



Potential Imaging Biomarkers of Cognitive Frailty

Jaesub Park^{1,2}, Woo Jung Kim^{2,3}

¹Department of Psychiatry, National Health Insurance Service Ilsan Hospital, Goyang, Korea

²Institute of Behavioral Science in Medicine, Yonsei University College of Medicine, Seoul, Korea

³Department of Psychiatry, Yongin Severance Hospital, Yonsei University College of Medicine, Yongin, Korea

Corresponding Author:

Woo Jung Kim, MD, PhD

Department of Psychiatry, Yongin
Severance Hospital, Yonsei University
College of Medicine, 363,
Dongbaekjukjeon-daero, Giheung-gu,
Yongin 16995, Korea

E-mail: woojungkim@yuhs.ac

ORCID:

<https://orcid.org/0000-0002-4963-4819>

Received: November 22, 2022

Revised: December 9, 2022

Accepted: December 15, 2022

Cognitive frailty (CF) is a state of impairment in both cognitive and motor functions. The concept of CF has been developed in several ways. However, it is difficult to identify consistent neuroimaging findings according to the application of the operational definition of different frailty models within the same concept, as well as the diversity of the concept itself of CF. This study aimed to review neuroimaging studies of CF and to determine suitable imaging biomarkers of CF. White matter abnormalities (e.g., white matter hyperintensity and microbleeds) seem likely to be considered imaging biomarkers of CF. The volume of the cerebral/cerebellar cortex and that of the subcortical nuclei are also candidates of imaging biomarkers of CF. These imaging biomarkers are expected to be more useful in discriminating the need for screening CF in visitors of clinics or health examination centers than in detecting the presence of CF in community-dwelling older adults.

Key Words: Cognitive frailty, Motoric cognitive risk syndrome, Physio-cognitive decline syndrome, Imaging biomarker, Magnetic resonance imaging

INTRODUCTION

Frailty is a dynamic intermediate condition that lies between pathological aging and adverse health outcomes such as disability or death.^{1,2)} The concept of frailty can be divided into physical, cognitive, and psychosocial aspects.³⁻⁵⁾ In April 2013, the International Academy of Nutrition and Aging (IANA) and the International Association of Gerontology and Geriatrics (IAGG) agreed on the definition of “cognitive frailty” (CF), which is a simultaneous state of both mild cognitive impairment (MCI) and physical frailty.⁶⁾ CF can be a precursor to degenerative neurocognitive disorders, and physical frailty can accelerate cognitive impairment as well as increase the risk of MCI and dementia.^{7,8)}

Initially, the concept of frailty was introduced to provide a target for primary and secondary prevention of disability in older adults. From this point of view, to detect the presence of CF, the use of cost-effective and time-saving screening tools (e.g., several frailty scales and gait speed tests) is also recommended. In addition, labo-

ratory or imaging tests usually conducted in clinics, hospitals, or medical examination centers may help find a target for preventing adverse health outcomes, that is, for intervening the development of CF. Therefore, this study aimed to review previous studies related to imaging biomarkers of CF.

CONCEPTS OF COGNITIVE FRAILTY DEFINED FROM VARIOUS PERSPECTIVES

CF was first introduced for the purpose of indicating cognitive vulnerability in patients with MCI who are more likely to progress towards dementia due to exposure to vascular risk factors.^{9,10)} According to the IANA/IAGG definition, cognitive impairment shown in CF is characterized by potentially reversible cognitive impairment, excluding the conditions in Alzheimer disease and other types of dementia—i.e., clinical dementia rating (CDR) score = 0.5.⁶⁾ After the introduction of the first operational definition of CF, even though the detailed definitions were different

from each other, the prevalence of CF in community-dwelling older adults without neurodegenerative disease was reported to be 1.0%–1.8%.¹¹⁾ The prevalence of CF has been reported to increase dramatically in clinical settings, ranging from 10.7 to 39.7%.¹¹⁾ Frailty is a parameter developed for the purpose of promoting the health in older adults. Based on the definitions developed thus far for CF, it is expected that its utility in the clinic will be higher than that in the community.

Ruan et al.¹²⁾ proposed two subtypes that further extended the concept of CF: potentially reversible and reversible CF. The potentially reversible CF is expressed as MCI (CDR score = 0.5) and the reversible CF is expressed as subjective cognitive decline (SCD) and/or positivity in fluid or imaging biomarkers of amyloid accumulation and neurodegeneration. Concurrently, Ruan et al.¹²⁾ extended the concept of both (potentially reversible and reversible) CF to cases with pre-physical frailty as well as physical frailty (Fig. 1). SCD is characterized by a subjective experience of impaired memory in the absence of objective cognitive deficits (CDR score = 0),¹³⁾ and is a concept known to establish an early target for dementia treatment. Many clinical trials for the treatment of Alzheimer disease fail successively, and SCD can be an important prevention target of brain diseases in older adults.

Motoric cognitive risk syndrome (MCRS) is defined as the co-existence of cognitive impairment and slow gait in older adults without dementia (Fig. 1).¹⁴⁾ It is known to be a predictor of both the development of Alzheimer disease and vascular dementia, the two most common causes of dementia,^{14,15)} and it is also used to

predict cardiovascular disease and the associated risk factors.^{16,17)} In order to avoid confusion between the concepts of MCRS and CF, which is constantly updated, the concept of physio-cognitive decline syndrome (PCDS) was proposed by Chen and Arai¹⁸⁾ at the 5th Asian Conference on Frailty and Sarcopenia in 2019. PCDS is defined as physical frailty manifested as slowness and/or weakness with impairment of any cognitive domain with at least 1.5 standard deviations below the mean for the age-, sex-, and education-matched norms (Fig. 1). The following paragraphs mainly contain reviews of magnetic resonance imaging (MRI) studies in CF and similar contexts¹⁹⁾ such as MCRS or PCDS.

White Matter Abnormality—An Imaging Biomarker Candidate of Cognitive Frailty

The number of studies investigating cerebral small vessel disease (CSVD) as a cause of neurodegenerative disease continues to increase.²⁰⁾ White matter hyperintensity (WMH) on T2-fluid-attenuated inversion recovery (FLAIR) sequence of brain MRI is one of the characteristic imaging markers of CSVD. Although WMH is prevalent in older adults and may be associated with other neuropathologies, it is often associated with the development of sub-clinical cognitive impairment.²¹⁾ When the outcome is set to dementia, a systematic review and meta-analysis study of more than 11,000 participants²²⁾ found that among the MRI markers of CSVD, only extensive WMH was significantly associated with incident dementia, and neither lacunes nor cerebral microbleeds were associated

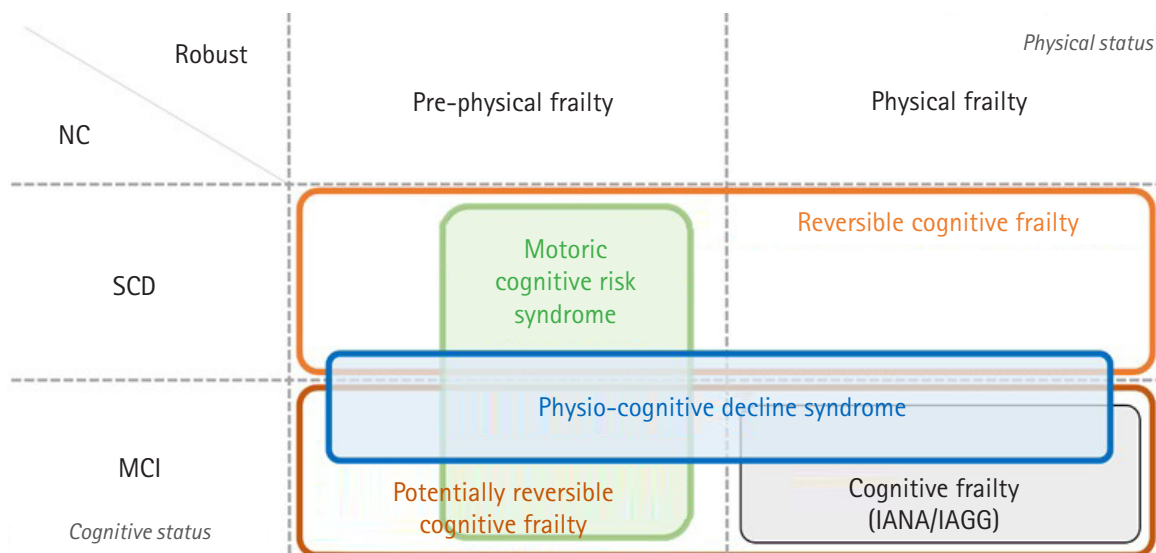


Fig. 1. Graphical conceptualization of different definitions of cognitive frailty. NC, normal cognition; SCD, subjective cognitive decline; MCI, mild cognitive impairment; IANA/IAGG, International Academy of Nutrition and Aging and International Association of Gerontology and Geriatrics. Adapted from Sugimoto et al.¹⁹⁾ with permission of the Japan Geriatrics Society.

with it.

Although CF was not defined separately, the relationship between the severity of WMH and frailty defined according to the different scales of the frailty index has already been reported.²³⁻²⁵⁾ More recently, Sugimoto et al.²⁶⁾ showed that CF was associated with a significantly higher WMH volume (11.0 ± 13.2 mL with CF vs. 5.8 ± 7.7 mL without CF; $p < 0.001$) and WMH volume divided by parenchymal volume (coefficient = 0.57, standard error = 0.13; $p < 0.001$) in 333 memory clinic patients. A similar finding was reproduced in a cross-sectional study conducted in China.²⁷⁾

In the MCRS, which overlaps with CF to some extent, a conflicting result was found. A study in the clinical setting in India revealed that the WMH burden was not related with MCRS.²⁸⁾ Instead, frontal lacunar infarction was found to be associated with MCRS in Indian older adults, contributing to slow gait and impaired memory.²⁸⁾ In contrast, in a community-based study with a larger number of participants, the relationship between MCRS and WMH volume was found to be significant.²⁹⁾ Interestingly, in the same study, the MCRS group showed lower volume in the frontal and parietal lobes as well as greater white matter abnormalities, whereas the MCI group showed volume loss across the brain regions susceptible to Alzheimer disease pathology (i.e., hippocampus, parahippocampal gyrus, entorhinal cortex, precuneus, and inferior parietal lobules).²⁹⁾

A brain MRI study in Japanese community-dwelling older adults showed more lacunar infarction and cerebral microbleeds with a severe WMH degree in the CF group.³⁰⁾ In this study, the CF group had medial temporal lobe atrophy compared with that of the normal controls, but there was no difference in the degree of medial temporal lobe atrophy between the CF and MCI groups without physical frailty. An Australian memory clinic cohort study³¹⁾ revealed that there was a significant difference in WMH severity but no difference in medial temporal lobe atrophy between patients with frailty, defined as a frailty index > 0.25 , and participants without frailty.

According to the results of a longitudinal study of 400 individuals with asymptomatic CSVD, mobility frailty, defined as having weaker hand-grip strength and/or slower walking speed, was significantly found to be associated with incident dementia (odds ratio = 4.8; 95% confidence interval, 1.5–14.8; $p = 0.007$) in the follow-up duration of an average of 5.7 years.³²⁾ As such, when identifying an imaging biomarker for CF, further studies are needed to classify imaging findings regarding not only proper CF but also each component of physical frailty.

Gray Matter (Cortical) and Subnuclei Volume—Another Imaging Biomarker Candidate of Cognitive Frailty

Osawa et al.³³⁾ published the first longitudinal study examining the correlation between brain volume and muscle strength changes in older adults. The authors found a decreased knee extensor strength in older adults with atrophy of the frontal, temporal, and occipital gray matter. This finding may provide evidence for the potential contribution of specific regional brain atrophy affecting age-related changes in muscle strength. In addition, a multicohort (two cohorts in the United States and one in France) MRI study revealed that MCRS is associated with cortical atrophy in brain regions involving the control aspects of gait, such as motor planning and modulation (i.e., supplementary motor, insular, and prefrontal cortex), rather than that of the motor aspects of gait, such as gait initiation and maintenance (i.e., cerebellar, temporal, and parahippocampal cortex).³⁴⁾

The severity of frailty was associated with the degree of cortical and subcortical atrophy, especially in the frontal and temporal cortex and peri-insular subcortical area, in a study of most patients diagnosed with MCI or dementia.³⁵⁾

Although the study was conducted with a relatively small number of participants (52 participants), there is a unique study of the hippocampus on brain MRI divided into subregions between older adults with and without CF.³⁶⁾ There was a clear decrease in the volume of hippocampal subregions, including the bilateral presubiculum, left parasubiculum, and right cornu ammonis subfield 1 (CA1). The presubiculum and parasubiculum play important roles in cognitive processing and visuospatial function, and their volume has been found to decrease in some diseases, such as diabetes mellitus, Parkinson disease, and Alzheimer disease.³⁷⁻³⁹⁾ CA1 is known to act as a subiculum-hippocampal interface and is functionally related to attention. Patients with Parkinson disease with cognitive impairment showed significantly lower right CA1 volume than those with cognitively normal Parkinson disease.⁴⁰⁾

In another study of the same participants,⁴¹⁾ significant volume reduction was found in the bilateral thalami, left caudate, right pallidum, and right accumbens in older adults with CF. In addition, the volume of the bilateral thalami, caudate, pallidum, and right accumbens was negatively correlated with the frailty index. Among them, the volume of regions other than that of the caudate was positively correlated with the Montreal Cognitive Assessment (MoCA) score. A previous study showed that the caudate nucleus contributed to body and extremity posture, as well as the accuracy and speed of directed movements.⁴²⁾ These findings may explain why changes in the volume of the caudate nucleus are related to

the frailty index and not cognitive impairment.

In an earlier study, Chen et al.⁴³⁾ proved that weakness, slowness, and low activity in physical frailty components were associated with atrophy of cerebellar gray matter, unlike exhaustion and body weight loss. Thereafter, in the I-Lan Longitudinal Aging Study (ILAS), among 1,196 participants with a mean age of 62 ± 9 years, 190 (15.9%) individuals with PCDS had reduced gray matter volume in the bilateral amygdala and thalamus, right hippocampus, temporo-occipital cortex, and left cerebellum VI and V regions compared with that of those without PCDS. In addition, individuals with PCDS had a significant association with disruption of hippocampal-amygdala-cerebellar connectivity.⁴⁴⁾ In future studies on CF and similar entities in the same context (i.e., MCRS and PCDS), studies on other brain regions, such as the subcortical nuclei and cerebellum, should be actively conducted in addition to those targeting the cerebral cortex.

DISCUSSION

In this review, we mainly looked at brain MRI studies of not only CF but also MCRS and PCDS, which report some concepts overlapping with CF with different names. Although further research is still needed, white matter abnormalities such as WMH and cerebral microbleeds, which are markers of CSVD, seem likely to be considered the imaging biomarkers for CF. On the other hand, the gray matter volume of the cerebrum/cerebellum related to motor planning and modulation, the volume of the hippocampal formation related to attention and cognitive processing, and the basal ganglia related to motor accuracy area are also candidates of imaging biomarkers of CF.

Del Brutto et al.'s previous study²⁵⁾ can be referred to interpret the reason for the diverse results of imaging studies of CF. Interestingly, they found that the relationships of frailty with global cortical atrophy and WMH change were significantly different between those in the 60s and 70s–80s age groups in the community-dwelling older adults. As of 67 years of age, older frail adults exhibit more pronounced neuroimaging signs of extensive cortical/subcortical damage than robust adults, whereas no such relationship was observed in younger-older adult population. Thus, in the future, when identifying imaging biomarkers, there is a possibility that imaging biomarkers should be considered separately by age group.

In addition, the characteristics of neuroimaging findings may differ by country and/or race and may appear differently depending on whether the study participants are patients in clinics or residents of the community. There have been many studies related to depressive symptoms in CSVD,⁴⁵⁾ but only a few studies on neuro-

imaging findings and depressive symptoms have been conducted in CF.³⁰⁾ As depressed mood itself, vulnerability to stress, and other psychological factors can affect CF, longitudinal studies that comprehensively evaluate these factors and frailty should be conducted.

Immunological blood biomarkers have been explored for both frailty and CF.⁴⁶⁾ In the future, it would be beneficial to study CF with respect to other blood biomarkers that have been studied in the research field of preclinical Alzheimer disease or SCD.⁴⁷⁾ Thus, the corresponding blood biomarkers and imaging biomarkers on MRI can be used for the health examination of the participants.

CONCLUSION

Establishment of screening tools to identify CF in the community population and prevent dementia or other adverse outcomes is of great significance. We believe that the imaging biomarkers listed in our review will be useful in determining the need to proceed with CF screening in patients showing specific MRI findings at a non-geriatric clinic or health examination center. In order to reduce the burden of disease in older adults and prevent dementia and other serious diseases, the discovery and establishment of several key biomarkers should continue in any population.

ACKNOWLEDGMENTS

CONFLICT OF INTEREST

The researchers claim no conflicts of interest.

FUNDING

This research was supported by a faculty research grant from the Yonsei University College of Medicine (No. 6-2021-0088) and the Basic Science Research Program through the National Research Foundation of Korea (NRF) funded by the Ministry of Education (No. 2021R111A1A01040374).

AUTHOR CONTRIBUTIONS

Conceptualization, WJK; writing-original draft, JP, WJK; writing-review & editing, WJK.

REFERENCES

1. Walston J, Hadley EC, Ferrucci L, Guralnik JM, Newman AB, Studenski SA, et al. Research agenda for frailty in older adults: toward a better understanding of physiology and etiology: summary from the American Geriatrics Society/National Institute on aging research conference on frailty in older adults. *J Am*

- Geriatr Soc 2006;54:991-1001.
2. Morley JE, Vellas B, van Kan GA, Anker SD, Bauer JM, Bernabei R, et al. Frailty consensus: a call to action. *J Am Med Dir Assoc* 2013;14:392-7.
 3. Panza F, Solfrizzi V, Frisardi V, Maggi S, Sancarlo D, Adante F, et al. Different models of frailty in predementia and dementia syndromes. *J Nutr Health Aging* 2011;15:711-9.
 4. Malmstrom TK, Morley JE. Frailty and cognition: linking two common syndromes in older persons. *J Nutr Health Aging* 2013;17:723-5.
 5. Lauretani F, Longobucco Y, Ferrari Pellegrini F, De Iorio AM, Fazio C, Federici R, et al. Comprehensive model for physical and cognitive frailty: current organization and unmet needs. *Front Psychol* 2020;11:569629.
 6. Kelaiditi E, Cesari M, Canevelli M, van Kan GA, Ousset PJ, Gillette-Guyonnet S, et al. Cognitive frailty: rational and definition from an (I.A.N.A./I.A.G.G.) international consensus group. *J Nutr Health Aging* 2013;17:726-34.
 7. Buchman AS, Boyle PA, Wilson RS, Tang Y, Bennett DA. Frailty is associated with incident Alzheimer's disease and cognitive decline in the elderly. *Psychosom Med* 2007;69:483-9.
 8. Boyle PA, Buchman AS, Wilson RS, Leurgans SE, Bennett DA. Physical frailty is associated with incident mild cognitive impairment in community-based older persons. *J Am Geriatr Soc* 2010;58:248-55.
 9. Panza F, D'Introno A, Colacicco AM, Capurso C, Parigi AD, Capurso SA, et al. Cognitive frailty: predementia syndrome and vascular risk factors. *Neurobiol Aging* 2006;27:933-40.
 10. Mantovani E, Zucchella C, Schena F, Romanelli MG, Venturelli M, Tamburin S. Towards a redefinition of cognitive frailty. *J Alzheimers Dis* 2020;76:831-43.
 11. Sugimoto T, Sakurai T, Ono R, Kimura A, Saji N, Niida S, et al. Epidemiological and clinical significance of cognitive frailty: a mini review. *Ageing Res Rev* 2018;44:1-7.
 12. Ruan Q, Yu Z, Chen M, Bao Z, Li J, He W. Cognitive frailty, a novel target for the prevention of elderly dependency. *Ageing Res Rev* 2015;20:1-10.
 13. Jessen F, Amariglio RE, van Boxtel M, Breteler M, Ceccaldi M, Chetelat G, et al. A conceptual framework for research on subjective cognitive decline in preclinical Alzheimer's disease. *Alzheimers Dement* 2014;10:844-52.
 14. Verghese J, Wang C, Lipton RB, Holtzer R. Motoric cognitive risk syndrome and the risk of dementia. *J Gerontol A Biol Sci Med Sci* 2013;68:412-8.
 15. Meiner Z, Ayers E, Verghese J. Motoric cognitive risk syndrome: a risk factor for cognitive impairment and dementia in different populations. *Ann Geriatr Med Res* 2020;24:3-14.
 16. Beauchet O, Sekhon H, Barden J, Liu-Ambrose T, Chester VL, Szturm T, et al. Association of motoric cognitive risk syndrome with cardiovascular disease and risk factors: results from an original study and meta-analysis. *J Alzheimers Dis* 2018;64:875-87.
 17. Iqbal K, Hasanain M, Ahmed J, Iqbal A, Rathore SS, Monis A, et al. Association of motoric cognitive risk syndrome with cardiovascular and noncardiovascular factors: a systematic review and meta-analysis. *J Am Med Dir Assoc* 2022;23:810-22.
 18. Chen LK, Arai H. Physio-cognitive decline as the accelerated ageing phenotype. *Arch Gerontol Geriatr* 2020;88:104051.
 19. Sugimoto T, Arai H, Sakurai T. An update on cognitive frailty: its definition, impact, associated factors and underlying mechanisms, and interventions. *Geriatr Gerontol Int* 2022;22:99-109.
 20. Paolini Paoletti F, Simoni S, Parnetti L, Gaetani L. The contribution of small vessel disease to neurodegeneration: focus on Alzheimer's disease, Parkinson's disease and multiple sclerosis. *Int J Mol Sci* 2021;22:4958.
 21. Alber J, Alladi S, Bae HJ, Barton DA, Beckett LA, Bell JM, et al. White matter hyperintensities in vascular contributions to cognitive impairment and dementia (VCID): knowledge gaps and opportunities. *Alzheimers Dement (N Y)* 2019;5:107-17.
 22. DeBette S, Schilling S, Duperron MG, Larsson SC, Markus HS. Clinical significance of magnetic resonance imaging markers of vascular brain injury: a systematic review and meta-analysis. *JAMA Neurol* 2019;76:81-94.
 23. Newman AB, Gottdiener JS, Mcburnie MA, Hirsch CH, Kop WJ, Tracy R, et al. Associations of subclinical cardiovascular disease with frailty. *J Gerontol A Biol Sci Med Sci* 2001;56:M158-66.
 24. Jung HW, Kim SW, Yoon SJ, Choi JY, Kim KI, Kim CH. Associations between frailty, retinal microvascular changes, and cerebral white matter abnormalities in Korean older adults. *J Am Geriatr Soc* 2014;62:2209-10.
 25. Del Brutto OH, Mera RM, Cagino K, Fanning KD, Milla-Martinez MF, Nieves JL, et al. Neuroimaging signatures of frailty: a population-based study in community-dwelling older adults (the Atahualpa Project). *Geriatr Gerontol Int* 2017;17:270-6.
 26. Sugimoto T, Ono R, Kimura A, Saji N, Niida S, Toba K, et al. Cross-sectional association between cognitive frailty and white matter hyperintensity among memory clinic patients. *J Alzheimers Dis* 2019;72:605-12.
 27. Zhao H, Wei W, Liu Y, Gao J, Huang Y. Cognitive frailty among elderly Chinese patients with cerebral small vessel disease: a structural MRI study. *Front Med (Lausanne)* 2020;7:397.
 28. Wang N, Allali G, Kesavadas C, Noone ML, Pradeep VG, Blumen HM, et al. Cerebral small vessel disease and motoric cognitive risk syndrome: results from the Kerala-Einstein study. *J Alz-*

- heimers Dis 2016;50:699-707.
29. Gomez GT, Gottesman RF, Gabriel KP, Palta P, Gross AL, Soldan A, et al. The association of motoric cognitive risk with incident dementia and neuroimaging characteristics: the Atherosclerosis Risk in Communities study. *Alzheimers Dement* 2022; 18:434-44.
 30. Yoshiura K, Fukuhara R, Ishikawa T, Tsunoda N, Koyama A, Miyagawa Y, et al. Brain structural alterations and clinical features of cognitive frailty in Japanese community-dwelling older adults: the Arao study (JPSC-AD). *Sci Rep* 2022;12:8202.
 31. Jordan N, Gvalda M, Cody R, Galante O, Haywood C, Yates P. Frailty, MRI, and FDG-PET measures in an Australian memory clinic cohort. *Front Med (Lausanne)* 2021;7:578243.
 32. Chung CP, Lee WJ, Chou KH, Lee PL, Peng LN, Wang PN, et al. Frailty and dementia risks in asymptomatic cerebral small vessel disease: a longitudinal cohort study. *Arch Gerontol Geriatr* 2022;102:104754.
 33. Osawa Y, Tian Q, An Y, Studenski SA, Resnick SM, Ferrucci L. Longitudinal associations between brain volume and knee extension peak torque. *J Gerontol A Biol Sci Med Sci* 2021;76:286-90.
 34. Blumen HM, Allali G, Beauchet O, Lipton RB, Verghese J. A gray matter volume covariance network associated with the motoric cognitive risk syndrome: a multicohort MRI study. *J Gerontol A Biol Sci Med Sci* 2019;74:884-9.
 35. Gallucci M, Piovesan C, Di Battista ME. Associations between the frailty index and brain atrophy: the Treviso Dementia (TRED-DEM) registry. *J Alzheimers Dis* 2018;62:1623-34.
 36. Wan M, Ye Y, Lin H, Xu Y, Liang S, Xia R, et al. Deviations in hippocampal subregion in older adults with cognitive frailty. *Front Aging Neurosci* 2021;12:615852.
 37. Li M, Huang L, Yang D, Luo C, Qin R, Zhang B, et al. Atrophy patterns of hippocampal subfields in T2DM patients with cognitive impairment. *Endocrine* 2020;68:536-48.
 38. Low A, Foo H, Yong TT, Tan LC, Kandiah N. Hippocampal subfield atrophy of CA1 and subicular structures predict progression to dementia in idiopathic Parkinson's disease. *J Neurol Neurosurg Psychiatry* 2019;90:681-7.
 39. Zhao W, Wang X, Yin C, He M, Li S, Han Y. Trajectories of the hippocampal subfields atrophy in the Alzheimer's disease: a structural imaging study. *Front Neuroinform* 2019;13:13.
 40. Foo H, Mak E, Chander RJ, Ng A, Au WL, Sitoh YY, et al. Associations of hippocampal subfields in the progression of cognitive decline related to Parkinson's disease. *Neuroimage Clin* 2016; 14:37-42.
 41. Wan M, Xia R, Lin H, Qiu P, He J, Ye Y, et al. Volumetric and diffusion abnormalities in subcortical nuclei of older adults with cognitive frailty. *Front Aging Neurosci* 2020;12:202.
 42. Villablanca JR. Why do we have a caudate nucleus? *Acta Neurobiol Exp (Wars)* 2010;70:95-105.
 43. Chen WT, Chou KH, Liu LK, Lee PL, Lee WJ, Chen LK, et al. Reduced cerebellar gray matter is a neural signature of physical frailty. *Hum Brain Mapp* 2015;36:3666-76.
 44. Liu LK, Chou KH, Hsu CH, Peng LN, Lee WJ, Chen WT, et al. Cerebellar-limbic neurocircuit is the novel biosignature of physio-cognitive decline syndrome. *Aging (Albany NY)* 2020;12: 25319-36.
 45. Fang Y, Qin T, Liu W, Ran L, Yang Y, Huang H, et al. Cerebral small-vessel disease and risk of incidence of depression: a meta-analysis of longitudinal cohort studies. *J Am Heart Assoc* 2020;9:e016512.
 46. Healy D. Interactions between systemic inflammation, frailty and neuroinflammation in ageing and neurodegeneration [dissertation]. Dublin, Ireland: Trinity College Dublin; 2022.
 47. Kim KY, Park J, Jeong YH, Kim HJ, Lee E, Park JY, et al. Plasma amyloid-beta oligomer is related to subjective cognitive decline and brain amyloid status. *Alzheimers Res Ther* 2022;14:162.