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Frailty in Aging Adults : A Narrative Review

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ABSTRACT

The recent literature (last five years) on frailty in aging (ageing) adults is predominantly focused on predictors/ risk factors for frailty along with some studies on negative effects and interventions. Aging has been typically defined as starting as early as 60 or 65. And, frailty has been defined as reduced physiological and functional reserve or measured by grip strength, weakness, exhaustion and social isolation or by longer assessments like The Frailty Index for Elders. The prevalence rates for frailty in aging adults have been highly variable in this literature, ranging from a low of 5% to a high of 51% depending on the severity of the frailty. Negative effects have included falls and mortality. Predictors/risk factors have included social isolation, lack of exercise, bad nutrition, anemia, anorexia, depression and multiple demographic variables. Interventions have included physical activity, Mediterranean-style diet, combinations of exercise and diet and the anti-aging drug metformin. Potential underlying mechanisms for frailty have been the negative effects of inflammation and the positive effects of Klotho, an aging suppressor gene. More well-designed longitudinal studies are needed as well as more robust randomized controlled trials.

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This narrative review involved entering the terms frailty and aging (ageing) into PubMed and PsycINFO. The search yielded 238 papers for the last five years. However, following exclusion criteria including case studies and non-English language papers, this review is a summary of the research reported in 34 papers. This recent literature is predominantly focused on predictors/risk factors for frailty in aging adults along with studies on negative effects and interventions. This narrative review is accordingly divided into sections on prevalence of frailty in aging adults, negative effects, predictors/risk factors and interventions. These are followed by sections on potential underlying mechanisms for frailty and methodological limitations of the research.

Operational Definitions of Frailty and Aging

Aging has been typically operationally defined as starting as early as age 60 or 65 in the literature on frailty in aging adults. And frailty has been variously defined as reduced physiological and functional reserve (Thillainadeson et al, 2020) or a decline in physiological functions that leads to dependency as well as vulnerability to stressors leading to high risk for adverse health outcomes (Vatic et al, 2020). And, it has been measured by various frailty instruments including grip strength, weakness, exhaustion and social isolation (Jang et al, 2022) and the presence of 3 out of 5 symptoms including unintentional weight loss, exhaustion, sedentariness, muscle weakness and slow walking (Shardell et al, 2019). And some have used even longer instruments like The Frailty Index for Elders (FIFE) (Schoufour et al, 2019). This index includes 10 items as follows: 1) help in or out of bed, 2), help washing or bathing, 3) lost or gained 10 pounds in the last six months, 4) tooth or mouth problems, hard to eat, 5) poor appetite and quickly feel full, 6) physical health or emotional problems interfering with social activities, 7) health fair or poor, 8) tired easily, 9) hospitalized during the last three months, and 10) emergency room during the last three months. The scores are 1 to 3 for risk and four or greater for frailty.

Prevalence Rates for Frailty in Aging Adults

The prevalence rates for frailty in aging adults have been highly variable in this literature, ranging from a low of 5% to a high of 51% depending on the severity of the frailty (Zhou et al, 2018) (see table 1). This range was based on a meta-analysis of 5 studies (N=3268) from China. Other studies from China have cited other prevalence based on classification or severity of frailty. At least two other studies from China have classified aging adults as frailty, pre-frailty and robust. In one of these based on several assessments of Chinese community adults (N=1072 greater than 60-year-old adults), 14% were called frail, 55% pre-frail and 31% robust (Lin et al, 2022). In another study on a much larger sample of Chinese adults across a greater age range from 30-79 years (N=512,723) based on the Frailty Index, only 3% were classified as frail, 40% as pre-frail and 57% as robust (Fan et al, 2020). The low prevalence of frailty in this study can likely be attributed to the younger age group included in this sample (the less than 60-year-old adults). In a sammpe of Taiwanese adults greater than 60 (N=1833), the corresponding figures were 7% for frail and 40% for pre-frail.

Using a different classification of mild to severe, trajectories of frailty in aging were given in a longitudinal study of adults who were followed for 12 years (N=681 adults, mean age =75 years) (Verghese et al, 2021). In this sample, 36% were considered mild, 24% moderate and 5% severe. And 34% were considered relatively stable. These results were based on a latent class modeling of 4 distinct frailty trajectories derived from the Frailty Index.

Negative Effects of Frailty

The research on negative effects of frailty on aging adults have primarily included falling and mortality, although those effects have often been confounded by comorbidities (see table 2). For example, in a meta-analysis of 34 studies on 22

factors, several comorbid conditions were noted along with frailty-related falls including a previous history of falls, cardiac disease, hypertension, diabetes, stroke, depression, Parkinson's and pain (Xo et al, 2022). In a study from Spain on adults greater than 70-years-old (N=527), frailty was noted in 20% of the sample (Machon et al,2018). However, this prevalence was based on as many as 44 health deficits on a Frailty Index including activities of daily living (basic and instrumental), chronic diseases and psychological factors, whereas other studies have only addressed physical frailty or cognitive frailty. For example, in a sample from Taiwan (N=1115 greater than 65-year-old adults), cognitive frailty was assessed on the Mini Mental State Examination and was noted to be present in 4% of the sample.

In another review on frailty, the negative effects included the risk of falling, increased morbidity and mortality (Natic et al, 2020). In the study from Spain, frailty led to poor diet, depression, polypharmacy and falling, although the direction of effects is not clear here given the cross-sectional nature of the data (Machon et al, 2018). In a study on trajectories of frailty and aging across a period of 12 years, frailty of all degrees led to greater mortality (Verghese et al, 2021). And, in one of the studies on Chinese adults, an association was noted between scores on the Frailty Index and all-cause mortality (Fan et al, 2020).

Predictors/Risk Factors

Multiple Predictor Variable Studies

Predictors/risk factors have included depression, anemia, anorexia, bad nutrition, inactivity and multiple demographic variables (see table 3). Although most of the studies in the current literature on predictors/risk factors for frailty have focused on a single predictor variable, a few researchers have explored multiple variables. For example, in a study from Korea (N= 9775), latent growth modeling was used to determine the predictors of frailty as assessed by grip strength, weakness, exhaustion and social isolation (Jang et al, 2022). The authors classified older adults as maintaining robustness, pre-frailty or changing from frailty to pre-frailty. The predictors for frailty were lack of regular exercise, cognitive dysfunction and limited social participation.

In a sample from China, the risk factors for frailty were age, appendicular skeletal muscle mass index, sarcopenia, less education, bad nutrition, weakness and falls (Lin et al, 2022). Of these predictor variables, sarcopenia, nutrition and falls were the most predictive. Surprisingly, mental and psychological status were not associated with frailty.

Single Predictor Variable Studies

The single variable predictor studies have focused on depression, walking, diet, biomarkers and telomeres. In a review paper entitled "The frail depressed patient", depression and frailty were bidirectionally associated (Aprahamian et al, 2022). The authors noted that more falls were due to antidepressants and recommended that dopaminergic antidepressants be used for frail, depressed patients.

In the sample from Spain (N=577 greater than 70-years-old), poor diet and obesity were significant predictors of frailty (Machon et al, 2018). The authors suggested a diet of fruits and vegetables as antioxidants, fish for protein for increasing muscle strength, nuts and legumes for preserving muscle mass and milk products for decreasing the risk of osteoporosis. Similarly, in the Taiwan study, cognitive frailty was inversely associated with dairy products, whole grains, vegetables, fruit, fish and seafood, nuts, tea, and coffee.

In a review entitled "Dietary protein, exercise, and frailty domains", the authors suggested that low protein as well as a lack of physical activity leads to physical frailty (Schoufour et al, 2019). They emphasized that frailty not only includes physical frailty, but also mood, cognition, and comorbidity. In the study on trajectories of frailty in aging, a clinical risk profile was formulated, which suggested that the greatest risk factors

were obesity, physical inactivity, and slower walking while talking (Verghese et al, 2021). These risk factors were confounded by low levels of education and living alone.

In a study entitled “Network analysis of frailty and aging” (N=10,983 greater than 50-year-old adults), the Deficit Frailty Index was formulated (Garcia – Pena et al, 2019). In this index of 34 factors, self-report of health and difficulty walking a block were the best predictors of frailty.

The physical conditions of anemia and anorexia have also been risk factors for frailty. In a meta-analysis of 19 studies on the relationship between anemia and frailty, 49% of those with anemia had pre-frailty and 24% of those with anemia were classified as frail (Palmer et al, 2018). Those with anemia had a two-fold odds of frailty. The authors suggested the need for longitudinal research on changes in anemia and treatment effects. In a study on anorexia in aging adults and its role in frailty, decreasing appetite was related to impaired smell and taste, alterations in stress hormones and inflammatory mediators (Sanford et al, 2017).

Telomere shortening has also been associated with aging. However, the research on its relationship with frailty has been very mixed. For example, in a review of five studies (N= 3268), frailty was noted in 5 to 51% of the aging, but no associations were noted between frailty and telomere length (Zhou et al, 2018. The authors suggested that well designed, prospective studies were needed. In another study, telomere length and frailty were related at baseline, but telomere length failed to predict frailty or mortality 35 years later (Assar et al, 2021). Further, in a review on telomere length and frailty, telomere length could not be considered as a single predictive measure or a biological marker for age-related conditions such as frailty (Lorenzi et al, 2018). However, in still another systematic review and meta-analysis, telomere length was shorter for frail adults based on the Frailty Index, but only in the Hispanic sample (Carvalho et al, 2019).

Interventions

Exercise, diet, and metformin (a medication for diabetes) have been the most frequently reported interventions in the literature on frailty in aging (see table 4). The Mediterranean diet has been cited in several studies. For example, in a systematic review, a Mediterranean diet was notably protective (Lochlainn et al, 2021). Specifically, a diet of fruit and veggies and less consumption of processed foods were noted by these authors. In addition, many of the studies included exercise training. In a study entitled "Nutrition and frailty: current knowledge", the Mediterranean diet contributed to 60% reduced risk of frailty based on three meta-analyses (Feart et al, 2019).

In a review of 14 intervention studies designed to reduce the level of frailty including 12 randomized controlled trials, activity interventions (all types and combinations) were noted to reduce frailty markers (Puts et al, 2017). A methodological problem noted by these authors was the variability in definitions of frailty in the 14 studies.

In another meta-analysis (N=5262, participants in eight different intervention studies), physical activity and physical activity plus nutrition contributed to a 71 to 100 percent reduced likelihood of frailty (Ngem et al, 2019). The authors suggested that more robust randomized controlled trials were needed.

Metformin, a medication used for glucose management in patients with diabetes, reputedly has an anti-aging effect (Piskovatska et al, 2020). It has been known to decrease the risk of age-related diseases, including cardiometabolic disorders, neurodegeneration, chronic inflammation and frailty. It is controversial as to whether it's protective of those who are free of diabetes (Mohammed et al, 2032). According to these authors, the reduced risk of age – related disease may be an indirect effect of cellular metabolism, anti-hypoglycemic – action that enhances insulin sensitivity and the reduction of oxidative stress. Others have also attributed the clinical benefits of metformin to its anti-hyperglycemic effects leading to reduced risk for

Table 1. Prevalence of frailty in aging adults (and first authors).

Prevalence	First authors
5-51%	Zhou
14%	Lin
3%	Fan
5%	Verghese

Table 2. Negative effects of frailty on aging adults (and first authors).

Negative effects	First authors
Comorbidities	Xo, Machon
Falls	Xo, Natic
Mortality	Natic, Verghese, Fan

Table 3. Predictors/risk factors for frailty in aging adults (and first authors).

Predictors/risk factors	First authors
Inactivity	Jang, Schoufour, Verghese
Cognitive dysfunction	Jang
Limited social participation	Jang
Sarcopenia	Lin
Less education	Lin, Verghese
Bad nuitrition	Lin, Machon, Schoufour
Weakness	Lin
Falling	Lin
Depression	Aprahamian
Obesity	Machon, Verghese
Living alone	Verghese
Difficulty walking	Garcia-Pena
Anemia	Palmer, Sanford
Anorexia	Palmer
Telomere shortening	Assar, Lorenzi, Carvalho, Zhou

Table 4. Interventions for frailty in aging adults (and first authors).

Interventions	First authors
Mediterranean diet	Lachlainn, Feart
Exercise training	Lachlainn, Puts
Physical activity plus nutrition	Ngent
Metformin	Piskovatska, Mohammed, Triggle

Table 5. Potential underlying mechanisms for frailty in aging adults (and first authors).

Mechanism	First author
Hypthalamic pituitary adrenal (HPA) dysregulation	Kamwa
Insulin resistance	Kamwa
Low vitamin D	Kamwa
Insulin-like growth factor-1 (IGF-1)	Chen, Goncalves
Inflammation (“inflammaging”)	Natic, Sendoma
Klotho	Shardell, Veronsi

a number of diseases and thereby enhancing "healthspan" (Triggle et al, 2022).

Potential Underlying Mechanisms

Several potential underlying mechanisms have been suggested for frailty, including hypothalamic pituitary adrenal axis (HPA) dysregulation, the production of insulin-like growth factor-one (IGF-1), inflammation and Klotho (see table 5). HPA has been reputedly involved in the pathogenesis of both frailty and sarcopenia (low muscle mass and strength associated with aging and reduced physical performance), indicating the severity of the condition (Kamwa et al, 2021). Sarcopenia is a key feature of the frailty phenotype. These authors suggested that insulin resistance and low vitamin D status may have confounded the negative effects of the HPA dysregulation. More robust randomized trials are needed.

IGF-1 was associated with reduced frailty, lean muscle mass and bone mineral density in the Taiwan study (Chen et al, 2018). In that sample (N=1833 greater than 60-year-old adults), IGF-1 was positively correlated with lean body mass, bone mineral density and hand grip strength, and negatively correlated with weakness.

Inflammation has been the focus of many studies on frailty in the aging and has been termed "inflamm-ageing", "oxi-inflamm-ageing" and "inflamm-inactivity" by some (Natic et al, 2020). Given that the biomarkers including inflammation, oxidative, stress, and muscle protein turnover are related to physical inactivity, these authors and many others have recommended exercise training and nutritional counseling to reduce the inflammation related to frailty.

In another paper on the resolution of inflammation, a low level of chronic inflammation called "inflammaging" in this case was again said to contribute to diseases of aging, such as sarcopenia and frailty (Sendama et al, 2019). These authors suggested that the presence of "inflammaging" indicates a failure of the cell clearance mechanisms that ordinarily resolve the inflammation after the infiltration of pathogens or tissue injury.

Other authors have elaborated on the frailty biomarkers as being the growth factors (IGF-1, SIRJ-1, GDF15) and inflammation markers (IL –6, CRP and TNF- alpha) (Goncalves et al, 2022). As they suggested, these biomarkers provide the best evidence for the significance of inflammation and nutrient sensing for frailty.

Still another potential underlying mechanism is the aging suppressor gene called klotho. In a sample of 774 Italians greater than 65-years-old, those who had higher levels of plasma klotho had lesser odds of exhaustion, weight loss, weakness and frailty (Shardell et al, 2019). In a systematic review on 16 studies, the authors reported a positive association between klotho, muscle strength and physical activity and a negative association between klotho and frailty, disability and mortality (Veronesi et al, 2021).

Methodological Limitations

Several methodological limitations can be noted about these recent studies on frailty in aging adults. The sampling methods, the sample sizes, the prevalence and the results of the studies have been highly variable. Aging has been typically defined as starting at 60 or 65 which seems early given that life expectancy is now somewhere in the 70s-80s in most countries and increasing numbers of centenarians are being identified.

The researchers have primarily used self-report symptoms and scales rather than medical data that might have been more reliable, although standard medical physicals do not typically include frailty measures. Frailty has been variously defined as reduced physiological and functional reserve or it has been measured by grip strength, weakness, exhaustion and social isolation or by longer instruments like The Frailty Index for Elders. This wide variety of measures has made it difficult to conduct systematic reviews and meta-analyses resulting in very few of those in the literature. Based on the variability of these measures, the prevalence rates for

frailty in aging adults have also been highly variable in this literature, ranging from a low of 5% to a high of 51% depending on the severity of the frailty.

The research has been primarily focused on predictors/risk factors for frailty, although they have only included a few variables, e. g. depression, anemia, anorexia and multiple demographic variables. The outcome measures have also been limited to falls and mortality. Both the predictors and the outcome variables appear to be obvious. However, although multiple variables would be predictive, they have often been treated as covariates in the data analyses rather than assessing the degree to which multiple variables contribute to the variance in the outcome. And, although variables often seem like mediators or moderators, mediation/moderation or structural equations analyses have rarely been used.

Although most of the studies are correlational or cross-sectional, making directionality difficult to determine, the variables that could be bi-directional or reciprocal seem to be arbitrarily treated as predictors or outcome variables. The longitudinal studies with mortality as an outcome have likely been limited by high attrition, although that methodological problem has rarely been reported.

Interventions have included physical activity, Mediterranean-style diet, combinations of exercise and diet and the anti-aging drug metformin that has reduced the risk of age-related diseases. These interventions haven't been compared as in a random assignment to different interventions, making it difficult to know the relative effectiveness of the interventions for frailty in aging adults.

Potential underlying mechanisms for frailty have been the negative effects of "inflammaging" and the positive effects of Klotho, the "aging suppressor gene". These have not been considered in the same study, so their relative validity as underlying mechanisms is unknown. As some have suggested, more well-designed prospective studies are needed as well as more robust randomized controlled trials.

Conclusions

The recent literature (last five years) on frailty in aging (ageing) adults is predominantly focused on predictors/ risk factors for frailty along with some studies on negative effects and interventions. Aging has been typically defined as starting at 60 or 65. And, frailty has been defined as reduced physiological and functional reserve or measured by grip strength, weakness, exhaustion and social isolation or by longer instruments like The Frailty Index for Elders. The prevalence rates for frailty in aging adults have been highly variable in this literature, ranging from a low of 5% to a high of 51% depending on the severity of the frailty. Negative effects have included falls and mortality. Predictors/risk factors have included depression, anemia, anorexia and multiple demographic variables. Interventions have included physical activity, Mediterranean-style diet, combinations of exercise and diet and the anti-aging drug metformin that has reduced the risk of age-related diseases. The potential underlying mechanisms for frailty have been the negative effects of "inflammaging" and the positive effects of Klotho, the "aging suppressor gene". More well-designed longitudinal studies are needed as well as more robust randomized controlled trials. Nonetheless, this recent literature has identified frailty as both an effect of inactivity and limited diet in aging adults and a contributor to mortality, highlighting the importance of continuing research on this problem.

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