Advances in Research on Frailty Trajectories and Their Influencing Factors: Postprint

Authors: He Yang, Yang Rong, Shen Can, Yi Shanye, Liu Lidi, Zhao Qian, Myriad wisdom, Xiaoyang Liao, Wan Zhi, Liao Xiaoyang

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Abstract

Frailty is an age-related geriatric condition that increases the risk of adverse events in older adults. With the progression of population aging, frailty has attracted widespread attention. Previous research has primarily focused on frailty status, dominated by cross-sectional studies, with unclear investigations into frailty trajectories (clustering of individuals with similar frailty status over time) and their influencing factors, and consequently unclear early intervention measures for frailty through these studies. This article summarizes the latest clinical research progress on risk factors for frailty trajectories, aiming to analyze factors influencing frailty trajectories from different perspectives and provide new insights for the comprehensive management of frail patients.

Full Text

Progress in Research on the Trajectory of Frailty and Its Influencing Factors

HE Yang[1], YANG Rong[1], SHEN Can[1], YI Shanye[1], LIU Lidi[1], ZHAO Qian[1], WAN Zhi[2], *LIAO Xiaoyang*[1]

[1] General Medicine Ward, Special Need Medical Center, West China Hospital, Sichuan University, Chengdu 610000, China
[2] Department of Emergency Department, West China Hospital, Sichuan University, Chengdu 610000, China

Corresponding authors: LIAO Xiaoyang, Chief physician/Professor/Doctoral supervisor; E-mail: 625880796@qq.com
WAN Zhi, Chief physician/Doctoral supervisor; E-mail: wanzhi4115@wchscu.cn

Abstract

Frailty is a geriatric syndrome associated with aging that increases the risk of adverse events in older adults. With the progression of population aging, frailty has become a widespread concern. Previous research has primarily focused on frailty status through cross-sectional studies, with limited investigation into frailty trajectories (the temporal clustering of individuals with similar frailty levels) and their influencing factors, leaving early intervention measures unclear. This review summarizes the latest clinical research progress on risk factors for frailty trajectories, aiming to analyze influencing factors from multiple perspectives and provide new insights for comprehensive management of frail patients.

Keywords: Frailty; Trajectory of frailty; Longitudinal studies; Risk factors; Review

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Since the beginning of the 21st century, "global aging" has remained a persistent topic in sustainable development research by the United Nations and international academia. The world population is undergoing unprecedented changes, with the number of people aged 60 and older projected to increase from 600 million in 2000 to 2 billion in 2050, representing a rise from 10% to 21% of the total population [1-2]. Notably, approximately 80% of these 2 billion older adults will live in developing countries by 2050 [3]. As the aging process continues, health issues in the context of aging have attracted increasing attention, with significant socioeconomic implications [4].

Frailty represents a critical health issue accompanying aging, defined as a state of increased vulnerability when encountering stressful events that elevates risks of falls, hospitalization, long-term care, and mortality [5]. A study investigating physical frailty among community-dwelling older adults in China reported an overall prevalence of 9.9%, with the lowest rate (4.3%) in those aged 60-64 years and the highest (26%) in those aged 80 years and above [6]. Previous frailty research has been largely limited to cross-sectional studies [7-8], treating individuals as having discrete frailty states rather than continuous changes [9]. To better understand temporal trends in frailty, the concept of frailty trajectories was proposed [10], representing the temporal changes in frailty among groups of individuals with similar progression patterns. However, research on frailty trajectories remains in its infancy, and clarifying influencing factors constitutes the first step toward identifying intervention targets and developing individualized strategies. This review synthesizes research on frailty trajectories and analyzes influencing factors to inform interventions for frail patients.

1 Frailty Trajectories

Frailty trajectories are constructed by fitting similar frailty groups to depict different trajectory types, representing the overall frailty changes among population subgroups with shared characteristics [10]. Most cohort studies have demonstrated linear frailty trajectories. The Longitudinal Aging Study Amsterdam (LASA), which followed participants for 17 years with assessments every three years, showed that the mean Frailty Index (FI) increased consistently from baseline to follow-up (mean FI: 0.17 to 0.39). After adjusting for sex and baseline age, FI continued to increase significantly over time ($\beta = 0.05$, $P < .001$), and the addition of quadratic terms to test for non-linear relationships further confirmed the linear nature of frailty trajectories in this cohort [11]. Data from the English Longitudinal Study of Ageing, measuring cultural participation frequency among 4,575 adults, revealed a linear rate of frailty progression over 10 years (β = -0.0039) [12]. Similarly, BUCHMAN et al. [13] enrolled 2,167 community-dwelling residents with a mean follow-up of 6 years, finding linear changes in frailty that worsened by 0.09 units annually (0.088, SD = 0.044).

In addition to linear trajectories, some studies have identified non-linear patterns. For instance, STOLZ et al. [14] used the Survey of Health, Ageing and Retirement in Europe (SHARE) dataset to assess the impact of occupational class and wealth on FI trajectories among 24,383 participants over nine years, finding that a non-linear quadratic model provided the best fit, revealing a non-linear relationship in frailty changes over time.

2 Frailty Assessment

Currently, no unified international standard exists for frailty assessment, and various tools are used for evaluating frailty trajectories. Most researchers select optimal assessment instruments based on data structure and evaluation standard accuracy. Assessment tools primarily include three categories (see Table 1): the Frailty Index (FI) [14], the Fried Frailty Phenotype and its modified versions [13], and other frailty assessment scales or combinations thereof. These tools incorporate different factors influencing frailty, clinical manifestations, and psychological status, though no standardized evaluation instrument currently exists.

2.1 Frailty Index (FI)

ROCKWOOD et al. [15-16] developed the FI to quantify frailty as the proportion of deficits present in an individual, based on the accumulation of deficits (impairments, disabilities, diseases) as a measure of health status. The calculation involves dividing the number of health deficits by the total number of possible deficits, with higher proportions indicating greater frailty. Research has validated that 30 or more items can reliably assess frailty severity [11]. The FI encompasses not only physical condition but also social and psychological dimensions, reflecting a holistic health concept [17]. Within the cumulative deficit model, multiple factors may contribute to frailty onset and progression. However, given the extensive number of assessment items, CLEGG et al. [18] proposed the electronic Frailty Index (eFI) as a simpler method for evaluating frailty severity. The eFI enables comprehensive geriatric assessment and helps identify frailty diagnosis and influencing factors, representing actionable targets for personalized intervention and management plans.

2.2 Fried Frailty Phenotype

The Fried Frailty Phenotype, developed by FRIED et al. [16], includes five components: unintentional weight loss, decreased grip strength, slow gait speed, low physical activity, and exhaustion, defining frailty as meeting $ $3 criteria, prefrailty as 1-2 criteria, and robustness as 0 criteria. BUCHMAN et al. [13] utilized a modified version of the Fried Frailty Phenotype, accounting for their younger baseline population compared to FRIED et al. [16], with primary differences in physical activity measurement methods and frailty cutoff points.

2.3 Other Assessment Tools

Beyond these two primary tools and their modifications, other assessment instruments have been introduced [19]. The Edmonton Frailty Scale (EFS) is a multidimensional tool comprising 11 variables across nine domains, including cognition, social support, self-reported health, nutrition, disability, and mood, with scores ranging from 0 to 17. Scores of 0-4 indicate no frailty, 5-6 indicate vulnerability, 7-8 indicate mild frailty, 9-10 indicate moderate frailty, and $ $11 indicate severe frailty [20]. AGUAYO et al. [19], when examining the relationship between blood glucose and frailty trajectories, employed the EFS alongside the 36-item Frailty Index and Fried Frailty Phenotype. To facilitate comparison across the three scales, scores were rescaled by dividing the obtained value by the maximum possible score and multiplying by 100, adjusting frailty scores from 0 (robust) to 100 (maximum frailty).

3 Influencing Factors of Frailty Trajectories

Influencing factors are categorized as non-modifiable and modifiable. Non-modifiable factors include age, sex, family support, and family economy, while modifiable factors encompass cultural engagement, physical activity, cognition, body weight, blood glucose, blood pressure, and diet. The following sections analyze primary influencing factors and review current evidence on factors affecting frailty trajectories.

3.1 Non-Modifiable Factors

Age: Age is frequently identified as adversely affecting frailty, though its relationship with frailty trajectories remains unclear. A UK longitudinal study on frailty [21] stratified participants by baseline age into five groups (50-54, 55-59, 60-64, 65-69, 70-74, and 75-79 years) and found that older baseline age was associated with greater trajectory changes over 10 years of follow-up. However, HOOGENDIJK et al. [5] concluded that age does not affect the rate of frailty trajectory change. These inconsistent findings may be explained by the UK study' s observation that after adjustment, the association only persisted in the

70-79 age group. Although FI changes were greater in older groups at baseline, the increases were similar between the 65-75 and 75+ groups during follow-up, suggesting relatively stable FI change rates throughout the study period. This may be partially explained by higher mortality and dropout rates among more frail individuals, potentially removing those with faster progression from the population [21].

Sex: Research consistently shows that women exhibit higher frailty levels than men. A coordinated analysis of five longitudinal studies observing frailty trajectories [11] demonstrated that women had consistently higher frailty levels across all five cohorts, attributable to women' s longer life expectancy and disparities in health, economic, and social status. However, sex differences in frailty progression rates were largely null, with only the US Health and Retirement Study (HRS) showing higher progression rates in women. Conversely, ROJAS et al. [22] found that women had steeper frailty trajectory slopes than men. These inconsistent results across cohorts require cautious interpretation, as differences are small and mostly non-significant, possibly related to FI values ranging between 0 and 1 and the slow accumulation of deficits.

Family Support: Several studies have explored family support' s impact on frailty trajectories, with robust family social support reducing trajectory slopes. A study published in *BMJ Open* [10] examining factors affecting US older adults' frailty trajectories from 2005-2012 found that older adults living alone had increased risk of high-frailty trajectories compared to those living with family or spouses. However, after adjusting for baseline frailty, this association only existed in the 70-79 age group. OBERNDORFER et al. [23] analyzed SHARE data to assess spousal loss effects on frailty trajectories, finding that widowhood initially affected both men and women' s trajectories, but women' s trajectories gradually converged with those of partnered individuals over time, while men' s trajectories showed persistent effects. Additionally, grandchild caregiving was associated with smaller declines in frailty, though reverse causality cannot be excluded [24]. The individual variation in frailty trajectory responses to partner loss suggests that both exacerbating and mitigating factors exist within family support' s influence, warranting further investigation.

Education Level: Education' s effect on frailty trajectories remains controversial. One study [25] showed that Taiwanese older adults with lower education had higher frailty trajectory change rates and faster progression, while the Longitudinal Aging Study Amsterdam [26] found that absolute educational differences in frailty neither widened nor narrowed during follow-up, with similar decline rates across education levels. Income may influence frailty trajectories in these populations, but other factors such as self-efficacy, cognitive impairment, obesity, and chronic disease burden also contribute.

Family Economy: GUO et al. [27] demonstrated a significant gradient in odds ratios for family wealth, with lower family wealth associated with higher likelihood of membership in groups with steeper frailty trajectories. PEEK et al. [28] showed that greater family financial stress was associated with higher frailty levels during 12-year follow-up, with financial stress relating to increased frailty over time among both those with low and increasing frailty levels. Social support serves as a beneficial factor for slowing frailty trajectories.

These findings indicate substantial overlap among different influencing factors, suggesting that specific factors may mediate effects on others (for example, income effects may operate indirectly through behavioral factors). Non-modifiable factors such as education and family economic status adversely affect frailty trajectories, revealing a social public health issue where improving population education and economic levels could enhance quality of life in later years.

3.2 Modifiable Factors

Given frailty' s associations with falls, delirium, disability, increased care needs, and healthcare utilization, the potential for targeted interventions cannot be ignored. Research on modifiable factors can facilitate early intervention for frail patients, reducing trajectory slopes in high-risk populations and representing potential targets for frailty prevention and treatment.

Cultural Engagement: Cultural engagement refers to individuals' or groups' active participation in cultural production, dissemination, consumption, and interaction, involving practices, experiences, and creation of cultural activities including theater, concerts, museums, art galleries, and cinemas. This represents a multimodal intervention [12]. A University College London study demonstrated that increased cultural engagement frequency (once every few months or more) was associated with reduced incidence of fatigue syndrome and a dose-response relationship with frailty development risk. This study was the first to show that cultural engagement in older adults is linked to reduced frailty risk and slower progression [12]. DU et al. [29] further confirmed in 2,268 older adults from the Chinese Longitudinal Healthy Longevity Survey that cultural engagement (such as playing chess, continuing higher education) could maintain stable frailty trajectories. The health benefits of cultural engagement may stem from providing social support networks and cognitive stimulation while reducing social isolation, sedentary behavior, and stress. Even after controlling for these factors, health-related benefits persist, suggesting that other aspects such as hedonic experiences, emotional expression, and provision of meaning and purpose are also important. These findings align with current calls for multimodal, multifactorial community activities supporting older adult health. While domestic museums and similar institutions remain underutilized in public health, they hold strong potential for supporting older adult health by combining multiple health promotion factors with aesthetic content that provides intrinsic motivation for engagement. Future behavioral change intervention research should focus on increasing cultural engagement among older adults, particularly those at risk for frailty.

Physical Activity: Previous studies have identified diverse factors associated with frailty trajectories. ROGERS et al. [21] found that individuals engaging in high-intensity physical activity showed significantly slower frailty progression [β coefficient (95% CI) = -0.061 (-0.081 to -0.042), P < 0.0001] compared to those with low-intensity activity [β coefficient (95% CI) = -0.014 (-0.031 to 0.004), P < 0.13]. However, the discussion noted that causality could not be established, as increasing frailty may reduce activity levels. STEPHAN et al. [30] found that sedentary individuals had higher frailty indices and steeper trajectory slopes, a pattern not observed in those engaging in light physical activity. Research indicates that even in adults considered frail, resistance training [31] and physical therapy [32] can prevent adverse events such as falls and fractures. However, encouraging frail adults to initiate and maintain physical activity remains challenging, requiring further research to determine optimal activity levels and duration for frail individuals.

Cognition: Although cognition' s role in frailty has gained increasing attention, related research remains limited. HOWREY et al. [33] enrolled 1,362 participants from the Hispanic Established Populations for Epidemiologic Studies of the Elderly (HEPESE), using group-based trajectory modeling to identify three frailty groups (non-frail, n = 331; moderate progressive frailty, n = 855; high progressive frailty, n = 149) and three cognitive groups (no cognitive impairment, n = 476; moderate cognitive decline, n = 677; rapid cognitive decline, n = 209). The study found that participants in the progressive cognitive decline group had a 63% probability of belonging to the high frailty group, while those in the no cognitive impairment group had a 68% probability of belonging to the non-frail group. Another study also found that steeper frailty trajectories characterized as "frailty improvement," "frailty worsening," "persistent pre-frailty," and "persistent frailty" included more severe cognitive impairment [34].

Body Weight: A study of five birth cohorts (1919-23, 1924-28, 1929-33, 1934-38, 1939-43) from the KORA-Age study in southern Germany including 2,682 participants [30] found that obese individuals had higher frailty levels and faster accumulation of deficits with age, indicating obesity as a risk factor for frailty trajectories with high preventive potential. Behavioral adjustments could maintain future healthcare costs at sustainable levels. Further research using both the China Health and Retirement Longitudinal Study (CHARLS) and English Longitudinal Study of Ageing (ELSA) [35] examined how different obesity metabolic phenotypes affect frailty progression, finding that metabolically unhealthy overweight/obesity and metabolically unhealthy normal weight showed accelerated frailty progression compared to metabolically healthy normal weight, while metabolically healthy overweight/obesity showed no such acceleration. The study further confirmed that transitioning from metabolically healthy to unhealthy status accelerated frailty progression regardless of weight status. Based on these findings, stratified obesity management according to metabolic status is recommended to further control frailty progression.

Blood Glucose: Older frail patients often have diabetes or abnormal glucose levels. A UK longitudinal aging study of 5,377 participants [19] showed that patients with diabetes or higher baseline HbA1c levels were more frail, and non-frail patients with diabetes or higher HbA1c showed faster age-related frailty deterioration. This study demonstrated adverse effects of hyperglycemia on frailty development, though the complex determinants, interaction pathways, and mutual influences remain difficult to elucidate.

Blood Pressure: Numerous studies have examined blood pressure' s effect on frailty, with previous research showing higher frailty trajectory intercepts in hypertensive patients. SHEN et al. [36] found that in a hypertensive sample, the poorly controlled blood pressure group had higher frailty scores than the well-controlled group, with a greater rate of change in frailty, indicating that poor blood pressure control has more significant effects on frailty changes over time. Some studies have also reported positive associations between hypotension and frailty, cognitive impairment, and even mortality in older adults, though mechanisms remain unclear. Blood pressure control in older hypertensive patients is challenging, and optimal targets for frail patients remain unsettled, with the causal relationship between excessive blood pressure reduction and frailty requiring clarification through prospective studies [37].

Diet: Previous cross-sectional studies using three dietary quality indices —the Mediterranean Diet Score (MDS), Mediterranean-DASH Intervention for Neurodegenerative Delay (MIND) diet, and Alternative Healthy Eating Index (AHEI)—identified plasma metabolomic features (metabolomic diet score, metDS) of three dietary patterns in 806 adults aged 65 and older, with metDS correlating with measured dietary patterns. The identified metabolomic profile encompassed various lipids, amino acids and derivatives, bile acids, and vitamins, partially mediating the relationship between MIND and AHEI dietary patterns and frailty index [38]. This suggests that specific dietary patterns may reduce frailty deficit accumulation by modulating various metabolites and pathways, indicating shared underlying mechanisms between dietary patterns and healthy functional status. Monitoring plasma metabolites may be a powerful tool for promoting healthy aging through quality diet adherence. The Longitudinal Aging Study Amsterdam [39] examined the relationship between serum desphospho-uncarboxylated matrix Gla protein (dp-ucMGP) tertiles as a vitamin K status marker and frailty over 13 years of follow-up, finding that middle and highest dp-ucMGP tertiles were associated with higher frailty levels and greater odds ratios. Frailty increased over time, but differences between dp-ucMGP tertiles existed at baseline and remained stable during follow-up, possibly because vitamin K affects various interrelated health deficits in the FI. This highlights the importance of ensuring adequate vitamin K supplementation in older adults through consumption of leafy green vegetables and fermented dairy products to slow frailty development. Previous cross-sectional studies on diet-frailty trajectory relationships cannot establish causality; future research should focus on longitudinal studies analyzing molecular mechanisms to better guide dietary interventions for delaying frailty progression.

Other Factors: Additional influencing factors have been identified. BOUILLON et al. [40] found that cardiovascular disease risk scores measured in individuals without cardiovascular disease were associated with future frailty. A plausible mechanism linking risk scores, cardiovascular disease, and frailty involves atherosclerosis and related systemic chronic inflammation. Atherosclerosis can obstruct coronary blood flow, triggering cardiovascular disease, and impede muscle blood flow, causing sarcopenia—a clinical feature of frailty. DALRYMPLE et al. [41] also found that lower glomerular filtration rate was associated with steeper frailty trajectories, with declining kidney function potentially related to accelerated muscle mass loss, considered an underlying frailty process. NEWMAN et al. [42] demonstrated that multiple factors share inflammatory processes with frailty, leading to accelerated catabolism associated with atherosclerosis and frailty for similar reasons.

These studies reveal that frailty in older adults results from multiple interacting factors with potentially interlinked mechanisms. Assessment tool content may also be interrelated, and the mechanisms underlying interactions among various comorbidities remain unclear, representing a future research area. Identifying subtle changes between frailty trajectories and discovering factors associated with these changes are crucial for enhancing understanding of frailty progression and prevention. Research on modifiable factors will facilitate development of frailty prevention strategies for older patients. Further studies on frailty trajectories are needed to identify potential risk factors and determine which populations benefit from targeted or personalized interventions. Additionally, most publications have not focused on frailty in nursing homes or clinical care settings, where individuals may be most frail, limiting generalizability.

As population aging advances, older adults' health issues have gained increasing attention, with growing research focus on frailty. Most existing frailty research remains cross-sectional, with longitudinal studies still lacking. Mechanisms underlying influencing factors remain incompletely understood, and reverse causality between factors and frailty trajectories is unclear. One of the most challenging goals in frailty trajectory research is reorganizing healthcare systems to develop management standards for frail patients. To date, translation from research to clinical practice remains a future challenge. Research on influencing factors, particularly modifiable ones, will ultimately improve quality of life for frail older adults. Future studies should further investigate frailty trajectories and their influencing factors to provide evidence for early interventions, reduce healthcare expenditures, and improve quality of life for older patients, anticipating the realization of multi-level, high-quality, healthy aging.

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revised the manuscript; WAN Zhi and LIAO Xiaoyang were responsible for quality control, review, and overall supervision.

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HE Yang: https://orcid.org/0009-0001-4823-1954

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Note: Figure translations are in progress. See original paper for figures.