Aged care series

Differences in frailty in older men and women

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In simple terms, ageing is an accumulation of cellular damage over time. Yet there is significant heterogeneity in the older population in terms of health status and care needs; some individuals remain functionally independent into their tenth decade whereas others have complex comorbidities and psychosocial problems from middle age. This variability suggests that ageing is not a fixed process and has stimulated research exploring the lifestyle and behavioural factors that promote healthy ageing and the pathophysiological processes that may lead to frailty. It is increasingly recognised in this research that the ageing trajectory is influenced by an individual's sex.

Here, we introduce the frailty construct before reviewing differences in the frailty of men and women. We also summarise the evidence for frailty interventions in older adults and consider whether, in the future, clinicians may be recommending sex-specific management strategies. For this review, we searched PubMed and other databases for peer-reviewed articles using various search terms, including "frailty", "sex differences" and "intervention".

Summary

- Frailty describes an individual's vulnerability to adverse health outcomes and is a useful construct that assists health professionals to understand the heterogeneity of the ageing population.
- While the pathophysiological pathways that lead to frailty are not well defined, an individual's sex appears to be a key factor influencing the ageing trajectory.
- Compared with age-matched men, women tend to have poorer health status (ie, they are more frail) but longer life expectancy (ie, they are more resilient). It seems likely that a combination of biological, behavioural and social factors underpin this male–female health–survival paradox.
- Randomised controlled trial data for frailty interventions in older adults are emerging, with multicomponent programs incorporating exercise and nutrition-based strategies showing promise. Pharmaceutical and other innovative therapeutic strategies for frailty are highly anticipated.
- Sex differences in the effectiveness of frailty interventions have not been addressed in the research literature to date. In the future, successful interventions may target many (if not all) biopsychosocial domains, with careful consideration of issues relevant to each sex.

Frailty

Frailty has been defined as a state of increased vulnerability that is associated with adverse health outcomes.[1] It has been estimated that just over 10% of community dwelling adults aged 65 years and over are frail.[2] A frail older person takes longer to recover after any sort of insult (such as infection, infarction or adverse drug reactions) and during the period of recovery is more vulnerable to further stressors. Increasing frailty is associated with syndromic disease presentations; falls, delirium, functional decline and new urinary incontinence may reflect acute illness in a frail older person and should never be dismissed as "normal for age".[1]

The prevalence of frailty increases with age, and chronic inflammation has been proposed as the key pathogenic factor in both ageing[3] and frailty.[4] However, since the exact aetiology of frailty is yet to be established, many different models have been developed to describe the clinical entity of frailty. Some measures define frailty as a phenotype, a set of symptoms and signs that occur together. The most widely used phenotypic model was defined by Fried and colleagues[5] as the presence of three or more of the following: weight loss, weakness, slowness, fatigue and low physical activity. Individuals with one or two of these criteria were defined as "pre-frail". In their landmark study, falls, worsening disability, hospitalisations and death were more common in pre-frail and frail individuals.[5]

The cumulative deficit model, represented by the Frailty Index (FI), is another commonly used method to quantify frailty. The underlying principle is that the more problems an individual acquires, the more likely they are to be frail.[6] Here, an index is derived from a list of variables (deficits) which should encompass functional, cognitive, physiological and psychosocial domains.[7] Signs, symptoms, disabilities and diseases may be included as deficits if they fulfil certain criteria: accumulation with age; association with adverse outcome; and absence of early saturation (eg, presbyopia is fairly ubiquitous after age 55 years so would not be included as a deficit).[7] As long as these criteria are met and more than 30 deficits are included, an FI can be derived from datasets comprising different numbers and types of deficits (eg, someone with ten deficits from a total of 40 has an FI of 0.25; someone with 21 deficits from a total of 70 has an FI of 0.30). The FI is a continuous variable, which not only provides information about frailty severity but also enables quantification of the health status of individuals identified as non-frail by the phenotypic model. Studies have found that the FI predicts adverse outcomes, including institutionalisation and mortality, in a dose-dependent manner.[6,8] Interestingly, it is the number of deficits, rather than the nature of the deficits, that influences the relationship between FI and adverse outcomes.[6] The predictive validity of the FI has been confirmed by multiple studies using cohorts from different cultural backgrounds.

Other frailty assessment tools are generally derived from these two key conceptual models, but there is no current consensus as to a standardised tool for frailty measurement. In a 2011 review, 20 frailty instruments were identified;[9] 4 years later, 29 instruments were described;[10] and by 2018, 89 different measures were being utilised in the acute care setting alone.[11] Different tools yield different estimates of frailty prevalence and vary in their content validity, predictive validity and feasibility.[9,10] While there is some overlap in identification of frailty, it is likely that these models (and their associated assessment tools) capture slightly different groups.

Interest in frailty has spread beyond geriatric medicine to other medical, surgical and critical care specialties in recent years. With improvements in the medical management of acute and chronic diseases, more adults are living to an advanced age

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and, as a result, subspecialty areas, such as oncology and cardiothoracic surgery, are seeking to validate frailty as a prognostic tool to guide their management.[12] In Australian acute medical units, the prevalence of frailty has been estimated to be between 50% and 88% (depending upon the frailty measure used).[13,14] Frail inpatients face many adverse outcomes, including falls, pressure injuries, delirium, prolonged hospitalisation, discharge to a nursing home, and death in hospital.[15]

Sex differences in frailty

In community dwelling populations aged over 65 years, women are more likely to be frail and to have a greater burden of frailty than men of the same age.[2,16] Yet women appear to be more resilient — at any given age or level of frailty, their mortality rates are lower.[16]

This sex–frailty paradox is another conceptualisation of the male–female health–survival paradox, which has long been reported in the literature. The female survival advantage has been documented by European historical records dating back to the 18th century,[17] and in Australia, the life expectancy of females continues to be about 4 years longer than that of males.[18] Yet throughout their lives, women are burdened by chronic disease and disability to a greater extent than men and, unsurprisingly, women have poorer self-rated health.[19]

Several biological, behavioural and social explanations for sex differences in morbidity and mortality have been proposed and tested by researchers. More recently, attention has turned to sex differences in frailty (Box 1). It seems likely that the pathophysiology of the sex–frailty paradox comprises many, if not all, of these factors. In terms of biopsychosocial pathways to frailty, much more needs to be done to better understand why and how men and women age in different ways.

Frailty interventions

Over the past 20 years, research efforts have focused on refining frailty measurement and establishing its prognostic implications. While it is important to be able to describe the heterogeneity of an ageing population and to define risks of adverse outcomes, it is equally important to develop and test therapeutic strategies for frailty. Given its negative consequences, it is tempting to view frailty from a nihilistic standpoint. However, improvements in health can occur in individuals of any age, with varying degrees of frailty.[35]

While there are many intervention studies of frail older adults, there are few studies specifically addressing the treatment of frailty. Two recent reviews have sought to clarify the effectiveness of frailty interventions in adults aged 65 years and over.[36,37] A 2018 systematic review included 21 randomised controlled trials published between 2002 and 2016,[36] and a 2017 scoping review included 12 randomised controlled trials and two cohort studies published during the same period.[37] Most of the evidence in the included studies was graded as low quality, meta-analysis could not be undertaken, and only four studies were common to both reviews. It was challenging for the authors of these reviews to synthesise the results for many reasons, but a key issue was heterogeneity of the frailty measurement. The impact of the intervention was also measured in various ways, including change in the prevalence of frailty and pre-frailty, and change in the prevalence of frailty components. Surrogate measures for frailty (such as physical performance scores, functional status, muscle mass and power) were frequently used. These methodological challenges highlight that this field of enquiry is still in its infancy.

Nevertheless, based upon the current available evidence, there are interventions that may have the potential to reduce the prevalence of frailty (or its components) or to prevent the progression of frailty in older adults (Box 2). At present, exercise and nutrition-based interventions have the highest level of evidence.[36]

Many of these interventions target phenotypic features of frailty, including weakness, slowness and wasting. Yet frailty is more than just physical signs and symptoms. Cognitive training strategies and comprehensive geriatric assessment with interdisciplinary interventions address important non-physical health domains. More recently, researchers have reported benefits from multifactorial interventions incorporating exercise, a nutritional intervention, and cognitive training with social support[40] or medication review.[41]

Criticisms of the available frailty interventions include imperfect treatment compliance, variable durability of effects post-intervention and cost-effectiveness. While provisional results regarding these issues are reassuring,[36,41,42] further investigation is justified considering the complexity of the interventions and the vast number of potential recipients. It is also important to note that very few studies have examined interventions to prevent the development of frailty in non-frail older adults. Further, the evidence-base for interventions to prevent or reduce frailty in institutionalised or hospitalised older adults is limited. Therefore, the available evidence primarily informs management of frail (and pre-frail) community dwelling adults.

While frailty is not synonymous with chronic disease, the number and severity of comorbidities increase the probability of being frail.[43] Bidirectional relationships have been postulated between frailty and several chronic diseases. In some cases, this may be due to shared pathophysiology (eg, cardiovascular and cerebrovascular disease),[44] and in other cases, frailty may be linked with chronic disease via functional impairment (eg, osteoporosis with fracture). Consequently, chronic diseases are likely to be important therapeutic targets for frailty.[45] However, to our knowledge, frailty is yet to be included as an outcome measure in chronic disease intervention trials and, as a result, the impact of disease management on the incidence and prevalence of frailty may only be inferred.

Smoking, excessive alcohol intake and abdominal obesity have all been strongly linked with frailty in older adults[23,46,47] and are key risk factors for the development of many chronic diseases. Again, in theory, management of these variables would reduce the incidence and prevalence of frailty in old age through primary prevention of chronic disease as well through reduced exposure to inflammatory stimuli.

More recently, increasing knowledge of frailty pathophysiology has prompted a search for effective pharmaceutical interventions. Androgen deficiency has been implicated in the development of frailty, particularly sarcopenia, in both sexes. However, the evidence for the therapeutic benefit of hormone replacement is limited. For example, testosterone replacement in pre-frail and frail men has not led to improvements in physical function,[48] and while the combination of dehydroepiandrosterone and exercise improved physical performance in a small study of pre-frail and frail women,[49] a subsequent systematic review did not confirm these results.[50] Concerns about the adverse event profile of androgen replacement therapy in older men and women may impact future advances in this area of research.[29] Early studies of selective androgen receptor

1 Biological, behavioural and social hypotheses regarding sex differences in mortality, morbidity and frailty

Category		Comments
Biological	Genetic	• The presence of two X-chromosomes, longer telomeres and slower telomere shortening processes may confer a survival advantage in females.[20]
	Hormonal	• Oestrogens may reduce risk of death in females by postponing the onset and lowering the burden of atherosclerosis.[20] • Testosterone may increase risk of death in males by reducing the robustness of the male immunological system.[21]
	Immunological	• Male immune systems may deteriorate to a greater extent and at a more accelerated rate than those of females, leading to poorer survival.[21] • Chronic inflammation may play a more critical role in the pathophysiology of frailty in females than in males.[22] This may be due (in part) to greater accumulation of abdominal adiposity in older females than males.[23]
	Reproduction	• Pregnancy, childbirth and lactation may contribute to increased morbidity in females. Cardiovascular and metabolic changes (eg, insulin resistance, inflammation and recurrent weight gain predisposing to post partum obesity), as well as pregnancy complications (eg, pre-eclampsia), appear to impact later life health in females.[24]
	Chronic disease	• Males may acquire more lethal conditions (such as cerebrovascular disease and ischaemic heart disease) than females, leading to higher mortality.[25] • Females may acquire more disabling conditions (such as obesity, arthritis, cataracts and depression) than males, leading to higher morbidity.[26] • Males may acquire different types of disabling conditions to females. For example, hearing impairment is more prevalent in males and has been associated with dementia and frailty.[27] Even so, the disabling effect of chronic diseases may be greater among females than males.[26]
	Disability	• Females report and experience more physical and functional impairment and lower rates of recovery than males. These factors may underpin higher rates of frailty in females.[25,28] • Females may be more frail than males due to the higher rates of sarcopenia.[29]
	Physiological reserve	• Females may have greater physiological reserve than males. This would enable females to acquire more deficits in multiple organ systems (ie, greater morbidity) before succumbing to death.[30]
Behavioural	Risk-related activities	• Males engage more frequently in high-risk behaviours (such as cigarette smoking and alcohol consumption), which may contribute to increased prevalence of lethal comorbidities and mortality.[19]
	Illness perception	• Females may be more sensitive to physical changes or discomforts than males, which may lead to more interactions with health care providers and possibly more diagnoses.[31]
	Health reporting behaviour	• Females may be more willing to identify and report minor and major health issues to others,[31] leading to seemingly higher disease prevalence rates and frailty.
	Health care use	• Females access health care more than males. This may result in receiving more preventative health care and early intervention, which in turn may contribute to better survival in females.[19,31]
Social	Gender roles	• Expectations and responsibilities associated with gender roles may contribute to the willingness (and ability) of the sexes to adopt a "sick" role, seek help and access health care. This in turn may influence sex differences in morbidity and mortality.[32]
	Social assets and deficits	• While social vulnerability is weakly to moderately correlated with frailty in both sexes, females are more socially vulnerable than males due to their living situation (widowhood and living alone).[33] Even so, females may be better able to cope with higher levels of frailty due to greater social support networks. • Males may be more vulnerable to the effects of social isolation, particularly widowhood, both in terms of frailty and mortality.[34]

modulators look promising, but larger trials of longer duration are still required.[29]

If chronic inflammation is a key pathogenic factor in frailty, it is reasonable to hypothesise that anti-inflammatory agents would be effective in preventing or reducing frailty. While randomised controlled trials in human participants have not been conducted, observational studies suggest that anti-inflammatory agents may not reduce the risk of frailty. For example, in the Women's Health Initiative Observational Study, current statin use had no effect on incident frailty over 3 years.[51] However, a recent intervention trial in ageing mice demonstrated that long term treatment with an angiotensin-converting enzyme inhibitor reduced pro-inflammatory cytokine levels and attenuated the progression of frailty.[52] While this preclinical evidence seems promising, caution is advised in assuming that inflammation causes frailty.[53] An alternative view is that inflammatory markers become elevated in response to chronic stimuli or are an epiphenomenon unrelated to the core pathophysiology.[53] In these scenarios, anti-inflammatory agents would be, at the very least, ineffective or, at the very worst, harmful.

Fortunately, frailty researchers continue to pursue innovative therapeutic options. For example, a phase 2 randomised double-blind controlled trial of allogeneic mesenchymal stem cell transplantation in older frail adults recently demonstrated a reassuring safety profile, as well as some promising results with respect to physical performance and function.[54] Even so, at the present time, non-pharmacological interventions, particularly exercise and nutrition programs (or combinations of such), are the recommended treatment for frailty in community dwelling older adults.[36]

2 Summary of evidence for frailty interventions[36,37]

Intervention	Impact on frailty	Comments
Exercise		
• Resistance training, balance and gait retraining, tai chi, aerobic training, computerised balance training • Group training sessions ± home-based practice • Home-based practice ± face-to-face supervision or phone calls	Exercise is generally considered to be an effective intervention for frailty. Positive study outcomes include: • improved frailty score • reduced frailty prevalence • improved strength, gait speed, physical activity and balance, and reduced exhaustion	The most effective program (ie, type of training, intensity or duration) has not been established although training in groups appears to be more effective than home-based programs. Computerised balance training did not have an effect on frailty.
Nutrition		
• Nutritional supplementation (including protein formula, micronutrients, milk fat globule membrane)	Nutritional supplementation is generally considered to be an effective intervention for frailty. Positive study outcomes include: • improved frailty score • improved physical activity, reduced exhaustion and increased energy intake • improved physical performance score	The most effective nutritional program (ie, type of supplement or duration) has not been established. Nutritional interventions were likely to be more effective for those with poor background nutritional status.
Multicomponent interventions		
• Exercise, nutrition ± cognitive training: ▸ resistance training, balance and gait retraining, aerobic training ▸ nutritional supplements, consultation, cooking classes ▸ cognition-enhancing activities • Other interventions: ▸ music-based program targeting motor, cognitive and social skills	Multicomponent interventions, comprising exercise and nutrition programs (± cognitive training), are generally considered to be effective interventions for frailty. Positive study outcomes include: • reduced frailty prevalence • improved frailty score • improved (or preserved) gait speed, improved hand-grip strength and physical activity, and reduced exhaustion	Components appeared to have additive effects. That is, the benefit of a multicomponent intervention was not solely attributed to the exercise program. Good compliers (with exercise and nutrition programs) were more likely to be robust at baseline and to benefit from the intervention.
Cognitive training		
• Weekly and fortnightly sessions incorporating cognition enhancing activities (targeting memory, attention, problem solving, judgement and reasoning)	The evidence for cognitive training alone as an intervention for frailty is limited. Positive study outcomes include: • improved frailty score • reduced frailty prevalence	Only one study has been reported to examine the effects of cognitive training alone on frailty.[38] Cognitive training was found to impact frailty; however, when considering changes in frailty components, a significant improvement was seen in knee strength only.
Comprehensive Geriatric Assessment (CGA)		
• CGA performed by a multidisciplinary team, a geriatrician, a nurse, or via a screening evaluation tool, and accompanied by tailored interdisciplinary interventions • Alternative models: ▸ CGA accompanied by a tailored education session for each at-risk adult and a report for their primary care physician ▸ CGA accompanied by referrals for interdisciplinary interventions • Settings include inpatient geriatric evaluation and management units, outpatient geriatric medicine clinics, emergency departments and the community	The evidence for CGA as an intervention for frailty is mixed. Positive study outcomes include: • reduced frailty prevalence • improved frailty status from at-risk to not at-risk	The CGA intervention did not impact frailty in all studies. The effectiveness of this intervention appeared to differ depending upon the setting, the target population, the assessment process and the delivery of interdisciplinary interventions. Even so, CGA is of proven benefit for older people in hospital, increasing the likelihood that they will be alive and in their own homes at follow-up.[39]
Education sessions and home visits		
• Group or individual education session(s) ± home visit • Single or regular home visits by a trained professional (allied health or nursing) ± provision of an alert button • Education content included the ageing process, available support services and home risk assessment and modification	The evidence for education sessions and home visits as interventions for frailty is mixed. Positive study outcomes include: • reduced frailty prevalence • reduced progression in frailty status from not at-risk to at-risk	The provision of an alert button was the only home visit intervention found to impact frailty. The effectiveness of group education sessions appeared to vary according to the frailty status of participants.

The sex–frailty paradox and frailty interventions

Sex differences in the effectiveness of interventions have not been specifically addressed by the research literature to date. Exercise programs appear to be effective in both sexes.[36] However, sarcopenia, low physical activity and functional impairment are more prevalent in older women than men,[29] and it is possible that women may benefit from a different type or

intensity of exercise intervention than men. With respect to nutrition, men may benefit from interventions to a greater extent than women. Several studies have indicated that men tend to have a poorer understanding of nutrition and make unhealthy dietary decisions.[55] A recent study recruited 4421 participants with, or at high risk of, knee osteoarthritis,[56] and explored the components of their diet at baseline. Over an 8-year follow-up period, men who consumed a diet with high inflammatory potential had up to four times the risk of developing frailty than men who did not; however, diet had no effect on incident frailty for women. It has also been noted that nutrition intervention studies with male and female participants were more likely to be positive than studies with mostly (or only) female participants.[36] Overall, it is possible that nutritional support is more beneficial in the prevention and treatment of frailty in men than in women.

Sex differences in frailty highlight that older men and women may respond to interventions in different ways and may benefit from more sex-specific strategies. The sex–frailty paradox adds yet another dimension by highlighting that the link between frailty and mortality is not fixed; even though men are less frail than women, we must not forget that they are more likely to die. Thus, while it is important for health care professionals to ask how we can prevent and treat frailty in ageing men and women, it may also be useful to consider how can we prevent and treat frailty, particularly in ageing women. And how do we prevent death, particularly in ageing men?

Like frailty, we can conceptualise the sex–frailty paradox to be an accumulation of deficits across multiple systems: biological, behavioural and social. Successful interventions, therefore, are likely to target many (if not all) domains with careful consideration of issues relevant to each sex (as outlined in Box 1). In Box 3 we propose sex-specific strategies for prevention and treatment of frailty.

3 Potential sex-specific targets for the prevention and treatment of frailty

Men

- Education and support for boys and men regarding appropriate illness and help-seeking behaviour
- Education and support for boys and men regarding risk-related behaviour, including smoking, excessive alcohol intake and illicit drug use
- Primary prevention of vascular disease in middle-aged men through smoking cessation, weight management, physical activity, screening for metabolic disease and pharmaceutical interventions (when appropriate)
- Aggressive management and secondary prevention of vascular disease in middle-aged and older men
- Nutritional education and support
- Management of sensory impairments, particularly hearing impairment
- Promotion of health care utilisation for preventive and early interventions in middle-aged and older men
- Promotion and facilitation of social and practical support networks for middle-aged and older men, particularly those recently widowed or single

Women

- Early (and ongoing management) of abdominal obesity, which may develop during reproductive and peri-menopausal periods
- Follow-up and implementation of primary prevention strategies in women with cardiovascular and metabolic complications of pregnancy
- Screening, diagnosis and management of depression, osteoporosis and sensory impairments, particularly vision impairment, and falls in middle-aged and older women
- Promotion and facilitation of physical activity for the prevention and treatment of sarcopenia, obesity, arthritis, depression, and cognitive and functional impairments in middle-aged and older women
- Promotion and facilitation of practical supports for women living alone

Conclusion

Caring for frail older adults is a core remit of our health care system. A better understanding of frailty should improve our care of the ageing population through earlier identification of at-risk patients, development of intervention strategies, and more effective use of health care resources. To provide optimal, patient-centred care, sex differences should inform our practice. While the evidence base for sex-specific frailty interventions is lacking at present, the knowledge gleaned and hypotheses generated from observational data should inspire programs of research, instigate public health initiatives, and prompt reflection by health professionals.

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