Zeidan RS, et al., J Gerontol Geriatr Med 2024, 10: 213
DOI: 10.24966/GGM-8662/100213

HSOA Journal of Gerontology and Geriatric Medicine

Commentary

Insights from Zeidan Et Al.'S Review: Sex Differences in Frailty among Older Adults

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During the last few decades, the average life expectancy of humans has significantly increased [1]. However, this increase was accompanied with an increase in frailty in older adults [2]. The aging process can impact the entirety of the body in most humans, resulting in declines in physiological, physical and cognitive capabilities [3]. Frailty reflects the increase in vulnerability to stressors and shortens [2-6] the time without disease (health span), while longevity refers to the length of life (lifespan). Noteworthy, women generally live longer than men but also experience shorter health spans [4,5]. Multiple factors spanning an array of uncontrollable and controllable factors can contribute to the observed differences in both life and health span between men and women. In our review [6], we thoroughly assessed the available literature on the potential causes of sex differences in frailty among older adults.

Our review paper [6] in Experimental Gerontology, offers valuable insights into the causes of frailty among older adults - a multifaceted phenomenon comprised of physical, physiological, psychological and social dimensions - particularly emphasizing the significance of sex differences. Frailty, which is negatively associated with the health span [7], is characterized by increased vulnerability to stressors [8]. In an aging population where frailty is very prevalent and poses significant challenges to health and well-being, understanding how frailty manifests differently between men and women is crucial for improving health outcomes and personalizing health interventions. Frailty results from a complex interplay of biological, epigenetic, psychological, social and lifestyle factors [6]. In our review, we mainly focused on demarcating factors contributing to sex differences in the health span of older adults. We diligently describe frailty complexity, detailing the key factors contributing to differences observed in frailty among the two sexes, which mainly entails increased frailty among older women. We highlighted the importance of considering sex-specific biological mechanisms, psychological and social determinants of health, healthcare utilization and daily habits and patterns (Figure 1) that can help understand and address frailty in the older population.

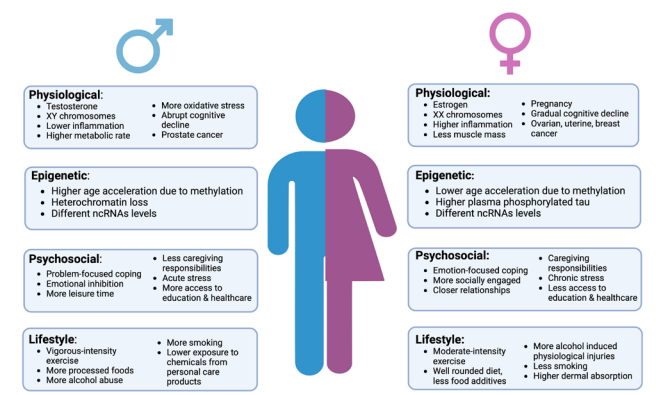

Figure 1: Differences in frailty determinants between men and women.

Review highlights

The physiological and biological underpinnings of sex differences in frailty were discussed, with an emphasis on how hormonal factors, genetic predispositions, and inflammatory pathways affect frailty trajectories in men and women. By delineating the role of sex hormones, particularly estrogen and testosterone, in modulating muscle mass, bone density, and immune function, we provided a comprehensive understanding of the physiological basis of sex-specific frailty risks. Notably, while the female hormone estrogen (decreases with age) can offer cardiovascular protection, low levels of the male hormone testosterone in older men have been linked to higher risk of developing cardiovascular diseases, as well as hormone replacement therapies [5,9-11]. Increased estrogen levels in women also delay age-related cognitive deterioration, leading to slower cognitive decline [12,13].

Furthermore, differences in the chromosomal makeup of each sex may play a role in longevity differences, as some inflammation-related genes are located on the X chromosome [14]. Since women have 2 copies of the X chromosomes and more expression of the X chromosome genes, this may contribute to the higher levels of inflammation observed in women [5,15]. Women also typically have higher fat mass and lower muscle mass, which may also contribute to increased levels of systemic inflammation [16,17]. In contrast, men often have higher muscle mass, are more physically active, and have a higher metabolic rate than women, all of which that can contribute to lower frailty with age [18,19]. This higher metabolic rate can increase oxidative stress, which could damage mitochondrial DNA, since men exhibit lower antioxidant gene expression, therefore potentially contributing to the shorter lifespan observed in males [20-22]. Moreover, men do not get pregnant, resulting in lower contributions to frailty, as pregnancy can

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Citation: Zeidan RS, Sykes S, Anton S (2024) Insights from Zeidan Et Al.'S Review: Sex Differences in Frailty among Older Adults. J Gerontol Geriatr Med 10: 213.

Received: May 30, 2024; **Accepted:** June 13, 2024; **Published:** June 20, 2024

accelerate the aging process [6,23]. Additionally, sex specific cancers may contribute to differences in frailty and some cancers affect one sex more than the other [24,25].

For epigenetics, distinct differences found in DNA methylation, histone modifications, nuclear architecture, and non-coding RNAs shape the aging process [26]. A study on epigenetic Age Acceleration (AA) found that men have higher AA than women due to differences in methylation patterns [27,28]. Epigenetic age acceleration is associated with both mortality and frailty [29]. Other epigenetic mechanisms that affect longevity are histone post-translational modifications, where women have been shown to have a higher baseline amount of plasma phosphorylated tau, a biomarker of frailty linked to faster cognitive decline in those with Alzheimer's disease [30,31]. In males, heterochromatin loss during aging may also lead to decreased longevity due to disproportionately mis-expressed heterochromatin on the Y chromosome [32]. Other epigenetic biomarkers, which serve as mediators of many age-related diseases including cardiovascular disease, neurodegenerative disease, and cancer, may help explain sex differences in frailty are non-coding RNAs (ncRNAs) [33-35]. These biomarkers have been found to be sex-specific and change with age, where plasma levels of certain ncRNAs were found to be different between men and women [36,37]. Specifically, ncRNAs involved in regulating pathways related to inflammation, oxidative stress, and muscle maintenance may exhibit differential expression between men and women [38-41].

We also critically examined the impact of social determinants of health on frailty, emphasizing the differential experiences of men and women in terms of socioeconomic status, caregiving responsibilities and access to healthcare. We highlighted the importance of recognizing and addressing gender disparities in social support networks, financial resources, and healthcare utilization, since these factors significantly influence frailty prevalence and outcomes. Additionally, we shed light on sex-specific patterns of healthcare utilization and healthcare-seeking behaviors among older adults. We showcased that disparities in preventive care, disease management, and rehabilitation services may contribute to differential frailty outcomes between sexes. For instance, some behavior differences that have been noted, are that women are more likely to be proactive about their health and medical appointments than men, leading to better health outcomes and early diagnoses [42,43]. Additionally, not having access to quality education may impact access to opportunities that could increase one's quality of life [44]. Women have traditionally had less access to healthcare and education than men, further increasing their risk of frailty and mortality [45]. Women are more affected by this due to the pay inequalities that exist and the fact that women do not receive as many benefits as men, leading to an increased risk of frailty [46]. Moreover, social engagement and close relationships with others is associated with better health and longevity and is seen more in women [47,48]. On the other hand, women tend to take on caregiving roles, which can provide positive and negative health impacts. Although caregiving can provide a sense of purpose and social support, caregivers are also at a higher risk of depression and other mood disorders, both of which can contribute to frailty [49]. By elucidating these disparities, we underscore the need for gender-sensitive healthcare policies and interventions aimed at promoting healthy aging and preventing frailty.

For lifestyle habits, choices such as exercising regularly and eating nutritious foods have a large impact on overall health and well-being, reducing the risk of frailty. Males take part in more vigorous-intensity physical activity, and women participate in more moderate-intensity physical activity [50]. While physical activity decreases in both sexes with age, women display a sharper decline than men [51], potentially contributing to an increase in frailty. In terms of dietary habits, women are more likely to adopt a well-rounded, nutritious diet and avoid processed foods and food additives [52,53]. Despite this, some studies found that overweight and obesity status are more prevalent in women than men, contributing to increased frailty [54]. Additionally, differences in alcohol consumption and smoking patterns exist between the two sexes, with men having a higher prevalence of smoking and alcohol abuse and women having more alcohol-induced physiological injuries [55-57]. Frailty differences between men and women can also influence sleep patterns, where women are known to develop more insomnia and sleep apnea with age, since both sexes display major differences in circadian rhythms and sleep patterns [58,59]. Further, sex differences in environmental exposures to toxic chemicals, with women usually having higher dermal absorption and higher accumulation of fat-soluble chemicals than men, along with differences in chemical metabolism and detoxification, can adversely affect health and increase the risk of frailty [60-62].

Information Applicability

Our review provides critical insights into sex differences in frailty among older adults, with significant applicability across various domains, mainly healthcare. Clinically, the information is invaluable for healthcare providers as all the evidence provided on the sex differences in frailty highlights the necessity of adopting sex-specific approaches to the prevention, assessment, and management of frailty. Understanding that men and women experience, and manifest frailty differently allows for more personalized and effective interventions, potentially improving outcomes and quality of life for older adults.

For caregivers, understanding sex differences in frailty can enhance care strategies, ensuring that they are more attuned to the specific needs of older men and women. For policymakers, the review provides evidence to support the allocation of resources and the development of policies that address sex-specific health disparities among the elderly. In public health, the information provided in our review can inform the design of community programs and policies. For instance, tailored health promotion and disease prevention strategies that consider sex-specific risk factors and protective factors can be developed. Programs targeting nutritional support, physical activity, and social engagement can be fine-tuned to address the distinct needs of older men and women, thus fostering healthier aging populations. Additionally, from a research perspective, the review highlights the importance of incorporating sex as a critical variable in studies on aging and frailty. Future research can build on these findings to explore underlying biological mechanisms and social determinants contributing to sex differences in frailty, in addition to their interplay. This can lead to more comprehensive and generalizable knowledge, potentially unveiling new therapeutic targets and intervention strategies.

Review Critique

Our review paper represents a significant contribution to the literature on frailty among older adults, providing a comprehensive analysis of sex differences in frailty prevalence, etiology and outcomes. Importantly, we elucidated the sex-specific manifestations of frailty to help better design potential interventions and preventive strategies.

By integrating physiological and biological, epigenetic, psychosocial, and lifestyle-related perspectives, we offer valuable insights that can inform targeted interventions and policies aimed at promoting healthy aging and mitigating frailty-related risks. This can also provide implications for clinical practice and healthcare policy, advocating for tailored interventions to address sex-specific frailty risks. By recognizing the heterogeneity of frailty experiences and adopting a personalized approach to care, healthcare providers can optimize outcomes for older adults of all sexes. Moving forward, further research is warranted to continue unraveling the complexities of frailty across sexes and to develop evidence-based strategies for enhancing the quality of life for older adults worldwide. Specifically, more research is needed on the sex differences in the interplay of different factors, including environmental, physiological and psychological factors.

Although the review was comprehensive and multifaceted, there are some limitations, other than mainly including research published only in English. Mainly, our review was narrative and did not include any meta-analysis of available data for the factors contributing to the sex differences in frailty in older adults. Additionally, we did not thoroughly discuss the impact of different cultural norms, beliefs, and practices on frailty perceptions and outcomes. Potentially, considering the effect of different cultures on frailty in men and women can provide insight into practices that might help mitigate frailty in older adults of the two sexes. Similarly, in our review we mainly focused on studies from certain geographical regions, possibly limiting the generalizability of findings, especially since people from different geographical areas may have different genetics, epigenetic, psychological perspectives and lifestyle habits that may impact how different factors affect their health span. Likewise, our review may lack sufficient discussion on how ethnic and racial diversity intersect with sex to influence frailty experiences.

The potential effects that environmental factors, such as neighborhood walkability, access to green spaces, and community resources, have in influencing frailty risks were not discussed. Additionally, the potential role of technology and digital health in sex differences in frailty was also not thoroughly discussed. Lastly, the combined effect of biological, psychological, and environmental factors could not be discussed in our review, due to the lack of current literature on how multiple axes can intersect to contribute to frailty risk in older adults.

Closing Remarks

Collectively, our review paper represents a seminal contribution to the literature on frailty among older adults, providing a comprehensive description of multiple factors contributing to sex differences in frailty. In essence, our review clearly depicts that many factors can contribute to the sex-related differences in frailty. These factors span from physiological, biological, genetic, epigenetic, psychosocial, environmental and lifestyle influences. Creating complex intervention to narrow these differences may increase the health span and decrease frailty in both men and women. Despite the current gaps of knowledge in the research available today, the information we displayed, reveals that the unique biological, psychological, behavioral, and social characteristics of both sexes should be considered when examining the differences in how frailty can affect older men and women differently. This approach emphasizes the importance of considering the cumulative effects of various exposures and experiences across an individual's lifespan, starting from early life, and continuing into old age. Moreover, methodological frameworks such as longitudinal studies are crucial, as they track different variables over time, providing robust data on how sex-specific factors evolve and interact to affect frailty. This comprehensive approach underscores the necessity for multifaceted interventions that address these sex-specific pathways, ultimately aiming to reduce the prevalence and impact of frailty in older adults.

Declaration of Competing Interest

The authors declare no competing interests.

Acknowledgment

This work has been supported by the Claude D. Pepper Center (P30AG028740) and a training grant from the National Institute on Aging (T32 AG062728) for Dr. Zeidan's contribution. Model figure was created using BioRender.com.

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