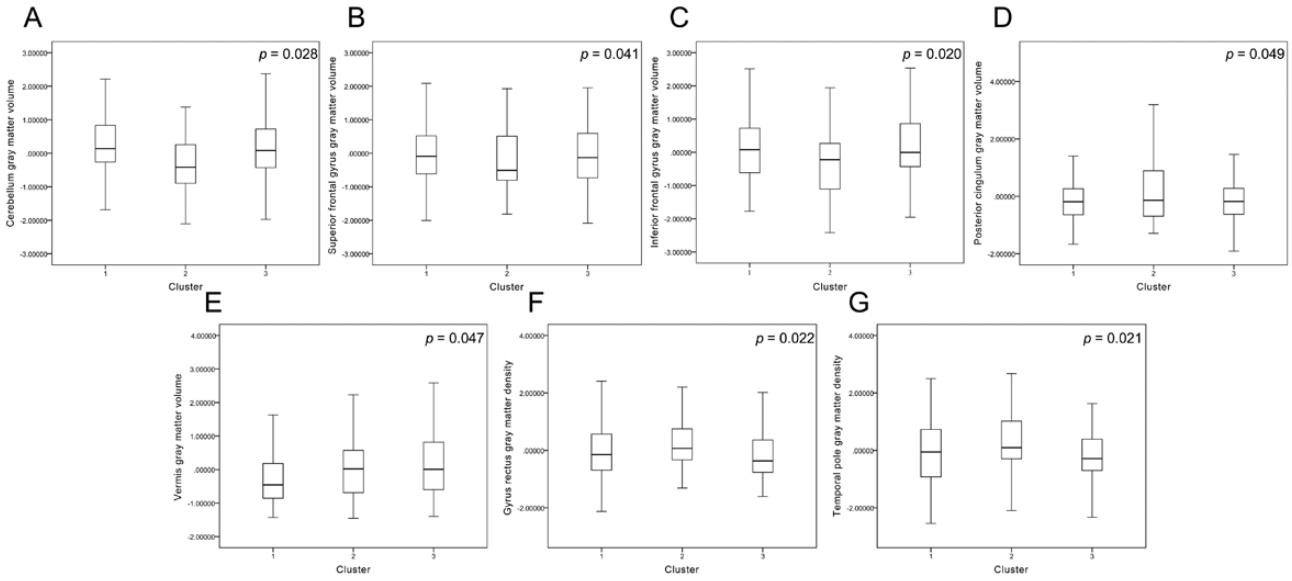
The between-cluster differences of mean *z*-scores of the seven MRI indices were shown in Figure 3. In cerebellum GMV, superior frontal gyrus GMV, inferior frontal gyrus GMV and posterior cingulum GMV (Figure 3A–D), Cluster 2 had the lowest mean *z*-scores, while Cluster 1 had the highest. In vermis GMV (Figure 3E), Cluster 1 had the lowest mean *z*-score, while Cluster 2 had the highest. In gyrus rectus GMD and temporal pole GMD (Figure 3F and G), Cluster 3 had the lowest mean *z*-score, while Cluster 2 had the highest. Taken together, Cluster 2, the leptin-resistant group, had most

Table 2. Multiple Linear Regression Model of the Association Between Sarcopenia-Related Markers in Clusters and Different MRI Indices

Sarcopenia-related markers in clusters	*B*	*SE*	β	*p*	R^2	Adjusted R^2
Cerebellum gray matter volume				<.001a	0.107	0.083
Age	−285.75	152.90	−0.120	.063		
Handgrip strength	136.38	60.48	0.203	.025		
Skeletal muscle mass index	−161.93	443.00	−0.031	.715		
Gait speed	3,662.09	1,886.83	0.131	.053		
Change of total body fat	0.06	0.10	0.041	.530		
Serum leptin	−45.54	42.41	−0.075	.284		
Superior frontal gyrus gray matter volume				.019[a]	0.403	0.329
Age	4.08	16.00	0.017	.799		
Handgrip strength	1.55	6.33	0.023	.807		
Skeletal muscle mass index	−4.60	46.36	−0.009	.921		
Gait speed	366.46	197.44	0.128	.045		
Change of total body fat	−0.01	0.01	−0.039	.560		
Serum leptin	−11.14	4.44	−0.181	.013		
Inferior frontal gyrus gray matter volume				.003[a]	0.280	0.156
Age	−0.18	23.31	0.000	.994		
Handgrip strength	18.04	9.22	0.179	.052		
Skeletal muscle mass index	−120.67	67.53	−0.155	.075		
Gait speed	246.99	287.61	0.059	.391		
Change of total body fat	0.01	0.02	0.024	.718		
Serum leptin	−15.74	6.46	−0.174	.016		
Posterior cingulum gray matter volume				.021[a]	0.362	0.238
Age	10.28	9.74	0.069	.292		
Handgrip strength	3.26	3.85	0.078	.399		
Skeletal muscle mass index	15.01	28.22	0.047	.595		
Gait speed	143.99	120.21	0.083	.232		
Change of total body fat	−0.01	0.01	−0.053	.426		
Serum leptin	−5.53	2.70	−0.147	.042		
Vermis gray matter volume				.045[a]	0.404	0.209
Age	−37.66	14.71	0.169	.011		
Handgrip strength	−7.49	5.82	−0.119	.199		
Skeletal muscle mass index	30.18	42.62	0.708	.480		
Gait speed	−229.61	181.51	−0.088	.207		
Change of total body fat	−0.02	0.01	−0.112	.044		
Serum leptin	−0.94	4.08	−0.017	.818		
Gyrus rectus gray matter density (portion of the inferior frontal lob)				<.001[a]	0.114	0.088
Age	1.36E-5	4E-6	0.211	.002		
Handgrip strength	2.34E-6	2E-6	0.135	.154		
Skeletal muscle mass index	4.15E-6	1.2E-6	0.031	.734		
Gait speed	−1.07E-4	5.2E-6	−0.146	.042		
Change of total body fat	4.53E-11	2.81E-9	0.001	.987		
Serum leptin	−2.49E-6	1E-6	−0.148	.047		
Temporal pole gray matter density				<.001[a]	0.134	0.108
Age	1.73E-5	6E-6	0.205	.003		
Handgrip strength	4.26E-6	2E-6	0.188	.046		
Skeletal muscle mass index	1.37E-5	1.6E-5	0.077	.388		
Gait speed	−1.57E-4	6.8E-5	−0.164	.021		
Change of total body fat	−5.03E-9	3.64E-9	−0.094	.169		
Serum leptin	−1.85E-6	2E-6	−0.084	.253		

Notes: *B* = unstandardized coefficient; MRI = magnetic resonance imaging; *SE* = standard error; β = standardized coefficient; R^2 = coefficient of determination.
[a]*p* Value of *F*-test representing overall significance of each model.

Figure 3. The between-cluster differences of mean *z*-scores of the seven MRI indices using one-way ANOVA test. (A) Cerebellum gray matter volume.



(B) Superior frontal gyrus gray matter volume. (C) Inferior frontal gyrus gray matter volume. (D) Posterior cingulum gray matter volume. (E) Vermis gray matter volume. (F) Gyrus rectus gray matter density. (G) Temporal pole gray matter density. The error bars represent the standard errors of the mean. A p value < .05 indicates that the differences of *z*-scores between clusters are statistically significant.

degree of reduction in GMV, whereas Cluster 3, the sarcopenia group, had most degree of reduction in GMD.

Subgroup Analyses by Gender

To further examine the differences between gender, subgroup analyses stratified by gender were conducted. In the analysis of association between cluster and brain MRI indices (Supplementary Table 1), statistical significance was shown in some subgroups, but lacked in others. In male, gyrus rectus GMD (total significance p = .029) and temporal pole GMD (total significance p = .004) were both positively correlated with age (standardized β-coefficient = 0.310 and 0.232, p = .005 and .030, respectively), and temporal pole GMD also had negative relationship with gait speed (standardized β-coefficient = −0.227, p = .034). In female, inferior frontal gyrus GMV (total significance p = .025) was inversely correlated with SMI (standardized β-coefficient = −0.295, p = .003), and vermis GMV (total significance p = .042) was positively correlated with age (standardized β-coefficient = 0.208, p = 0.018). In the analysis of between-cluster difference (Supplementary Figure 1), the trends in gender subgroups were mostly the same as the ones in the total population, though some subgroups failed to show statistical significance. Cluster 2 still had the lowest mean *z*-scores in both gender in cerebellum GMV, superior frontal gyrus GMV, and inferior frontal gyrus GMV (Supplementary Figure 1A–F); Cluster 3 still had the lowest mean *z*-scores in both gender in gyrus rectus GMD and temporal pole GMD (Supplementary Figure 1K–N); and Cluster 1 still had the lowest mean *z*-score in both gender in vermis GMV (Supplementary Figure 1I and J). Only in posterior cingulum GMV showed different results, where Cluster 3 and Cluster 1 had the lowest mean *z*-scores in men and women, respectively (Supplementary Figure 1G and H). Taken together, the between-cluster differences among seven MRI indices were still similar when stratifying the population by gender. The association between in-cluster variables and MRI indices was significant in some pairs, but absent in others.

Discussion

The present study demonstrated the association between muscle health cluster and several brain MRI indices, namely GMV changes in cerebellum, superior frontal gyrus, inferior frontal gyrus, posterior cingulum, vermis, and GMD changes in gyrus rectus and temporal pole. Brain MRI indices showing significant relationship with the overall cluster illustrated their correlation with general muscle health, and p value of individual variable (Table 2) explained specific contribution. To the best of our knowledge, we are the first to investigate the correlation between neuroimaging and general muscle health, and compare differences between three muscle health patterns classified by cluster analysis.

Normal brain aging exhibits neuroimaging changes including loss of volume and structural integrity, but studies confirmed there are regional differences (Caserta et al., 2009). Regions regulating cognition particularly showed alterations (e.g., the frontal lobe), while others showed modest changes (e.g., occipital and parietal lobe; DeCarli et al., 2005). Accordingly, changes in other regions may indicate disease process, and specific MRI indices correspond to different diseases. Muscle disorders are no exception. The association between several muscle health markers and brain structure changes have been documented in previous studies, but little has been delineated the different muscle health patterns and brain MRI indices.

Among the brain MRI indices, the reduction of GMV in cerebellum has been most widely discussed. A longitudinal study conducted in I-Lan County, Taiwan, in 2011–2012 concluded that prefrail and frail participants revealed reduced GMV in cerebellum, especially in vermis part, which are

both regions that revealed significant association in our study (Chen et al., 2015). Another study found correlation between low gait speed (<1.0 m/s) and reduced GMV in cerebellum in community-dwelling older Japanese (Nishita et al., 2019). The fact that cerebellum governs motor and cognitive function has been well-established (Diamond, 2000), and accumulating evidence supports that morphological changes in neuroimaging implicate decline in these functions (Bernard & Seidler, 2014). Our study revealed muscle health clusters associated with cerebellum GMV suggested that cerebellum not only regulate motor "functions," but may also correlate to muscle mass and fat distribution.

The connection between superior frontal gyrus and muscle is inferable as the supplementary motor area locates within its medial surface, and is responsible for planning complex movements (Roland et al., 1980). A longitudinal study demonstrated lower GMD in superior frontal gyrus in participants experiencing history of falling (Makizako et al., 2013), implying structural changes in this region correlate to declined balance and muscle control. Our study proposed consistent findings that reduced GMV in superior frontal gyrus is associated with impaired muscle health. Compared with superior frontal gyrus, the inferior frontal gyrus primarily involves in language procession and speech (Greenlee et al., 2007), and therefore the connection with muscle was mostly identified in laryngeal and tongue muscles (Deletis et al., 2014). Future studies are warranted to investigate its relationship with general muscle health.

Roles of the cingulum are heterogenous (Vogt et al., 1992). A specific part relating to motor function was first identified in monkeys, which is a group of premotor regions termed cingulate motor area (CMA; Strick et al., 1998). CMA locates in the cingulate sulcus, and therefore spans from the anterior to the posterior part of cingulum. A case with posterior cingulate infarction was reported to present astasia (Satow et al., 2014), suggesting damage to this area led to motor dysfunction. The link between decreased GMV in posterior cingulum and impaired muscle health in our study may possibly be attributed to the impact on CMA.

GMV of cerebellar vermis, the narrow midline zone of cerebellum, has been found to negatively associate with age (Raz et al., 1998) and psychiatric disorders (Mills et al., 2005). A study reported its correlation with frailty, but limited to only two components, slowness (low gait speed) and weakness (low grip strength; Chen et al., 2015). In children, decreased vermis volume was documented to associate with impaired gross and motor skills (Bolduc et al., 2012). The role of vermis is the regulation of axial motor control, eye movements, and affect and emotion (Sacchetti et al., 2009; Schmahmann et al., 2007). Malformation of this region results in diseases characterized by decreased muscle tone and movement abnormalities, such as Joubert syndrome and Dandy–Walker malformation (Maria et al., 1999; Peters et al., 2002). These motor deficits explained the association between reduced GMV in cerebellar vermis and muscle health in our study, and further research is needed to clarify the underlying mechanism.

Comparatively speaking, functional roles of gyrus rectus and temporal pole are less referred to muscle health or motor skills. The temporal pole involves in high-level cognitive processes (Herlin et al., 2021), whereas function of gyrus rectus remains unclear but is widely discussed in neurosurgery for its proximity to the limbic system (Joo et al., 2016). Their associations with muscle health pattern in our study implied that there may be undiscovered regulatory mechanisms toward muscle and motor in these regions.

The three muscle health clusters in our study had distinct features but also shared some properties, and their differences among brain MRI indices may elucidate their characteristics in neuroscience. Cluster 2, the leptin-resistant group, had lowest *z*-scores in four MRI indices. Leptin receptors have been detected in extrahypothalamic sites like cerebellum, and scientists proposed that leptin in these locations mediate functions other than body weight homeostasis (Elmquist et al., 1998; Savioz et al., 1997). Plausible reasons for the relatively smaller GMV in leptin-resistant group may be attributed to the dysfunction of leptin receptors in atrophied brain sites. Another reason could be the loss of neuroprotective effect of leptin, which was demonstrated to be limited to nonobese population (Lieb et al., 2009), addressing that increased leptin resistance loses benefits of neuroprotection. Cluster 3, the sarcopenia group, also revealed lowest *z*-scores in two MRI indices. The pathophysiology of sarcopenia has been proposed to be not only muscular but also neurogenic (Kwan, 2013), and the shared mechanisms in muscle and cognition decline such as oxidative stress, mitochondrial dysfunction, and altered hormone levels explained the intimate relationship between the two (Kwan, 2013). Collectively, results in our study suggested that the leptin-resistant and sarcopenia patterns were at higher risk of alterations in brain MRI indices.

Pertaining gender issues, the prevalence of sarcopenia has been noted to be higher in females (Yang et al., 2019). Nevertheless, our study revealed similar trends of between-cluster difference of brain MRI indices in both gender and the total population, implying that the association between muscle patterns and MRI indices is independent of gender. Despite the disparities in muscle structure, strength, and physical performance between men and women, neuroimaging alterations authentically exist in both with impaired muscle functions.

Some limitations in this study need to be addressed. First, the muscle health markers in our study are limited to the data provided in the Health ABC Study. Variables such as creatine kinase, myoglobin, or troponin I may also deliver vital information, which should be taken into consideration in future studies to establish more representative models. Secondly, the investigation of association between clusters and brain MRI indices was an observational study, and thus the causal relationship cannot be determined. Moreover, the complex underlying mechanisms are yet to be addressed, and more research is needed.

Conclusion

With the use of cluster analysis, we were able to group and identify muscle health patterns that relate to specific MRI indices, and demonstrated the association between muscle health and alterations in GMV in cerebellum, superior frontal gyrus, inferior frontal gyrus, posterior cingulum, vermis, and GMD in gyrus rectus and temporal pole. The leptin-resistant group had most degree of reduction in GMV, whereas the sarcopenia group had most degree of reduction in GMD. Clinicians should raise awareness on the brain MRI findings in clinical settings. Because these patients mostly had central nervous system conditions or other critical illnesses, the risk of sarcopenia as a comorbidity will substantially affect the prognosis and medical care.

Supplementary Material

Supplementary data are available at *Innovation in Aging* online.

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Conflict of Interest

None declared.

Author Contributions

S.-E. Wu: Roles/writing—original draft; formal analysis; visualization. W.-L. Chen: Conceptualization; data curation; investigation; methodology; project administration; resources; software; supervision; validation; writing—review and editing.

Data Availability

The data that support the findings of this study are available from Health ABC but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are however available from the authors upon reasonable request and with permission of Health ABC.

Ethics Approval and Consent to Participate

Health, Aging, and Body Composition (Health ABC) Study is a National Institute of Health-sponsored cohort study. All participants provided written informed consent. All protocols were approved by the institutional review board at each study site (University of Tennessee, Memphis, TN, and the University of Pittsburgh, Pittsburgh, PA).

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