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Original Article

# Differential interplay between multimorbidity patterns and frailty and their mutual mediation effect on mortality in old age

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ABSTRACT

*Background:* Multimorbidity and frailty often concurrently occur among older adults.
*Objectives:* To assess the reciprocal association between multimorbidity (condition count and patterns) and frailty and examine the mutual mediation effect of multimorbidity and frailty in their associations with mortality among Chinese older adults.
*Methods:* This nationwide population-based longitudinal study included 16,563 participants aged ≥65 years in the Chinese Longitudinal Healthy Longevity Survey who were surveyed in 2008 and followed up in 2011, 2014, and 2018. Frailty phenotype was assessed by the modified Fried criteria and vital status was ascertained from family members. Cross-lagged panel model (CLPM) was used to test bidirectional associations between multimorbidity and frailty. The direct and indirect effects of multimorbidity and frailty on mortality were evaluated using the combined CLPM with survival analysis.
*Results:* Three multimorbidity patterns were identified: cardiometabolic diseases, cognitive-sensory disorder, and arthritis-digestive-respiratory diseases. The number of chronic conditions and cognitive-sensory disease pattern showed bidirectional associations with frailty across waves (range for β: 0.046−0.109; all $P < 0.001$), while cardiometabolic and arthritis-digestive-respiratory patterns unidirectionally predicted frailty change. Furthermore, frailty mediated 23%–27% of the association between multimorbidity and mortality. Only the number of conditions and cognitive-sensory disease pattern were significant mediators in the association between frailty and mortality, with the proportion of mediation ranging 4%–12%.
*Conclusions:* Multimorbidity measures including condition count and cognitive-sensory disease pattern are bi-directionally associated with frailty in older adults. These multimorbidity measures and frailty partially mediated each other's association with mortality, with frailty acting as a more prominent pathway in the association between multimorbidity and mortality.


## 1. Introduction

Multimorbidity, the co-occurrence of two or more chronic diseases in the same individual, has become the norm rather than exception among older adults (e.g., 55%–98% in those aged ≥65 years) [1]. Multimorbidity is associated with adverse health outcomes such as hospitalization, functional decline, mortality, and healthcare utilization [2]. While multimorbidity is commonly assessed with the number of chronic diseases, evidence suggests that specific chronic conditions tend to cluster together due to shared risk factors or pathophysiology [3]. Understanding multimorbidity patterns and associated health impacts could provide valuable insight into disease clustering and clinically relevant targets for multimorbidity prevention or intervention.

Frailty is recognized as a key measure to identify at-risk individuals with multimorbidity who might benefit from treatment optimization [4]. Frailty describes a dynamic state of increased vulnerability for adverse health outcomes (e.g., disability, need for long-term care, and mortality), resulting from age-associated multi-system declines in reserve and

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function [5,6]. Synthesized evidence of cross-sectional and longitudinal studies showed that two-thirds of frail older adults had multimorbidity and a fifth of multimorbid adults presented with frailty, suggesting a plausible bidirectional relationship between multimorbidity and frailty [7]. However, to date, only one recent study examined this speculation among European older adults [8]. Future studies are warranted to explore if similar bidirectional associations exist across different populations, particularly in China, which has the world's largest older population. An empirical investigation of the interplay between multimorbidity and frailty may provide insights into their common risk factors and a scientific basis for clinicians to better treat patients and prevent or delay the onset of both multimorbidity and frailty in a holistic and more effective approach.

Furthermore, multimorbidity and frailty are promising clinical markers in the aging process. Both conditions have been associated with a higher risk of mortality, while such associations have typically been investigated separately [2,9]. Given the potential reciprocal association between multimorbidity and frailty, it is plausible that both conditions are involved in the pathways that lead from each other to mortality. Relatedly, poor physical functioning has been found to mediate the association between multimorbidity and mortality among American older adults [10]. As older adults often experience concurrent multimorbidity and frailty, exploring their interrelationship with mortality may help elucidate the development of different age-related phenotypes, inform clinical practice, and guide interventions to minimize mortality risk.

This study aims to examine the bidirectional relationship between multimorbidity and frailty using three-wave panel data from a nationally representative sample of Chinese older adults and to further explore the mediation roles of multimorbidity and frailty on each other's association with mortality by combining the cross-lagged models with the survival analysis.

## 2. Methods

### 2.1. Study design and participants

Data were obtained from the Chinese Longitudinal Healthy Longevity Survey (CLHLS), which is a large nationwide and population-based survey focusing on Chinese adults older than 65 years. Participants were randomly recruited from half of the counties and city districts of 22 out of the 31 provinces in mainland China, which represents approximately 85% of the Chinese population. Nine provinces in the West and North-West parts of China were excluded, where the proportions of ethnic minorities are relatively high and the age reporting tends to be less accurate amongst older adults. Those who were deceased or too sick to be interviewed or who had migrated before the interview were excluded. As the CLHLS aims to understand aging and longevity, it specifically oversamples the oldest-old population, including centenarians, octogenarians, and nonagenarians. This approach ensures that sufficient data are collected from these age groups, which are often underrepresented in population surveys.

Eight waves of surveys have been conducted since 1998, with periodically refreshing cohort in most waves to maintain sample representativeness over time. Data were collected through in-person interviews using structured questionnaire. Quality control measures including interviewer training, fieldwork supervision, and data entry check were used to ensure the accuracy and reliability of the data. More details about the study design, sampling, measures, and data quality are available elsewhere [11]. This study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guidelines.

For this study, we included 16,563 participants aged $\geq$ 65 years who were surveyed in 2008 (T1) and followed up in 2011 (T2), 2014 (T3), and 2018 (T4). Supplementary Figure S1 shows the flowchart of the study sample and follow-up schedule.

### 2.2. Ethical considerations

The CLHLS study was approved by the Biomedical Ethics Committee at Peking University (IRB00001052–13074) and the Institutional Review Board at Duke University (Pro00062871). Written informed consent was obtained from participants.

### 2.3. Measurements

#### 2.3.1. Assessments of frailty phenotype

Frailty was defined using the modified Fried criteria [12] that comprise five components of exhaustion, shrinkage, weakness, low mobility, and inactivity [13–15]. Specifically, exhaustion was assessed by the question "I felt old and useless". Those who answered "always", "often", or "sometimes" were defined as having exhaustion [14,15]. Shrinkage was defined as body mass index $<18.5\,kg/m^2$ [14,15]. Weakness was defined as having difficulties in lifting a bag weighing five kilograms and low mobility was ascertained as not being able to walk one kilometer [15]. Inactivity was defined as engagement of the following activities once per week or less: housework, outside activity, gardening, keeping a pet, livestock breeding, playing cards or mahjong, and social activity [13,15]. Frailty score was calculated by summing up the domains met by each participant, with scores of 1–2 indicating pre-frailty and $\geq$3 indicating frailty.

#### 2.3.2. Assessments of health conditions

Twelve chronic conditions were included and categorized. Blood pressure was measured by a trained physician with the electronic sphygmomanometer. We defined hypertension as blood pressure $\geq$140/90 mmHg (average of two readings) or self-reported physician diagnosis [3]. Diabetes, heart diseases, cerebrovascular diseases including stroke, respiratory diseases (bronchitis, emphysema, and asthma), cancer, gastrointestinal or duodenal ulcers, arthritis, and dyslipidemia, were ascertained based on self-reported physician diagnosis or if the person reported being hospitalized or bedridden due to any of these conditions. Visual impairment was ascertained if participants could not see or distinguish the break in the circle, or were blind and/or reported having glaucoma or cataract. Hearing impairment was defined as requiring a hearing aid when listening. Cognitive impairment was ascertained by the self-reported diagnosis of dementia, self-reported being hospitalized or bedridden due to dementia, or using the education-specific cut-offs of the Chinese version of the Mini-Mental State Examination (MMSE); that is $\leq$17 for individuals without formal education; $\leq$20 for those with 1–6 years of education; $\leq$24 for those with $\geq$7 years of education [16]. The reliability of self-reported chronic conditions in CLHLS has been supported in the previous study [11].

#### 2.3.3. All-cause mortality

During each follow-up survey, information about vital status and health status was collected through interviews with a close family member. The quality of mortality data in the CLHLS has been evaluated to be reliable and there is no substantial underreporting bias [11].

#### 2.3.4. Covariates

Data on social-demographic characteristics (age, sex, education level, self-rated economic status, and urban/rural residency) and lifestyle factors (smoking and alcohol drinking) were collected. In addition, functional status was measured by the Katz Index of Independence in Activities of Daily Living (ADL), including the performance adequacy of six essential functions: bathing, dressing, toileting, transferring, continence, and feeding [17]. For each activity, participants were scored one point if they could perform the task without supervision, direction, or personal assistance. The total score was summarized, with higher scores indicating greater levels of functional independence.

### 2.4. Statistical analysis

Categorical and continuous variables were presented as frequency (percentage) and mean (standard deviation, SD), respectively. Multimorbidity operationalized as the number of chronic diseases was calculated for each wave of the survey. Exploratory factor analysis (EFA) was performed to identify multimorbidity patterns using baseline data (2008 wave) based on a tetrachoric correlation matrix and the principal component method. The optimal number of factors was determined based on the shape of scree plot, having an eigenvalue >1, and the interpretability of factors [18,19]. Only chronic diseases with a prevalence of >1% were included in the analysis to obtain epidemiologically coherent patterns and avoid statistical noise and spurious associations [20–22]. We applied an oblique (Oblimin) factor rotation, with each resulting factor loading representing the strength of association between the condition and the latent factor. A chronic health condition was deemed as characterizing a given pattern of multimorbidity if its loading was ≥0.25 in the corresponding pattern. A standardized composite factor score for each factor was calculated. After identifying the multimorbidity patterns at baseline, we estimated the factor scores for each pattern over the follow-up surveys using factor loadings of the multimorbidity patterns at baseline to capture the dynamic change in multimorbidity patterns [23].

To examine the bidirectional relationship between multimorbidity and frailty, we first used structural equation modeling techniques to fit the cross-lagged panel model (CLPM) which has been widely used in longitudinal data analysis to test reciprocal effects or causality [24,25]. Separate CLPM models were fitted for multimorbidity operationalized as the disease count and each multimorbidity pattern. Cross-lagged effect size was considered small (0.03), medium (0.07), and large (0.12) [26]. Then, we combined CLPM with discrete-time survival analysis to assess the direct and indirect effects (via mediation analysis) of multimorbidity and frailty on mortality [27]. The mediation analysis decomposes the total effect into direct and indirect effects to understand whether and to what extent the independent variable influences the dependent variable through an intervening mediator variable. In this study, we incorporated three dichotomous variables indicating whether the participants died between 2008 and 2011, between 2011 and 2014, and between 2014 and 2018 (coded 1 if dead, 0 if alive, missing if died in a preceding period, or lost to follow-up) in the CLPM. These mortality indicators ($T_n$) were then regressed on the multimorbidity and frailty measures from the preceding time waves ($T_1$, $T_2$, . . . , and $T_{n-1}$). Hazard ratios (HR), standardized path coefficients (β), direct and indirect effects, and proportion of mediation (indirect effect/total effect) were presented.

Missing data were handled using the full information maximum likelihood (FIML) method. FIML uses all available information from the database to estimate model parameters that produce less biased and more reliable estimates compared with conventional methods of dealing with missing data [28,29]. Data analysis was performed using STATA 11.0 and Mplus 8.0. A two-tailed *P* value <0.05 was set as statistically significant.

## 3. Results

### 3.1. Characteristics of the participants

At baseline, the participants had a mean age of 87.49 years (SD = 11.37). Most of them were female (57.8%), illiterate (63.2%), lived in rural areas (60.3%); 67.3% had never smoked and 69.6% abstained from alcohol consumption. Three-quarters of the participants maintained functional independence in ADLs (Table 1). The most prevalent chronic condition was hypertension (45.1%), followed by visual impairment (44.4%) and hearing impairment (35.9%). Based on the Fried phenotype, 45.3%, and 22.0% of the participants were classified as pre-frail and frail, respectively (Table 1). Description of chronic conditions and frailty in the follow-up waves is presented in Supplementary Table S1.

### 3.2. Patterns of multimorbidity and frailty phenotype score

The Kaiser–Meyer–Olkin value of 0.72 indicated that the baseline data were suitable for factor analysis. Three multimorbidity patterns were identified, explaining 52.1% of the total variance (Table 2). Factor 1 was characterized by cardiometabolic diseases (e.g., diabetes, heart disease, dyslipidemia, hypertension, and stroke). Factor 2 was represented by cognitive and sensory disorders (e.g., hearing and visual impairment). Factor 3 was characterized by arthritis, gastroduodenal ulcer, and respiratory diseases. Description of condition counts, multimorbidity pattern scores, and frailty phenotype scores for each wave is presented in Supplementary Table S2.

**Table 1**
Baseline characteristics of study participants in the 2008 wave survey (N = 16,563).

| Characteristics | N (%)/Mean ± SD |
|---|---|
| Sociodemographic characteristics | |
| Age (year) | 87.49 ± 11.37 |
| 65∼79 | 4,286 (25.9) |
| 80∼99 | 8,787 (53.0) |
| ≥100 | 3,490 (21.1) |
| Sex | |
| Male | 6,988 (42.2) |
| Female | 9,575 (57.8) |
| Education | |
| Illiterate | 10,465 (63.2) |
| Elementary school | 4,486 (27.1) |
| Junior school and above | 1,562 (9.4) |
| Missing | 50 (0.3) |
| Self-rated economic status | |
| Poor/Very poor | 3,013 (18.2) |
| Mediocre | 11,315 (68.3) |
| Rich/Very rich | 2,187 (13.2) |
| Missing | 48 (0.3) |
| Residential area | |
| City | 3,272 (20.0) |
| Town | 3,215 (19.7) |
| Rural | 9,838 (60.3) |
| Lifestyle factors | |
| Smoking | |
| Never smoke | 11,157 (67.3) |
| Ever smoke | 2,589 (15.6) |
| Current smoker | 2,817 (17.0) |
| Drinking | |
| Never drink | 11,520 (69.6) |
| Ever drink | 2,255 (13.6) |
| Current drinker | 2,788 (16.8) |
| Functional independence in ADL | |
| 0 | 507 (3.1) |
| 1 | 486 (2.9) |
| 2 | 494 (3.0) |
| 3 | 370 (2.2) |
| 4 | 557 (3.4) |
| 5 | 1,317 (8.0) |
| 6 | 12,832 (77.5) |
| Chronic health conditions | |
| Hypertension | 7,464 (45.7) |
| Visual impairment | 7,347 (44.4) |
| Hearing impairment | 5,950 (35.9) |
| Cognitive disorder | 3,005 (22.1) |
| Arthritis | 3,551 (21.7) |
| Respiratory disease | 1,791 (11.0) |
| Heart disease | 1,490 (9.2) |
| Cerebrovascular diseases | 1,030 (6.3) |
| Gastroduodenal ulcer | 859 (5.3) |
| Diabetes | 430 (2.7) |
| Gallbladder disease | 384 (2.4) |
| Dyslipidemia | 252 (1.6) |
| Frailty components | |

(continued on next page)

**Table 1** ***(continued)***

| Characteristics | N (%)/Mean ± SD |
|---|---|
| Exhaust | |
| No | 5,260 (31.8) |
| Yes | 8,760 (52.9) |
| Missing | 2,543 (15.4) |
| Shrinkage | |
| No | 10,782 (65.1) |
| Yes | 5,348 (32.3) |
| Missing | 433 (2.6) |
| Weakness | |
| No | 11,070 (66.8) |
| Yes | 5,493 (33.2) |
| Inactivity | |
| No | 10,986 (66.3) |
| Yes | 5,556 (33.5) |
| Low mobility | |
| No | 11,010 (66.5) |
| Yes | 5,553 (33.5) |
| Frailty status | |
| Non-frailty | 2,706 (16.3) |
| Pre-frailty | 7,497 (45.3) |
| Frailty | 3,649 (22.0) |
| Missing | 2,711 (16.4) |

Abbreviation: ADL, activities in daily living.

### 3.3. Bidirectional relationship between multimorbidity and frailty phenotype

As shown in Fig. 1, four individual CLPM models were fitted for multimorbidity measured as condition count and each identified multimorbidity pattern. All the models showed satisfactory model fits (see model fit indices in Supplementary Table S3). After adjusting for covariates, the increased number of chronic conditions was associated with greater frailty at follow-up (T1→T2: $\beta = 0.046$; T2→T3: $\beta = 0.072$; all $P < 0.001$) and vice versa (T1→T2: $\beta = 0.055$; T2→T3: $\beta = 0.069$; all $P < 0.01$), suggesting a stable bidirectional association between the number of chronic conditions and frailty (Fig. 1a). In terms of multimorbidity patterns, cognitive-sensory impairment pattern showed medium to large predictive value on follow-up frailty (T1→T2: $\beta = 0.064$; T2→T3: $\beta = 0.100$; all $P < 0.001$) and vice versa (T1→T2: $\beta = 0.109$; T2→T3: $\beta = 0.101$; all $P < 0.001$) (Fig. 1c). The cross-lagged effects of cardiometabolic disease pattern at T2 on frailty at T3 (Fig. 1b: $\beta = 0.026$, $P < 0.05$) and arthritis-digestive-respiratory disease pattern at T1 on frailty at T2 (Fig. 1d: $\beta = 0.034$, $P < 0.01$) were small, while no other cross-lagged effects involving these two multimorbidity patterns and frailty were significant.

### 3.4. Direct and indirect effects of multimorbidity and frailty phenotype on all-cause mortality

The combined model of cross-lagged and survival analysis revealed independent associations between multimorbidity measured as the condition count and mortality (HR range: 1.03–1.18; all $P < 0.05$) as well as between frailty and mortality (HR range: 1.29–1.47; all $P < 0.001$) over the subsequent follow-up period (Fig. 2a). The mediation analysis further showed that condition count and frailty mutually mediated each other's association with mortality. In addition to the direct effect, the increased number of chronic conditions had a significant indirect effect on mortality through its association with frailty at follow-up, constituting 24–27% of the total association. Similarly, the indirect path from frailty to mortality through increased condition count also remained significant (proportion of mediated: ~4%) (Table 3).

In contrast, multimorbidity patterns showed differential associations with mortality risk. As illustrated in Fig. 2b–d, only cognitive-sensory disorder pattern (HR range: 1.27–1.94; all $P < 0.001$) and frailty (HR range: 1.35–1.47; all $P < 0.001$) showed consistent associations with mortality in the later wave. Cardiovascular disease pattern score measured at T1 predicted mortality between T1-T2 (HR = 0.78) and measured at T3 predicted mortality between T3-T4 (HR = 1.80) (Fig. 2b), while arthritis-digestive-respiratory disease pattern did not have a direct association with mortality across waves (Fig. 2d).

Regarding the indirect effects of multimorbidity patterns and frailty in mortality, we found that cognitive-sensory disorder pattern and frailty significantly mediated each other's association with mortality across waves (Fig. 2c and Table 3). For the other two multimorbidity patterns, frailty at T3 mediated the association of cardiometabolic disease pattern score assessed at T2 wave with mortality between T3-T4 ($\beta = 0.007$), and frailty at T2 mediated the indirect association of arthritis-digestive-respiratory disease pattern score assessed at T1 with mortality between T2-T3 ($\beta = 0.008$). No other significant indirect effects involving these two multimorbidity patterns were observed.

### 3.5. Sensitivity and subgroup analysis

To account for the potential selection bias due to loss to follow-up, we repeated the analysis by only including participants with complete data on multimorbidity and frailty at both the baseline and the first follow-up to allow for longitudinal analysis. The results of bidirectional and mediation analysis were identical to the findings from the analysis using all information (Supplementary Table S4 and Supplementary Figure S2 and S7). In addition, sex- and age- stratified analyses showed consistent results between males and females (Supplementary Table S5 and Supplementary Figure S3, S4, S8 and S9), and between elderly aged 65–79 and aged 80 and above (Supplementary Table S6 and Supplementary Figure S5, S6, S10 and S11).

## 4. Discussion

This prospective cohort study revealed a stable bidirectional relationship between multimorbidity and frailty over time among a large and nationally representative sample of Chinese older adults.

**Table 2**
Rotated factor loadings for each of the 12 chronic diseases by disease patterns from factor analysis using 2008 wave data.

| Chronic diseases | Cardiometabolic diseases (factor 1) | Cognitive-sensory disorders (factor 2) | Arthritis-digestive-respiratory diseases (factor 3) |
|---|---|---|---|
| Diabetes | **0.71** | −0.04 | −0.07 |
| Heart disease | **0.69** | −0.01 | 0.11 |
| Dyslipidemia | **0.68** | −0.06 | 0.15 |
| Hypertension | **0.59** | −0.02 | −0.32 |
| Cerebrovascular diseases | **0.59** | 0.18 | 0.05 |
| Gallbladder disease | **0.40** | −0.04 | 0.14 |
| Cognitive disorder | −0.05 | **0.89** | 0.00 |
| Hearing impairment | −0.04 | **0.88** | −0.05 |
| Visual impairment | 0.15 | **0.75** | 0.07 |
| Arthritis | 0.02 | 0.02 | **0.68** |
| Gastroduodenal ulcer | 0.08 | −0.08 | **0.65** |
| Respiratory disease | −0.02 | 0.05 | **0.62** |
| **Eigenvalue** | 2.47 | 2.19 | 1.59 |
| **Cumulative percentage** | 20.6% | 38.9% | 52.1% |

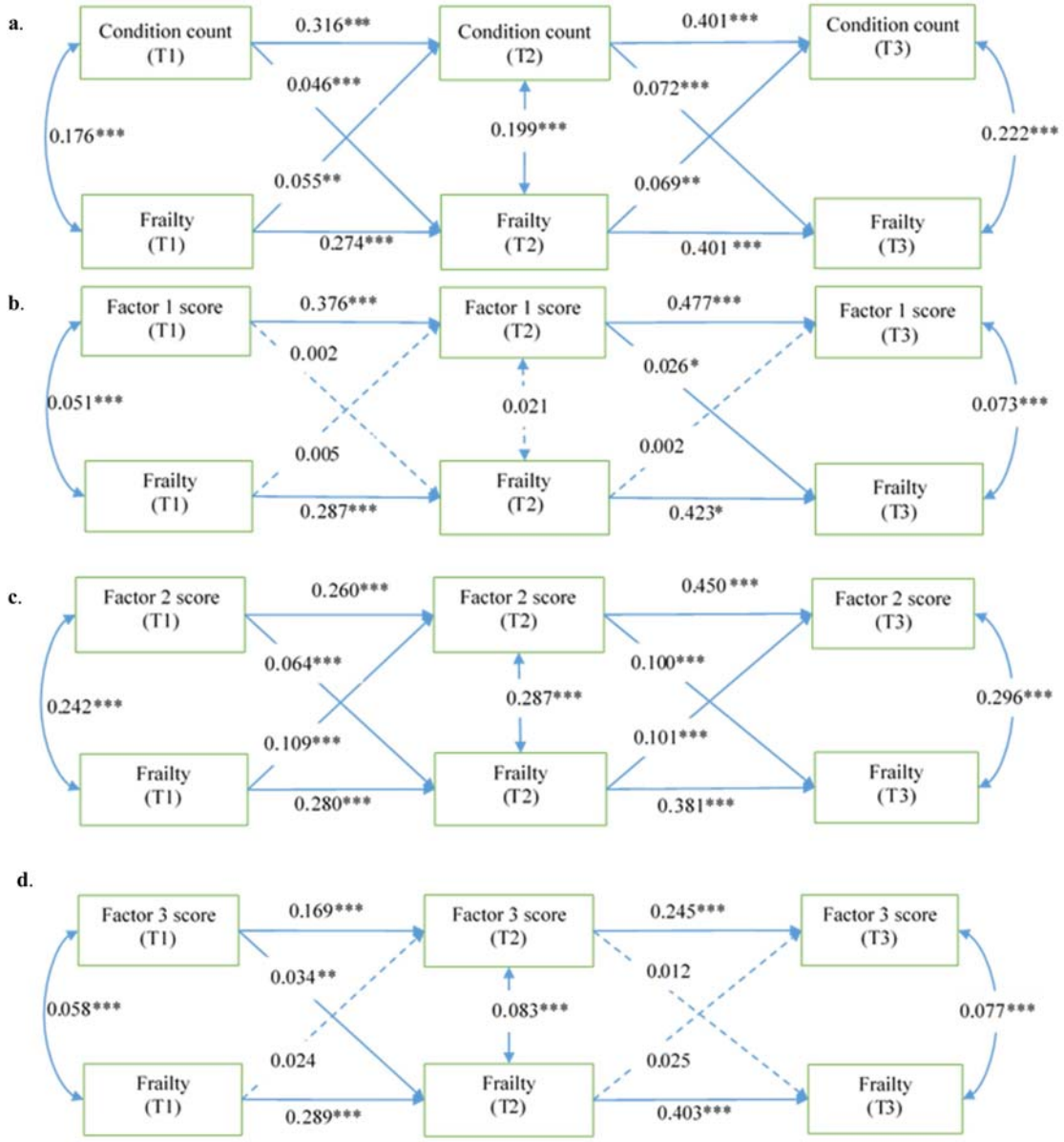


**Fig. 1.** Cross-lagged panel models for the association between multimorbidity and frailty phenotype (n = 16,563).
Note: Solid lines represent the significance of the structural path ($p < 0.05$) while dash lines represent non-significant paths. Standardized coefficients were shown. For simplicity, background covariates (i.e., age, sex, education, self-reported economic status, residential area, smoking, drinking, and ADL) of outcomes are not presented. ***$p < 0.001$. **$p < 0.01$. *$p < 0.05$. Abbreviation: Factor 1: cardiometabolic diseases; Factor 2: cognitive-sensory impairment; Factor 3: arthritis-digestive-respiratory diseases.

Furthermore, this study firstly attempted to explore the mutual mediating role of multimorbidity and frailty in their associations with mortality. The findings suggested that multimorbidity and frailty were associated with an increased risk of mortality directly and indirectly via each other's mediation effect. However, the three multimorbidity patterns showed differential associations with frailty and mortality, indicating that the effect of multimorbidity may depend on the characteristics of disease interactions. This study advances the understanding of the interrelationship between multimorbidity and frailty and disentangles the pathways contributing to reduced survival in multimorbid and frail older adults.

Multimorbidity was highly prevalent among the study participants and over one-fifth presented with frailty, which is comparable to other studies [30,31]. The confirmed bidirectional relationship between the number of chronic conditions and frailty suggested that multimorbidity was predictive of frailty, and vice versa. On the other hand, the three identified multimorbidity patterns, which were identical to those identified in prior studies of older adults in China [3,32], showed varying associations with frailty. Cognitive-sensory disease pattern had a consistent and reciprocal association with frailty across waves, while cardiometabolic disease pattern and digestive-respiratory disease pattern unidirectionally predicted frailty in a specific wave and with a smaller effect size. These findings suggested that multimorbidity had a broader effect on frailty and frailty exerted a stronger effect on cognitive-sensory diseases. The potential causal association between multimorbidity and frailty might involve mechanisms of specific chronic diseases, polypharmacy, and elevated inflammation changes and oxidative stress accumulated in multimorbidity [33]. Specifically, cognitive-sensory diseases and frailty share common pathological pathways underlying the aging process, including neuropathology and decreased ability to recover from damage, which may explain their strong and reciprocal associations [34]. Indeed, frailty is a strong predictor of cognitive impairment and dementia in older individuals [35]. Cognitive-sensory diseases are thus

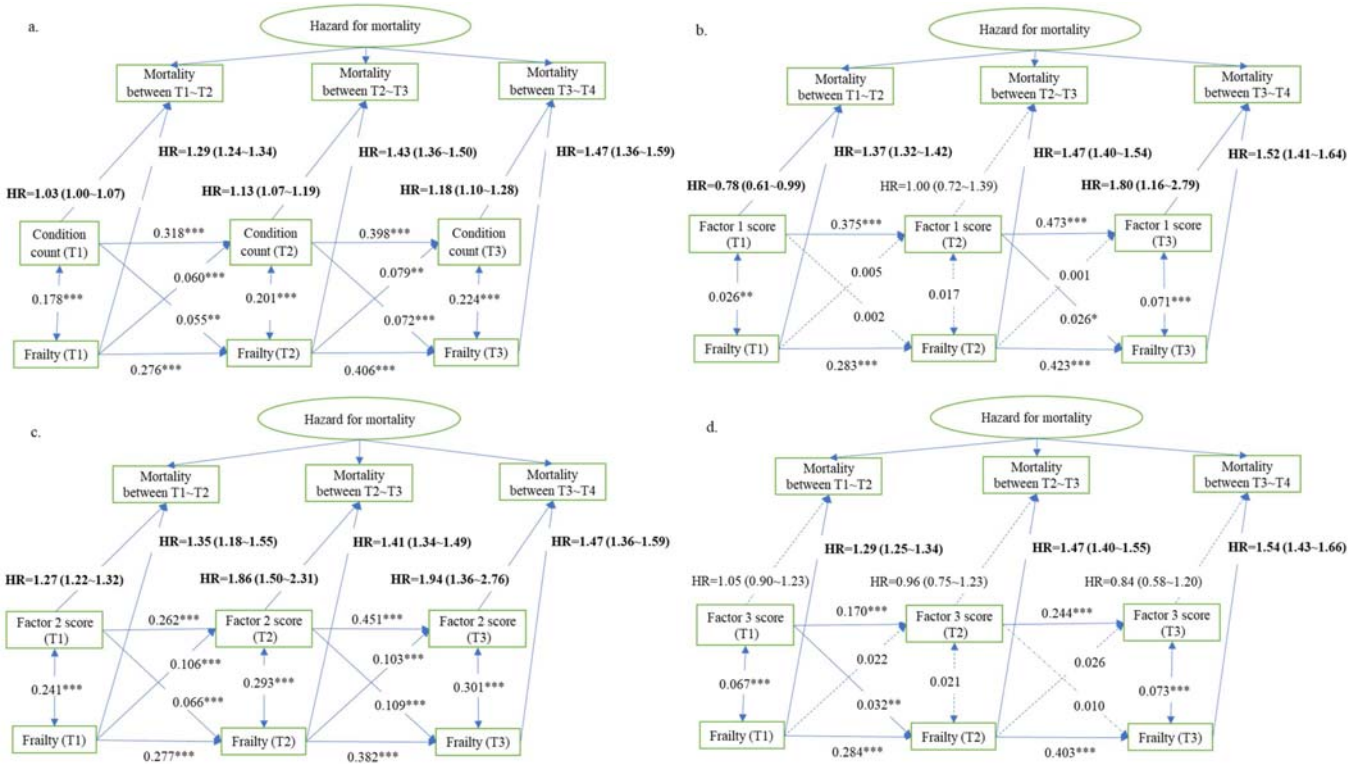


**Fig. 2.** Combined cross-lagged and hazard model for mortality explained by multimorbidity (condition count and patterns) and phenotype (n = 16,563).
Note: Standardized coefficients were shown. Solid lines represent the significance of the structural path ($p < 0.05$) while dash lines represent non-significant paths. For simplicity, the background covariates (i.e., age, sex, education, self-reported economic status, residential area, smoking, drinking, and ADL) and lagged paths from multimorbidity and frailty score to mortality at later time intervals are not presented. ***$p < 0.001$, **$p < 0.01$, *$p < 0.05$. Abbreviation: Factor 1: cardiometabolic diseases; Factor 2: cognitive-sensory impairment; Factor 3: arthritis-digestive-respiratory diseases.

especially relevant outcomes for frail individuals and prevention and optimal management of co-occurring chronic conditions would be effective in tailoring interventions to reduce the risk of frailty.

Furthermore, the combined models with mediation analysis revealed that multimorbidity measured as the number of chronic conditions predicted higher levels of frailty, which subsequently increased the risk of mortality. Frail individuals were at higher risk of death not only directly but also indirectly through changes in accumulated chronic diseases. These findings suggested the potential mutual mechanism circles of multimorbidity and frailty in their contribution to the increased risk of mortality and that properly managing frailty in multimorbid older adults and prevention of multimorbidity in individuals with frailty could help reduce the risk of mortality. Notably, frailty showed a larger mediation effect (23–27%) in the association between multimorbidity and mortality compared to the mediating role of multimorbidity in the association between frailty and mortality (4–12%), denoting that frailty was a more prominent pathway in explaining the association between multimorbidity and mortality. However, partial mediation effects indicate the existence of other plausible mediators accounting for the mortality risk of older adults with multimorbidity or frailty. For instance, healthy behaviors were found to mediate the association between frailty and respiratory disease mortality [9]. More longitudinal studies are warranted to disentangle the mechanisms influencing the survival status of older people with multimorbidity or frailty.

The three multimorbidity patterns showed prospective associations with frailty across waves and frailty mediated some of their associations with mortality. Such mediation effects were more consistent and pronounced for cognitive-sensory disorder pattern. This reinforces the view that frailty was an intermediate status in the death path of older adults with chronic diseases, especially for cognitive-sensory diseases. The prevention of frailty may be effective in reducing the mortality rate of patients with multimorbidity. An unexpected finding was the negative association between cardiometabolic pattern score at T1 and subsequent risk of mortality. The management of cardiometabolic diseases often involve effective medication treatments and lifestyle modifications, which may empower patients and provide a sense of control [36], potentially buffering the mortality risk. However, the positive association between cardiometabolic pattern at T3 and mortality risk highlighted the detrimental impact and cumulative burden of cardiometabolic diseases over time.

On the other hand, frailty was prospectively associated with cognitive-sensory disease pattern, which in turn increased the risk of mortality. Such mediation effects were not observed for the cardiometabolic and digestive-respiratory patterns as these two patterns were not predicted by frailty. These findings were consistent with the results of cross-lagged models and emphasized the interplay between frailty and cognitive-sensory diseases. Interventions to prevent and manage cognitive and sensory comorbidities may help improve the survival of older populations with frailty syndromes.

The strength of this study was that we used three-wave panel data from a nationally representative sample of older adults to clarify the reciprocal relationship of multimorbidity, frailty, and mortality. Furthermore, the use of joint modeling of cross-lagged model and survival analysis could assess these simultaneous associations of multimorbidity and frailty with mortality, which has the advantage of investigating the dynamic and simultaneous process in which how multimorbidity and frailty influenced survival, with greater accuracy than independent models [10]. In addition, we measured multimorbidity as both the number of chronic conditions and patterns that capture the interaction among different chronic conditions, which provides a more nuanced understanding of the health impacts of multimorbidity.

The findings have important clinical implications. First, it is imperative to implement routine monitoring and surveillance for both multimorbidity and frailty among older adults, as the presence of one

**Table 3**
Parameter estimates on the associations of multimorbidity and frailty phenotype with all-cause mortality from the cross-lagged path models (n = 16,563).

| Paths | Standardized indirect effect of the specific path β (95% CI) | Standardized direct effect β (95% CI) | Standardized total effect β (95% CI) | Proportion of mediation (%) |
|---|---|---|---|---|
| **Chronic condition count** | | | | |
| Condition count at T1 → Frailty score at T2 → Mortality between T2-T3 | **0.012 (0.006∼0.017)** | 0.006 (−0.026∼0.039) | **0.044 (0.013∼0.074)** | 27.3 |
| Condition count at T2 → Frailty score at T3 → Mortality between T3-T4 | **0.017 (0.009∼0.024)** | 0.014 (−0.035∼0.062) | **0.070 (0.027∼0.114)** | 24.2 |
| Frailty score at T1 → Condition count at T2 → Mortality between T2-T3 | **0.004 (0.001∼0.008)** | 0.027 (−0.009∼0.062) | **0.096 (0.062∼0.131)** | 4.2 |
| Frailty score at T2 → Condition count at T3 → Mortality between T3-T4 | **0.008 (0.002∼0.014)** | **0.093 (0.044∼0.142)** | **0.195 (0.149∼0.241)** | 4.1 |
| **Cardiometabolic disease pattern (Factor 1)** | | | | |
| Factor 1 score at T1 → Frailty score at T2 → Mortality between T2-T3 | 0.001 (−0.004∼0.005) | 0.016 (−0.014∼0.047) | 0.017 (−0.011∼0.044) | / |
| Factor 1 score at T2 → Frailty score at T3 → Mortality between T3-T4 | **0.007 (0.000∼0.013)** | −0.023 (−0.073∼0.026) | 0.012 (−0.031∼0.054) | N.A. |
| Frailty score at T1 → Factor 1 score at T2 → Mortality between T2-T3 | 0.000 (0.000∼0.000) | **0.032 (−0.002∼0.067)**# | **0.104 (0.071∼0.137)** | / |
| Frailty score at T2 → Factor 1 score at T3 → Mortality between T3-T4 | 0.000 (−0.002∼0.003) | **0.102 (0.054∼0.150)** | **0.209 (0.165∼0.254)** | / |
| **Cognitive-sensory disorder pattern (Factor 2)** | | | | |
| Factor 2 score at T1 → Frailty score at T2 → Mortality between T2-T3 | **0.015 (0.007∼0.023)** | 0.010 (−0.027∼0.047) | **0.054 (0.018∼0.090)** | 27.8 |
| Factor 2 score at T2 → Frailty score at T3 → Mortality between T3-T4 | **0.026 (0.015∼0.037)** | 0.045 (−0.013∼0.102) | **0.115 (0.063∼0.166)** | 22.6 |
| Frailty score at T1 → Factor 2 score at T2 → Mortality between T2-T3 | **0.012 (0.006∼0.017)** | 0.022 (−0.014∼0.059) | **0.097 (0.062∼0.133)** | 12.4 |
| Frailty score at T2 → Factor 2 score at T3 → Mortality between T3-T4 | **0.010 (0.003∼0.017)** | **0.078 (0.028∼0.128)** | **0.179 (0.132∼0.227)** | 5.6 |
| **Arthritis-digestive-respiratory disease pattern (Factor 3)** | | | | |
| Factor 3 score at T1 → Frailty score at T2 → Mortality between T2-T3 | **0.008 (0.003∼0.013)** | −0.004 (−0.031∼0.023) | 0.004 (−0.023∼0.031) | N.A. |
| Factor 3 score at T2 → Frailty score at T3 → Mortality between T3-T4 | 0.003 (−0.004∼0.010) | 0.016 (−0.023∼0.054) | 0.013 (−0.024∼0.051) | / |
| Frailty score at T1 → Factor 3 score at T2 → Mortality between T2-T3 | 0.000 (−0.001∼0.001) | **0.033 (−0.002∼0.068)**# | **0.105 (0.072∼0.139)** | / |
| Frailty score at T2 → Factor 3 score at T3 → Mortality between T3-T4 | −0.001 (−0.002∼0.001) | **0.099 (0.051∼0.138)** | **0.204 (0.160∼0.249)** | / |

Note: N.A.: the proportion of mediation was not calculated due to the opposite direction of indirect and direct effects. /: the proportion of mediation was not calculated due to non-significant indirect effect. #: $p < 0.10$.

condition increases vulnerability to the other. Specifically, for individuals presented with frailty phenotype symptoms, early screening and prevention of cognitive and sensory impairments is greatly warranted. Second, an integrated and personalized care approach recognizing and jointly managing multimorbidity and frailty has the potential to reduce repetitive medical visits, improve patient outcomes, and reduce mortality risk in older adults. This necessitates a coordinated effort from a multidisciplinary team involving geriatricians, physicians, nurses, physical/occupational therapists, nutritionists, and social workers. Third, as frailty acts as a prominent mediator in the pathway from the accumulation of multimorbidity to mortality, interventions alleviating frailty in multimorbid patients (e.g., strength training, nutritional support, cognitive training) may prevent the progression of functional decline and decrease mortality risk in patients with multimorbidity. Fourth, health education is warranted to enhance awareness of the interplay between multimorbidity and frailty among older adults, caregivers, and the broader community to empower individuals and their support systems with the knowledge necessary for proactive disease self-management, timely help-seeking behaviors, and clinical decision-making process, in order to achieve patient-centered and integrated care.

Our study had several limitations. First, we used self-reported physician diagnoses or medical treatments to measure multimorbidity, which may underestimate the multimorbidity prevalence as some participants, especially those in rural areas, might have limited access to the healthcare system for timely diagnosis. Second, the numbers and types of chronic conditions measured in CLHLS are comprehensive though not exhaustive. Third, the findings might have been affected by selective attrition. The association between multimorbidity and frailty may be underestimated if those who had more chronic conditions or frailty symptoms were more likely to drop out due to health issues. We also performed sensitivity analysis to understand the potential attrition impact. Lastly, as the data were derived from the Chinese population, the interpretation and generalization of findings should take the cultural and contextual factors into consideration. Variations in healthcare systems across different countries can significantly affect patients' help-seeking behaviors and the management of multimorbidity and geriatric symptoms, thereby influencing outcomes and mortality rates associated with multimorbidity and frailty. In China, the healthcare system is predominantly oriented towards specialist care for chronic diseases, despite primary care system has been strengthened in recent years [37]; this can lead to patients experiencing frequent medical visits and hospitalizations due to multimorbidity. Lack of coordination of information systems and support from community services (e.g., physiotherapists or district nurses) have been reported by multimorbid patients [37–39]. Besides the impact of organizational environment on multimorbidity care, perceptions of illness and strategies for coping with multimorbidity can also significantly impact patients' ability to self-manage their conditions, which may be influenced by cultural differences. In Chinese culture, which values harmony and unity, individuals may be inclined to adapt to their current status rather than intentionally making changes. This contrasts with Western cultures, where individuals might employ a variety of active strategies in response to stress [40]. A study found that about half of Chinese patients with multimorbidity viewed their conditions as a significant threat from different perspectives

(e.g., illness concern, emotional distress, and long timeline) and tended to use positive adaptation, denial, or disengagement coping strategies [37]. Future cross-cultural studies are warranted to test if such cultural and social differences would affect the management and health consequences of multimorbidity and frailty.

## 5. Conclusion

This large-scale cohort study revealed a bidirectional association between multimorbidity and frailty among Chinese older adults and demonstrated that both multimorbidity and frailty partially mediated each other's effects on mortality, but the findings varied by the pattern of multimorbidity. This study advances the understanding of the interplay between multimorbidity and frailty, emphasizing the need to identify and address these conditions simultaneously for early intervention. Future studies are warranted to investigate whether interventions to reduce the development and progression of multimorbidity and frailty conjointly could help improve the survival of aging populations.

## Conflict of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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## Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.jnha.2024.100305.

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