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ORIGINAL RESEARCH

Is Co-Occurrence of Frailty and Multimorbidity Associated with Increased Risk of Catastrophic Health Expenditure? A Prospective Cohort Analysis in China

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Purpose: The coexistence of multimorbidity and frailty is more likely to increase the risk of physical limitations, mortality and other adverse health outcomes in older adults than their individual occurrence. However, whether and how this coexistence is associated with catastrophic health expenditure (CHE) has not been well assessed. This study aimed to evaluate the independent and coexisting effects of frailty and multimorbidity on CHE.

Participants and Methods: A total of 4838 participants obtained from the China Health and Retirement Longitudinal Study (CHARLS) without CHE at baseline (2011) were included in the analytical sample. Marginal structural model (MSM) and time-varying Cox regression model were used to assess the independent and co-occurring impact of frailty and multimorbidity on CHE, respectively.

Results: Suffering from single chronic disease (HR, 1.26; 95% CI, 1.13–1.40; $P < 0.001$), multimorbidity (HR, 1.80; 95% CI, 1.63–1.99; $P < 0.001$) and frailty (HR, 1.32; 95% CI, 1.21–1.45; $P < 0.001$) were associated with a higher risk of CHE. Frailty co-occurring with a single chronic disease (HR, 1.28; 95% CI, 1.03–1.60; $P = 0.027$) or multimorbidity (HR, 1.91; 95% CI, 1.56–2.32; $P < 0.001$), and multimorbidity co-occurring with frailty also increased CHE risk (HR, 1.32; 95% CI, 1.17–1.48; $P < 0.001$) compared with single frailty or multimorbidity status.

Conclusion: Preventing, postponing, or reducing frailty, and enhancing standard management of chronic diseases are essential in reducing healthcare costs and preventing families from poverty. More efficient interventions for frailty and multimorbidity are urgently required.

Keywords: frailty, multimorbidity, catastrophic health expenditure, co-occurrence

Introduction

China is one of the world's most rapidly ageing countries, with more people aged 65 and over than in any other country. In 2019, the Chinese population constituted 18% of the world's population, with 164.5 million citizens aged 65 and above, and 26 million aged 80 or above.[1,2] This will continue to exacerbate the burden borne by the management of chronic non-communicable diseases, physical frailty, neurodegenerative diseases, cardiovascular diseases and so on.[3] This grim reality could increase the risk of households' catastrophic health expenditure (CHE). CHE is an important index for measuring health equity, and reducing its risk in families is the original intention of medical system designs in various countries. CHE is critical to proactively addressing population ageing, promoting health equity, and making more targeted policy recommendations.

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Frailty and multimorbidity are two risk factors for CHE among the older populations. Frailty describes a state of overall decline in physical, mental, or cognitive functions between unhealthy and non-serious impairment. Frailty is a predictor of mortality, falls, worsening disability, diseases (dementia, cardiovascular events, etc.), and is significantly associated with a decreased quality of life.[4,5] According to the impact of frailty on clinically adverse outcomes, it is easy to predict that frailty is associated with increased healthcare costs in older populations.[6,7] Some previous cross-sectional studies have found that frailty is positively associated with increased healthcare use, and can predict subsequent high healthcare costs.[8–10] Jin et al examined the association between frailty and healthcare expenditure among Chinese older adults, and found that frailty was associated with higher odds of incurring outpatient, inpatient, and self-treatment expenditure.[11] Fan et al found that prefrail or frail adults were associated with higher odds for CHE through a prospective cohort analysis[12] in one of the first studies to explore the association between frailty and CHE in China. However, the study period was relatively short (2011–2013). The ageing situation, disease spectrum, and socioeconomic status of older adults have changed dramatically during the past years.

With an ageing population and high levels of risk factors for non-communicable diseases, the prevalence of multimorbidity in China has increased rapidly. According to Hu's systematic review, the prevalence of multimorbidity in older adults (60+) ranged from 6.4% to 76.5% in China.[13] A recent study using a nationally representative sample of older Chinese people also presented a 42.2% prevalence of multimorbidity. Multimorbidity is associated with a high economic burden for older populations (both themselves and their households). Significant positive relationships between multimorbidity and healthcare use, total and out-of-pocket (OOP) healthcare costs were found in several previous studies, many of which found that use or costs significantly increased with each additional condition.[14–16] An epidemiological study demonstrated that older adults with multimorbidity experienced a higher probability of incurring CHE than those without it.[17] In Zhao's study, which was the first study from China that used panel survey data, physical multimorbidity was found to be associated with a significantly increased likelihood of CHE, which persisted even among the higher socioeconomic groups and across all health insurance programmes.[18] Fu et al also found that multimorbidity affects about two-thirds of Chinese patients with diabetes and can lead to CHE for their families across all health insurance types irrespective of socioeconomic status in China.[19]

Based on recent studies, both frailty and multimorbidity are increasingly prevalent along with the growth of an ageing population. The attention received by both conditions is derived from their strong association with disability, hospitalisation, economic burden, and mortality.[20] Frailty and multimorbidity represent two different clinical conditions. According to Vetrano's review, the prevalence of multimorbidity in frail individuals and frailty in multimorbid individuals was 72% and 16%, respectively. This suggested that most frail individuals are also multimorbid, but fewer multimorbid ones also present frailty, although the causal association between the two is not conclusive.[21] Some longitudinal studies suggest a bidirectional association between multimorbidity and frailty.[22–24]

To date, it is unclear whether and how co-occurrence of frailty and multimorbidity affects CHE among middle-aged and older adults, especially in China. Some studies have assessed the impact one of the issues on CHE, with another issue adjusted as a confounding or subgroup analysis. For example, in Fan et al's study, frailty was associated with increased risk of CHE after multimorbidity and many other covariates were controlled.[25] Jing et al investigated the effect of co-occurrence of frailty on CHE among single empty-nest older adults with multimorbidity in China, and demonstrated that there is a positive effect of co-occurrence of frailty on CHE among them, and that this effect varies by economic status.[26]

The coexistence of multimorbidity and frailty was found to more likely increase the risk of physical limitations, mortality, and other adverse health outcomes in older adults than multimorbidity or frailty status individually.[27,28] Nevertheless, longitudinal assessments are scarce, and investigation of independent and combined effects of frailty and multimorbidity on CHE are urgently required. Therefore, through cohort analysis based on nationally representative data, this study aimed to evaluate independent and co-occurring effects of frailty and multimorbidity on CHE. We proposed two hypotheses: (1) both frailty and multimorbidity can independently predict CHE; (2) co-occurrence of frailty and multimorbidity will increase the risk of CHE, compared with those who suffer from only one condition.

Materials and Methods

Participants

Data for this study were obtained from the China Health and Retirement Longitudinal Study (CHARLS), conducted in 2011, 2013, 2015 and 2018. CHARLS is a representative database for geriatrics research in China, with a high quality of micro-level database on middle-aged and older adults. The sampling details and variables have been described minutely in previous studies.[29] We included data from participants who were not lost to follow-up over the four waves and aged 45 years and older in wave 2011. We excluded participants who had missing values of dependent or independent variables. Then participants not suffering from CHE at baseline were considered for the analysis.

Variables

Exposure – Frailty and Multimorbidity

Frailty status was measured by the Rookwood's Cumulative Deficit Frailty Index (FI). The deficits used for calculating FI were selected according to the following inclusions: (1) a minimum of 30 total deficits; (2) associated with adverse health outcomes; (3) increase in prevalence with age at least into the tenth decade; (4) prevalence of at least 1% in the population; (5) does not saturate.[30] A total of 34 deficits were selected to calculate FI, with binary variables coded as 0 or 1 and some ordered categorical variables coded as 0, 0.5, and 1 (details in Supplementary Table S1).[31] FI was calculated by summing the number of deficits reported by the participants and dividing it by the total number of answered possible deficits. An FI ranged from 0 to 1 was then generated, with higher FI indicating more serious status of frailty. Participants were classified as not frail (FI <0.25), or frail (FI ≥ 0.25).[30] Additionally, participants with missing items of frailty-related deficits exceeding seven (20% out of 34 items) were excluded from our analysis.

Multimorbidity is defined as the presence of two or more physical chronic non-communicable diseases.[32] We used 11 self-reported diagnosed non-communicable chronic diseases to measure multimorbidity (hypertension, diabetes, dyslipidaemia, heart disease, stroke, cancer, chronic lung disease, digestive disease, liver disease, kidney disease, and arthritis). We enumerated the number of non-communicable diseases for each participant to identify those with multimorbidity.

Outcome – Catastrophic Health Expenditure (CHE)

CHE at the household level was calculated by integrating individuals' and their spouses' OOP. We defined a household as incurring CHE when OOP spending on health equalled or exceeded 40% of a household's capacity to pay, defined as the total consumption expenditure of the household minus the food-based household spending.[18,33] This expenditure level was the denominator and the numerator was the sum of participants' and their spouses' OOP spending for outpatient and inpatient care in the past year. We defined a binary variable, which indicated whether the participant's household had CHE or not.

Covariates

Covariates in this study included participants' demographic characteristics (age, gender, marital status), socioeconomic background (hukou status, level of education, rural/urban residence, public health insurance coverage, household per capita consumption and current work status, and health behaviours (alcohol intake, smoking status). Hukou status is obtained from the registration system based on place of birth and lineage, and is a special identifier in China. Hukou status differentiates opportunity structures for Chinese population by giving priority to urban hukou holders in many spheres, including education, job opportunities, housing, health insurance, and other social services and provisions.[34] The grouping details for the covariates are presented in Table 1.

Statistical Analysis

In description analysis of the participants' baseline characteristics within different exposure groups ("None", "Single chronic disease", "Multimorbidity", "Frailty", "Frailty and single chronic disease", "Frailty and multimorbidity"), "number" (percentage) and "mean ± standard deviation" (SD) were used for describing binary or categorical variables and continuous variables, respectively. The statistical differences were tested by ordinal chi-square tests for the

Table 1 Baseline Characteristics of the Sample

	None	Single Chronic Disease	Multimorbidity	Frailty	Frailty and Single Chronic Disease	Frailty and Multimorbidity	P value
Number of participants	1383 (28.59%)	1016 (21.00%)	898 (18.56%)	331 (6.84%)	463 (9.57%)	747 (15.44%)	–
Age	55.39 ± 7.81	55.81 ± 7.60	57.51 ± 8.11	58.50 ± 8.66	58.66 ± 7.79	58.62 ± 7.67	<0.001
Gender							<0.001
Male	760 (54.95%)	570 (56.10%)	447 (49.78%)	131 (39.58%)	159 (34.34%)	254 (34.00%)	
Female	623 (45.05%)	446 (43.90%)	451 (50.22%)	200 (60.42%)	304 (65.66%)	493 (66.00%)	
Education levels[a]							<0.001
Less than lower secondary	1181 (85.39%)	847 (83.37%)	764 (85.08%)	315 (95.17%)	447 (96.54%)	706 (94.51%)	
Upper secondary and vocational training	182 (13.16%)	154 (15.16%)	118 (13.14%)	16 (4.83%)	16 (3.46%)	38 (5.09%)	
Tertiary	20 (1.45%)	15 (1.48%)	16 (1.78%)	0 (0.00%)	0 (0.00%)	3 (0.40%)	
Public health insurance coverage[b]							0.005
Not covered	108 (7.81%)	62 (6.12%)	43 (4.79%)	14 (4.23%)	32 (6.94%)	32 (4.31%)	
Covered	1274 (92.19%)	951 (93.88%)	855 (95.21%)	317 (95.77%)	429 (93.06%)	711 (95.69%)	
Hukou status[c]							<0.001
Agricultural	1116 (80.69%)	785 (77.26%)	649 (72.27%)	314 (94.86%)	427 (92.22%)	656 (87.82%)	
Non-agricultural	255 (18.44%)	227 (22.34%)	243 (27.06%)	17 (5.14%)	32 (6.91%)	87 (11.65%)	
Other	12 (0.87%)	4 (0.39%)	6 (0.67%)	0 (0.00%)	4 (0.86%)	4 (0.54%)	
Rural/urban residence							<0.001
Urban	502 (36.30%)	392 (38.58%)	367 (40.87%)	47 (14.20%)	90 (19.44%)	177 (23.69%)	
Rural	881 (63.70%)	624 (61.42%)	531 (59.13%)	284 (85.80%)	373 (80.56%)	570 (76.31%)	
Alcohol intake							<0.001
Do not drink	832 (60.16%)	623 (61.32%)	592 (65.92%)	238 (71.90%)	340 (73.43%)	547 (73.23%)	
Drink	551 (39.84%)	393 (38.68%)	306 (34.08%)	93 (28.10%)	123 (26.57%)	200 (26.77%)	
Smoking status							<0.001
Do not smoke	882 (63.82%)	665 (65.45%)	640 (71.27%)	227 (68.58%)	328 (70.84%)	575 (76.97%)	
Smoke	500 (36.18%)	351 (34.55%)	258 (28.73%)	104 (31.42%)	135 (29.16%)	172 (23.03%)	
Marital status							<0.001
Married	1270 (91.83%)	961 (94.59%)	824 (91.76%)	291 (87.92%)	400 (86.39%)	657 (87.95%)	
Divorced or widowed	113 (8.17%)	55 (5.41%)	74 (8.24%)	40 (12.08%)	63 (13.61%)	90 (12.05%)	
Current work status							<0.001
Not working	310 (22.55%)	236 (23.46%)	278 (31.27%)	93 (28.27%)	130 (28.26%)	270 (36.49%)	
Working	1065 (77.45%)	770 (76.54%)	611 (68.73%)	236 (71.73%)	330 (71.74%)	470 (63.51%)	
Household per capita consumption[d]	6961.12 ± 8800.59	7628.27 ± 9016.46	7784.37 ± 7960.86	4851.07 ± 4922.33	5524.71 ± 6193.52	6487.44 ± 8766.85	<0.001

Notes: [a]Education levels were classified by a simplified version of the 1997 International Standard Classification of Education codes. [b]Public health insurance includes Urban Employee Medical Insurance, Urban Resident Medical Insurance, New Cooperative Medical Insurance, Urban and Rural Resident Medical Insurance, Government Medical Insurance, Medical Aid or other government insurance plan. [c]Hukou status indicates the respondent's hukou place and is a special identifier in China. Hukou status affects many aspects of life in China such as buying a house, buying a car, children's school enrollment and other welfare. [d]Household per capita consumption is calculated by taking total household consumption divided by the number of people in the household. The amount of total household consumption as aggregated from all consumption activities: food consumption in last week, non-food in the past 30 days, and other non-food consumption in the past year.

categorical variables and Kruskal–Wallis one-way analysis for the numerical variables which were abnormally distributed.

Cox proportional hazard models were employed to calculate relative risk of CHE with survey waves as the timescale. Participants classified as CHE at baseline were excluded from the analysis, and those who remained without CHE were treated as censored data.

When analysing independent effects, we treated one condition (frailty or multimorbidity) as exposure, with another one as time-varying confounder, which is associated with both the exposure and outcome. Then, we performed marginal structural model (MSM) via inverse probability of treatment weighting (IPTW) to mitigate time-varying confounders and overcome immortal time bias. The stabilised weights for MSM were calculated based on IPTW by multiplying the treatment and censoring weights, which were then pooled into the marginal structural model to calculate the associations between frailty or multimorbidity and CHE.

When analysing the co-occurrence effect, we treated frailty and multimorbidity as time-varying exposures to avoid immortal time bias. The analysis strategy is presented in Supplementary Table S2. Hazard ratios (HRs) with 95% confidence intervals (CIs) were calculated through MSM and time-varying Cox regression, respectively.

Sampling and non-response weight were not considered in this study because many studies that employed CHARLS data suggested that results of regression analyses with and without weighting were similar.[35] *P* values were two-tailed, where statistical significance was set at an alpha level of 0.05. Data were analysed using R version 3.6.3 (R Foundation for Statistical Computing, Vienna, Austria).

Sensitivity Analysis

To validate the results, we performed two sensitivity analyses. First, considering the heavy economic burden brought by cancer, we excluded participants suffering from cancer and repeated the above analysis. Second, multiple imputations were conducted to impute the missing covariate values based on five replications and a chained equation approach, to avoid statistical test performance reduction and bias due to direct exclusion of missing values. Additionally, to evaluate the potential effect of unmeasured confounding in the association between co-occurrence (of multimorbidity and frailty) and CHE, E-value analysis was performed using the methodology developed by VanderWeele and Ding.[36,37] E-value is an alternative approach to sensitivity analyses for unmeasured confounding in our study that avoids making assumptions that, in turn, require subjective assignment of inputs for some formulas.

Heterogeneity Analysis

There are significant variances between rural and urban area in China in terms of economic level, proportion of older people and ageing process, family structures, and healthcare resources. Therefore, we further explored the variance of the impact of frailty and multimorbidity on CHE for rural and urban participants separately.

Results

Descriptive Analysis

We identified 6117 participants without missing outcomes and exposure variables, and who had completed all the four waves of surveys. The prevalence of CHE in participants with different co-occurrence of frailty and multimorbidity status are shown in Table 2. It shows that the prevalence of CHE in participants with co-occurrence of frailty and multimorbidity was higher than all the other groups, which ranged from 32.7% to 40.95%; participants without any conditions had the lowest prevalence of CHE.

A total of 4838 participants without CHE at baseline were included in the following analytical sample. Table 1 presents the baseline characteristics of the sample according to co-occurrence of frailty and multimorbidity status. The prevalence of multimorbidity without frailty and frailty without chronic diseases was 18.56% and 6.84%, respectively. The prevalence of frailty co-occurring with multimorbidity was 15.44%, which was higher than that of frailty co-occurring with a single chronic disease. The age of participants without frailty and multimorbidity was lower than the other groups. Females were more likely to suffer from the co-occurrence of frailty and multimorbidity. All the variances between different exposure groups were statistically significant.

Table 2 Prevalence of CHE Across 4 Survey Waves (N=6117)

	2011	2013	2015	2018
None	197 (12.47%)	250 (17.35%)	169 (17.92%)	107 (13.86%)
Single chronic disease	211 (17.20%)	273 (21.55%)	248 (22.01%)	189 (19.34%)
Multimorbidity	281 (23.83%)	421 (29.38%)	516 (27.76%)	460 (25.77%)
Frailty	96 (22.48%)	60 (20.83%)	42 (22.58%)	32 (19.28%)
Frailty and single chronic disease	131 (22.05%)	140 (28.63%)	118 (26.52%)	84 (20.84%)
Frailty and multimorbidity	363 (32.70%)	491 (40.95%)	624 (40.08%)	729 (36.20%)
All	1279 (20.91%)	1635 (26.73%)	1717 (28.07%)	1601 (26.17%)

Abbreviation: CHE, catastrophic health expenditure.

Independent Effect of Multimorbidity and Frailty on CHE

After adjusting for time-varying exposure (multimorbidity status) and confounders (frailty status), both suffering from a single chronic disease (adjusted HR, 1.26; 95% CI, 1.13–1.40; P < 0.001) and multimorbidity (adjusted HR, 1.80; 95% CI, 1.63–1.99; P < 0.001) were associated with a higher risk of CHE. After adjusting for multimorbidity status as a time-varying confounder, frailty (adjusted HR, 1.32; 95% CI, 1.21–1.45; P < 0.001) was also associated with a higher risk of CHE. Details are presented in Table 3.

Effect of Co-Occurrence of Multimorbidity and Frailty on CHE

We classified the participants into six groups according to the co-occurrence of frailty and chronic diseases. Based on time-varying Cox regression (Table 4), we found that compared to those suffering neither from frailty nor chronic diseases, single chronic disease (adjusted HR, 1.23; 95% CI, 1.08–1.39; P = 0.001), multimorbidity (adjusted HR, 1.60; 95% CI, 1.42–1.81; P < 0.001), co-occurrence of frailty and single chronic disease (adjusted HR, 1.42; 95% CI, 1.21–1.67; P < 0.001), and co-occurrence of frailty and multimorbidity (adjusted HR, 2.11; 95% CI, 1.86–2.38; P < 0.001) were significantly associated with increased CHE risk, whereas only suffering from frailty did not increase CHE risk.

Compared to participants only suffering from frailty but not any chronic disease, both frailty co-occurring with a single chronic disease (adjusted HR, 1.28; 95% CI, 1.03–1.60; P = 0.027) and with multimorbidity (adjusted HR, 1.91; 95% CI, 1.56–2.32; P < 0.001) were associated with increased CHE risk. Similarly, frailty co-occurring with

Table 3 Independent Impact of Multimorbidity and Frailty on CHE Based on Marginal Structural Model

	HR	95% CI	P value
Multimorbidity (ref. Without chronic diseases)			
Single chronic disease	1.26	1.13 to 1.40	<0.001
Multimorbidity	1.80	1.63 to 1.99	<0.001
Frailty (ref. Not frail)			
Frailty	1.32	1.21 to 1.45	<0.001

Notes: In marginal structural models, frailty was considered as time-varying confounders when analysing the impact of multimorbidity on CHE, and vice versa. The adjustment factors included all the covariates.
Abbreviations: HR, hazard ratio; CI, confidence interval.

Table 4 Impact of Combined Status of Multimorbidity and Frailty on CHE Based on Time-Varying Cox Regression Analysis

	HR	95% CI	P value
Ref. Group: without frailty and chronic diseases			
Single chronic disease	1.23	1.08 to 1.39	0.001
Multimorbidity	1.60	1.42 to 1.81	<0.001
Frailty	1.11	0.90 to 1.35	0.331
Frailty and single chronic disease	1.42	1.21 to 1.67	<0.001
Frailty and multimorbidity	2.11	1.86 to 2.38	<0.001
Ref. Group: with frailty but without chronic diseases			
Frailty and single chronic disease	1.28	1.03 to 1.60	0.027
Frailty and multimorbidity	1.91	1.56 to 2.32	<0.001
Ref. Group: with Multimorbidity but without frailty			
Frailty and multimorbidity	1.32	1.17 to 1.48	<0.001

Notes: In time-varying Cox regression analysis, co-occurring status of frailty and chronic diseases was considered as time-varying exposure. The adjustment factors included all the covariates.
Abbreviations: HR, hazard ratio; CI, confidence interval.

multimorbidity also increased CHE risk compared with those with multimorbidity but not frailty (adjusted HR, 1.32; 95% CI, 1.17–1.48; P < 0.001).

Sensitivity Analysis

We additionally analysed participants not suffering from cancer and data with multiple imputation as two sensitivity analyses (presented in Table 5). The results were consistent with our main analysis, which validated our conclusions. E-value analysis was further conducted to assess the robustness of the impact of co-occurrence of frailty and multimorbidity on CHE in the MSM and time-varying Cox regression models. The E-values were greater than the estimated confounders for CHE (presented in Supplementary Table S3); therefore, it is unlikely that a potential unmeasured confounder could have a considerably greater effect on CHE than these known risk factors.

Heterogeneity Between Rural and Urban Areas

We compared the effect of co-occurrence of frailty and multimorbidity on CHE between urban and rural areas (Table 6). Notably, compared with participants without frailty and chronic diseases, frailty co-occurring with multimorbidity was significantly associated with increased CHE risk in both rural and urban areas; nevertheless, the impact of single chronic diseases and frailty co-occurring with single chronic diseases was only significant in rural areas. Additionally, frailty co-occurring with a single chronic disease or multimorbidity was significantly associated with increased CHE risk only in rural areas compared with those with frailty but without chronic diseases; it was also only significant for the effect of multimorbidity's co-occurrence with frailty in rural areas compared to those with multimorbidity without frailty.

Table 5 Sensitivity Analysis

	HR	95% CI	P value
Non-cancer respondents			
Ref. Group: without frailty and chronic diseases			
Single chronic disease	1.23	1.08 to 1.39	0.001
Multimorbidity	1.59	1.41 to 1.80	<0.001
Frailty	1.10	0.90 to 1.35	0.335
Frailty and single chronic disease	1.42	1.21 to 1.66	<0.001
Frailty and multimorbidity	2.10	1.85 to 2.38	<0.001
Ref. Group: with frailty but without chronic diseases			
Frailty and single chronic disease	1.28	1.03 to 1.60	0.027
Frailty and multimorbidity	1.90	1.56 to 2.32	<0.001
Ref. Group: with Multimorbidity but without frailty			
Frailty and multimorbidity	1.32	1.17 to 1.48	<0.001
Multiple imputation			
Ref. Group: without frailty and chronic diseases			
Single chronic disease	1.23	1.08 to 1.39	0.001
Multimorbidity	1.60	1.42 to 1.80	<0.001
Frailty	1.10	0.90 to 1.35	0.341
Frailty and single chronic disease	1.42	1.21 to 1.66	<0.001
Frailty and multimorbidity	2.11	1.86 to 2.38	<0.001
Ref. Group: with frailty but without chronic diseases			
Frailty and single chronic disease	1.28	1.03 to 1.60	0.027
Frailty and multimorbidity	1.91	1.56 to 2.33	<0.001
Ref. Group: with Multimorbidity but without frailty			
Frailty and multimorbidity	1.32	1.17 to 1.48	<0.001

Notes: Time-varying Cox regression analyses were used. The adjustment factors included all the covariates.
Abbreviations: HR, hazard ratio; CI, confidence interval.

Table 6 Heterogeneity Between Rural and Urban Areas

	Urban			Rural		
	HR	**95% CI**	**P value**	**HR**	**95% CI**	**P value**
Ref. Group: without frailty and chronic diseases						
Single chronic disease	1.22	0.98 to 1.51	0.077	1.24	1.06 to 1.44	0.007
Multimorbidity	1.58	1.28 to 1.94	<0.001	1.61	1.39 to 1.87	<0.001
Frailty	1.61	1.04 to 2.48	0.032	1.04	0.82 to 1.3	0.768
Frailty and single chronic disease	1.20	0.84 to 1.72	0.310	1.48	1.23 to 1.78	<0.001
Frailty and multimorbidity	1.90	1.49 to 2.42	<0.001	2.18	1.88 to 2.52	<0.001
Ref. Group: with frailty but without chronic diseases						
Frailty and single chronic disease	0.75	0.45 to 1.25	0.265	1.43	1.12 to 1.83	0.004
Frailty and multimorbidity	1.18	0.76 to 1.83	0.461	2.11	1.69 to 2.63	<0.001
Ref. Group: with Multimorbidity but without frailty						
Frailty and multimorbidity	1.20	0.96 to 1.51	0.112	1.35	1.18 to 1.56	<0.001

Notes: Time-varying Cox regression analyses were used. The adjustment factors included all the covariates except for the rural/urban residence.
Abbreviations: HR, hazard ratio; CI, confidence interval.

Discussion

To the best of our knowledge, this is the first study to use cohort analysis to evaluate the impact of co-occurrence of frailty and multimorbidity on CHE in China based on a nationally representative database among middle-aged and older adults. This study proved that both frailty and multimorbidity can independently predict increased CHE risk. More importantly, both frailty co-occurring with single or multiple chronic diseases and multimorbidity co-occurring with frailty increases CHE risk compared with frailty or multimorbidity's individual status; but these effects are only significant in rural areas. However, co-occurrence of frailty and multimorbidity increases CHE risk in both rural and urban areas compared with the most robust participants (without frailty and chronic diseases).

Frailty and multimorbidity have been shown to be associated with older people's risk of disability, hospitalisation, and mortality, as well as escalating health-related costs.[38,39] The coexistence of multimorbidity and frailty was found to be more likely to increase the risk of adverse health outcomes in older adults than multimorbidity or frailty alone;[28] therefore, both frailty co-occurring with chronic diseases and morbidity co-occurring with frailty may bring about great economic burden and increase CHE risk. Many older adults suffering from chronic diseases or multimorbidity have to enrol in long-term medication and regular examination. Additionally, chronic diseases often have complications, or acute episodes. Multimorbidity may be thought of as the accumulation of biological abnormalities deemed as clinically relevant and that define overt disease diagnoses.[7,40] These situations release more demand for medical services, and bring great economic burdens for their families. Therefore, the increased risk of CHE was observed in all subgroups with a single chronic disease or multimorbidity compared to the robust group. Moreover, symptoms related to chronic diseases might have a relevant role in the onset or worsening of frailty status,[40,41] which could also explain why CHE risk is higher in frailty co-occurring with a single chronic disease or multimorbidity than in frailty alone. For those with multimorbidity, co-occurrence of frailty may accelerate disease progression, affect disease prognosis, or cause acute onset of chronic diseases.[42–44] Therefore, multimorbidity co-occurring with frailty also increases CHE risk.

Notably, frailty was observed to independently predict CHE risk after multimorbidity was controlled; however, frailty alone is not significantly associated with increased CHE risk compared with those without chronic disease and frailty. First, it may be caused by different reference groups and analysis models. Second, frailty stems from the progressive accumulation of biological deficits that pile up with time as an expression of ageing. It can be considered as a global and transversal measure for capturing both clinical and subclinical impairments.[7,41] That means, frailty does not mean disease, and the mechanism between frailty, disease, healthcare utilisation, and medical economic burden is complex, and requires further prospective analysis in the future. Noticeably, frailty is characterised as systemic, dynamic, and reversible.[4,12] Thus, certain intervention measures can be taken to prevent early occurrence of frailty, control its progress, or promote recovery to potentially lead to cost savings. This can provide policy makers with clear evidence of the

requirement for certain interventions to prevent and control frailty. This also indicates that the coexistence of frailty and chronic disease is more harmful for older adults.

The heterogeneity of impact of co-occurrence of frailty and multimorbidity on CHE was observed in this study, with rural participants more likely to experience CHE. This may be because rural participants, with lower capacity to pay than urban participants, represent a large sample of lower socioeconomic levels, and the economic risks of frailty co-occurring with chronic diseases or multimorbidity co-occurring with frailty are too great for rural families with similar medical costs. Based on previous studies, we found that there are differences between urban and rural areas in terms of basic health status,[45] and resources that can be accessed for medical services,[46] which could cause differences in the impact of co-occurrence of frailty and multimorbidity between urban and rural areas. It is essential to balance the urban and rural economies, promote rural revitalisation, and establish a national social security network to maintain efficiency and equity.[47]

Policy Implications

According to the global Strategy for Healthy Aging, the core objective of healthy ageing is to improve the quality of life of older adults, shorten the survival period with disease, and extend healthy life expectancy.[48] Both frailty and multimorbidity have been proved to be associated with worse quality of life,[37,49] and as shown in this study, their coexistence causes catastrophic economic burden for families. Thus, prevention of frailty and multimorbidity, intensive management of older adults suffering from frailty and multimorbidity, and policy intervention should be enhanced to promote healthy ageing. China is experiencing an ageing population which could magnify the frailty and multimorbidity epidemic and will require significant adjustments to the countrywide management strategy. First, China has established a multi-tiered and widely covered medical security system, and has made significant achievements in reducing the economic burden of disease, releasing the demand for medical services and improving health.[50] However, in the future, preferential policy towards the older population with frailty and multimorbidity, and promotion of fairness needs to be further strengthened. Second, China has invested a lot of resources to integrate basic public health services into primary healthcare (such as strengthening the management of hypertension and diabetes populations) and carrying out many health management projects for the elderly (such as routine physical examination).[51] In the future, continuous attention to multimorbid populations and accurate screening of frailty need to be strengthened. Finally, China's "Active Response to Population Aging Strategy" and "Healthy China Strategy" emphasise co-construction and sharing, and active initiative of the older population.[52] Combined with previous effective interventions on multimorbidity and frailty in the older population, we should encourage older adults to enhance self-management of chronic diseases. Additionally, a good social atmosphere should strengthen publicity and education for the older population in urban and rural communities.

Limitations

This study has several limitations. First, it acknowledges the existence of recall bias, because information was self-reported. For example, indexes associated with physical function and mental health were the main constituent elements of frailty. However, a self-rated levels may differ from that of reality. Second, participants who died before 2018 had not been included our analysis. Given that frailty and multimorbidity are associated with mortality, excluding them may have introduced a survival bias. Third, indirect medical economic burden was not assessed in this study. Fourth, the causal effect and bidirectional association between frailty and multimorbidity, and which affects CHE more could not be assessed in this study. Finally, the FI covers numerous indicators. During the interview process, many indicators were observed missing among the participants, which led to sample loss.

Conclusion

Co-occurrence of frailty and multimorbidity is associated with a high risk of CHE. Preventing, postponing, or reducing frailty, and enhancing standard management of chronic diseases are essential in reducing healthcare costs and preventing families from poverty. More efficient interventions for frailty and multimorbidity are urgently required.

Data Sharing Statement

All the original data could be obtained from the official website of CHARLS (http://charls.pku.edu.cn/). The identified analysis dataset is available to other researchers and others upon request by emailing the corresponding author (heruibo27@163.com).

Ethics Approval and Consent to Participate

The Biomedical Ethics Review Committee of Peking University approved CHARLS, and all participants were required to provide written informed consent. The ethical approval number was IRB00001052-11015. As the data were accessible to the public, review and approval was not required for this research by the authors' institutional review board or ethics committee.

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.

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Disclosure

The authors report no conflicts of interest in this work.

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