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Anita Mohandas
Jefferson School of Population Health, Thomas Jefferson University, Anita.Mohandas@jefferson.edu

JoAnne Reifsnyder
Care Transitions CareKinesis, Inc., Moorestown, New Jersey

Mimi Jacobs
ox GERI: Geriatric Education & Research Institute, Cherry Hill, New Jersey

Tim Fox
ox GERI: Geriatric Education & Research Institute, Cherry Hill, New Jersey

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Current and Future Directions in Frailty Research

Anita Mohandas, MSc,[1] JoAnne Reifsnyder, PhD,[2] Mimi Jacobs, PT, MPT, GCS,[3] and Tim Fox, PT, DPT[3]

Abstract

The concept of frailty has been evolving dramatically for the past 30 years. Through its evolution, a variety of single and multidimensional models have been used to describe frailty. This article reviews the current literature related to the defining dimensions of frailty and identifies the gaps in the literature requiring additional research. A detailed literature review was performed to identify key dimensions and models currently being used to define frailty, classify interventions that have been developed to reverse frailty, and identify potential areas for future research within this field. Despite the large body of research defining the dimensions of frailty, no consensus exists on a comprehensive, operational definition. A standardized definition will be critical to design effective interventions at earlier stages along the continuum of frailty and interpret findings from evaluation studies. Identified gaps in the literature include studies supporting the utility of expanding the definition of frailty to incorporate social determinants, studies evaluating the role of obesity in the development of frailty, and the need for longitudinal studies for defining the pathways to developing frailty. This review highlights the need for an accurate definition of frailty and for longitudinal research to explore the development of frailty and evaluate the effectiveness of the frailty reversal interventions that may avert or delay adverse outcomes within this susceptible population. These future research needs are discussed within the context of the growing pressures to bring down health care costs, and the role of comparative effectiveness research and cost-effectiveness research in identifying interventions with the potential to help slow the growth of health care spending among the elderly. (*Population Health Management* 2011;14:277–283)

Introduction

Frailty is characterized by progressive decline in system function, and affects an estimated 7% of individuals older than 65 years of age.[1] Frailty has not been well defined and, because it does not present as a syndrome in which symptoms are easily visualized,[2] it is not easily diagnosed. Although some studies have defined frailty using a single dimensional approach, others have characterized frailty as a multidimensional syndrome that encompasses physical, social, and cognitive attributes.[3] To date, a validated definition of frailty has not emerged, despite years of research on both its attributes and associated processes.[4] There is agreement, however, on some of the basic signs of frailty, typically including the presence of inflammation, sarcopenia, neuroendocrine deregulation, and loss of bone density.[5] Factors such as age,[1] sex,[1] and lifestyle[6] have been associated with frailty. Frailty also is associated with significant debility,[1] with frail older adults having a higher risk for institutionalization,[7] hospitalization, and death[8] in comparison to non-frail older adults. Evidence suggests that customized interventions may reverse some of the physical consequences of frailty.[9] However, our understanding of the effectiveness of current interventions is limited by the lack of agreement on a standard definition and the absence of a clearly defined set of determinants, pathways, and outcomes related to frailty. This article provides an overview of the current state of frailty research and identifies gaps in the literature that require additional research.

Methods

A detailed literature review was performed to identify key dimensions and models currently being used to define frailty, to classify interventions that have been developed to reverse frailty, and to identify potential areas for future research within this field. The keywords used for the search were frailty in combination with models, dimensions, interventions, and cost-effectiveness.

Results

Dimensions and models related to frailty

As individuals age, a complex set of biological and physical factors interact to produce a gradual decline in health and

[1]Jefferson School of Population Health, Thomas Jefferson University, Philadelphia, Pennsylvania.
[2]Care Transitions CareKinesis, Inc., Moorestown, New Jersey.
[3]Fox GERI: Geriatric Education & Research Institute, Cherry Hill, New Jersey.

functional ability.[1] These factors combine in different ways, leading to a variety of pathways that ultimately may lead to cognitive and functional decline, compromised self-management capacity, and adverse outcomes such as disability,[1] falls, fractures, hospitalization, institutionalization,[7] and mortality.[8] This complex and poorly understood web of frailty causes and associated outcomes is reflected in the diversity of causal models and approaches to frailty research. These dimensions and models have focused mainly on biological, physical, cognitive, and multisystem attributes related to frailty.

Biological dimensions. Frailty has been hypothesized to be a process where inflammation, neuroendocrine deregulation, and sarcopenia contribute to a gradual decline in health.[5] Increases in inflammatory markers in older adults have been associated with both disability and mortality.[10,11] For example, high levels of C-reactive proteins and cytokines that characterize inflammation have been associated with poorer physical function in older adults.[12] Combined with deficiencies in Vitamin D in the elderly, inflammation may accelerate the process of developing frailty.[13] Puts et al conducted a prospective cohort study in which frailty was strongly associated with low levels of 25-hydroxyvitamin D and moderately increased levels of C-reactive protein. This was the first study that linked the increase in levels of inflammatory markers with indicators related to frailty.[14]

Furthermore, exercise has been shown to reduce the levels of inflammatory markers,[15] whereas the presence of multiple chronic diseases is associated with higher levels of such markers.[12] Taken together, these data suggest that factors typically associated with aging, such as declining levels of activity and an increasing number of chronic diseases, may impact biological processes associated with developing frailty. Biological models of frailty, then, offer the possibility of quantifiable markers of frailty and suggest that some interventions, such as physical therapy and therapeutic exercise, may impact frailty through multiple pathways.

Physical dimensions and models. The concept of physical frailty has been studied extensively, which has led to the development of various approaches to measurement. These approaches range from single-dimension scales, such as the assessment of gait speed,[16] to multidimensional instruments such as the Physical Performance Battery (PPB), which includes gait speed as 1 of 3 measures of function. Gait speed has been shown to be a highly predictive marker of frailty, as it is strongly associated with the progressive disability that characterizes frailty syndrome; furthermore, gait speed has been shown to be almost as good of a predictor of disability as the PPB.[18] The ease and feasibility of measuring gait speed in the clinical setting makes it an attractive measure for many practitioners.[4] The multivariate PPB test, on the other hand, evaluates lower extremity function in the elderly population using 3 variables: gait speed, repeated chair stands, and balance tests. This tool has been shown to be extremely predictive of frailty in the nondisabled elderly population.[18] A study conducted on elderly persons by Brown et al[19] showed that the scores obtained on the PPB test were significantly associated with measures of strength, and balance, gait, sensation, and multiple range of motion values.

In 1998, the concept of frailty as a phenotype was initially examined by Strawbridge et al utilizing the functional domains model.[20] This model defined frailty through the presence of deficits in 2 or more functional domains, including physical, nutritional, cognitive, and sensory functioning. They found that respondents who scored as frail reported reduced activities, had worse mental health, and reported lower satisfaction with life. Taking another approach, Fried et al[1] defined frailty as a process whereby a gradual decline in physiological reserves results in increased susceptibility to external stressors. Using data from the Cardiovascular Health Study[21] and the Women's Health and Aging Study[1], Fried et al developed the Fried Index, which classifies frailty as the presence of at least 3 of 5 criteria: unintentional weight loss, self-reported exhaustion, grip strength (weakness), low walking speed, and low physical activity. They observed that higher scores were associated with advanced age, African American race, female sex, lower socioeconomic status, and the presence of comorbidities and disability. The link between frailty and lower lean body mass in females is consistent with biological theories. In the Women's Health and Aging Study, researchers found that factors such as exhaustion and weight loss were associated with a 3 to 5 times greater likelihood of developing frailty. They concluded that physical weakness is a sign of vulnerability for frailty and recommended using outcomes such as weight loss and exhaustion to identify women who are at risk for progression into frailty.[21]

Although these models have shown good predictive value for identifying both the risk for and presence of frailty, it is not clear that models focused solely on the physical components of frailty are sufficient on their own or whether they can be improved by using them in conjunction with models that capture the biological and cognitive aspects of frailty.

Cognitive dimensions. The National Institute on Aging emphasized the need to understand the role of cognition, neurodegeneration, and neurological impairment markers in the development of frailty.[22] Studies have reported that some frail individuals experience cognitive decline. Funes et al[23] evaluated whether adding cognitive impairment to the Fried Criteria would improve its predictive validity. They found that the population classified as frail according to the Fried criteria had lower scores on the Mini-Mental State Exam than did the non-frail and the pre-frail. The frail population with cognitive impairment was also at higher risk for adverse outcomes such as disability and hospitalization. Another observational study reported that independent predictors of frailty, such as a slow walking speed, in combination with cognitive impairment, were associated with progression to dementia.[24] Finally, Buchman et al[25] showed that increasing levels of frailty were associated with greater incidence of Alzheimer's disease and a more rapid rate of decline in cognitive function in older persons. Although these studies show that cognitive impairment is associated with the development of frailty, future research using longitudinal study designs will be necessary to determine whether cognitive impairment is a risk factor for frailty and/or an adverse outcome of frailty.

Multidimensional phenotype. Recognizing that evaluation of impairment of multiple systems is necessary to define frailty as a syndrome, Rockwood et al[3] posited that frailty is an accumulation of deficits as captured by symptoms, signs, disabilities, diseases, and laboratory measurements. They developed the frailty index (FI), which includes 70 items derived from a comprehensive geriatric evaluation, the Folstein Mini-Mental State Exam, clinical evaluation, and laboratory tests (eg, HbA1c). Although the 70-item index is a simple average rate that represents the likelihood of developing frailty, its use in a clinical setting may not be feasible because collection of such detailed data is cumbersome for both clinicians and patients. Therefore, Rockwood and colleagues subsequently developed a 7-category Clinical Frailty Scale that captured fitness level, comorbidities, and functional dependence. This scale identifies populations that range from robust health to complete dependence on others based on the subjective judgment of the physician. Validation studies showed that the shorter scale correlated highly with the 70-item FI, and performed better than independent measures of cognition, function, and comorbidities at assessing risk of mortality.[26]

Comparison of different models. Multiple studies comparing these models of frailty in different populations have been conducted. In a comparison of the FI and Fried Criteria, Rockwood et al[27] found that the measures correlated moderately well in terms of function but less well with cognition. They found that the FI more robustly predicted combined risk for adverse outcomes such as institutionalization and all-cause mortality. Cigolle et al[28] compared 3 models of frailty, which included the FI index, the Fried Criteria, and the functional domains model. They found that the models identified discrete groups of frail populations that differed in their sociodemographic and chronic disease characteristics. A third of the respondents were classified as frail according to at least 1 model and there was a 3.1% overlap among all 3 models. Cigolle et al's results suggest that different models of frailty may correspond to varying trajectories of frailty that will ultimately lead to adverse outcomes related to aging. The results of these comparisons suggest that frailty is a multidimensional phenotype. Additionally, understanding and defining the different pathways to develop frailty can help to provide a more focused definition of different frailty pathways and enable the design of effective interventions to prevent or delay the onset of frailty.

Interventions tailored to address frailty

If patients at high risk of frailty could be accurately identified, then interventions to prevent frailty and/or its progression could be developed and tested in a target population. However, the lack of consensus in defining frailty as a syndrome[4] has made it difficult to design interventions that target the populations at greatest risk for frailty. The frail population is generally deconditioned, sedentary, and homebound because of the presence of multiple chronic diseases and their associated disabilities. Targeted interventions could have a significant impact on preventing the progression of frailty and the negative consequences of frailty. Physical therapy interventions and therapeutic exercise for the frail population may be a viable option to arrest the progression of frailty and improve both function and quality of life.

Studies that evaluate the effectiveness of individualized home-delivered exercise programs for the elderly population have found reductions in the risk and incidence of falls and improvement in physical and emotional function. Teri et al[29] conducted a study to evaluate the effectiveness of a 3-month-long intervention that combined an exercise program with training the caregiver in behavioral management. This program resulted in improvement in physical functioning and depression scores. The improvements in physical function were maintained up to 2 years. The subset of patients who had a high depression score at baseline showed significant improvements in depression scores that were maintained up to 24 months.[29] Toulette et al[30] conducted a study that evaluated the effect of a 16-week physical training program on 20 demented elderly people. They demonstrated that this program resulted in significant improvements in physical measures such as walking, mobility, flexibility, and static balance. Gill et al[9,31] conducted 2 studies evaluating the effectiveness of a home-based physical therapy and occupational therapy program for the physically frail. They found that at 7 months, the home-based program led to prevention of functional decline, which was demonstrated by a 45% reduction in activities of daily living scores in the intervention group compared to the usual care group. However, the effects of this program were significant only for the moderately frail and not for those who were severely frail. In the second study, they showed that among the subgroup of patients with physical frailty, this same program led to significant improvements in physical functioning, as measured by instrumental activities of daily living, mobility, performance-oriented mobility assessment, and integrated physical performance. Faber et al[32] evaluated the effects of moderate-intensity group exercise programs that were based on either daily mobility activities or balance exercises in the frail, pre-frail, and non-frail elderly. Outcomes measured included falls, functional performance, and disability. They found that the moderate-intensity group exercise programs had positive effects on falling and physical performance for the pre-frail, but not the frail elderly. Taken together, these results provide strong evidence that a supervised physical therapy or occupational therapy rehabilitation program that targets underlying physical impairments can lead to improvements in physical function and a reduction in adverse outcomes such as disability among the elderly. However, the severity of frailty could have an impact on the effectiveness of the exercise program. For effective design and evaluation of interventions, priority must be placed on achieving a consistent definition of frailty.

Future Directions

Although a large amount of research has been carried out to study frailty, there are still some gaps in the research that need to be further addressed. Additionally, emphasis will need to be placed on research efforts that focus on defining frailty, as this will be especially important to provide effective solutions to prevent and delay frailty. This section will cover the some of the areas of future research, such as attributes that can be used to define frailty, measurement issues related to frailty, methods to improve clinical trial design for the measurement of frailty, and explore the role of comparative effectiveness research (CER) and cost-effectiveness analysis (CEA) in this area (Table 1).

Conceptualization/Definition: Frailty as a syndrome

Although a significant body of research has focused on identifying the physical, cognitive, and biological attributes of frailty, there is no consensus on a standard definition of frailty. In an effort to reconcile the various perspectives on frailty measurement, the International Academy on Nutrition and Aging (IANA) Geriatric Advisory Panel recently reviewed the findings across studies and populations. The panel concluded that single dimensions, such as gait speed measured alone or combined with a PPB, were strongly predictive of frailty.[4] They further concluded that disability should be conceptualized as an outcome of frailty rather than being used to identify frailty. Studies that apply a longitudinal design are needed to clearly understand development of the syndrome, the outcomes of frailty, and differentiation of outcomes from causes.[33] To address some of these gaps in knowledge, Santos–Eggimann has initiated a longitudinal cohort study to evaluate frailty from a population-based perspective through the identification of risk factors (ie, environmental, medical, psychological), and track the sequence of physical and mental manifestations, trajectories, and transitions between frailty, outcomes related to disability, and resulting long-term outcomes related to falls and hospitalization.[34] This study may provide crucial information on the development of frailty. The American Geriatrics Society/National Institute on Aging Conference on a Research Agenda on Frailty in Older Adults brought together clinical experts in frailty to promote examination of the body of research on frailty, and highlight the need for research on understanding how specific medical, social, and psychological conditions affect outcomes related to frailty.

Factors involving individual circumstances (eg, socioeconomic factors) also may play a role in increasing the risk of developing frailty. For example, Lang et al[35] found that older adults who were poor and resided in deprived neighborhoods had a higher FI than adults who resided in wealthier neighborhoods. This study demonstrated the need for frailty models to account for environmental and individual characteristics associated with social settings.

Given that frailty has been associated with decreases in lean muscle mass and weight loss, overweight individuals typically have not been viewed as a high-risk population. However, biological markers linked to frailty, such as C-reactive proteins, also have been associated with obesity.[36] Blaum et al[37] evaluated if obesity was associated with the physical frailty phenotype in an elderly population of women with a BMI >18.5 kg/m2 and found that women who were overweight were categorized as pre-frail and obese women were classified as frail according to the Fried Criteria. Longitudinal studies will need to be conducted to disentangle the effects of obesity on frailty development and to evaluate the effect of weight loss and physical activity on frailty development in this population.

Measurement: Weighting of factors

The main trend in the development of frailty models has been evaluation of the trade-off between acquiring precision within the models and adapting a more broadly defined and applicable tool for use in clinical settings. In both cases, weighting of the variables is important because not all risk factors or predictors increase the risk of developing frailty equally (eg, terminal illness vs. age-related sarcopenia). Rockwood et al[26] suggested the use of mathematical techniques, such as artificial neural networks, to calculate weighted scores for risk factors. However, clinicians will need to exercise judgment in conjunction with these scales to identify which factors increase the risk of developing frailty and to identify populations for whom symptoms of frailty could be prevented or reversed.

The Geriatrics Society/National Institute on Aging conference emphasized the need to identify combinations of traits or risk factors that contribute to frailty development, which would improve the targeting of interventions aimed at modifying particular sets of traits and risk factors.[22] Passarino et al[38] carried out a hierarchical cluster analysis in which 2 groups of subjects with different degrees of cognitive, functional, and psychological status were classified into 3 frailty clusters: non-frail, intermediate, and frail. Their analyses demonstrated that these 3 clusters correlated with outcomes such as disability, comorbidity, and 18-month mortality.

Table 1. Summary of Future Directions for Frailty Research

Research Topic	*Recommended Directions*
Conceptualization of frailty	* Use of single dimensions such as gait speed alone or along with Physical Performance Battery for defining frailty * Use of longitudinal design studies to evaluate determinants and outcomes of frailty * Role of socioeconomic factors in the development of frailty * Role of obesity in the development of frailty
Measurement issues	* Weighting of risk factors for predicting frailty
Comparison of models	* Use of longitudinal designs to compare progression of frailty for different models
Improvement in clinical trial design	* Use of screening tools to identify and target populations for interventions * Use of risk stratification to evaluate severity of frailty
Role of CER and CEA in frailty	* Measurement of primary outcomes (eg, ADLs, mobility, performance-based measures) and secondary outcomes (eg, quality of life, depression) for evaluation of interventions * CEA can be added to RCTs for evaluation of interventions from a clinical and an economic perspective

ADL, activities of daily living; CEA, cost-effectiveness analysis; CER, comparative effectiveness research; RCT, randomized controlled trial.

They concluded that cluster analysis was a viable method to differentiate phenotypes and warrants further exploration.

Longitudinal outcomes evaluation for models

When comparing outcomes related to different models, most studies utilized a cross-sectional sample for cohorts. Such designs do not allow for an understanding of the progression of frailty. However, the use of longitudinal cohorts to identify determinants and outcomes associated with each of the various models could provide greater insight into pathways to developing frailty. The results of studies to differentiate pathways associated with frailty models could shed more light on refining such models and enable the design of targeted preventive interventions for populations identified through different models.

Improvement in designing and conducting trials related to evaluating interventions targeting frailty

Identifying the ideal population at risk of developing frailty will be important to recruit effectively for clinical trials that evaluate interventions that target and prevent frailty. The Frailty Working Group[39] stated that the recruitment process for these populations may be complex and expensive, and recommended a multistage selection process that would involve excluding populations who are robust and identifying a frail subset of the population based on specific domains of frailty (eg, mobility, muscle strength, nutritional intake, weight change, balance, endurance, fatigue, physical activity). The IANA Geriatric Advisory Panel[4] concluded that there is a lack of appropriate screening tools for frailty. However, the task force recommended that populations that are 80 years of age or older with subjective fatigue as well as those younger populations that have the presence of risk factors (eg, living alone, memory complaints, weight loss, low walking speed) should be screened. The task force suggested the use of a case finding tool that includes domains such as fatigue, resistance, ambulation, number of illnesses, and weight loss.

When designing interventions for the frail populations, researchers must develop methods to measure the severity of frailty in populations to evaluate whether interventions will be effective at different levels of frailty. Gill et al[9] found that individualized interventions were effective for the moderately frail but not for the severely frail. Because there are various models to evaluate frailty, a standardized approach to frailty staging is needed so that findings from frailty research can be generalized across different populations. Predictive modeling techniques could be applied to large data sets to identify population variation in degree of frailty based on risk factors.[40] The identification of subpopulations at varying levels of risk could then be followed with a more comprehensive frailty assessment tool to diagnose frailty and suggest the primary or secondary interventions to prevent adverse events at that stage. However, before application of risk stratification, a standard definition of frailty must be agreed upon.

Role of CER and CEA in designing clinical trials for frailty

CER has been suggested as an approach to evaluate interventions based on the relative value they provide to patients. CER could allow for evaluation and comparison of multiple types of exercise protocols in populations with varying levels of frailty. However, lack of comparability among the outcomes measured in current studies makes it difficult to evaluate which interventions are most effective for elderly populations. Therefore, standardization of the outcomes measured in intervention studies is a critical next step in the frailty research agenda. The Frailty Working Group[39] recommended collecting functional outcomes as primary end points for this population, such as activities of daily living, mobility, and performance-based measures. Secondary outcomes could provide information regarding the causal pathways between interventions and the development of disability. The Working Group suggested the use of secondary outcomes such as mobility, quality of life, and depression. These outcomes also could be used to investigate the effects of interventions on the well-being of frail populations. Secondary outcomes also could provide insight into whether changes in performance-based measures actually translate to meaningful changes in outcomes related to quality of life. The need to evaluate multiple outcomes, including quality of life, is especially important for this population because many frail adults have multiple chronic diseases and poor function. Outcomes research could reveal whether provision of interventions at an earlier stage contributes to the delay or prevention of adverse events related to the development of frailty.

Home health agencies have been reimbursed for their services and achieved an average profit margin of 16.5% per year over the last 8 years. Because of the steady growth of home health services over the last 7 years, along with consistent positive margins for these organizations, in 2006, the Medicare Commission concluded that home health reimbursement payments should be reduced for 2010.[41] However, recent health care reform initiatives have not been finalized, resulting in uncertainty about future reimbursement. The combined effects of the aging population and increasing chronic illness burden are predicted to increase the demand for services and support that will allow older adults to age safely and comfortably at home. In light of the pressures to reduce Medicare expenditures, CEA techniques could be applied to studies of home-based interventions targeting frail older adults to identify interventions with the greatest value (ie, those that are the lowest cost and most effective when applied to the target population). CEA studies will need to measure effectiveness with respect to both short-term intermediate outcomes, such as improvement of physical function and reduction in functional decline, and long-term outcomes such as falls and mortality. A study by Jutkowitz et al[42] evaluated the cost-effectiveness of a physical therapy and occupational therapy intervention to prevent functional decline in an elderly population through measurement of functional difficulties and costs. They showed that this intervention was cost-effective when compared to usual care. CEA could be added to randomized controlled studies to evaluate frailty interventions from a clinical and an economic perspective. However, to conduct meaningful CEA studies, there will need to be more clarity in defining outcomes related to different frailty models. Consensus workshops could be useful to determine appropriate end points associated with various frailty models for conducting cost-effectiveness studies.

Conclusion

Frailty research has evolved dramatically over the last 30 years, producing new insights into both the definition and measurement of determinants and outcomes. This review provides a summary of the current state of frailty research. Specifically, it describes frailty models, identifies gaps in research, and makes recommendations to improve research in this arena. Although a large body of research has focused on defining the dimensions of frailty, there still is no agreement on a comprehensive operational definition of frailty. However, a standardized definition of frailty is critical to design effective interventions at earlier stages along the frailty continuum and to interpret findings across studies.[4] The care of the elderly who frequently have multiple comorbidities accounts for the greatest portion of current health care spending. Interventions that would prevent or delay adverse outcomes such as disability, institutionalization, and mortality for this susceptible population may increase function and quality of life while at the same time potentially decreasing health care spending. Research on interventions to reverse and delay frailty will play an important role in promoting healthy and active aging.

Author Disclosure Statement

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Address correspondence to:
Anita Mohandas, M.Sc.
Jefferson School of Population Health
Thomas Jefferson University
1015 Walnut Street, Suite 115
Philadelphia, PA 19107

E-mail: anita.mohandas@jefferson.edu