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Association of cognitive frailty with subsequent all-cause mortality among middle-aged and older adults in 17 countries

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What is the primary question addressed by this study?

What is the association between different cognitive frailty status at baseline and subsequent all-cause mortality?

What is the main finding of this study?

In six prospective cohort study including 71,553 participants from 17 countries, we found that cognitive frailty was associated with an increased risk of all-cause mortality than cognitive impairment and frailty alone for people aged 50 years and older. The mortality risk of cognitive frailty was higher in people aged 70 years and older, males, single and non-consumers of alcohol.

What is the meaning of the finding?

Our results highlight the need to pay more attention to cognitive frailty in older people as early as possible to reduce its impact on mortality with the development of population aging.

Title page

Association of cognitive frailty with subsequent all-cause mortality among middle-aged and older adults in 17 countries

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Abstract

Objectives: Cognitive frailty refers to the co-occurrence of cognitive impairment and frailty without concurrent Alzheimer's disease or dementia. Studies of cognitive frailty and mortality have been limited to single country or older people. However, frailty and cognitive decline may occur much earlier. We aimed to examine the association between different cognitive frailty status and subsequent all-cause mortality among middle-aged and older people in 17 countries.

Methods: Participants aged 50 and over were drawn from six prospective cohorts of aging. We classified participants according to their cognitive impairment and frailty status into the following groups: none, only cognitive impairment, only frailty and cognitive frailty. Competing-risks regression models were used to evaluate the association of different cognitive frailty status at baseline with subsequent all-cause mortality.

Results: The cognitive frailty group had a higher mortality risk compared to those without cognitive impairment and frailty groups. Meta-analysis results showed participants with cognitive frailty (pooled subhazard ratio [SHR]=2.34, 95% confidence interval [CI]: 2.01-2.72, I^2=68.0%) had a higher mortality risk compared with those with only cognitive impairment status (pooled SHR=1.36, 95% CI: 1.25-1.48, I^2=3.0%) or only frailty status (pooled SHR=1.83, 95% CI: 1.72-1.95, I^2=31.0%). The association between cognitive frailty and mortality were stronger among those who were aged 70 years and older, males, single and non-consumers of alcohol.

Conclusions: Cognitive frailty, frailty or cognitive impairment alone, is associated with an increased risk of all-cause mortality in Asian, European and American countries. Physical and

cognitive function screening should be conducted as early as possible in middle-aged and older people, and targeted intervention approaches should be developed to reduce the incidence of adverse health outcomes.

Keywords: Cognitive frailty, frailty, cognitive impairment, mortality, cohort study

Introduction

Population aging has led to a significant increase in age-related health problems. Cognitive impairment and frailty are among the two most common geriatric syndromes.[1] Cognitive impairment is the decline of intellectual functions such as thinking, remembering, reasoning and planning.[2] Frailty is a complex clinical condition characterized by a decline in functioning across multiple physiological systems, with a resultant increased vulnerability to stressors.[3] Both cognitive impairment and frailty directly impact on health, increasing disability, reducing quality of life, and contributing to a higher risk of adverse outcomes.[4] Both conditions also lead to high direct and indirect costs to healthcare, often long-term care and hospitalization.[5] The close association is seen between cognitive impairment and frailty, with potential shared physiological links.[6] Frailty increases the risk of future cognitive decline and cognitive impairment increases the risk of frailty, suggesting that cognition and frailty work together to accelerate physical and cognitive decline.[2]

In 2013, an international consensus group proposed the concept and operational definition of cognitive frailty; that is, co-occurrence of cognitive impairment and frailty without concurrent Alzheimer's disease or dementia.[7] Meta-analyses showed that participants classified as cognitive frailty had a 3.66 to 5.58 times higher risk of dementia than participants who were robust or without cognitive frailty.[8,9] The pooled hazard ratio for dementia was 5.36 for cognitive frailty, which was higher than the 3.83 for non-frail cognitive impairment and the 1.47 for isolated frailty.[10] Cognitive frailty may be a physiological precursor to the degenerative nervous system diseases, which could play a key role in predicting the short- and long-term adverse health outcomes such as falls, disability, hospitalization, dementia, and

all-cause mortality.[8,11] All-cause mortality rate of the oldest old with cognitive frailty was 1.99 to 2.65 times higher than that of normal and healthy older adults in the United States (cognition assessed using the Mini-Mental State Examination [MMSE]; frailty assessed using the Fried phenotype [FP]), Japan (self-reported-cognitive decline; the Kihon Checklist), and China (MMSE; the frailty index [FI]).[12-14] Similar findings have been reported among older adults aged 65 years and older in France (MMSE and the Isaacs Set Test; FP), Italy (subjective cognitive decline; FP), Canada (MMSE; FI), and South Korea (MMSE; FP).[15-18] Individuals with cognitive frailty had a higher risk of dementia/mortality compared with individuals with isolated frailty or cognitive impairment.[10,19]

However, current studies have several limitations. First, studies have been limited to single country at a time, with low comparability across countries given differences in measurement instruments between studies. Such mortality estimates among participants with cognitive frailty could be inflated due to the high study heterogeneity for the meta-analysis findings. Second, most of the study population was 65 or 60 years of age or older, whereas frailty and cognitive decline may have occurred earlier.[20] In a previous study from Singapore, individuals with cognitive frailty had a fivefold increased mortality risk among adults aged 55 years and older.[19] From this perspective, an earlier age group of such issues have not been well examined.

This study therefore conducted a multi-cohort study based on six large, representative sample of adults aged 50 years and older across 17 nations, aiming to: (1) investigate the association between different cognitive frailty status and subsequent all-cause mortality; (2) estimate the overall effect sizes of cognitive frailty and mortality risk for all countries; and (3)

examine which groups of the population were at higher risk for cognitive frailty and mortality.

Methods

Study design and participants

We obtained data from six prospective cohorts of aging: the China Health and Retirement Longitudinal Study (CHARLS);[21] the Korean Longitudinal Study of Aging (KLoSA);[22] the English Longitudinal Study on Ageing (ELSA);[23] the Survey of Health, Ageing and Retirement in Europe (SHARE: Austria, Belgium, Switzerland, Germany, Denmark, Spain, France, Greece, Italy, Israel, Netherlands, and Sweden);[24] the Health and Retirement Study (HRS);[25] and the Mexican Health and Aging Study (MHAS).[26]

In this study, the baseline wave was wave 1 in CHARLS, KLoSA, ELSA, and SHARE, wave 4 in HRS, and wave 2 in MHAS. The dementia or Parkinson's disease and cognition variables were not measured at earlier waves in HRS and MHAS. To estimate mortality risk, follow-up data were used from waves 2 to 4 in CHARLS, waves 2 to 8 in KLoSA, waves 2 to 9 in ELSA, waves 2 to 8 in SHARE, waves 5 to 14 in HRS, and waves 3 to 5 in MHAS. Table 1 gives details of the sample characteristics. The number of respondents was highest in SHARE, mortality follow-up longest in HRS. Each year the survey is conducted would be considered a wave.[27]

Flowcharts of sample selection are shown in Supplementary Figures S1-S6. Participants were recruited if they attended baseline survey. Participants were excluded if they were aged <50 years, or had dementia or Parkinson's disease, or had missing information on cognitive frailty and covariates. Furthermore, participants without date of death and survival time (loss to follow-up occurred at baseline and during the first follow-up visit) were excluded. Finally,

the analytical samples were 9,522 CHARLS, 7,793 KLoSA, 8,643 ELSA, 23,321 SHARE, 11,469 HRS, and 10,805 MHAS participants.

Measures

Three sets of cognitive function tests were completed to assess cognitive impairment, including an immediate word recall test, a delayed word recall test, and an orientation to date test (Supplementary Table S1). For the immediate and delayed word recall, participants were asked to recite 10 words in CHARLS, ELSA, SHARE, and HRS; 3 words in KLoSA; and 8 words in MHAS. At orientation to date, participants were asked if they could remember the date of that day (day of week, day of month, month, and year in CHARLS, KLoSA, ELSA, SHARE, and HRS; day of month, month, and year in MHAS). Participants who performed 1.5 standard deviations below the mean of the score in two or three tests, compared to the total population aged 50 and over with the same level of education within the database were defined as cognitive impairment.[28,29] Frailty was evaluated by the frailty index (FI). Under the deficit accumulation model developed by Searle et al, we constructed the FI following a standard procedure.[30] To harmonize the frailty assessment of data from the six cohorts, we selected 29 items to construct the FI, including variables of self-reported health status, functional limitations, mobility, chronic diseases, and psychological characteristics (Supplementary Table S2). Mobility limitations data were not available in KLoSA, and we used seven functional limitations instead. Functional limitations in CHARLS, ELSA, SHARE, MHAS was that the respondent reported some difficulty with the activity and in HRS was that the respondent reported any difficulty with the activity. In KLoSA was the respondent's need for help with activity. We excluded participants that they had >20% missing data in items of

frailty index. For participants with missing data on some deficits, we excluded the deficits with missing information from the numerator. FI was calculated as the sum of scoring divided by the total number of items. Frailty status was defined as a value of 0.25 or greater on the FI.[31] We further classified participants according to their cognitive impairment and frailty status into the following groups: none (without cognitive impairment and frailty), only cognitive impairment, only frailty, and cognitive frailty (co-occurrence of cognitive impairment and frailty).[7]

All-cause mortality was the time-to-event outcome including date of death. Mortality data were retrieved from national mortality registers (ELSA and HRS) or end-of-life interviews with relatives (CHARLS, KLoSA, SHARE, and MHAS). A timeline was created, with the baseline wave marking the beginning of the observation period. The end was either (1) the time of death (reported in year/month in CHARLS, KLoSA, SHARE, HRS and MHAS, and years in ELSA) (2), the end of follow-up, or (3) dropout for other reasons, whatever came first. We defined outcome as survival=0, death=1, dropout=2.

Covariates included age (in years), sex (male, female), education (less than upper secondary, upper secondary and vocational training, and tertiary), marriage (single, married or partnered), smoking (no, yes), and alcohol drinking (no, yes). Education is classified according to the 1997 International Standard Classification of Education (ISCED-97). Single marital status covered separated, divorced, widowed, and never married marital status. Smoking was described as current smoking behavior or smoking in the past. Drinking was about whether alcohol was consumed last week, last three months, last year, or earlier.

Statistical Analysis

Mean with standard deviation (SD) or median with interquartile range (IQR) was used for reporting descriptive statistics of continuous variables, and number with percentage was used for reporting categorical variables. Differences in characteristics were assessed using analysis of variance for continuous variables and chi-square test for categorical variables.

Competing-risks regression models were fitted to assess the association of different cognitive frailty status at baseline with subsequent all-cause mortality. The cumulative incidence function was used to estimate the cumulative incidence of mortality. The non-parametric Nelson-Aalen method was used to estimate the cumulative hazard rate function, and the log-rank test was applied to evaluate the difference of hazard curve amongst categories. We used the Fine-Gray model to calculate the subhazard ratio (SHR) for death in each group category. The "None" profile served as the reference group. We fitted two models for these analyses. Model 1 was unadjusted. Model 2 was adjusted for covariates. Time-to event was expressed in months and calculated by the time elapsed between the end of the timeline and the date of baseline survey.

To estimate the overall effect sizes for all outcomes, we pooled our findings into multinational meta-analyses using the random effects model. Pooled SHR and 95% confidence interval (CI) were reported. Between-country heterogeneity was assessed using Cochran's Q and I^2 statistics. A *p* value of Q statistic less than 0.05 indicates heterogeneity. A value of I^2>50% indicates heterogeneity. When there was heterogeneity, the random effects model was used for pooled estimation, and the fixed effects model was used otherwise. The meta-analysis was weighted to given that some countries had more participants than others and thus had lower sampling variability and more precise estimates. Countries with a greater

number of participants were given more weight than countries with a small number of participants. These were relative weights that summed to 100. When there was heterogeneity, we tested the interactions of cognitive frailty with covariates to further examine which populations had a higher risk of cognitive frailty and mortality.

Several sensitivity analyses were conducted. First, we further conducted our analysis based on inverse probability-weighted samples to handle potential selection bias. Second, we added numeracy to reassess cognitive function. No numeracy survey data were available in waves 1-3 of SHARE, and wave 2-3 of MHAS. The baseline wave was wave 4 in SHARE and wave 4 in MHAS. Third, we performed subgroup analyses by age (50-69, 70 and above), sex, education, marriage, smoking, and alcohol drinking. Forest plots were drawn to visualize the adjusted SHR and 95% CI in sub-populations. Fourth, we repeated the survival analysis limiting the follow-up duration of KLoSA, ELSA, SHARE, HRS and MHAS to 85.2 months to coincide with the longest follow-up time of CHARLS. All analyses were performed by Stata 15.0 (StataCorp, College Station, USA). Two-sided *p* values <0.05 were considered to be statistically significant.

Results

Table 2 presents the baseline characteristics of participants in the six cohort studies. Participants in the cognitive frailty group were older in all cohorts of aging and were less likely to be married or partnered. Participants in the frailty-only group were more likely to have lower levels of education. The proportion of females in the cognitive frailty group was higher in CHARLS and KLoSA, and that of females in the frailty-only group was higher in ELSA, SHARE, HRS and MHAS. Participants in the cognitive frailty group were less likely

to smoke and drink in CHARLS and HRS.

The proportion of cognitive frailty ranged from 1.0% in Switzerland (SHARE) to 9.1% in Spain (SHARE) (Supplementary Figure S7). China (CHARLS) had the lowest proportion of death (1.9%) and the United States (HRS) the highest (68.9%) during follow-up. The pooled proportion of cognitive frailty in SHARE was 3.4%, while the cognitive frailty rate was 4.4% in CHARLS, 3.3% in KLoSA, 4.2% in ELSA, 5.0% in HRS, and 5.3% in MHAS (Supplementary Table S3).

The four cognitive frailty status differed significantly with regard to all-cause mortality risk ($p < 0.0001$). During follow-up, the cumulative incidence of mortality in the cognitive frailty group was higher than that in the frailty only and cognitive impairment only groups (Figure 1). The cumulative hazard rate was also higher in the cognitive frailty group (Supplementary Figures S8). Competing-risks regression models for all-cause mortality are summarized in Table 3. In the unadjusted model, cognitive frailty was consistently associated with elevated mortality risk in six cohorts. After controlling for the effect of potential confounding variables (baseline age, sex, education, marriage, smoking, and alcohol drinking), mortality risk was attenuated for the cognitive frailty group but remained statistically significant in CHARLS (SHR=2.58, 95% CI: 1.57-4.25), KLoSA (SHR=2.28, 95% CI:1.90-2.72), ELSA (SHR=2.74, 95% CI: 2.12-3.53), SHARE (SHR=2.20, 95% CI: 1.95-2.47), HRS (SHR=2.30, 95% CI: 2.07-2.56), and MHAS (SHR=2.11, 95% CI: 1.87-2.38). Mortality risk was found to be higher in the cognitive frailty group than the frailty only and cognitive impairment only groups.

Results were pooled into meta-analyses from adjusted models (Figure 2). Compared with the group without cognitive impairment and frailty, only cognitive impairment status (pooled

SHR=1.36, 95% CI: 1.25-1.48, I^2=3.0%) or only frailty status (pooled SHR=1.83, 95% CI: 1.72-1.95, I^2=31.0%) was associated with subsequently higher mortality risk. Participants classified as cognitive frailty (pooled SHR=2.34, 95% CI: 2.01-2.72, I^2=68.0%) had a higher mortality risk compared with those without cognitive impairment and frailty. We also found differential associations between cognitive frailty and the risk of death among Asians, Europeans, and Americans (Asia: pooled SHR=2.47, 95% CI: 1.90-3.19, I^2=0.0%; Europe: pooled SHR=2.36, 95% CI: 1.77-3.16, I^2=75.9%; America: pooled SHR=2.21, 95% CI: 2.03-2.40, I^2=10.4%) (Supplementary Figures S9). Figure 3 visualizes the interactions of cognitive frailty with covariates on mortality. In general, we found the mortality risk of cognitive frailty was higher among adults aged 70 years and older, and the risk was lower among people who were female, married or partnered, and alcohol drinking. More detailed results are shown in Supplementary Table S4.

In sensitivity analyses, we observed the following findings. First, after conducting the primary analysis using the original weighted samples, results were not substantially changed (Supplementary Table S5). Second, except CHARLS, the other five cohorts' results were consistent with the existing findings after reassessment of cognitive function (Supplementary Table S6). Third, associations of different cognitive frailty status with mortality risk in sub-populations were consistent with the main findings (Supplementary Figures S10-S15). Fourth, we balanced the follow-up times across the six data sets, showed similar results (Supplementary Table S7).

Discussion

In this study, we used baseline cognitive frailty measurements from six large cohort studies of

adults aged 50 years and older to predict all-cause mortality. Cognitive frailty rates varied substantially across countries, ranging from 1.0% in Switzerland and 3.3% in South Korea to 5.3% in Mexico and 9.1% in Spain. A recent meta-analysis found a prevalence of cognitive frailty ranging from 1% to 50%, with a pooled prevalence of 9% and significant heterogeneity between studies.[32] Most of the studies included in this meta-analysis had a higher rate of cognitive frailty than the present study. This may be related to the time of variable measurement, and the prevalence of cognitive frailty increased year by year.[32]

We found that only cognitive impairment, only frailty and cognitive frailty status were associated higher mortality risk compared with those without cognitive impairment and frailty in most of the countries included in the study. Participants with cognitive frailty had the highest mortality risk. These findings are in line with meta-analyses on the association of cognitive frailty with other adverse outcomes. Older adults with cognitive frailty had a higher risk of for falls, disability and hospitalization than those with frailty or cognitive impairment alone.[11] The influences of cognitive frailty on adverse outcomes (falls, disability and hospitalization) were both greater than that of frailty or cognitive impairment alone. Our findings expand the research on the effect size of the association between cognitive frailty and adverse outcomes.

Our results indicated that cognitive frailty had a greater impact on all-cause mortality than cognitive impairment and frailty alone, which suggested that cognitive frailty was a better predictor than cognitive impairment and frailty alone for predicting mortality. This supports a series of studies emphasizing that the co-occurrence of cognitive impairment and frailty to exacerbate physical and cognitive function.[2,4] The etiology is related to the potential role of

chronic inflammation, impaired stress response, imbalanced energy metabolism, oxidative stress, neuropathology, cardiovascular dysfunction, and anorexia in both syndromes.[6,33] Cognitive impairment and frailty should be screened in health examination of older adults, and preventive intervention should be implemented, which could be an effective strategy to reduce mortality risk.

After 50 years of age, the all-cause mortality rate of adults with cognitive frailty was 2.34 times higher than that of people without cognitive impairment and frailty. Our results are similar to existing meta-analysis findings on the association between cognitive frailty and all-cause mortality in older adults.[8,34] Cognitive frailty may occur much earlier. Studies on cognitive frailty and all-cause mortality should focus on middle-aged and older adults rather than only older adults. Furthermore, regional differences in the ratio of cognitive frailty to all-cause mortality were found (lower in European and American countries than in Asian countries). This might be related to dietary habits. The study found that the Mediterranean dietary pattern in some countries in Europe and the Americas reduced age-related disease mortality risk.[35,36] Large educational disparities in mortality across countries may also make a substantial contribution to the gap in mortality between different regions.[37]

We observed the interaction effects of cognitive frailty with age, sex, marriage and alcohol drinking on all-cause mortality. Adults aged ≥70 years were at higher odds of death compared with adults 50-69 years. But precursors of frailty tend to arise earlier in the life-course.[38] The impact of cognitive frailty on health outcomes may occur earlier. Males had a higher mortality risk of cognitive frailty than females. Our finding is similar to the fact that nutritional frailty is associated with a higher risk of all-cause mortality in males.[39] Evidence suggests that

cognitive impairment and frailty share biological mechanisms, but biomarkers associated with transitions in gait speed and cognition during aging are sex-specific.[40] Metabolic biomarkers were associated with cognitive change in males, but not in females. Lifestyle and health factors may partially account for excess mortality in males compared with females.[41] Of course, variation in cultural, societal and historical contexts can also lead to different life experiences of males and males and variation in the mortality gap across countries.[42] Public health policies must recognize variation among genders and further incorporate cultural and societal factors within and across countries.

In addition, cognitive frailty was associated with a higher risk of death among those who were single. Married or partnered people are at a distinct advantage with respect to health in comparison to single people.[43] This health premium on partnership is especially strong among adults aged 45 and 65 years. The positive effects of partnership need to be supported in the future, with interventions where vulnerability occurs earlier. Cognitive frailty was more likely to predict mortality among people who did not drink alcohol. It has also been showed that frailty and pre-frailty were also positively associated with infrequent alcohol intake.[38] But alcohol use is among the leading risk factors for premature mortality and disability because of its causal relationship with multiple health conditions.[44] Perhaps people with multiple health problems choose not to drink or abstain from alcohol. The mechanism of the association between cognitive frailty and mortality risk should be further explored.

Further research is warranted to explore the potential mechanisms of cognitive frailty on mortality, including socio-cultural differences in population and region. Understanding these nuances can inform policy on healthy ageing globally.

This study has some limitations. First, the present study was unable to excluded participants with dementia or Parkinson's disease in KLoSA and MHAS due to the lack of data on dementia or Parkinson's disease in these two databases. Even if we excluded subjects with a diagnosis of dementia in the baseline when possible, there could be a residual risk for other databases. Second, we relied on the memory and orientation domains to determine the presence of cognitive impairment. Cognitive decline can also affect other cognitive domains. Therefore, there is a major risk of misclassification based on the criteria selected. However, the reassessment of cognition largely demonstrated consistent results. Third, we operationalized frailty based on the deficit accumulation framework. A limited amount of items in the frailty index can lead to differences in frailty classification and, consequently, in the study results. However, the strategy we used to build the frailty index is consistent with the original proposal[29] and has been replicated in other studies using subgroup samples. Fourth, cross-country variation in the results might be due to the heterogeneity in the cohorts' settings, such as the follow-up length. However, consistent follow-up times showed similar results, in which participants with cognitive frailty had the highest mortality risk. Despite such limitations, our study also has several strengths. First, we include longitudinal data from multiple large cohort studies with follow-up ranging from 6 to 19 years. Second, all variables were harmonized. By conducting the same statistical analyses across six data sets, we avoided inconsistencies caused by methodological differences in the analysis design, population selection, the definition of cognitive impairment and frailty, and confounder adjustment. Third, competing-risks regression models reduced the bias of overestimation of mortality risk.

Conclusions

Cognitive frailty, frailty or cognitive impairment alone, is associated with an increased risk of all-cause mortality compared with those without frailty and cognitive impairment. The magnitude of the association between cognitive frailty and mortality varied across populations and countries. The findings suggest that screening for physical and cognitive function in middle-aged and older adults should be performed as early as possible. Future studies are needed to confirm the current results, preferentially including a more detailed neurocognitive assessment and a broader measurement of frailty.

Disclosures

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Data statement

The data that support the findings of this study are available to the public and available from the Gateway to Global Aging Data [https://g2aging.org/].

Author contributions

PH and YY conceptualized and drafted the first version of the manuscript. YY and HS made the analysis plan and did the statistical analyses. ZS and YW contributed to the visualization and statistical methods of the study. YX and XG provided valuable advice on writing revisions of the manuscript. All authors contributed to and approved the final manuscript.

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Figure legends

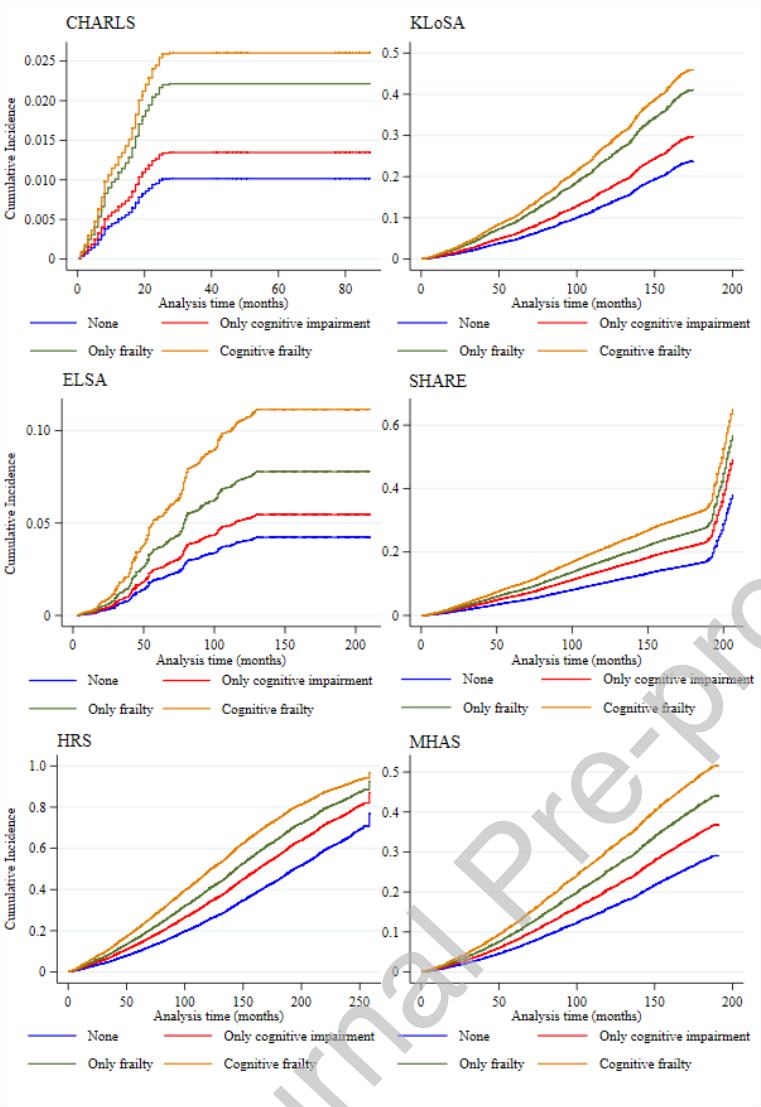

Figure 1. Cumulative incidence of mortality for different cognitive frailty status from adjusted models

CHARLS: China Health and Retirement Longitudinal Study; KLoSA: Korean Longitudinal Study of Aging; ELSA, English Longitudinal Study of Ageing; SHARE: Survey of Health, Ageing and Retirement in Europe; HRS: Health and Retirement Study; MHAS: Mexican Health and Aging Study. Six log-rank tests: $p<0.0001$.

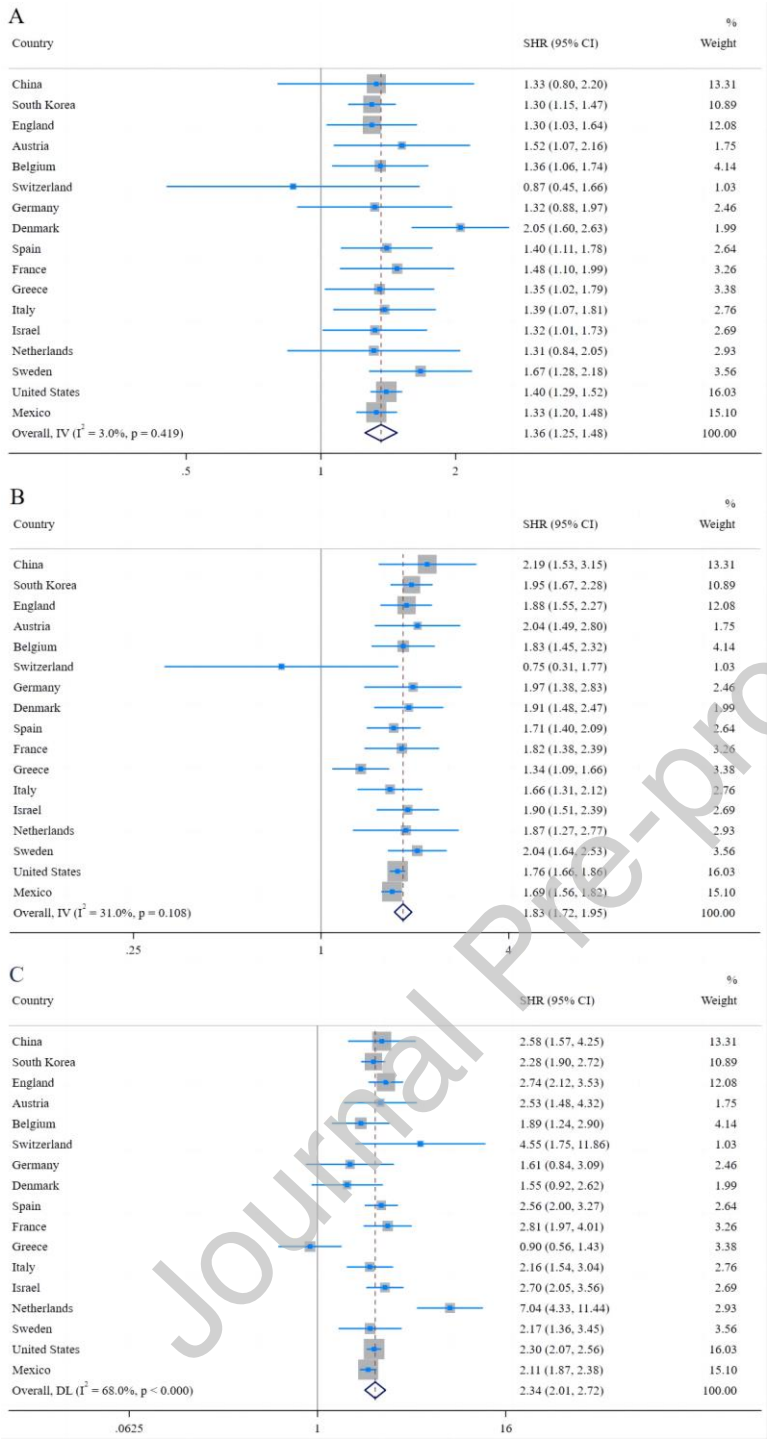

Figure 2. Forest plot of the association between different cognitive frailty status and mortality risk

SHR: subhazard ratio; CI: confidence interval. A, only cognitive impairment. B, only frailty. C, cognitive frailty.

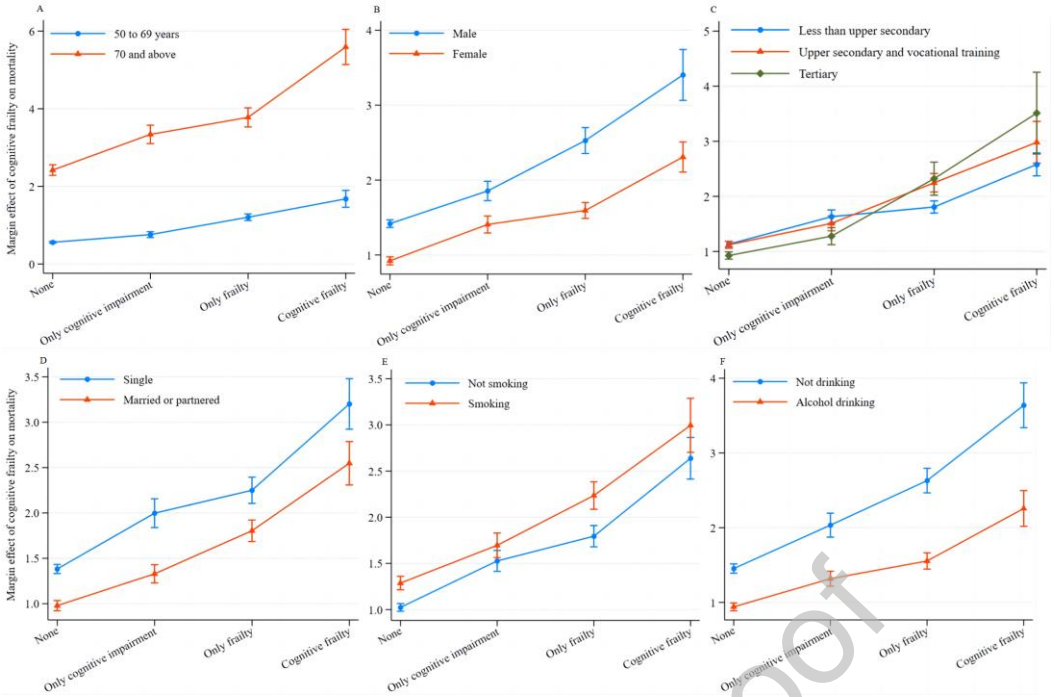

Figure 3. Margin effects of cognitive frailty on all-cause mortality by age, sex, education, marriage, smoking and alcohol drinking

A, age. B, sex. C, cognitive frailty. D, marriage. E, smoking. F, alcohol drinking. All coefficients were estimated after adjusting for age, sex, education, marriage, smoking, or alcohol drinking. n=71,553.

Table 1. Sample Characteristics

	CHARLS	KLoSA	ELSA	SHARE	HRS	MHAS
Baseline wave	wave1: 2011/2012	wave1: 2006	wave1: 2002/2003	wave1: 2004/2005	wave4: 1998/1999	wave2: 2003
Follow-up mortality data	wave2: 2013/2014	wave2: 2008	wave2: 2004/2005	wave2: 2006/2007	wave5: 2000/01	wave3: 2012
	wave3: 2015/2016	wave3: 2010	wave3: 2006/2007	wave4: 2011/2012	wave6: 2002/2003	wave4: 2015
	wave4: 2018	wave4: 2012	wave4: 2008/2009	wave5: 2013	wave7: 2004/2005	wave5: 2018
		wave5: 2014	wave5: 2010/2011	wave6: 2015	wave8: 2006/2007	
		wave6: 2016	wave6: 2012/2013	wave7: 2017	wave9: 2008/2009	
		wave7: 2018	wave7: 2014/2015	wave8: 2019	wave10: 2010/2011	
		wave8: 2020	wave8: 2016/2017		wave11: 2012/2013	
			wave9: 2018/2019		wave12: 2014/2015	
					wave13: 2016/2018	
					wave14: 2018/2019	
Cognitive frailty measurement, date: n	2011: 9,522	2006: 7,793	2002/2003: 8,643	2004/2005: 23,321	1998/1999: 11,469	2003: 10,805
Total number of respondents, n	9,522	7,793	8,643	23,321	11,469	10,805
Follow-up time (months), median (IQR)	85.2 (84.2-85.2)	169.4 (112.6-170.5)	148.1 (74.1-196.8)	128.9 (75.0-178.6)	151.8 (76.6-226.9)	186.7 (121.8-187.7)
Final status						
Alive, n (%)	7,814 (82.1)	4,533 (58.2)	3,332 (38.6)	6,551 (28.1)	2,334 (20.4)	5,968 (55.2)
Dead, n (%)	185 (1.9)	2,424 (31.1)	701 (8.1)	5,907 (25.3)	7,903 (68.9)	4,029 (37.3)
Dropout, n (%)	1,523 (16.0)	836 (10.7)	4,610 (53.3)	10,863 (46.6)	1,232 (10.7)	808 (7.5)
Age at baseline (years)						
Mean ± SD	61.4 ± 7.8	64.8 ± 9.6	64.5 ± 10.0	64.5 ± 10.0	70.4 ± 10.3	63.6 ± 9.3
Rang (min-max)	50-101	50-98	50-90	50-102	50-105	50-107
Female, n (%)	4,694 (49.3)	4,387 (56.3)	4,627 (53.5)	12,661 (54.3)	6,587 (57.4)	6,082 (56.3)

IQR: interquartile range; SD: standard deviation; CHARLS: China Health and Retirement Longitudinal Study; KLoSA: Korean Longitudinal Study of Aging; ELSA, English Longitudinal Study of Ageing; SHARE: Survey of Health, Ageing and Retirement in Europe; HRS: Health and Retirement Study; MHAS: Mexican Health and Aging Study.

Table 2. Baseline characteristics of participants by cognitive frailty status

	CHARLS (n=9,522)						**KLoSA (n=7,793)**					
	None (n=6,786)	Only cognitive impairment (n=745)	Only frailty (n=1,574)	Cognitive frailty (n=417)	F/χ^2	*p* value	None (n=6,518)	Only cognitive impairment (n=709)	Only frailty (n=309)	Cognitive frailty (n=257)	F/χ^2	*p* value
ge (years), mean ± SD	60.4 ± 7.3	64.0 ± 9.1	63.2 ± 8.0	67.2 ± 9.1	177.52	<0.0001	63.3 ± 8.7	70.8 ± 10.0	72.5 ± 8.5	77.8 ± 9.7	433.90	<0.0001
emale, n (%)	3,076 (45.4)	399 (53.6)	938 (59.6)	281 (67.4)	169.52	<0.001	3,586 (55.0)	439 (61.9)	189 (61.2)	173 (67.3)	29.10	<0.001
ducation, n (%)					166.66	<0.001					100.03	<0.001
Less than upper econdary	5,864 (86.4)	665 (89.3)	1,501 (95.4)	391 (93.8)			4,498 (69.0)	493 (69.5)	277 (89.6)	226 (88.0)		
Upper secondary and ocational training	781 (11.5)	71 (9.5)	63 (4.0)	18 (4.3)			1,497 (23.0)	164 (23.1)	25 (8.1)	25 (9.7)		
Tertiary	141 (2.1)	9 (1.2)	10 (0.6)	8 (1.9)			523 (8.0)	52 (7.4)	7 (2.3)	6 (2.3)		
larried or partnered, n (%)	6,033 (88.9)	615 (82.5)	1,287 (81.8)	314 (75.3)	119.37	<0.001	5,154 (79.1)	418 (59.0)	189 (61.2)	115 (44.8)	314.73	<0.001
moking, n (%)	3,031 (44.7)	282 (37.9)	586 37.2)	122 (29.3)	67.25	<0.001	1,937 (29.7)	188 (26.5)	89 (28.8)	61 (23.7)	7.05	0.070
lcohol drinking, n (%)	2,854 (42.1)	292 (39.2)	604 (38.4)	134 (32.1)	22.04	<0.001	6,094 (93.5)	642 (90.5)	256 (82.8)	213 (82.9)	88.46	<0.001
	ELSA (n=8,643)						**SHARE (n=23,321)**					
	None (n=5,978)	Only cognitive impairment (n=833)	Only frailty (n=1,468)	Cognitive frailty (n=364)	F/χ^2	*p* value	None (n=18,335)	Only cognitive impairment (n=1,790)	Only frailty (n=2,403)	Cognitive frailty (n=793)	F/χ^2	*p* value
ge (years), mean ± SD	62.5 ± 9.0	69.3 ± 10.5	67.4 ± 10.2	73.5 ± 10.7	312.89	<0.0001	62.9 ± 9.0	68.7 ± 11.0	69.5 ± 10.1	77.5 ± 10.1	1044.56	<0.0001
emale, n (%)	3,141 (52.5)	350 (42.0)	938 (63.9)	198 (54.4)	110.26	<0.001	9,731 (53.1)	764 (42.7)	1,652 (68.8)	514 (64.8)	345.95	<0.001
ducation, n (%)					447.36	<0.001					793.95	<0.001
Less than upper econdary	2,324 (38.9)	297 (35.6)	971 (66.2)	217 (59.6)			9,204 (50.2)	670 (37.4)	1,767 (73.5)	570 (71.9)		
Upper secondary and ocational training	2,735 (45.7)	417 (50.1)	429 (29.2)	130 (35.7)			5,532 (30.2)	599 (33.5)	452 (18.8)	131 (16.5)		
Tertiary	919 (15.4)	119 (14.3)	68 (4.6)	17 (4.7)			3,599 (19.6)	521 (29.1)	184 (7.7)	92 (11.6)		
larried or partnered, n (%)	4,462 (74.6)	557 (66.9)	830 (56.5)	182 (50.0)	259.89	<0.001	14,229 (77.6)	1,231 (68.8)	1,459 (60.7)	383 (48.3)	644.65	<0.001
moking, n (%)	3,750 (62.7)	532 (63.9)	1,020 (69.5)	255 (70.1)	28.91	<0.001	8,940 (48.8)	859 (48.0)	947 (39.4)	271 (34.2)	130.82	<0.001

lcohol drinking, n (%)	5,522 (92.4)	733 (88.0)	1,178 (80.2)	268 (73.6)	275.22	<0.001	13,365 (72.9)	1,188 (66.4)	1.188 (49.4)	301 (38.0)	918.95	<0.001
	HRS (n=11,469)						**MHAS (n=10,805)**					
	None (n=7,525)	Only cognitive impairment (n=874)	Only frailty (n=2,494)	Cognitive frailty (n=576)	F/χ^2	*p* value	None (n=7,030)	Only cognitive impairment (n=942)	Only frailty (n=2,263)	Cognitive frailty (n=570)	F/χ^2	*p* value
ge (years), mean ± SD	68.3 ± 9.9	76.4 ± 9.2	72.6 ± 9.7	79.4 ± 9.0	22.15	<0.001	61.8 ± 8.1	68.0 ± 9.9	64.9 ± 9.5	73.6 ± 10.6	458.37	<0.0001
emale, n (%)	4,106 (54.6)	422 (48.3)	1,696 (68.0)	363 (63.0)	176.58	<0.001	3,691 (52.5)	402 (42.7)	1,645 (72.7)	344 (60.4)	363.16	<0.001
ducation, n (%)					510.67	<0.001					137.81	<0.001
Less than upper econdary	1,748 (23.2)	219 (25.0)	1,089 (43.7)	242 (42.0)			6,300 (89.6)	851 (90.3)	2,190 (96.8)	552 (96.8)		
Upper secondary and ocational training	4,240 (56.4)	477 (54.6)	1,190 (47.7)	269 (46.7)			165 (2.4)	24 (2.6)	15 (0.7)	2 (0.4)		
Tertiary	1,537 (20.4)	178 (20.4)	215 (8.6)	65 (11.3)			565 (8.0)	67 (7.1)	58 (2.5)	16 (2.8)		
larried or partnered, n (%)	5,091 (67.6)	495 (56.6)	1,261 (50.6)	249 (43.2)	336.92	<0.001	5,166 (73.5)	611 (64.9)	1,416 (62.6)	302 (53.0)	186.28	<0.001
moking, n (%)	4,323 (57.5)	493 (56.4)	1,490 (59.7)	310 (53.8)	8.61	0.035	3,068 (43.6)	418 (44.4)	833 (36.8)	232 (40.7)	35.29	<0.001
lcohol drinking, n (%)	4,085 (54.3)	377 (43.1)	836 (33.5)	147 (25.5)	452.67	<0.001	2,056 (29.3)	280 (29.7)	425 (18.8)	67 (11.8)	165.84	<0.001

SD: standard deviation; CHARLS: China Health and Retirement Longitudinal Study; KLoSA: Korean Longitudinal Study of Aging; ELSA, English Longitudinal Study of Ageing; SHARE: Survey of Health, Ageing and Retirement in Europe; HRS: Health and Retirement Study; MHAS: Mexican Health and Aging Study.

Table 3. Associations of cognitive frailty with all-cause mortality risk

	CHARLS (n=9,522)								**KLoSA (n=7,793)**							
	Adjusted [a]				Unadjusted				Adjusted [a]				Unadjusted			
	SHR	SE	95% CI	*p* value	SHR	SE	95% CI	*p* value	SHR	SE	95% CI	*p* value	SHR	SE	95% CI	*p* value
None	Ref				Ref				Ref				Ref			
Only cognitive impairment	1.33	0.34	0.80-2.20	0.273	1.87	0.49	1.13-3.11	0.015	1.30	0.08	1.15-1.47	<0.001	2.25	0.13	2.01-2.53	<0.001
Only frailty	2.19	0.41	1.53-3.15	<0.001	2.78	0.47	1.99-3.88	<0.001	1.95	0.15	1.67-2.28	<0.001	3.71	0.28	3.20-4.31	<0.001
Cognitive frailty	2.58	0.66	1.57-4.25	<0.001	4.34	1.01	2.74-6.86	<0.001	2.28	0.21	1.90-2.72	<0.001	6.45	0.53	5.49-7.58	<0.001
	ELSA (n=8,643)								**SHARE (n=23,321)**							
	Adjusted [a]				Unadjusted				Adjusted [a]				Unadjusted			
	SHR	SE	95% CI	*p* value	SHR	SE	95% CI	*p* value	SHR	SE	95% CI	*p* value	SHR	SE	95% CI	*p* value
None	Ref				Ref				Ref				Ref			
Only cognitive impairment	1.30	0.15	1.03-1.64	0.028	2.45	0.28	1.96-3.07	<0.001	1.41	0.06	1.30-1.54	<0.001	2.30	0.10	2.12-2.49	<0.001
Only frailty	1.88	0.18	1.55-2.27	<0.001	2.78	0.26	2.32-3.33	<0.001	1.75	0.07	1.62-1.89	<0.001	2.88	0.10	2.69-3.08	<0.001
Cognitive frailty	2.74	0.36	2.12-3.53	<0.001	6.69	0.77	5.34-8.40	<0.001	2.20	0.13	1.95-2.47	<0.001	6.32	0.32	5.72-6.98	<0.001
	HRS (n=11,469)								**MHAS (n=10,805)**							
	Adjusted [a]				Unadjusted				Adjusted [a]				Unadjusted			
	SHR	SE	95% CI	*p* value	SHR	SE	95% CI	*p* value	SHR	SE	95% CI	*p* value	SHR	SE	95% CI	*p* value
None	Ref				Ref				Ref				Ref			
Only cognitive impairment	1.40	0.06	1.29-1.52	<0.001	2.27	0.09	2.10-2.47	<0.001	1.33	0.07	1.20-1.48	<0.001	2.13	0.11	1.93-2.35	<0.001
Only frailty	1.76	0.05	1.66-1.86	<0.001	2.17	0.06	2.05-2.29	<0.001	1.69	0.07	1.56-1.82	<0.001	1.95	0.07	1.81-2.10	<0.001

Cognitive frailty	2.30	0.13	2.07-2.56	<0.001	4.48	0.24	4.03-4.98	<0.001	2.11	0.13	1.87-2.38	<0.001	4.51	0.25	4.04-5.04	<0.001

SHR: subhazard ratio; CI: confidence interval; CHARLS: China Health and Retirement Longitudinal Study; KLoSA: Korean Longitudinal Study of Aging; ELSA, English Longitudinal Study of Ageing; SHARE: Survey of Health, Ageing and Retirement in Europe; HRS: Health and Retirement Study; MHAS: Mexican Health and Aging Study.

[a] Adjusted for: age, sex, education, marriage, smoking and alcohol drinking.