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Cardiometabolic Risk Factors, Health Trajectories, and Frailty Progression in Older Adults: A Narrative Review

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Abstract

Frailty is a dynamic, multidimensional geriatric syndrome whose natural history—from preclinical origins to progression and potential reversibility—remains incompletely understood. This narrative review synthesizes evidence at the intersection of two emerging paradigms: dynamic cardiometabolic risk factor modeling and health trajectory analysis using multistate Markov models. We critically examine the shift from static baseline measurements to longitudinal dynamic patterns of hypertension, diabetes, dyslipidosis, and obesity, demonstrating that cumulative exposure and change trajectories are more informative than single assessments. We then review Markov-based models that capture bidirectional frailty transitions, highlighting how cardiometabolic conditions modify transition probabilities between robust, prefrail, frail, and death states. An integrated four-stage framework—exposure, process, trajectory, outcome—is proposed to link cardiometabolic dynamics to frailty progression. Emerging directions include precision frailty research, digital biomarkers, frailty-reversal interventions, and socioeconomic determinants, with particular attention to the understudied but high-risk Northeast Chinese aging population.

Keywords

Frailty, Cardiometabolic Risk Factors, Health Trajectories, Markov Model, Aging, Chronic Disease Epidemiology, Prevention

1. Introduction

Global population aging is accelerating, with the proportion of people aged ≥ 65 years projected to reach 16.4% by 2050 [1]. This demographic shift has brought frailty to the forefront of geriatric research. Frailty is a clinical state of reduced

physiological reserve across multiple organ systems, leading to heightened vulnerability to stressors and increased risks of falls, disability, institutionalization, and mortality [1]. Affecting 12% - 24% of community-dwelling older adults, its prevalence rises steeply from ~11% at age 50 - 59 to 51% at age ≥ 90 [2]-[5]. Notably, approximately half of older adults are prefrail—an intermediate state associated with a 38% higher mortality risk [2], underscoring the need for early identification. Crucially, frailty is not irreversible: longitudinal evidence demonstrates bidirectional transitions, with recovery possible, particularly from the prefrail stage [6]. Understanding this natural history—the sequence and timing of health state transitions—is therefore a public health priority.

Despite progress, critical gaps remain. First, most studies adopt a static risk factor perspective, examining baseline cardiometabolic measures (blood pressure, glycemia, lipids, adiposity) in relation to later frailty. This ignores the informative value of long-term fluctuations, trajectories, and cumulative burden. Second, risk factor analysis and health trajectory modeling have largely evolved separately. Studies linking cardiometabolic factors to frailty rarely incorporate formal transition models (e.g., Markov models) that quantify state-to-state probabilities; conversely, Markov studies of frailty transitions have focused primarily on demographic and behavioral covariates, with limited attention to how dynamic cardiometabolic changes shape those transitions. Third, a geographic gap persists: frailty research has flourished in Western settings, but evidence from rapidly aging Asian populations—particularly China—remains limited. Northeast China, with its high older-adult proportion, heavy chronic disease burden, and distinct socioeconomic/environmental context, is an understudied yet critical region for frailty natural history research.

This narrative review bridges two complementary paradigms—dynamic cardiometabolic risk factor analysis and health trajectory modeling—with five aims: 1) to synthesize current evidence on frailty's conceptualization, measurement, and epidemiology, emphasizing its dynamic and multidimensional nature; 2) to critically examine the relationship between cardiometabolic risk factors (hypertension, diabetes, dyslipidemia, obesity, metabolic syndrome) and frailty, highlighting the shift from static to dynamic exposure assessment; 3) to review methodological approaches for frailty trajectory analysis, including group-based and multistate Markov models; 4) to propose an integrated conceptual framework linking cumulative cardiometabolic exposure, physiological decline, health state transitions, and frailty outcomes; and 5) to identify emerging directions and persistent gaps, particularly in the context of Chinese and Northeast Asian aging populations. This review directly informs two ongoing projects by the author's team: one examining how dynamic patterns of cardiometabolic risk factors affect frailty natural history, and another using Markov models to link health status trajectories with frailty transitions.

2. Core Concepts and Definitions

2.1. Frailty: Conceptualization and Assessment

Frailty is a key concept in geriatric care, yet its definition and assessment remain

matters of ongoing debate [1] [7]. Since the early 2000s, two major conceptual models have dominated the field, each with distinct theoretical underpinnings and operational implications.

The Fried frailty phenotype, proposed by Fried and colleagues, conceptualizes frailty as a distinct clinical syndrome characterized by the presence of at least three of five physical criteria: unintentional weight loss (shrinking), self-reported exhaustion, low grip strength (weakness), slow walking speed (slowness), and low physical activity [1] [7]. This model identifies three mutually exclusive categories: robust (0 criteria), prefrail (1 - 2 criteria), and frail (≥3 criteria). The Fried phenotype has been widely adopted in epidemiological research due to its operational simplicity and strong predictive validity for adverse outcomes, including disability, hospitalization, and mortality. However, its exclusive focus on physical manifestations—without consideration of cognitive, psychological, or social domains—has been recognized as a limitation, particularly given the multidimensional nature of frailty in real-world clinical settings [1].

The Rockwood deficit accumulation model offers a complementary and fundamentally different approach. Rather than defining frailty through a fixed set of physical criteria, Rockwood and Mitnitski proposed that frailty arises from the accumulation of health deficits across multiple domains—including symptoms, signs, disabilities, laboratory abnormalities, and diseases. The Frailty Index (FI) is calculated as the proportion of deficits present out of the total number of variables assessed, yielding a continuous score that has been validated across diverse populations and settings [1]. The FI demonstrates high predictive validity for mortality, institutionalization, and other adverse outcomes, and can be constructed from routinely collected data, including electronic health records and administrative databases, enabling automated calculation at scale [1]. However, the FI requires a comprehensive assessment and may capture aspects of comorbidity and disability that some argue are conceptually distinct from frailty itself.

A critical review reflecting the absence of a unified conceptual framework [7]. This proliferation of tools poses challenges for cross-study comparability and clinical implementation. The review also highlighted substantial overlap between frailty and other constructs, including functional impairment, disability, morbidity, and sarcopenia, raising important questions about construct validity [7]. Despite these challenges, contemporary consensus increasingly recognizes frailty as inherently multidimensional, encompassing physical, cognitive, psychological, and social domains [6].

The natural history of frailty can be conceptualized as a continuum spanning multiple stages: robust (health) → preclinical/subclinical frailty → prefrailty → mild/moderate frailty → severe frailty → disability/death. This staging framework is not merely descriptive; it has critical implications for intervention timing, as reversibility is most likely in earlier stages.

2.2. Cardiometabolic Risk Factors

Cardiometabolic risk factors refer to a cluster of interrelated metabolic abnormalities

that increase risk for cardiovascular disease and type 2 diabetes [8]. The core components include:

- Hypertension: sustained elevation of blood pressure, a leading contributor to cardiovascular morbidity.
- Type 2 diabetes mellitus: chronic hyperglycemia resulting from insulin resistance and/or beta-cell dysfunction.
- Dyslipidemia: abnormalities in lipid profile, typically elevated low-density lipoprotein cholesterol, triglycerides, and/or reduced high-density lipoprotein cholesterol.
- Obesity, particularly central/abdominal obesity: excess adipose tissue, especially visceral fat.
- Metabolic syndrome: the co-occurrence of multiple cardiometabolic abnormalities (typically three or more of the above).

The biological mechanisms linking cardiometabolic risk factors to frailty are increasingly well understood. Shared pathophysiological pathways include [8]:

- Chronic low-grade inflammation ("inflammaging"): Persistent elevation of pro-inflammatory cytokines, including interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), and C-reactive protein (CRP) drives insulin resistance, promotes muscle catabolism, and accelerates atherosclerosis. This inflammatory milieu is common to both cardiometabolic disease and frailty.
- Insulin resistance and altered glucose metabolism: Impaired insulin signaling in muscle, liver, and adipose tissue promotes muscle weakness, reduced exercise capacity, and ectopic fat deposition. Hyperglycemia and glycation stress contribute to vascular and neuronal damage, further compromising physiological reserve [8].
- Mitochondrial dysfunction and oxidative stress: Shared mechanisms underlying both metabolic dysregulation and age-related decline in muscle function and energy metabolism [9].
- Sarcopenia: loss of muscle mass and function, which is closely linked to insulin resistance and metabolic syndrome, directly contributes to the physical manifestations of frailty, including weakness, slowness, and reduced activity [10].

2.3. Health Trajectories and Markov Modeling

The concept of health trajectories refers to the longitudinal patterns of change in health status over time. Rather than treating health as static or assuming linear decline, trajectory analysis recognizes that individuals follow diverse paths, with different rates of change, periods of stability, and potential for improvement. Understanding heterogeneity in health trajectories is essential for predicting outcomes and targeting interventions.

Group-based trajectory modeling (GBTM), also known as latent class growth analysis, is a widely used approach for identifying distinct subgroups of individuals who follow similar developmental trajectories. This method estimates a finite number of trajectory groups and assigns individuals to groups with varying probabilities. GBTM has been extensively applied to identify frailty trajectory patterns

in aging populations, typically revealing two to four distinct trajectories ranging from low-and-stable to high-and-increasing [11] [12].

Multistate Markov models (MSMs) offer a fundamentally different and complementary approach to longitudinal health data. Rather than focusing on continuous trajectories of a frailty index, MSMs model transitions between discrete health states (e.g., robust → prefrail → frail → death). Key outputs include:

- Transition intensities (hazard rates): instantaneous rates of moving from one state to another.
- Transition probabilities: the probability of being in a given state after a specified time interval, conditional on the starting state.
- Mean sojourn times: expected duration spent in each state before transitioning.
- Covariate effects: estimates of how individual characteristics (e.g., age, sex, comorbidities) modify transition rates [6].

MSMs are particularly well-suited to frailty research because they explicitly model the bidirectional nature of frailty transitions, recognizing that improvement is possible (e.g., from prefrail to robust) as well as deterioration. The Markov assumption—that future state depends only on the current state, not on the past history—is a simplification, but one that enables tractable estimation and interpretation of complex longitudinal processes.

The application of MSMs to frailty research has grown substantially in recent years, with studies using data from the China Health and Retirement Longitudinal Study (CHARLS), the English Longitudinal Study of Ageing (ELSA), the Survey of Health, Ageing and Retirement in Europe (SHARE), and other major aging cohorts. These models have demonstrated that frailty is not a one-way street toward decline but a dynamic process with substantial opportunities for improvement, particularly when interventions are targeted at the prefrail stage [6] [13].

3. Cardiometabolic Risk Factors and Frailty Natural History

3.1. Static versus Dynamic Perspectives

Early research on cardiometabolic risk factors and frailty adopted a static perspective, measuring exposures at baseline and linking them to subsequent frailty outcomes. While this approach established associations with diabetes, obesity, and hypertension, it assumes risk factor levels remain stable—an assumption rarely justified. Blood pressure, glycemia, lipids, and body weight fluctuate substantially over time due to lifestyle, disease progression, and medication changes. A single measurement cannot distinguish transient from persistent abnormalities, nor capture trajectories of change (e.g., worsening vs. improvement) that may better predict frailty.

A dynamic perspective has recently emerged, recognizing that patterns of change over time are more informative than isolated values. Enabled by longitudinal data and trajectory methods, Ke *et al.* used the 30-year CARDIA follow-up to construct insulin resistance (HOMA-IR) trajectories. Compared with a low trajectory, individuals in the high trajectory had significantly higher frailty prevalence in midlife

(OR = 1.55, 95% CI: 1.05 - 2.30), and this effect was detectable before old age, suggesting frailty roots are established decades earlier [14]. The implication is profound: interventions targeting metabolic health in midlife—or even young adulthood—may be more effective than late-life measures. Identifying unfavorable trajectories early provides a window for intervention that static assessment cannot offer.

3.2. Impact of Individual Cardiometabolic Factors on Frailty Onset

1) Hypertension: Highly prevalent in older adults, hypertension has a complex, potentially bidirectional relationship with frailty. Chronic hypertension promotes vascular stiffening, reduced cerebral perfusion, and end-organ damage, accelerating physiological decline. Conversely, hypotension (spontaneous or iatrogenic) increases fall risk. A meta-analysis of older coronary patients reported a pooled frailty prevalence of 36%, with hypertension as a significant risk factor [8] [15]. The Amirkola study, however, found central obesity to be a stronger predictor than hypertension itself [16].

2) Diabetes and hyperglycemia: Diabetes consistently increases frailty risk. In Amirkola, older adults with diabetes had 1.84-fold higher odds of frailty, and those with fasting glucose ≥ 126 mg/dL were 53% more likely to be frail [16]. Mechanisms include insulin resistance-driven muscle catabolism, chronic hyperglycemia causing micro-/macrovascular damage, and diabetic neuropathy. The long-term perspective is critical: Ke *et al.* showed that a 30-year high insulin resistance trajectory—often preceding overt diabetes—was associated with increased frailty prevalence and progression, indicating that underlying metabolic dysfunction, not just clinical diagnosis, drives risk [14]. Moreover, frailty and diabetes amplify each other: a meta-analysis found that frailty in diabetes was associated with 1.8-fold higher all-cause mortality and 2.0-fold higher cardiovascular mortality [17].

3) Dyslipidemia: Evidence is more mixed. The Amirkola study included elevated LDL, elevated triglycerides, and reduced HDL among CVD risk factors, but individual contributions varied [16]. Mechanistically, lipid abnormalities accompany chronic inflammation, which promotes muscle catabolism and systemic decline.

4) Obesity and central adiposity: Obesity, especially central obesity, is strongly linked to frailty. In Amirkola, each 1-cm increase in waist circumference was associated with 79% higher odds of frailty [16], underscoring the pro-inflammatory, metabolically active nature of visceral fat. The concept of sarcopenic obesity—excess adiposity with reduced muscle mass/function—combines metabolic and functional insults, synergistically increasing frailty risk beyond either condition alone [10].

3.3. Cumulative Effects and Comorbidity Burden

Cardiometabolic risk factors rarely occur in isolation; their co-occurrence as metabolic syndrome or multimorbidity has cumulative, synergistic effects on frailty. A systematic review documented that abdominal obesity, hyperglycemia, and multiple co-occurring factors are associated with frailty in a dose-response manner,

suggesting that the total burden of cardiometabolic dysregulation—not any single factor—is the key driver [15] [17].

The Costa Rican study using multistate Markov models provided striking evidence: compared to individuals with <3 chronic diseases, those with multimorbidity and prefrailty had a 27% lower chance of recovering to robustness (HR 0.73, 95% CI: 0.54 - 0.99) and an 83% higher risk of becoming frail (HR 1.83, 95% CI: 1.43 - 2.34), translating to a 30-month earlier onset of frailty [18]. Multimorbidity, now the norm among older adults, accelerates transitions to frailty and reduces recovery opportunities. Clinical guidelines must address the totality of cardiometabolic burden rather than managing isolated risk factors.

3.4. Temporal Patterns and Critical Windows

A key question from the dynamic perspective is: when do cardiometabolic patterns most influence frailty? Emerging evidence points to midlife as a critical window. Ke *et al*. found that insulin resistance trajectories from young adulthood to midlife predicted frailty detectable by age 40 - 50, well before traditional frailty assessment begins [14]. This aligns with the view that frailty has life-course antecedents. The CARDIA study specifically emphasized early prevention of abnormal glucose metabolism in young adults to prevent later frailty and CVD [14]—a paradigm shift from frailty as inevitable aging to a condition preventable or delayable through midlife metabolic optimization.

Nevertheless, critical windows likely exist at multiple stages. In later life, the direction of change in risk factors (stable, worsening, improving) may determine frailty trajectories. For example, individuals who successfully control previously uncontrolled hypertension or achieve glycemic targets may experience slower frailty progression than those whose metabolic profile continues to deteriorate. The timing and direction of change are as important as absolute levels.

Two ongoing projects directly address this temporal dimension: one examines dynamic patterns of cardiometabolic risk factors in relation to frailty natural history; the other uses Markov models to capture transitions over time. Together, they aim to identify temporal patterns and critical windows predictive of frailty outcomes in Chinese older adults, with particular focus on Northeast China—a region with high aging and chronic disease burdens.

4. Health Trajectories, Markov Modeling, and Frailty Outcomes

4.1. Trajectory Analysis Approaches

Health trajectory analysis recognizes that aging is not a homogeneous linear decline; individuals follow diverse paths shaped by genetic, behavioral, social, and environmental factors. Two methodological families dominate frailty research:

1) Group-based trajectory modeling (GBTM) identifies latent subgroups following similar developmental trajectories. Using CHARLS data (8993 participants aged ≥ 50), three frailty trajectories emerged: low-stable (56.8%), moderate-increasing

(34.4%), and high-increasing (8.8%) [11]. Residing in Northeast China was strongly associated with rapid progression (OR = 3.53, 95% CI: 2.56 - 4.88); other risk factors included older age (OR = 7.37), female sex (OR = 1.79), no formal education (OR = 4.91), rural residence (OR = 1.22), and low physical activity (OR = 2.65) [11]. A 16-year CLHLS study (2299 participants ≥ 65) similarly identified three trajectories and found that higher leisure activity scores reduced odds of progressive trajectories by 11% - 14%, with physically stimulating activities showing the strongest protection (43% reduction) [12].GBTM strengths include intuitive interpretation and flexibility with incomplete data; limitations include arbitrary group numbers and difficulty incorporating time-varying covariates.

2) Multistate Markov models (MSMs) take a fundamentally different approach, modeling transitions between discrete states (e.g., robust → prefrail → frail → death). MSMs explicitly accommodate bidirectional transitions (improvement and deterioration) and directly estimate transition probabilities, sojourn times, and covariate effects. The choice between methods depends on the research question: GBTM describes heterogeneity in continuous trajectories, while MSMs quantify transition dynamics and predict future state distributions. Both are complementary and increasingly used together.

4.2. Markov-Based Models for Frailty Transitions

MSM applications to frailty have advanced substantially. Tong *et al.* used four waves of CHARLS (2011-2018, 15,763 participants ≥ 45) with a four-state Markov model (robust → prefrail → frail → death). Baseline prevalences: robust 44.3%, prefrail 39.4%, frail 16.3% [6]. Key findings: within one year, prefrail individuals had 18.0% probability of reverting to robust and 19.7% of progressing to frail; at five years, these were 23.4% and 33.4%, respectively, with mortality reaching 19.7%. Older age increased progression and mortality but reduced recovery. A significant age-by-sex interaction showed men had higher recovery rates but greater frailty-related mortality. Urban residency, higher education, and marriage were protective; smoking and alcohol increased risk [6].

A comparative MSM study of ELSA (UK) and CHARLS (China) revealed cross-national differences. In ELSA, the prefrail-to-robust transition intensity (0.226) exceeded prefrail-to-frail (0.105), whereas CHARLS showed a different pattern. Age and marital status influenced transitions in both cohorts, but other covariates (physical activity, drinking, loneliness, and economic status) exerted cohort-specific effects [13]. Frailty dynamics are not universal; they are shaped by population-specific healthcare, social support, lifestyle, and environmental factors, reinforcing the need for country-specific evidence.

The Costa Rican study (Ogaz-González *et al.*) used MSMs to examine multimorbidity (≥3 chronic diseases). Compared to individuals with fewer diseases, those with multimorbidity and prefrailty had 27% lower chance of recovering to robust (HR = 0.73) and 83% higher risk of becoming frail (HR = 1.83), translating to a 30-month earlier frailty onset. Mortality impact was observed primarily in

prefrail individuals, suggesting multimorbidity accelerates frailty progression rather than increasing mortality among those already frail [18].

4.3. How Cardiometabolic Factors Shape Health Trajectories

Understanding how cardiometabolic conditions modify frailty transition probabilities is key to bridging the two themes of this review. Existing MSM studies have begun incorporating such covariates, but much work remains. The CHARLS MSM included smoking and alcohol but not hypertension, diabetes, or dyslipidemia [6]; the ELSA-CHARLS comparison focused on physical activity and drinking status [13].

Indirect evidence, however, is compelling. Diabetes increases transitions from robust to prefrail and prefrail to frail. Uncontrolled hypertension accelerates progression via vascular and end-organ damage. Obesity, especially with sarcopenia, both increases entry into frailty and reduces recovery probability.

Critically, cardiometabolic factors may affect different transitions differently. Aggressive blood pressure lowering in frail older adults might reduce cardiovascular events but increase falls and syncope, potentially accelerating disability. Conversely, achieving glycemic control may improve energy and function, increasing recovery from prefrailty. Understanding these differential effects requires MSM analyses estimating covariate effects separately for each transition.

4.4. Predictive Value of Trajectory Models

Frailty trajectory group membership (low-stable, moderate-increasing, high-increasing) strongly predicts future disability, hospitalization, institutionalization, and mortality—information not captured by baseline frailty status alone, as individuals with the same baseline FI can follow very different paths [11].

Markov models offer the additional advantage of dynamic predictions that can be updated with new information. A clinician could estimate a patient's future state probabilities conditional on current state and covariates, enabling more accurate risk stratification and personalized intervention planning.

However, clinical deployment faces challenges. First, most models are cohort-specific; generalizability to other populations and healthcare settings is uncertain. Second, reliable transition probability estimation requires multiple waves of frailty assessment, often unavailable in routine care. Third, implementation studies demonstrating clinical utility and cost-effectiveness are lacking.

For population health planning, these models already provide value. Simulating frailty transitions under different intervention scenarios (e.g., reducing uncontrolled hypertension prevalence by 20%) can inform resource allocation and policy decisions, even if individual-level predictions remain imperfect.

5. Integrated Framework: From Risk Factors to Frailty Progression

5.1. A Conceptual Roadmap

A four-stage integrated framework is proposed in **Table 1**:

Table 1. Four-stage integrated framework linking cumulative cardiometabolic exposure to frailty natural history.

Stage	Description	Key Factors/Interventions
1. Exposure	Cumulative cardiometabolic burden (dynamic patterns of hypertension, diabetes, dyslipidemia, obesity)	Population-level primary prevention (diet, physical activity); midlife screening
2. Process	Shared pathophysiological pathways: inflammation, insulin resistance, mitochondrial dysfunction, sarcopenia	Early detection and management of metabolic abnormalities; an anti-inflammatory lifestyle
3. Trajectory	Transitions between health states (robust ↔ prefrail ↔ frail ↔ death)	Markov model estimation; targeted interventions at prefrail stage
4. Outcome	Final health outcomes: incident frailty, severe frailty, recovery, disability, death	Tertiary prevention; integrated care; long-term care and end-of-life planning

5.2. Key Interplay between Dynamic Risks and Trajectories

A central—and still poorly understood—aspect of the integrated framework is how long-term patterns of cardiometabolic exposure modify transition probabilities between frailty states. Several testable hypotheses emerge from existing evidence [6] [19], summarised in **Table 2**.

Table 2. Hypothesised mechanisms linking dynamic cardiometabolic patterns to frailty transitions.

Hypothesis	Core Proposition
Cumulative Exposure	Higher lifetime burden (e.g., cumulative hyperglycaemia, inflammation) lowers thresholds for progressing from robust → prefrail → frail, potentially causing earlier transitions.
Trajectory Direction	The direction of change (improving vs. worsening) matters independently of the current level; an improving profile confers lower transition risk than a worsening one at the same current value.
Recovery Threshold	Probability of recovering from prefrail to robust depends on underlying cardiometabolic burden; well-controlled single conditions allow recovery similar to unaffected individuals, whereas poor control or multimorbidity reduces it.
Critical Window	Cardiometabolic exposure exerts its strongest effect on frailty transitions during specific developmental periods (e.g., midlife), with diminishing returns from later-life intervention.

These hypotheses directly combined detailed longitudinal cardiometabolic data with Markov-based frailty transition models [6] [20] to quantify how dynamic metabolic risk patterns modify the probabilities of entering, progressing through,

and recovering from frailty states in Chinese older adults.

5.3. Methodological Challenges and Future Directions

Implementing the integrated framework faces several key challenges:

1) Data missingness is pervasive in longitudinal ageing studies. Frail participants are more likely to miss follow-up, and death leads to permanent loss. Informative missingness (related to the underlying health state) can bias transition estimates. Multiple imputation, inverse probability weighting, and joint modeling of longitudinal and missingness processes can mitigate this bias.

2) Measurement error affects both frailty classification and cardiometabolic assessments. Within-person variability in the Fried phenotype or FI leads to misclassification, attenuating transition rates. Single blood pressure or glucose measurements suffer from regression dilution bias, underestimating true associations.

3) Time-dependent confounding arises when a time-varying covariate (e.g., antihypertensive use) is both affected by prior health status and influences subsequent transitions. Standard adjustment for current medication use is biased because medication use is itself a consequence of prior frailty. Marginal structural models and g-estimation can address this, but require careful specification and large samples.

4) Model selection and validation remain challenging. MSMs require specification of the state space, transition structure, and covariate effect form. Internal cross-validation and external validation in independent cohorts are essential for assessing performance and generalisability.

5) Generalizability is a particular concern, as most frailty trajectory studies have been conducted in Western populations or selected Chinese cohorts (CHARLS, CLHLS). Findings may not generalize to Northeast China—a region with distinct demographic, chronic disease, and socioeconomic profiles. The author's team is uniquely positioned to address this gap through region-specific research.

Future directions include integrating multi-omics data (genomics, proteomics, metabolomics) into trajectory models to uncover biological mechanisms underlying frailty progression heterogeneity. Electronic health records (EHRs), with large samples and longitudinal follow-up, offer opportunities to develop and validate frailty transition models at scale, despite data quality and standardization challenges. Finally, incorporating social determinants of health—socioeconomic status, education, social support, neighborhood characteristics, and environmental exposures—into Markov models is essential for capturing the full range of factors shaping real-world frailty trajectories.

6. Emerging Directions and Unaddressed Gaps

6.1. Precision Frailty Research

The marked heterogeneity in frailty progression, exemplified by CHARLS trajectories where only 8.8% follow a "high-increasing" path [11], calls for a precision approach to prevention and management. Precision frailty research aims to identify

individual-level modifiers of the cardiometabolic-frailty relationship, enabling targeted interventions.

Genetic factors may influence susceptibility. For instance, APOE genotype affects lipid metabolism and cardiovascular/cognitive risk, but whether it modifies frailty trajectories independently remains unknown. GWAS on frailty-related phenotypes are emerging, though sample sizes remain modest [21].

Lifestyle factors—diet, physical activity, sleep, social engagement—are powerful modifiers. The CLHLS study showed that physically stimulating leisure activities reduced odds of progressive frailty trajectories by 43% [12]. Identifying for whom and under what conditions these interventions work best is a priority.

Gut microbiome composition influences inflammation, insulin sensitivity, and energy metabolism, potentially mediating diet–metabolic health–aging relationships. Integrating microbiome assessments into frailty cohorts is an important future direction [22] [23].

6.2. Digital Biomarkers and Real-World Data

Traditional frailty assessment (grip strength, gait speed) is resource-intensive and hard to scale [24]. Digital biomarkers from passive monitoring offer continuous, unobtrusive assessment in real-world settings [25].

Wearable devices (accelerometers, smartwatches) monitor physical activity, step counts, sleep, and heart rate variability—proxies for frailty status [26]. Smartphone-based assessments capture gait, cognitive function, and symptoms. Passive in-home sensors detect mobility and activity changes preceding clinical frailty.

Advantages include high-frequency longitudinal data capturing day-to-day variability, unobtrusiveness, and scalability for population-level surveillance [25]. Challenges remain: validation against gold-standard frailty assessments is early-stage; data privacy and security need addressing; integration with clinical care pathways is unproven.

6.3. Frailty Reversal and Interventions

Frailty is reversible: Markov models show prefrail individuals have 18% probability of returning to robust within one year and 23% within five years [6] [27]. Key evidence on effective interventions is summarised in **Table 3**.

A randomised trial comparing nutritional supplementation, physical training, cognitive training, combination, and usual care in prefrail/frail older adults found all active interventions reduced frailty, with physical training (OR = 4.05) and combination (OR = 5.00) strongest; effects persisted at 12 months [28].

Implications: Resistance training is the core active ingredient; nutrition and cognitive training provide additive benefits [29]. Targeting the prefrail state is most cost-effective. Unanswered questions include optimal timing (midlife window may be as important as later life), dose-response relationships, effect modification by individual characteristics, and scalability to community settings.

Table 3. Summary of intervention evidence for frailty reversal (from 2025 overview of 23 systematic reviews, N = 18,768) [27].

Intervention Type	Effectiveness	Key Evidence
Resistance Training (≥2×/week)	Beneficial for reversing frailty and preventing progression	28 primary studies, 3246 participants
Nutrition + Physical Activity (including Resistance Training)	Effective	9 studies, 1812 participants
Nutrition Alone	Inconclusive	Suggests physical activity is essential

6.4. Socioeconomic and Environmental Determinants

Frailty is shaped by multilevel social, economic, and environmental factors. The CHARLS finding that Northeast China residents strongly predict rapid frailty progression (OR = 3.53) highlights geographic context [11]. Contributing factors include a high proportion of older adults, heavy chronic disease burden, lower economic growth relative to coastal regions, and harsh winters limiting physical activity and social engagement [30].

Socioeconomic status (SES) consistently predicts frailty trajectories. In CHARLS, no formal education (OR = 4.91) and rural residence (OR = 1.22) were strong risk factors [11]. Low SES affects frailty through reduced healthcare access, lower health literacy, financial barriers to healthy foods/medications, and greater environmental stressors [31].

Social support matters: being married was protective in both ELSA and CHARLS cohorts [6]. Loneliness—prevalent in rapidly aging societies with changing family structures—accelerates frailty progression.

Healthcare access and quality vary regionally and by SES. Underdeveloped primary care and urban-concentrated specialist care delay diagnosis and management of cardiometabolic risk factors, increasing cumulative exposure and accelerating frailty [32].

Addressing these social determinants is essential for reducing frailty-related differences. Population-level interventions improving healthcare access, social support systems, and economic security for older adults may yield frailty prevention benefits as large as any individual-level behavioral intervention.

7. Conclusions

Frailty is a dynamic, multidimensional geriatric syndrome and a major public health challenge. This narrative review synthesized evidence across two complementary paradigms: dynamic cardiometabolic risk factors and frailty trajectory modeling.

Three core findings emerge. First, frailty is not irreversible; bidirectional transitions among robust, prefrail, frail, and death states are well documented by multistate Markov models. The prefrail state offers substantial recovery opportunities through targeted interventions. Second, cardiometabolic risk factors—hypertension,

diabetes, dyslipidemia, obesity, and multimorbidity—are strongly associated with frailty progression. Critically, dynamic patterns over time (e.g., long-term insulin resistance trajectories) matter more than static measurements. Cumulative burden accelerates frailty transitions and reduces recovery probability. Third, integrating these perspectives yields a powerful conceptual framework: exposure → physiological decline → health state transitions → frailty outcomes. This four-stage model identifies multiple intervention points and highlights midlife as a key window for primary prevention.

Emerging directions—precision frailty research, digital biomarkers, resistance-based interventions, and social determinants—offer new opportunities. Resistance training combined with nutritional support effectively reverses frailty, particularly at the prefrail stage. Digital biomarkers from wearables could enable scalable, unobtrusive frailty surveillance. Addressing socioeconomic and geographic differences, including the elevated risk observed in Northeast China, is essential for equitable prevention.

This review provides the conceptual foundation for examining dynamic cardiometabolic patterns and Markov-based frailty transitions. Looking forward, integrating multi-omics, digital health, and precision modeling will deepen understanding of frailty natural history, enabling earlier risk identification, more targeted interventions, and healthier ageing worldwide.

Conflicts of Interest

The author declares no conflicts of interest regarding the publication of this paper.

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