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COGNITIVE FRAILTY AND ITS ASSOCIATION WITH NUTRITION AND DEPRESSION IN COMMUNITY-DWELLING OLDER PEOPLE

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Abstract: *Background:* Cognitive frailty is a condition where physical frailty and mild cognitive impairment (MCI) co-exist. It is associated with increased risk of dementia and dependency. Previous studies reported that malnutrition and depression are associated with physical frailty and MCI; however, their relationships with cognitive frailty remained to be explored. The aims of this study were to examine the association of nutrition and depression with cognitive frailty, in comparison to having physical frailty or MCI alone. *Methods:* This study employed a cross-sectional design. Data collection was conducted in the community settings on the older people without dementia. Dependent variables were cognitive frailty, physical frailty, and MCI. The independent variables were depression and nutrition. Multi-nominal regression was employed to examine the relationships between the dependent and independent variables. The associations were adjusted by four known co-variates, including age, gender, education and APOE ε4 carrier status. *Results:* A total of 185 participants were recruited from four community centres and one elderly hostel and completed the data collection. Approximately 44.9% of the older people with physical frailty and 82.5% of elderly with MCI belonged to cognitive frailty. Multi-nominal regression models showed that depression is positively associated with cognitive frailty and with physical frailty, but not associated with solely MCI. Nutrition is negatively associated with cognitive frailty, but not associated with physical frailty or MCI alone. *Conclusion:* Cognitive frailty is associated with malnutrition and depression. Therapeutic interventions managing depression and malnutrition may focus the older people with cognitive frailty to improve efficacy and cost-effectiveness.

Key words: Cognitive frailty, nutrition, depression, APOE gene.

Introduction

Cognitive frailty is a heterogeneous clinical manifestation characterized by the simultaneous presence of both physical frailty and cognitive impairment without being severe enough to fulfil the criteria of dementia (1). Physical frailty and mild cognitive impairment (MCI) often co-exist. Older people with frailty show a significantly higher risk of developing MCI and vice versa (2). These two syndromes share many common neuro-pathologies, such as Alzheimer's disease, Parkinson's disease, and cerebrovascular disease; as well as other common potential mechanisms, such as insulin resistance, chronic inflammation (2, 3). Cognitive frailty is commonly seen in older people in community settings with a prevalence of 1.8-8.9% (4, 5). It is associated with increased risk of adverse health outcomes, such as functional disability, worsened quality of life, hospitalization, mortality, and incidence of dementia (6). In the Italian Longitudinal Study on Ageing, evidence showed that the earlier cognitive frailty is identified, the more likely it is to be reversible (7). Therefore, cognitive frailty is increasingly recognized as a novel target for prevention of elderly dependency and dementia (8, 9).

Nutrition is a strong and modifiable risk factor associated with cognitive frailty (OR=8.16) (10). Obesity and insulin resistance are associated with cognitive decline, while neuro-inflammation and oxidative stress are some of the proposed underlying mechanisms that impact on older people's cognitive health (11). Older people with malnutrition have poorer cognitive performance (12). Weight loss, reduced intake of calorie and specific nutrients (e.g., protein intake, vitamin D), and dietary pattern are associated with changes in body composition and physical function, and also increase the risk of physical frailty (13, 14).

Depression is another common and modifiable risk factor for both frailty and cognitive impairment (15). Older people with depression have a higher risk of developing frailty (OR=4.07) (16). High levels of depressive symptoms are also associated with cognitive decline in older people (17). A study has shown that depression is an independent associated factor of cognitive decline in older people with physical frailty (18).

Cognitive frailty is potentially a novel target for the prevention of dementia and dependency. Therefore, it would be important to further understand whether the published risk factors are associated with cognitive frailty, or solely with cognitive impairment, or solely with physical frailty, so as to devise effective screening and intervention strategies. Here, we focused on two of the most important but modifiable risk factors, nutrition and depression, aiming to examine their associations with cognitive frailty. Specifically, this study tests the following null hypotheses:

1. There are no associations of depression with physical frailty, MCI, or cognitive frailty.

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2. There are no associations of nutrition with physical frailty, MCI, or cognitive frailty.

Methods

Study design

A cross-sectional design was employed in this study; therefore, we report this study by adopting the Strengthening The Reporting of OBservational studies in Epidemiology (STROBE) checklist for cross-sectional studies (19).

Setting

This study was conducted in community settings. Subjects were either members of elderly community centres, which provide recreational activities for older people; or residents of elderly hostels, which provide residential services for functionally independent older people. Subject recruitments and data collections were conducted during Jan 2017 – Jun 2018.

Participants

Inclusive criteria

1. Community-dwelling, living in either their own homes or elderly hostels
2. Age ≥ 65 years

Exclusive criteria

Established dementia, either

a. Having formal diagnosis of dementia, as documented on their medical records; or
b. Having overt cognitive impairment, as determined by the Clinical Dementia Rating (CDR) ≥ 1,20 OR Mini-Mental State Exam (MMSE) score ≤ 18 for illiterate, ≤ 20 for having 1-2 years formal education, and ≤ 22 for having more than 2 years formal education (21).

Variables

The dependent variable was cognitive frailty. The independent variables included nutrition and depression. The demographic, clinical and genetic variables included age, gender, marital status, living status, education, health literacy, smoking, drinking, and the ε-allele genotype of apolipoprotein E (APOE) gene.

Measurement

Outcomes

In this study, the dependent variables are cognitive frailty, physical frailty, and MCI. Physical frailty was defined as having either pre-physical frailty or frailty.

Physical frailty was measured by using the FRAIL scale (22). FRAIL comprises five dichotomous items with possible scores from 0 to 5. A higher score indicates a higher level of physical frailty. FRAIL categorizes frailty in three levels by severity (i.e., robust=0, pre-frail=1-2, frail=4-5). Subjects' FRAIL score ≥ 1 were identified as having physical frailty.

MCI was defined by having subjective memory complaint, objective cognitive impairment, and largely intact functional activities (23). CDR was used for assessment of MCI and Subjects' CDR=0.5 were identified as having MCI (20, 23)

This study adopts Ruan's definition of cognitive frailty, which is defined as having 1) physical frailty or pre-physical frailty, 2) MCI, and 3) no concurrent dementia.8 Subjects with the coexistence of physical frailty or pre-physical frailty and MCI were identified as having cognitive frailty.

Subjects with CDR=0 and FRAIL=0 were identified as robust, which means being cognitively healthy without any frailty symptoms.

Factors

There were two independent variables in this study: 1) depression and 2) nutrition. Depression was measured by the Geriatric Depression Scale (GDS-15) (24), which comprises 15 items that a higher score indicates a higher level of depression. Nutrition was measured by Mini-Nutrition Assessment-Short Form (MNA-SF), which comprises six items with possible scores from 0 to 14 (25). A higher score indicates a better nutritional status.

Confounders

Age, gender, and education were considered to be the potential confounders because previous studies showed that they were also associated with physical frailty and MCI (26). Since APOE ε4 allele is a well-known genetic risk factor of Alzheimer's disease (27), an important type of dementia and MCI among older adults, we also included APOE ε4 carrier status as a potential confounder in this study.

Study size

This study is testing the hypotheses on the associations of cognitive frailty status with two factors (i.e., depression and nutrition) adjusted for four confounders (i.e., age, gender, education, APOE ε4 carrier status) on three outcomes (i.e., cognitive frailty, physical frailty, and MCI). Previous studies reported that the effect sizes of nutrition (OR=3.1) (28) and depression (OR=2.64)16 on frailty had been observed to be small-moderate (29). We conservatively assumed that the effect sizes of nutrition and depression on cognitive frailty to be small-moderate (i.e., f2=0.02-0.15) (30). By using GPower, with linear multiple regression and with several assumptions (i.e., number of tested predictors=3, power=0.8, level of significance=0.05, f2=0.07), 160 subjects were needed to be included in the data analysis.

Statistical methods

All the demographic variables, clinical variables, outcomes, and factors were described by using mean with standard

deviation or frequency with percentage. These variables were compared between four outcome groups (i.e., cognitive frailty, physical frailty, MCI, and robust). Student t-test, Mann-Whitney U test, and Chi-Square test were used to compare the variables between groups. The level of significance was set to be 0.05.

To test the hypotheses, multi-nominal logistic regression models were employed to test the two hypotheses according to the outcomes. The dependent variable was nominal cognitive frailty status (i.e., 1) robust, 2) physical frailty, 3) MCI, and 4) cognitive frailty). Robust group was set as the reference for calculation of odds ratios. Nutrition and depression were assigned as the independent variables. Two models with unadjusted and adjusted for confounders (i.e., age, gender, education, APOE ε4 carrier status) were computed separately to understand whether the factors are independent to the confounders. The level of significance was set to be 0.05.

Missing data will be replaced by the mean when the missing rate of variables was inconsequential (i.e., 5% or less), multiple imputation was adopted for the variables with a missing rate over 5% according to the missing patterns (31).

Ethical considerations

All subjects had signed the informed consent to participate in this study after they had listened to the research team's explanation on the procedures, risks, and benefits of this study.

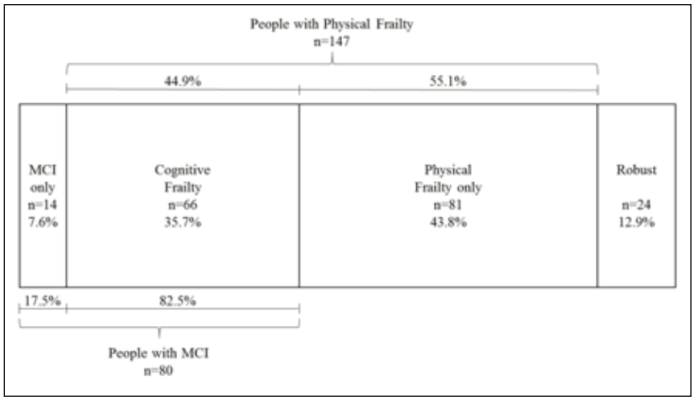
Results

This study recruited 185 participants who have completed the data collection (robust=24, 12.9%; physical frailty=81, 43.8%; MCI=14, 7.6%; cognitive frailty=66, 35.7%) in four community centres and one elderly hostel. Missing data in variables were within 5% and they were substituted by the mean.

As shown in Figure 1, in the people with MCI (n=80), vast majority of them has cognitive frailty (n=66, 82.5%). People having MCI alone is scarce (n=14, 17.5%). In people with physical frailty (n=147), slightly less than half of them have cognitive frailty (n=66, 44.9%). Slightly more than half of the people with physical frailty have physical frailty alone (n=81, 55.1%).

As shown in Table 1, the mean age of the participants was 86.2±4.5 years old. Majority of them was female (n=132, 71.4%), having education at primary level or below (n=161, 87%), non-drinkers (n=175, 94.6%), non-smokers (n=157, 84.9%), and non-APOE-ε4 carriers (n=138, 74.6%). Their mean MMSE score was 22.2±4.5, mean FRAIL score was 1.6±1.2, mean GDS-15 score was 3.8±3.4, and mean MNA-SF score was 11.7±2.2. There were significant differences between groups on cognitive function ($p<0.001$), frailty level ($p<0.001$), depression ($p=0.001$), and nutrition ($p=0.002$). There were no significant differences between groups on APOE ε4 carrier status as well as other demographic variables.

Figure 1
Distribution of physical frailty, cognitive frailty, and mild cognitive impairment



The unadjusted multi-nominal regression models (R2=0.175) in Table 2 showed that depression is positively associated with cognitive frailty (OR=1.577, p=0.002) and with physical frailty (OR=1.496, p=0.004), but not associated with MCI. Nutrition is negatively associated with cognitive frailty (OR=0.656, p=0.005), but not associated with physical frailty or MCI. The associations remained significant, even after adjusting for age, gender, education and APOE ε4 carrier status.

Discussion

This study showed that over 40% of older people with physical frailty and over 80% of older people with cognitive impairment were considered as cognitive frailty. We also investigated the association of cognitive frailty with nutrition and depression in older people, which remained significant even after adjusting for age, gender, education background and APOE ε4 genetic factor. Further analysis showed that nutrition was only associated with cognitive frailty but not frailty or MCI. Depression was only associated with cognitive frailty and frailty but not MCI.

In the existing epidemiological studies, most of them reported the prevalence of cognitive frailty without reporting the prevalence of the MCI only and physical frailty only in the people with cognitive frailty.32 To our knowledge, this is the first study showed that there was a large overlapping between physical frailty and MCI. Previous studies showed that MCI, physical frailty, and cognitive frailty are associated with higher risk of dementia and dependence.33-35 Future studies should test if cognitive frailty is a more significant entity to cause dementia and dependency, compared to the entity of MCI and physical frailty.

Previous studies had reported significant associations of nutrition with physical frailty and MCI, 10,36 in which subjects might include those with cognitive frailty. Here, by carefully dissecting the older people into appropriate subgroups, we were able to demonstrate for the first time that nutrition was

Table 1
Demographic variables and factors between groups

Mean (SD)/Frequency (%)	Total (N=185)	Robust (n=24)	Physical Frailty (n=81)	MCI (n=14)	Cognitive Frailty (n=66)	p-value#
Demographic						
Age	86.2 (4.5)	87.5 (3.2)	86.6 (3.1)	84.6 (5.1)	85.6 (6.0)	0.131
Gender						0.258
Male	53 (28.6)	11 (45.8)	21 (25.9)	4 (28.6)	17 (25.8)	
Female	132 (71.4)	13 (54.2)	60 (74.1)	10 (71.4)	49 (74.2)	
Education						0.053
Primary or below	161 (87.0)	21 (87.5)	66 (81.5)	11 (78.6)	63 (95.5)	
Secondary	19 (10.3)	1 (4.2)	13 (16.0)	2 (14.3)	3 (4.5)	
Tertiary or above	5 (2.7)	2 (8.3)	2 (2.5)	1 (7.1)	0 (0)	
Drinking						0.266
Yes	10 (5.4)	0 (0)	4 (4.9)	0 (0)	6 (9.1)	
No	175 (94.6)	24 (100)	77 (95.1)	14 (100)	60 (90.9)	
Smoking						0.950
Smoker	5 (2.7)	1 (4.2)	2 (2.5)	0 (0)	2 (3.0)	
Ceased	23 (12.4)	3 (12.5)	9 (11.1)	1 (7.1)	10 (15.2)	
Non-smoker	157 (84.9)	20 (83.3)	70 (86.4)	13 (92.9)	54 (81.8)	
APOE ε4 status						0.773
Carrier	29 (15.7)	3 (12.5)	11 (13.6)	3 (21.4)	12 (18.2)	
Non-carrier	156 (84.3)	21 (87.5)	70 (86.4)	11 (78.6)	54 (81.2)	
Outcomes						
Cognition (MMSE)	22.2 (4.5)	25.8 (2.4)	24.0 (3.3)	20.7 (2.9)	19.0 (4.7)	<0.001*
Frailty (FRAIL)	1.6 (1.2)	0 (0)	2.0 (1.0)	0 (0)	2.1 (1.1)	<0.001*
Factors						
Depression (GDS-15)	3.8 (3.4)	1.7 (1.9)	3.9 (3.2)	2.2 (1.5)	4.6 (3.9)	0.001*
Nutrition (MNA-SF)	11.7 (2.2)	12.8 (1.3)	12.0 (2.1)	11.8 (2.2)	11.0 (2.4)	0.002*

MMSE: Mini-mental State Exam, GDS-15: Geriatric Depression Scale 15-item, MNA-SF: Mini-Nutrition Assessment short-form, APOE: apolipoprotein E

associated with cognitive frailty, but not with physical frailty or MCI alone. To date, most of the nutritional interventions target broadly on people with physical frailty or cognitive impairment (36, 37). Studies showed that malnutrition (e.g., vitamin E deficiency, low energy and protein intake) correlated with both physical frailty and cognitive decline, and evidence advocated that physical frailty and cognitive decline induced the occurrence of each other.3 The findings of our study may provide some insights on targeting nutritional interventions for older people with cognitive frailty being more cost effective and efficacious.

Our study also confirmed the previous findings on associations of depression with physical frailty (38, 39). Recent evidence showed that physical frailty and depression share many common physiological mechanisms. For example, chronic inflammation is associated with both decreased muscle mass or strength and reduced central dopaminergic function leading to both physical frailty and depressive affect (40).

MCI is previously reported to be associated with a higher risk of depression (41). In people with MCI, depressive symptoms increased the risk of progression to dementia (RR=1.28) (42). Psychological treatments are effective to reduce symptoms of depression for people with dementia, but similar studies for people with MCI is lacking (43). On the other hand, antidepressant such as selective serotonin reuptake inhibitors may delay the progression from MCI to Alzheimer's disease (44). Interestingly, in a large scale systematic review, the prevalence of depression in patients with MCI in the community settings (25%) was significantly lower than that in the clinical settings (40%) (45). While the discrepancy could be attributed to chronic illnesses and functional limitation which were more related to the clinical settings (46), it is also possible that depression may be associated with a more defined group, such as cognitive frailty, as suggested by our study. Further

Table 2
Multi-nominal logistic regression model examining the associations of physical frailty, MCI, cognitive frailty with depression and nutrition

	Robust (N=24)	Physical Frailty (n=81)		MCI (n=14)		Cognitive Frailty (n=66)	
Model 1 (R2=0.175)		**OR**	**p-value**	**OR**	**p-value**	**OR**	**p-value**
Depression	Ref	1.496	0.004*	1.179	0.372	1.577	0.002*
Nutrition	Ref	0.803	0.137	0.750	0.114	0.654	0.005*
Model 2 (R2=0.261)							
Depression	Ref	1.432	0.010*	1.124	0.540	1.524	0.003*
Nutrition	Ref	0.838	0.224	0.779	0.174	0.668	0.006*

Model 1: unadjusted, Model 2: adjusted for age, gender, education, and APOE ε4, MCI: mild cognitive impairment

studies should explore if interventions targeting cognitive frailty (e.g., physical activity (38)) may be better alternatives to reduce the risk of depression and dementia onset in older people with MCI.

Our data suggested that cognitive frailty is a significant condition associated with poor nutrition and depression, further studies should consider the possibility of devising interventions that target nutrition and depression for preventing the progression of cognitive frailty to dementia and dependency. Current evidence suggested that treating protein and calorie insufficiency in older people is a fundamental part to prevent both physical frailty and cognitive decline.11 Physical activity is effective to slow down cognitive frailty progression or reverse cognitive frailty and reduce depression (38, 47). Systematic screening programme should be established to identify elderly with cognitive frailty, as well as signs of malnutrition or depression such that prompt interventions could be implemented. Further investigation should also be conducted to analyse the effect of combined interventions in this vulnerable population on the cognitive frailty progression, risk of dementia, and dependency.

Albeit the significant findings, there are several limitations to be considered. The sample size of this study is relatively small, which may limit the generalizability of the findings. Also, there is an unbalanced number of subjects in different groups, particularly a small number of subjects in the solely MCI group. This may have restricted the statistical power to detect the underlying difference between the MCI and robust groups. This study adopted a cross-sectional design that the cause-effect relationships among these variables cannot be confirmed.

Conclusion

Cognitive frailty is associated with malnutrition and depression. By targeting older people with cognitive frailty who show the signs of malnutrition or depression, interventions could be promptly implemented to prevent the worsening or even reverse the condition. Further studies should examine the impacts of such interventions on the risk of dementia and dependency.

Conflict of interest: Moonchu Foundation funded the project; none of the authors have any conflict of interest to declare

Ethical standards: This article complies with the law. The study received an ethical approval from the institutional review board at The Hong Kong Polytechnic University with the reference number of HSEARS20161101002.

References

1. Kelaiditi E, Cesari M, Canevelli M, et al. Cognitive frailty: rational and definition from an (IANA/IAGG) international consensus group. The journal of nutrition, health & aging. 2013;17(9):726-734.
2. Buchman A, Bennett DA. Cognitive frailty. The journal of nutrition, health & aging. 2013;17(9):738.
3. Halil M, Cemal Kizilarslanoglu M, Emin Kuyumcu M, Yesil Y, Cruz Jentoft AJ. Cognitive aspects of frailty: Mechanisms behind the link between frailty and cognitive impairment. The journal of nutrition, health & aging. 2015;19(3):276-283.
4. Roppolo M, Mulasso A, Rabaglietti E. Cognitive frailty in Italian community-dwelling older adults: Prevalence rate and its association with disability. The journal of nutrition, health & aging. 2017;21(6):631-636.
5. Feng L, Zin Nyunt MS, Gao Q, Feng L, Yap KB, Ng T-P. Cognitive Frailty and Adverse Health Outcomes: Findings From the Singapore Longitudinal Ageing Studies (SLAS). Journal of the American Medical Directors Association. 2017;18(3):252-258.
6. Panza F, Lozupone M, Solfrizzi V, et al. Different cognitive frailty models and health- and cognitive-related outcomes in older age: from epidemiology to prevention. Journal of Alzheimer's disease. 2018;62(3):993-1012.
7. Solfrizzi V, Scafato E, Lozupone M, et al. Additive Role of a Potentially Reversible Cognitive Frailty Model and Inflammatory State on the Risk of Disability: The Italian Longitudinal Study on Aging. The American Journal of Geriatric Psychiatry. 2017;25(11):1236-1248.
8. Ruan Q, Yu Z, Chen M, Bao Z, Li J, He W. Cognitive frailty, a novel target for the prevention of elderly dependency. Ageing Research Reviews. 2015;20:1-10.
9. Panza F, Lozupone M, Solfrizzi V, et al. Cognitive frailty: a potential target for secondary prevention of dementia. In: Taylor & Francis; 2017.
10. Chye L, Wei K, Nyunt MSZ, Gao Q, Wee SL, Ng T-P. Strong Relationship between Malnutrition and Cognitive Frailty in the Singapore Longitudinal Ageing Studies (SLAS-1 and SLAS-2). The Journal of Prevention of Alzheimer's Disease. 2018;5(2):142-148.
11. Dominguez LJ, Barbagallo M. The relevance of nutrition for the concept of cognitive frailty. Current opinion in clinical nutrition and metabolic care. 2017;20(1):61-68.
12. Cesari M. Perspective: Protein supplementation against sarcopenia and frailty: Future perspectives from novel data. Journal of the American Medical Directors Association. 2013;14(1):62-63.
13. Cruz-Jentoft AJ, Kiesswetter E, Drey M, Sieber CC. Nutrition, frailty, and sarcopenia. Aging clinical and experimental research. 2017;29(1):43-48.
14. Kwan RY, Cheung DS, Lo SK, et al. Frailty and its association with the Mediterranean diet, life-space, and social participation in community-dwelling older people. Geriatric Nursing. 2019.
15. Lee RS, Hermens DF, Porter MA, Redoblado-Hodge MA. A meta-analysis of cognitive deficits in first-episode major depressive disorder. Journal of Affective Disorders. 2012;140(2):113-124.
16. Soysal P, Veronese N, Thompson T, et al. Relationship between depression and frailty in older adults: A systematic review and meta-analysis. Ageing Research Reviews. 2017;36:78-87.
17. Paterniti S, Verdier-Taillefer M-H, Dufouil C, Alpérovitch A. Depressive symptoms and cognitive decline in elderly people: Longitudinal study. British Journal of Psychiatry. 2018;181(5):406-410.
18. Ma L, Zhang L, Zhang Y, Li Y, Tang Z, Chan P. Cognitive frailty in China: Results from China comprehensive geriatric asessment study. Frontiers in Medicine.

2017;4(174).
19. Von Elm E, Altman DG, Egger M, et al. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement: guidelines for reporting observational studies. International journal of surgery. 2014;12(12):1495-1499.
20. Morris JC. Clinical dementia rating: a reliable and valid diagnostic and staging measure for dementia of the Alzheimer type. International psychogeriatrics. 1997;9(S1):173-176.
21. Lam LC, Tam CW, Lui VW, et al. Prevalence of very mild and mild dementia in community-dwelling older Chinese people in Hong Kong. International Psychogeriatrics. 2008;20(1):135-148.
22. Morley JE, Malmstrom T, Miller D. A simple frailty questionnaire (FRAIL) predicts outcomes in middle aged African Americans. The journal of nutrition, health & aging. 2012;16(7):601-608.
23. Petersen RC. Mild cognitive impairment as a diagnostic entity. Journal of internal medicine. 2004;256(3):183-194.
24. Chan AC-M. Clinical validation of the geriatric depression scale (GDS) Chinese version. Journal of aging and health. 1996;8(2):238-253.
25. Kaiser MJ, Bauer J, Ramsch C, et al. Validation of the Mini Nutritional Assessment Short-Form (MNA®-SF): A practical tool for identification of nutritional status. JNHA-The Journal of Nutrition, Health and Aging. 2009;13(9):782.
26. Lee W-J, Peng L-N, Liang C-K, Loh C-H, Chen L-K. Cognitive frailty predicting all-cause mortality among community-living older adults in Taiwan: A 4-year nationwide population-based cohort study. PLOS ONE. 2018;13(7):e0200447.
27. Liu C-C, Kanekiyo T, Xu H, Bu G. Apolipoprotein E and Alzheimer disease: risk, mechanisms and therapy. Nature Reviews Neurology. 2013;9(2):106.
28. Kurkcu M, Meijer RI, Lonterman S, Muller M, de van der Schueren MAE. The association between nutritional status and frailty characteristics among geriatric outpatients. Clinical Nutrition ESPEN. 2018;23:112-116.
29. Chen H, Cohen P, Chen S. How big is a big odds ratio? Interpreting the magnitudes of odds ratios in epidemiological studies. Communications in Statistics—Simulation and Computation®. 2010;39(4):860-864.
30. Cohen J. A power primer. Psychological bulletin. 1992;112(1):155.
31. Dong Y, Peng C-YJ. Principled missing data methods for researchers. SpringerPlus. 2013;2(1):222.
32. Sugimoto T, Sakurai T, Ono R, et al. Epidemiological and clinical significance of cognitive frailty: a mini review. Ageing research reviews. 2018;44:1-7.
33. Barnes B, Gopaul K, Muir Hunter SW, et al. Disentangling Cognitive-Frailty: Results From the Gait and Brain Study. The Journals of Gerontology: Series A. 2016;71(11):1476-1482.
34. Solfrizzi V, Panza F, Colacicco A, et al. Vascular risk factors, incidence of MCI, and rates of progression to dementia. Neurology. 2004;63(10):1882-1891.
35. Kulmala J, Nykänen I, Mänty M, Hartikainen S. Association between frailty and dementia: a population-based study. Gerontology. 2014;60(1):16-21.
36. Manal B, Suzana S, Singh D. Nutrition and frailty: a review of clinical intervention studies. ON FRAILTY. 2015:25.
37. Forbes SC, Holroyd-Leduc JM, Poulin MJ, Hogan DB. Effect of nutrients, dietary supplements and vitamins on cognition: a systematic review and meta-analysis of randomized controlled trials. Canadian Geriatrics Journal. 2015;18(4):231.
38. Liu Z, Hsu F-C, Trombetti A, et al. Effect of 24-month physical activity on cognitive frailty and the role of inflammation: the LIFE randomized clinical trial. BMC medicine. 2018;16(1):185.
39. Aprahamian I, Suemoto CK, Lin SM, et al. Depression is associated with self-rated frailty in older adults from an outpatient clinic: a prospective study. International psychogeriatrics. 2018:1-10.
40. Brown PJ, Roose SP, Fieo R, et al. Frailty and depression in older adults: a high-risk clinical population. The American Journal of Geriatric Psychiatry. 2014;22(11):1083-1095.
41. Li N, Chen G, Zeng P, et al. Prevalence and factors associated with mild cognitive impairment among Chinese older adults with depression. Geriatrics & gerontology international. 2018;18(2):263-268.
42. Mourao RJ, Mansur G, Malloy-Diniz LF, Castro Costa E, Diniz BS. Depressive symptoms increase the risk of progression to dementia in subjects with mild cognitive impairment: systematic review and meta-analysis. International journal of geriatric psychiatry. 2016;31(8):905-911.
43. Orgeta V, Qazi A, Spector A, Orrell M. Psychological treatments for depression and anxiety in dementia and mild cognitive impairment: systematic review and meta-analysis. The British Journal of Psychiatry. 2015;207(4):293-298.
44. Bartels C, Wagner M, Wolfsgruber S, Ehrenreich H, Schneider A, Initiative AsDN. Impact of SSRI therapy on risk of conversion from mild cognitive impairment to Alzheimer's dementia in individuals with previous depression. American Journal of Psychiatry. 2017;175(3):232-241.
45. Ismail Z, Elbayoumi H, Fischer CE, et al. Prevalence of depression in patients with mild cognitive impairment: a systematic review and meta-analysis. Jama psychiatry. 2017;74(1):58-67.
46. Eynon Black D, Parajuli J, Brown J. Depression, chronic disease and functional limits: A comparison between the United States and India. Innovation in Aging. 2017;1(Suppl 1):34-34.
47. Alexandrino-Silva C, Ribeiz SR, Frigerio MB, et al. Prevention of depression and anxiety in community-dwelling older adults: the role of physical activity. Archives of Clinical Psychiatry (São Paulo). 2019;46(1):14-20.