Clinical Interventions in Aging

Dovepress
open access to scientific and medical research

Open Access Full Text Article

ORIGINAL RESEARCH

Intrinsic Capacity Declines with Elevated Homocysteine in Community-Dwelling Chinese Older Adults

Siyang Lin[1,2,*], Fang Wang[2–4,*], Jiaxin Zheng[1,2], Yin Yuan[1,2,5,6], Feng Huang[1,2,5,6], Pengli Zhu[1,2,5,6]

[1]Shengli Clinical Medical College of Fujian Medical University, Fuzhou, Fujian, People's Republic of China; [2]Department of Geriatric Medicine, Fujian Provincial Hospital, Fuzhou, Fujian, People's Republic of China; [3]Fujian Health College, Fuzhou, Fujian, People's Republic of China; [4]Nursing School of Fujian Medical University, Fuzhou, Fujian, People's Republic of China; [5]Fujian Provincial Center for Geriatrics, Fuzhou, Fujian, People's Republic of China; [6]Fujian Provincial Key Laboratory of Geriatrics, Fuzhou, Fujian, People's Republic of China

*These authors contributed equally to this work

Correspondence: Feng Huang; Pengli Zhu, Shengli Clinical Medical College of Fujian Medical University, No. 134 Dongjie Road, Gulou District, Fuzhou, 350001, Fujian, People's Republic of China, Tel/Fax +86-591-88216023, Email wmhf0327@126.com; zpl7755@hotmail.com

Purpose: Intrinsic capacity (IC) reflects the overall health status of older adults and has great public health significance. But few studies described the related biomarkers for IC. The aim of this study was to investigate the association between homocysteine (Hcy) and IC in older adults.

Participants and Methods: This cross-sectional study included 1927 community-dwelling Chinese older adults aged 60–98 years from May 2020 to December 2020. Data were collected through interviews, physical examinations, and laboratory tests. IC involved five domains of cognition, locomotion, sensory, vitality, and psychology evaluated by the Mini-cog scale, 4-m walk test, self-reported visual and hearing conditions, MNA-SF scale, and GDS-4 scale, respectively. The score of each domain dichotomized as 0 (normal) and 1 (impaired) was added together to an IC total score. Low IC was defined as a score of 3–5, and high IC as 0–2. Hcy was measured by a two-reagent enzymatic assay. A restricted cubic spline regression model was used to explore the non-linear relationship between Hcy and low IC.

Results: Hcy was higher in the low IC group than in the high IC group. Restricted cubic spline analysis revealed a J-shaped nonlinear association between Hcy and low IC. The risk of IC decline was slowly decreased until 8.53 μmol/L of Hcy (OR=0.753, 95% CI=0.520–1.091, P=0.132), and increased with elevations of per 5 μmol/L Hcy afterwards (OR=1.176, 95% CI=1.059–1.327, P=0.005). Among the five domains of IC, Hcy had ORs of 1.116 (1.009–1.247) for cognition impairment, 1.167 (1.055–1.305) for vitality, and 1.160 (1.034–1.303) for psychology per 5 μmol/L increase in Hcy above the change point. Additional sensitivity analysis also demonstrated the nonlinear association between Hcy and low IC.

Conclusion: Hcy had a J-shaped association with low IC. Higher Hcy (Hcy ≥8.53μmol/L) might provide clinical implications for early identifying the risk of low IC.

Keywords: homocysteine, intrinsic capacity, older adults, frailty

Introduction

At present, "healthy aging" has become a major public health concern globally. The goal of healthy aging is to develop and maintain function ability needed for healthy life in older adults. The World Health Organization (WHO) released the "World report on aging and health", and the concept of intrinsic capacity (IC) was first proposed in the report.[1] IC plays an crucial role in promoting healthy aging because IC can determine the functional ability of older adults in combination with the environmental factors.[2] IC is defined as the sum of mental and physical strength in individuals, reflecting the basis of what old people can do. Five domains were proposed for IC screening: cognition, locomotion, sensory, vitality, and psychology by the WHO in 2017.[3] IC embodies the overall state of older adults, which penetrates the entire life over

Received: 15 April 2022
Accepted: 26 June 2022
Published: 7 July 2022

time, instead of an observation indicator at a given moment.[4,5] The statistics data of IC is relatively limited. Based on the small amount of literature, the proportion of IC impairment in one domain or more is about 64.5%-89.3%,[6–11] indicating that the decline in IC is prevalent among older adults. Due to the differences in included populations and IC assessments, IC status still requires more exploration and research to know for certain. Constructing the health system with IC as the core to provide monitoring, evaluation, and interference in IC can promote a shift from a disease-centered model to a human-centered model to satisfy the health needs of older adults.[12]

Homocysteine (Hcy) is a sulfur-containing amino acid metabolite involved in methionine metabolism.[13] Hyperhomocysteine is characterized by a high level of Hcy, and can result in cardio-cerebrovascular disorders through damage to vascular endothelial cells and oxidative stress, which promote thrombosis.[14] Hcy is an independent risk factor for stroke and a high risk factor for cardiovascular disease, chronic kidney disease, cognitive impairment, and macular degeneration, which are particularly prevalent in older adults.[15] Hcy concentration levels vary in gender and ethnicity. Hcy was significantly higher in men than in women due to the gender difference in creatine biosynthesis, vitamin status, life styles, and so on.[16,17] The China Stroke High-risk Population Screening Program of 110551 residents from 31 provinces showed that the median Hcy level was 10.9μmol/L,[18] which was similar to other Asian countries,[19,20] but higher than European and American countries,[21,22] resulting from a higher genotype frequency of the methylenetetrahydrofolate reductase (MTHFR) C677T mutation and no full implementations of folic acid supplementation in Asian countries compared with European and American countries.

Previous clinical studies have found that Hcy is associated with a decline in physical function,[23] increased bone resorption,[24] sarcopenia,[25] and frailty.[26] On the molecular level, high Hcy induces senescence through multiple mechanisms, including mitochondrial dysfunction, oxidative stress, endoplasmic reticulum stress, inflammatory responses, and DNA methylation.[14,27] Moreover, mouse models have shown that high Hcy levels might cause skeletal muscle atrophy and decreased skeletal muscle mass, leading to a decline in muscle contractions, easy fatigue, and frailty.[28]

The proposal of IC and frailty is based on the common goal of healthy aging. Compared with the focus of frailty on deficits, IC pays more attention to existing function in the old, which provides a positive and comprehensive connotation.[29] IC has great public health significance in strategies for older adults with different health status. However, research in the IC field is still at a preliminary stage, and relatively few studies have described biomarkers associated with IC. On the basis of biological experiments and clinical studies on Hcy and senescence, we examined the association between Hcy and low IC to explore the biomarker for the decline of IC.

Materials and Methods

Participants

This cross-sectional study was conducted at the Fuzhou Wenquan Community Health Service Center, recruiting 2046 subjects from May 2020 to December 2020. There were three inclusion criteria: (1) aged 60 years or older; (2) negative nucleic acid detection for COVID-19; (3) provided written informed consent. The exclusion criteria were as follows: (1) acute, critical or terminal stages of chronic disease; (2) acute infection within one week (acute respiratory infection, gastrointestinal infection, skin infection, and so on induced by the virus, bacteria, fungus or parasite); (3) serious psychiatric or neurological disorders; (4) motor disability of upper and lower limbs; (5) unable to complete the study due to severe visual, hearing impairments, or language difficulties; (6) Hcy testing not completed; (7) severe renal failure (eGFR <30 mL/min•1.73 m^2); (8) participants who have used drugs affecting Hcy metabolism, such as vitamin B6, vitamin B12, folate, and so on. A total of 1927 participants aged 60–98 years were included in the analysis finally. The study obtained approval from the ethics committee of Fujian Provincial Hospital (K2020-05-008). The protocol (ChiCTR2000032949) can be found on the Chinese Clinical Trial Register Network (www.chictr.org.cn/index.aspx).

Assessment of IC

IC is composed of five domains: cognition, locomotion, sensory, vitality, and psychological capacity based on the WHO guideline.[3] Our study was based on the comprehensive assessment of older adults, and we adopted screening tools that have been widely used or proven to be convenient and reliable in each domain. The score of each domain dichotomized

as 0 (normal) and 1 (impaired) was added together to an IC total score. IC total score ranged from 0–5. Low IC was defined as a score of 3–5, and high IC as 0–2 (the reference group).

Cognition

Cognition was evaluated using the Mini-cog, which comprises three-word recall and clock drawing tests. The Mini-cog has been validated for identifying dementia in community-dwelling older adults with high diagnostic performance.[30] The Mini-cog score ranged from 0 to 5. Impairment in cognition was recognized as a Mini-cog score ≤ 3. Older adults with cognition impairment received one score, and those with normal cognition received no score.

Locomotion

Locomotion was assessed by a 4-m walk test, which was used in several articles.[7,31–34] Participants started from the same position and ended when the first whole foot crossed over the 4-m line. The average time of the two trials was taken as gait speed. An impairment in locomotion was defined as a gait speed < 1.0 m/s based on the 2019 Asian Working Group for Sarcopenia consensus.[35] Older adults with locomotion impairment received one score, and those with normal locomotion received no score.

Sensory

The sensory capacity domain included vision and hearing impairments. Most IC-related articles applied the self-report by participants to evaluate the sensory impairment,[8,10,31,34,36–40] and we also adopted this method. Participants were asked to choose the most appropriate answer for their vision and hearing conditions: (1) normal; (2) slight decrease; (3) daily life limited; (4) vision or hearing disability. We defined the slight decreased or more severe conditions as an impairment in sensory capacity. Older adults with sensory impairment received one score, and those with normal sensory capacity received no score.

Vitality

Vitality was measured by the Short-Form Mini Nutritional Assessment (MNA-SF), which was commonly used to assess the vitality domain in previous IC articles.[7,8,31] The MNA-SF has also been verified to have diagnostic consistency with the MNA scale in malnutrition and the risk of malnutrition among older adults.[41,42] The MNA-SF score ranged from 0 to 14. Malnutrition risk was considered a score ≤11, representing an impairment in the vitality domain. Older adults with vitality impairment received one score, and those with normal vitality received no score.

Psychology

Psychology was measured using the Geriatric Depression Scale-4 (GDS-4). Its diagnostic performance for depression in older populations has also received recognition.[43,44] Participants were asked four questions: "Do you feel satisfied with your life?" (yes/no, 0/1), "Do you often feel empty?" (yes/no, 1/0), "Do you often feel that something bad is about to happen?" (yes/no, 1/0), and "Do you feel happy most of the time?" (yes/no, 0/1). An impairment in the psychological domain was defined as a score of 2 or more out of 4. Older adults with psychology impairment received one score, and those with normal psychology received no score.

Hcy Detection

Fasting peripheral venous blood samples (5 mL) were collected by venipuncture in the morning, which were centrifuged for 15 min at 2500 r/min at room temperature. Serum and plasma samples were both collected in separate EP tubes and stored in a refrigerator at −80°C. Serum Hcy was measured by a two-reagent enzymatic assay using an Hcy kit (AxIS-Shield, Norway). All operations were performed strictly followed the detection instructions in DxC800 biochemical detector (Beckman Coulter, USA). Hcy was analyzed as continuous variable in this study.

Covariates

Participants were interviewed for demographic data including age (continuous variable), sex (female vs male), marital status (widowed vs others), education (high school or above vs less than high school), smoking (current or former vs never) and drinking (current or former vs never). Comorbidity was defined as the coexistence of two or more chronic diseases. Polypharmacy was defined as taking five or more long-term medications. The covariates were selected based on clinical relevance.

Statistical Analysis

Continuous variables are presented as the mean and standard deviation (SD) for normal distribution, and the median and interquartile range (IQR) for non-normal distribution. Categorical variables are presented as frequencies and percentages (%). Independent sample *t*-tests were applied for two-group comparisons of continuous variables with a normal distribution, and non-parametric tests were applied for two-group comparisons of continuous variables with a non-normal distribution. The differences in categorical variables were analyzed by the chi-squared test or Fisher's exact test.

The primary dependent variable in the study was low IC (dichotomic variable), using high IC as the reference group. The independent variable was Hcy (continuous variable). Considering that the low level of Hcy should also be a health risk factor similar to the high level of Hcy,[14] we supposed that the association between Hcy and low IC might be non-linear. Therefore, we used restricted cubic spline models with three knots at the 10th, 50th, and 90th percentiles of Hcy to test for potential non-linearity association of Hcy with low IC and impairments in IC five domains. The spline models were adjusted for age, gender, widowed, education, drinking, smoking, comorbidity, and polypharmacy. Additionally, piecewise linear regression was used to quantify the odds ratio (OR) per 5 μmol/L Hcy increase below and above the change point. We also performed sensitivity analyses for the association between Hcy and low IC. First, we examined the shape of Hcy-IC relation after excluding Hcy outliers. Second, the excluded population was later included for a reanalysis, the missing values of Hcy among them imputed by multiple imputation. Third, analysis was performed on log-transformed Hcy and low IC. Lastly, we redefined the low IC as a score of 4–5 to explore whether the relations between Hcy and low IC still existed.

All statistical analyses were conducted using R language (version 3.6.1) and SPSS (version 22.0). The hypothesis test was conducted by a two-sided test, and statistical significance was set at $P < 0.05$.

Results

Baseline Characteristics

The study included 1927 subjects (mean 72.0±7.2 years); 40.1% of them were male. As shown in Table 1, the median (IQR) for Hcy, Mini-cog score, gait speed and MNA-SF score in the older population were 8.45 (5.84, 11.25) μmol/L, 4.0 (3.0, 5.0), 0.84 (0.74, 0.94)m/s and 13.0 (12.0, 14.0). Supplementary Figure 1 presented the distribution of Hcy by gender. The Hcy level was 7.87(5.42, 10.42) in females and 9.44 (6.59, 12.71) in males. All participants were grouped into low IC and high IC. Compared with participants with high IC, those with low IC were older, more female, fewer smokers and drinkers, more likely to be widowed, less educated, with higher Hcy, lower gait speed, lower scores on the Mini-cog and MNA-SF, and vision or hearing impairments and depression, which had statistical significance. There was no statistically significant difference in comorbidity and polypharmacy between the low IC and high IC groups.

Association of Hcy with Low IC and Impairments in IC Domains

As shown in Figure 1, the association between Hcy and low IC was non-linear (P for non-linearity <0.05). In the restricted cubic spline models, a J-shaped non-linear association was observed. The change point, which was recognized as the nadir for risk of low IC, was estimated from piecewise linear models to be at a Hcy of 8.53 μmol/L. The OR of IC gently decreased until the Hcy change point and increased rapidly afterwards. Among the five domains of IC, Hcy also had a J-shaped non-linear association with impairments in cognition, sensory, vitality, and psychology, except for locomotion (P >0.05) in Figure 2.

Table 1 General Characteristics of Participants at Baseline

Characteristics	Total (n=1927)	Low IC (n=647)	High IC (n=1280)	*P*
Age (years), mean (SD)	72.0 ± 7.2	74.3 ± 7.8	70.9 ± 6.5	<0.001
Men, n (%)	773 (40.1)	214 (33.1)	559 (43.7)	<0.001
Widowed, n (%)	381 (19.8)	182 (28.1)	199 (15.5)	<0.001
High school or above, n (%)	1028 (53.3)	269 (41.6)	759 (59.3)	<0.001
Smoking, n (%)	306 (15.9)	83 (12.8)	223 (17.4)	0.009
Drinking, n (%)	278 (14.4)	70 (10.8)	208 (16.3)	0.001
Comorbidity, n (%)	1098 (57.0)	361 (55.8)	737 (57.6)	0.456
Polypharmacy, n (%)	548 (28.4)	195 (30.1)	353 (27.6)	0.239
Hcy (μmol/L), median (IQR)	8.45 (5.84, 11.25)	9.00 (5.96, 12.23)	8.08 (5.79, 10.82)	<0.001
Mini-cog score, median (IQR)	4.0 (3.0, 5.0)	3.0 (2.0, 3.0)	4.0 (4.0, 5.0)	<0.001
Gait speed (m/s), median (IQR)	0.84 (0.74, 0.94)	0.79 (0.67, 0.90)	0.87 (0.77, 0.97)	<0.001
Vision or hearing impairment, n (%)	1335 (69.3)	586 (90.6)	749 (58.5)	<0.001
MNA-SF score, median (IQR)	13.0 (12.0, 14.0)	11.0 (10.0, 12.0)	14.0 (12.0, 14.0)	<0.001
Depression, n(%)	166 (8.6)	147 (22.7)	19 (1.5)	<0.001

Note: Continuous variables were reported as mean (SD) or median (IQR), and categorical variables as percentages (%).
Abbreviations: SD, standard deviation; IQR, interquartile range; Hcy, homocysteine; IC, intrinsic capacity; MNA-SF, the Short-Form Mini Nutritional Assessment.

The piecewise linear regression analysis showed that (Table 2), the estimated OR of the IC per 5 μmol/L increase in Hcy was 0.753 (95% CI: 0.520–1.091) below 8.53 μmol/L and 1.176 (95% CI: 1.059–1.327) above this point. The risk of cognition, vitality, and psychology increased per 5 μmol/L increase in Hcy above the change point, with ORs of 1.116

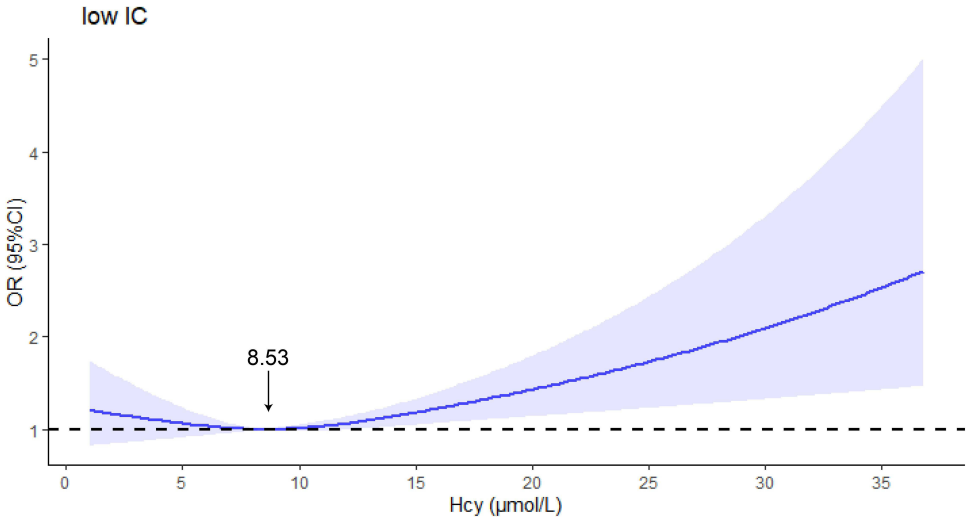

Figure 1 Association between Hcy and low IC based on the restricted cubic spline model. The solid lines represent OR, and the dashed line represent 95% CI. Hcy was modeled as a continuous variable with splines having 3 knots placed at the 10th, 50th, and 90th percentiles. A 95% CI for the OR that did not span 1.00 was considered *P* <0.05, and a 95% CI for the OR that did span 1.00 was considered *P* ≥0.05. The adjusted factors were age, gender, widowed, education, smoking, drinking, comorbidity, and polypharmacy.
Abbreviations: Hcy, homocysteine; IC, intrinsic capacity.

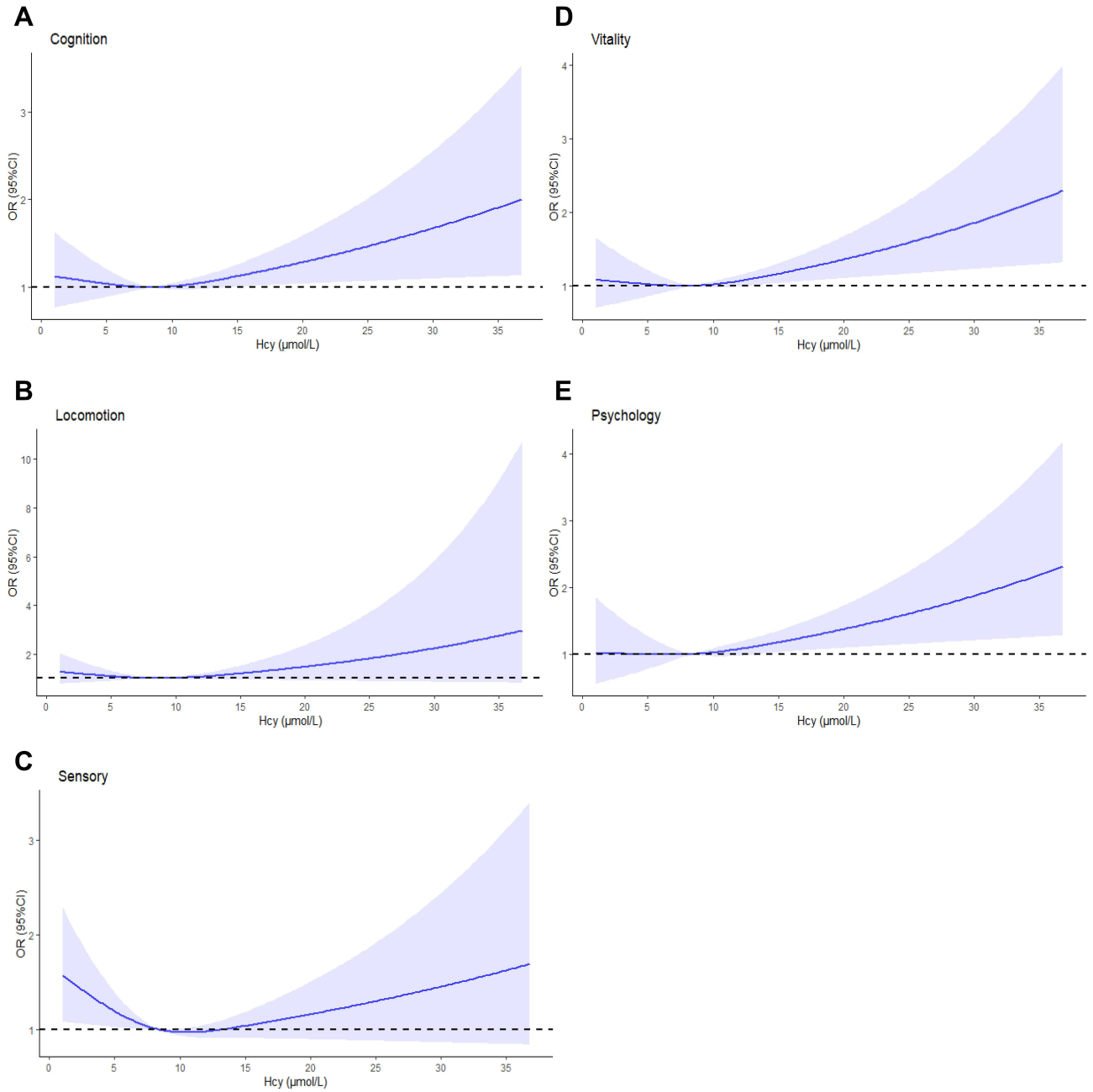

Figure 2 Association between Hcy and impairments in IC domains based on the restricted cubic spline model. The graphs indicate the associations of impairments in cognition domain (**A**), locomotion domain (**B**), sensory domain (**C**), vitality domain (**D**), and psychology domain (**E**) with Hcy separately among older adults. The solid lines represent OR, and the dashed line represent 95% CI. Hcy was modeled as a continuous variable with splines having 3 knots placed at the 10th, 50th, and 90th percentiles. A 95% CI for the OR that did not span 1.00 was considered P <0.05, and a 95% CI for the OR that did span 1.00 was considered P ≥0.05. The adjusted factors were age, gender, widowed, education, smoking, drinking, comorbidity, and polypharmacy.
Abbreviations: Hcy, homocysteine; IC, intrinsic capacity.

(1.009–1.247), 1.167 (1.055–1.305), and 1.160 (1.034–1.303). Hcy had a negative correlation with sensory below the Hcy change point (OR: 0.679, 95% CI: 0.470–0.976), and no significant association was found between Hcy and sensory above the Hcy change point.

Sensitivity Analyses

We performed restricted cubic spline analysis in participants excluding Hcy outliers (n=1850), which showed a U-shaped non-linear association between Hcy and low IC (P for non-linearity <0.05, Figure 3A). After including the initially

Table 2 Association of Hcy with Low IC and Impairments in IC Domains Below and Above the Change Point Among Older Adults Based on Piecewise Linear Regression

	OR per 5 μmol/L Hcy Increase Below Change Point (95% CI)	*P*	OR per 5 μmol/L Hcy Increase Above Change Point (95% CI)	*P*
Low IC	0.753 (0.520–1.091)	0.132	1.176 (1.059–1.327)	0.005
Impairments in IC domains				
Cognition	0.749 (0.516–1.089)	0.129	1.116 (1.009–1.247)	0.042
Locomotion	0.841 (0.537–1.306)	0.444	1.213 (0.998–1.591)	0.112
Sensory	0.679 (0.470–0.976)	0.038	1.075 (0.966–1.230)	0.235
Vitality	0.990 (0.644–1.531)	0.964	1.167 (1.055–1.305)	0.004
Psychology	0.683 (0.372–1.266)	0.221	1.160 (1.034–1.303)	0.009

Note: The adjusted factors were age, gender, widowed, education, smoking, drinking, comorbidity, and polypharmacy.
Abbreviations: Hcy, homocysteine; IC, intrinsic capacity.

excluded population and conducting multiple imputation for the missing values of Hcy, the reanalysis was performed on 2046 participants. Figure 3B indicates that Hcy had a J-shaped non-linear association with low IC (*P* for non-linearity <0.001). Thus, log-transformed for Hcy or using a different definition of low IC did not qualitatively alter the result of non-linear relation between Hcy and low IC (*P* for non-linearity <0.001, Figure 3C and D).

Discussion

Our study showed that males had higher Hcy levels than females, which was consistent with previous researches.[16,17] Hcy levels in older adults were higher in the low IC group than in the high group. A nonlinear association between Hcy and low IC was verified, and Hcy was also associated with cognition, sensory, vitality, and psychology among the five domains of IC. We confirmed that the risk of IC decline increased with elevations in Hcy levels when Hcy reached 8.53 μmol/L and above. However, once Hcy was lower than 8.53 μmol/L, the negative correlation between Hcy and low IC was of no statistical significance. Furthermore, a sensitivity analysis was performed to strengthen the results of the nonlinear relation between Hcy and low IC.

IC can reflect the physiologic reserve of individuals, and has been used as a predictor of frailty, disability, and other adverse outcomes in recent studies involving different populations. Among older hospitalized patients, Chen et al found a predictive value of IC for new disability and one year after hospital discharge.[31] Alexia et al completed a three-year follow-up in a cohort of Belgian 28 nursing homes, indicating that the locomotion and nutrition domains of IC were associated with the risk of mortality and falling.[34] The INCUR study found a relationship between higher IC levels and lower risk of adverse outcomes in nursing home residents.[45] Focusing on community-dwelling older adults, a number of cross-sectional and longitudinal studies showed that the decline in IC had a positive association with an increased risk of incident disability, frailty, and other negative health outcomes.[6,33] There have also been several studies from the perspective of the trajectory in IC change to discuss the connection between IC and frailty[8] or mortality.[46] Chew et al used cluster analysis to conclude that the evaluation of IC could be complementary to the prognosis risk stratification in prefrail individuals.[47] Screening for IC impairments might provide better predictability of disability compared to the comorbidity status, which means that the function-centered geriatric concept should receive more emphasis.[10]

By virtue of the close correlations between IC and multiple adverse outcomes, there is an increased need for the early identification of related factors to prevent the decline in IC. Currently, a few scholars have investigated the effects of various exercises and dietary patterns on IC. A single-blind randomized controlled trial suggested that a 26-week aerobic training course and resistance training plus self-paced home training could lead to improvements in IC in older adults

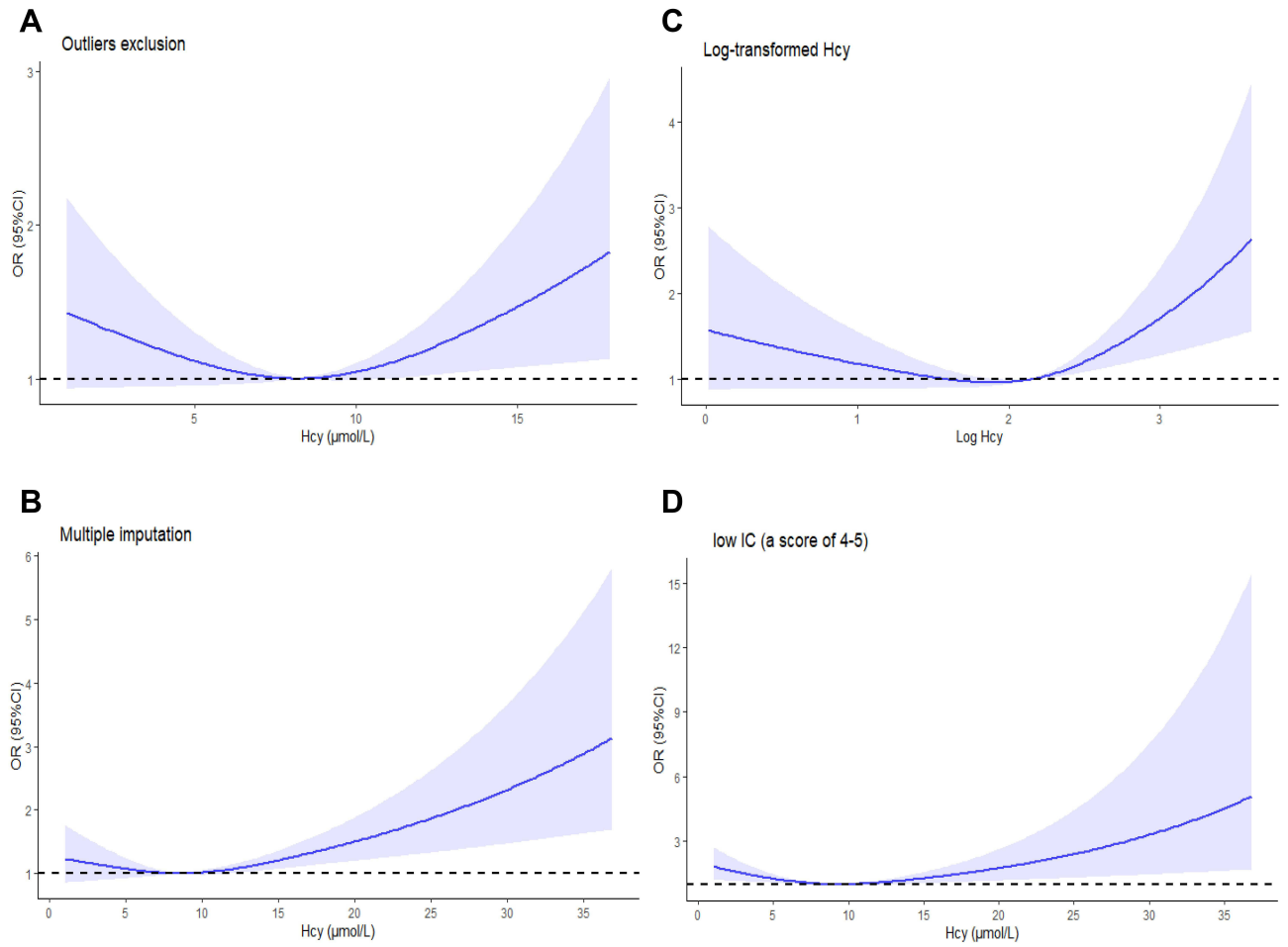

Figure 3 Sensitivity analyses of association between Hcy and low IC based on the restricted cubic spline model. The graphs indicate the associations of low IC with Hcy after the exclusion of Hcy outliers (**A**), multiple imputations for the missing values (**B**), log transformation for Hcy (**C**), and the change for low IC definition (**D**) separately among older adults.The solid lines represent OR, and the dashed line represent 95% CI. Hcy was modeled as a continuous variable with splines having 3 knots placed at the 10th, 50th, and 90th percentiles. A 95% CI for the OR that did not span 1.00 was considered $P < 0.05$, and a 95% CI for the OR that did span 1.00 was considered $P \geq 0.05$. The adjusted factors were age, gender, widowed, education, smoking, drinking, comorbidity, and polypharmacy.
Abbreviations: Hcy, homocysteine; IC, intrinsic capacity.

with subjective memory concerns, but the effects were weakened later.[48] Huang et al identified that "fruits and vegetables" and "protein-rich" dietary patterns were positively associated with high IC by using the food frequency questionnaire.[36] Moreover, Yeung proposed the view that there might be sex differences in the association between dietary patterns and IC.[49]

Except for lifestyle modifications, IC-related biomarkers have also been explored. N-terminal pro-B-type natriuretic peptide (NT-proBNP) was found to be associated with a decline in IC.[9] A secondary analysis of CRELES indicated that allostatic load was an independent risk factor of IC, even after adjusting for socioeconomic factors and chronic diseases. The allostatic load was a multi-system comprehensive index reflecting disorders of physiological systems by using ten biomarkers of five biological systems (hypothalamic-pituitary-adrenal axis, sympathetic nervous system, inflammatory system, metabolic system, and cardiovascular system), which applied the sex-specific parameters and was calculated as a composite score.[50] Besides, biomarkers that can reflect chronic inflammatory states, such as tumor necrosis factor receptor 1 (TNFR1),[37] C-reactive protein (CRP),[51] and Hcy, have been found to be related to the impairment of IC domains. In the MAPT study, the IC score decreased among participants with hyperhomocysteine during the five-year follow-up, but the group difference between normal Hcy and hyperhomocysteine on IC score did not persist after adjusting for confounders, and only handgrip strength remained significant.[51] Our study is the first study on the correlation between Hcy and IC in a Chinese population, which obtained a similar result to the MAPT study that high Hcy was associated with a decline in IC.

But there are still some discrepancies between the two studies. The MAPT study was a longitudinal study to examine the IC score change in different Hcy groups targeting community-dwelling populations aged ≥70 years with spontaneous memory complaints. Our study was conducted to explore the association of Hcy (a continuous variable) with low IC (a dichotomous variable) among older people aged ≥60 years residing in the community.

Two potential explanations may be proposed for the correlation between Hcy and IC. On the one hand, elevated Hcy promotes inflammatory reactions and mitochondrial malfunction,[14,27] which are crucial mechanisms of aging at the biomolecular level. These underlying changes may ultimately influence IC and the expression of functional ability when individuals are faced with various stressors.[12] On the other hand, Hcy is closely related to the cognitive and physical reserve of individuals, and are the main domains of IC. For instance, numerous studies have revealed that high Hcy might have a negative effect on cognitive function among older adults.[52,53] Regarding sensory aspects, Gopinath found that participants with elevated tHcy (>20 mmol/L) had an increased prevalence of age-related hearing dysfunction in a cross-sectional study, but the correlation did not hold up in a longitudinal study.[54] Martínez demonstrated that the correlation between hyperhomocysteinemia induced by folate deficiency and premature hearing dysfunction involved the impairment of cochlear Hcy metabolism.[55] Some studies have reported that Hcy might be associated with cataracts and age-related macular degeneration, which are major causes of vision loss in older adults, but the relevance is still in dispute.[14,15] Moreover, Hcy is strongly related to nutrition, due to the fact that Hcy is an intermediate product of methionine metabolism, which can be affected by vitamin B6, folate, and vitamin B12, especially in older adults with insufficient nutrient intake.[13,14] At the psychological level, a meta-analysis summarized that subjects with hyperhomocysteinaemia had a higher probability of depression.[56] The result of our study shows that elevated Hcy is associated with impairments in cognition, sensory, vitality, and psychology, accordance with the studies described above. However, the heterogeneity of the diagnostic tools was non-negligible. Some earlier studies discussed the effect of high Hcy on the decline in gait speed,[23] but this study was not powered to draw such an inference.

There are some strengths that need to be acknowledged. Our study is one of the early researches investigating the related biomarkers of IC and the first to explore the association between Hcy and IC in the older Chinese population. Hcy has attracted much attention in the fields of cardiology and neurology due to its predictive effect on cardiovascular and cerebrovascular diseases. In recent years, more and more studies have explored the relationship between Hcy and aging diseases. This study indicated that Hcy might be associated with the decline of IC among older adults, suggesting more necessity to regard Hcy as a routine health examination item for the senior population. Meanwhile, we also revealed that Hcy might be developed as a potential biomarker of IC. The increase of Hcy (Hcy>8.53umol/L) may have important implications for clinicians to identify the decline of IC earlier. Besides, the abnormally low level of Hcy needs concern. Although we did not obtain a statistical association between low Hcy and low IC, it deserves more studies to investigate and verify in the future. In addition, this study presents a certain degree of precision. Restricted cubic spline models were performed to explore the nonlinear relationship of Hcy and the low IC in order adults, and the sensitivity analysis confirmed the robustness.

Several limitations should also be considered. Firstly, this was a cross-sectional study that only evaluated an association but could not prove a causal effect of elevated Hcy on the decline in IC. Future longitudinal research is warranted to establish the IC trajectory and further test this hypothesis. Moreover, the generalizability of our findings to older adults of different ethnicities or older adults of Chinese ancestry not living in China is uncertain. It needs further prospective study with multiple populations and larger sample size to explore because Hcy is influenced by many factors such as heredity, diet, and lifestyles, which vary in different ethnicities and living environments.

Conclusion

In conclusion, Hcy was associated with low IC, as well as impairments in cognition, sensory, vitality, and psychology, even after adjusting for demographic status, comorbidity, and polypharmacy. Hcy may be considered as an IC-related biomarker, but its predictive effect needs further longitudinal studies for confirmation.

Abbreviations

Hcy, homocysteine; IC, intrinsic capacity; MNA-SF, the Short-Form Mini Nutritional Assessment.

Data Sharing Statement

The datasets generated and analyzed during the current study are available from the corresponding author on reasonable request.

Ethics Approval and Informed Consent

The design and procedures of the study were performed in accordance with the principles of the Declaration of Helsinki. The study was approved by the Fujian Provincial Hospital research ethics committee (K2020-05-032). Written informed consent was obtained from all participants.

Consent for Publication

The participants consented to the submission of their data to the journal.

Acknowledgments

We are grateful for the support from Fujian Provincial Center for Geriatrics and Fujian Provincial Institute of Clinical Geriatrics. We appreciate the technical assistance of the Institute of Fujian Provincial Key Laboratory of Geriatrics.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Funding

This study was supported by Fujian Science and Technology Innovation Joint Major Project (2019Y9027), and Firestone Foundation of Fujian Provincial Hospital (2019HSJJ27).

Disclosure

The authors have no conflict of interest.

References

1. Beard JR, Officer A, de Carvalho IA, et al. The World report on ageing and health: a policy framework for healthy ageing. *Lancet*. 2016;387(10033):2145–2154. doi:10.1016/S0140-6736(15)00516-4
2. Zhou Y, Ma L. Intrinsic capacity in older adults: recent advances. *Aging Dis*. 2022;13(2):353–359. doi:10.14336/AD.2021.0818
3. World Health Organization. *Integrated Care for Older People: Guidelines on Community-Level Interventions to Manage Declines in Intrinsic Capacity*. Geneva: World Health Organization; 2017.
4. George PP, Lun P, Ong SP, Lim WS. A rapid review of the measurement of intrinsic capacity in older adults. *J Nutr Health Aging*. 2021;25(6):774–782. doi:10.1007/s12603-021-1622-6
5. Chhetri JK, Xue QL, Ma L, Chan P, Varadhan R. Intrinsic capacity as a determinant of physical resilience in older adults. *J Nutr Health Aging*. 2021;25(8):1006–1011. doi:10.1007/s12603-021-1629-z
6. González-Bautista E, de Souto Barreto P, Andrieu S, Rolland Y, Vellas B. Screening for intrinsic capacity impairments as markers of increased risk of frailty and disability in the context of integrated care for older people: secondary analysis of MAPT. *Maturitas*. 2021;150:1–6. doi:10.1016/j.maturitas.2021.05.011
7. Leung A, Su JJ, Lee E, Fung J, Molassiotis A. Intrinsic capacity of older people in the community using WHO Integrated Care for Older People (ICOPE) framework: a cross-sectional study. *BMC Geriatr*. 2022;22(1):304. doi:10.1186/s12877-022-02980-1
8. Liu S, Kang L, Liu X, et al. Trajectory and correlation of intrinsic capacity and frailty in a Beijing elderly community. *Front Med*. 2021;8:751586. doi:10.3389/fmed.2021.751586
9. Ma L, Zhang Y, Liu P, et al. Plasma N-terminal pro-B-type natriuretic peptide is associated with intrinsic capacity decline in an older population. *J Nutr Health Aging*. 2021;25(2):271–277. doi:10.1007/s12603-020-1468-3
10. Zhao J, Chhetri JK, Chang Y, Zheng Z, Ma L, Chan P. Intrinsic capacity vs. multimorbidity: a function-centered construct predicts disability better than a disease-based approach in a community-dwelling older population cohort. *Front Med*. 2021;8:753295. doi:10.3389/fmed.2021.753295
11. Ma L, Chhetri JK, Zhang Y, et al. Integrated care for older people screening tool for measuring intrinsic capacity: preliminary findings from ICOPE pilot in China. *Front Med*. 2020;7:576079. doi:10.3389/fmed.2020.576079
12. Beard JR, Si Y, Liu Z, Chenoweth L, Hanewald K. Intrinsic capacity: validation of a new WHO concept for healthy aging in a longitudinal Chinese study. *J Gerontol a Biol Sci Med Sci*. 2022;77(1):94–100. doi:10.1093/gerona/glab226

13. Kumar A, Palfrey HA, Pathak R, Kadowitz PJ, Gettys TW, Murthy SN. The metabolism and significance of homocysteine in nutrition and health. *Nutr Metab*. 2017;14:78. doi:10.1186/s12986-017-0233-z
14. Koklesova L, Mazurakova A, Samec M, et al. Homocysteine metabolism as the target for predictive medical approach, disease prevention, prognosis, and treatments tailored to the person. *EPMA J*. 2021;12(4):1–29. doi:10.1007/s13167-021-00263-0
15. Smith AD, Refsum H. Homocysteine - from disease biomarker to disease prevention. *J Intern Med*. 2021;290(4):826–854. doi:10.1111/joim.13279
16. Cohen E, Margalit I, Shochat T, Goldberg E, Krause I. Gender differences in homocysteine concentrations, a population-based cross-sectional study. *Nutr Metab Cardiovasc Dis*. 2019;29(1):9–14. doi:10.1016/j.numecd.2018.09.003
17. Xu R, Huang F, Wang Y, Liu Q, Lv Y, Zhang Q. Gender- and age-related differences in homocysteine concentration: a cross-sectional study of the general population of China. *Sci Rep*. 2020;10(1):17401. doi:10.1038/s41598-020-74596-7
18. Tu W, Yan F, Chao B, Ji X, Wang L. Status of hyperhomocysteinemia in China: results from the China Stroke High-risk Population Screening Program, 2018. *Front Med*. 2021;15(6):903–912. doi:10.1007/s11684-021-0871-4
19. Lim HS, Heo YR. Plasma total homocysteine, folate, and vitamin B12 status in Korean adults. *J Nutr Sci Vitaminol*. 2002;48(4):290–297. doi:10.3177/jnsv.48.290
20. Adachi H, Hirai Y, Fujiura Y, Matsuoka H, Satoh A, Imaizumi T. Plasma homocysteine levels and atherosclerosis in Japan: epidemiological study by use of carotid ultrasonography. *Stroke*. 2002;33(9):2177–2181. doi:10.1161/01.STR.0000026861.18199.89
21. Ganji V, Kafai MR. Population reference values for plasma total homocysteine concentrations in US adults after the fortification of cereals with folic acid. *Am J Clin Nutr*. 2006;84(5):989–994. doi:10.1093/ajcn/84.5.989
22. Nurk E, Tell GS, Vollset SE, et al. Changes in lifestyle and plasma total homocysteine: the Hordaland Homocysteine Study. *Am J Clin Nutr*. 2004;79(5):812–819. doi:10.1093/ajcn/79.5.812
23. Vidoni ML, Pettee Gabriel K, Luo ST, Simonsick EM, Day RS. Vitamin B12 and homocysteine associations with gait speed in older adults: the Baltimore longitudinal study of aging. *J Nutr Health Aging*. 2017;21(10):1321–1328. doi:10.1007/s12603-017-0893-4
24. Álvarez-Sánchez N, Álvarez-Ríos AI, Guerrero JM, et al. Homocysteine levels are associated with bone resorption in pre-frail and frail Spanish women: the Toledo Study for Healthy Aging. *Exp Gerontol*. 2018;108:201–208. doi:10.1016/j.exger.2018.04.019
25. Lee WJ, Peng LN, Loh CH, Chen LK. Sex-different associations between serum homocysteine, high-sensitivity C-reactive protein and sarcopenia: results from I-lan longitudinal aging study. *Exp Gerontol*. 2020;132:110832. doi:10.1016/j.exger.2020.110832
26. Álvarez-Sánchez N, Álvarez-Ríos AI, Guerrero JM, et al. Homocysteine and C-reactive protein levels are associated with frailty in older Spaniards: the Toledo study for healthy aging. *J Gerontol a Biol Sci Med Sci*. 2020;75(8):1488–1494. doi:10.1093/gerona/glz168
27. Chen LT, Xu TT, Qiu YQ, et al. Homocysteine induced a calcium-mediated disruption of mitochondrial function and dynamics in endothelial cells. *J Biochem Mol Toxicol*. 2021;35(5):e22737. doi:10.1002/jbt.22737
28. Majumder A, Singh M, Behera J, et al. Hydrogen sulfide alleviates hyperhomocysteinemia-mediated skeletal muscle atrophy via mitigation of oxidative and endoplasmic reticulum stress injury. *Am J Physiol Cell Physiol*. 2018;315(5):C609–C622. doi:10.1152/ajpcell.00147.2018
29. Belloni G, Cesari M. Frailty and intrinsic capacity: two distinct but related constructs. *Front Med*. 2019;6:133. doi:10.3389/fmed.2019.00133
30. Tsoi KK, Chan JY, Hirai HW, Wong SY, Kwok TC. Cognitive tests to detect dementia: a systematic review and meta-analysis. *JAMA Intern Med*. 2015;175(9):1450–1458. doi:10.1001/jamainternmed.2015.2152
31. Zeng X, Shen S, Xu L, et al. The impact of intrinsic capacity on adverse outcomes in older hospitalized patients: a one-year follow-up study. *Gerontology*. 2021;67(3):267–275. doi:10.1159/000512794
32. Arokiasamy P, Selvamani Y, Jotheeswaran AT, Sadana R. Socioeconomic differences in handgrip strength and its association with measures of intrinsic capacity among older adults in six middle-income countries. *Sci Rep*. 2021;11(1):19494. doi:10.1038/s41598-021-99047-9
33. Gutiérrez-Robledo LM, García-Chanes RE, González-Bautista E, Rosas-Carrasco O. Validation of two intrinsic capacity scales and its relationship with frailty and other outcomes in Mexican community-dwelling older adults. *J Nutr Health Aging*. 2021;25(1):33–40. doi:10.1007/s12603-020-1555-5
34. Charles A, Buckinx F, Locquet M, et al. Prediction of adverse outcomes in nursing home residents according to intrinsic capacity proposed by the World Health Organization. *J Gerontol a Biol Sci Med Sci*. 2020;75(8):1594–1599. doi:10.1093/gerona/glz218
35. Chen LK, Woo J, Assantachai P, et al. Asian Working Group for sarcopenia: 2019 consensus update on sarcopenia diagnosis and treatment. *J Am Med Dir Assoc*. 2020;21(3):300–307.e2. doi:10.1016/j.jamda.2019.12.012
36. Huang CH, Okada K, Matsushita E, et al. Dietary patterns and intrinsic capacity among community-dwelling older adults: a 3-year prospective cohort study. *Eur J Nutr*. 2021;60(6):3303–3313. doi:10.1007/s00394-021-02505-3
37. Ma L, Liu P, Zhang Y, Sha G, Zhang L, Li Y. High serum tumor necrosis factor receptor 1 levels are related to risk of low intrinsic capacity in elderly adults. *J Nutr Health Aging*. 2021;25(4):416–418. doi:10.1007/s12603-020-1533-y
38. Ramírez-Vélez R, Correa-Bautista JE, García-Hermoso A, Cano CA, Izquierdo M. Reference values for handgrip strength and their association with intrinsic capacity domains among older adults. *J Cachexia Sarcopenia Muscle*. 2019;10(2):278–286. doi:10.1002/jcsm.12373
39. Huang CH, Okada K, Matsushita E, et al. The association of social frailty with intrinsic capacity in community-dwelling older adults: a prospective cohort study. *BMC Geriatr*. 2021;21(1):515. doi:10.1186/s12877-021-02466-6
40. Prince MJ, Acosta D, Guerra M, et al. Intrinsic capacity and its associations with incident dependence and mortality in 10/66 Dementia Research Group studies in Latin America, India, and China: a population-based cohort study. *PLoS Med*. 2021;18(9):e1003097. doi:10.1371/journal.pmed.1003097
41. Lera L, Sánchez H, Ángel B, Albala C. Mini nutritional assessment short-form: validation in five Latin American cities. SABE study. *J Nutr Health Aging*. 2016;20(8):797–805. doi:10.1007/s12603-016-0696-z
42. Kaiser MJ, Bauer JM, Ramsch C, et al. Validation of the Mini Nutritional Assessment short-form (MNA-SF): a practical tool for identification of nutritional status. *J Nutr Health Aging*. 2009;13(9):782–788. doi:10.1007/s12603-009-0214-7
43. Krishnamoorthy Y, Rajaa S, Rehman T. Diagnostic accuracy of various forms of geriatric depression scale for screening of depression among older adults: systematic review and meta-analysis. *Arch Gerontol Geriatr*. 2020;87:104002. doi:10.1016/j.archger.2019.104002
44. Johansson S, Lövheim H, Olofsson B, Gustafson Y, Niklasson J. A clinically feasible short version of the 15-item geriatric depression scale extracted using item response theory in a sample of adults aged 85 years and older. *Aging Ment Health*. 2022;26(2):431–437. doi:10.1080/13607863.2021.1881759

45. Sánchez-Sánchez JL, Rolland Y, Cesari M, de Souto Barreto P. Associations between intrinsic capacity and adverse events among nursing home residents: the INCUR study. *J Am Med Dir Assoc*. 2022;23(5):872–876.e4. doi:10.1016/j.jamda.2021.08.035
46. Locquet M, Sanchez-Rodriguez D, Bruyère O, et al. Intrinsic capacity defined using four domains and mortality risk: a 5-year follow-up of the SarcoPhAge cohort. *J Nutr Health Aging*. 2022;26(1):23–29. doi:10.1007/s12603-021-1702-7
47. Chew J, Lim JP, Yew S, et al. Disentangling the relationship between frailty and intrinsic capacity in healthy community-dwelling older adults: a cluster analysis. *J Nutr Health Aging*. 2021;25(9):1112–1118. doi:10.1007/s12603-021-1679-2
48. Huang CH, Umegaki H, Makino T, et al. Effect of various exercises on intrinsic capacity in older adults with subjective cognitive concerns. *J Am Med Dir Assoc*. 2021;22(4):780–786.e2. doi:10.1016/j.jamda.2020.06.048
49. Yeung S, Sin D, Yu R, Leung J, Woo J. Dietary patterns and intrinsic capacity in community-dwelling older adults: a cross-sectional study. *J Nutr Health Aging*. 2022;26(2):174–182. doi:10.1007/s12603-022-1742-7
50. Gutiérrez-Robledo LM, García-Chanes RE, Pérez-Zepeda MU. Allostatic load as a biological substrate to intrinsic capacity: a secondary analysis of CRELES. *J Nutr Health Aging*. 2019;23(9):788–795. doi:10.1007/s12603-019-1251-5
51. Giudici KV, de Souto Barreto P, Guerville F, et al. Associations of C-reactive protein and homocysteine concentrations with the impairment of intrinsic capacity domains over a 5-year follow-up among community-dwelling older adults at risk of cognitive decline (MAPT Study). *Exp Gerontol*. 2019;127:110716. doi:10.1016/j.exger.2019.110716
52. Alghadir AH, Gabr SA, Anwer S, Li H. Associations between vitamin E, oxidative stress markers, total homocysteine levels, and physical activity or cognitive capacity in older adults. *Sci Rep*. 2021;11(1):12867. doi:10.1038/s41598-021-92076-4
53. Nelson ME, Andel R, Nedelska Z, et al. The association between homocysteine and memory in older adults. *J Alzheimers Dis*. 2021;81(1):413–426. doi:10.3233/JAD-201558
54. Gopinath B, Flood VM, Rochtchina E, McMahon CM, Mitchell P. Serum homocysteine and folate concentrations are associated with prevalent age-related hearing loss. *J Nutr*. 2010;140(8):1469–1474. doi:10.3945/jn.110.122010
55. Martínez-Vega R, Garrido F, Partearroyo T, et al. Folic acid deficiency induces premature hearing loss through mechanisms involving cochlear oxidative stress and impairment of homocysteine metabolism. *FASEB J*. 2015;29(2):418–432. doi:10.1096/fj.14-259283
56. Moradi F, Lotfi K, Armin M, Clark C, Askari G, Rouhani MH. The association between serum homocysteine and depression: a systematic review and meta-analysis of observational studies. *Eur J Clin Invest*. 2021;51(5):e13486. doi:10.1111/eci.13486