Risk of frailty in older women dependent on multisystem abnormalities

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A study published online ahead of press in the Gerontology Society of America's *Journal of Gerontology: Medical Sciences* reports that the condition of frailty in older adults is associated with a critical mass of abnormal physiological systems, over and above the status of each individual system, and that the relationship is nonlinear. This research is the first evidence that frailty is related to the number of abnormal physiological systems, rather than a specific system abnormality, a chronic disease, or chronological age. It suggests significant alterations in system biology with aging, and underlying frailty. Clinical implications are that prevention and treatment may be more likely to be effective if any given intervention improves multiple systems, not just one.

According to the report, three or more systems at abnormal levels were significant predictors of being frail, and the dominating predictor was the number of systems abnormal, not any particular system. The study was based on data of women aged 70 - 79 years from the Women's Health and Aging Studies I and II and assesses the association of eight physiological measures with frailty. Abnormality in each system (anemia, inflammation, insulin-like growth factor-1, dehydroepiandrosterone-sulfate, hemoglobin A1c, micronutrients, adiposity, and fine motor speed) was significantly associated with frailty status. However, adjusting for the level of each system measure, the mean number of impaired systems significantly predicted frailty; only one system, fine motor speed, remained an independent predictor when the mass of systems abnormal was considered.

The data indicate that half of those frail had three or more systems at abnormal levels, compared with 25% of the pre-frail and 16% of the non-frail. Less than 21% of the frail had zero or one system abnormal (of eight).

Frail older adults are a group at increased risk of serious adverse clinical outcomes, including mortality, disability, falls, and loss of independence. Through the work of Dr. Fried and her colleagues at Johns Hopkins University, frailty has been defined to function as a distinct medical syndrome, which is clinically recognizable when a critical mass of symptoms and signs emerge. Frailty is recognized as the concurrent presence of three or more of the following: low strength, low energy, slowed motor performance, low physical activity, or unintentional weight loss. The findings outlined in the current paper build on Dr. Fried's body of work around frailty, and have significant applicability for the design of therapeutics, such as new drugs.

"We found that the likelihood of frailty increases in relationship to the number of abnormal physiological systems, and the number of abnormal systems was strongly predictive of the likelihood of frailty, whereas the individual systems were not," says Linda P. Fried, MD, MPH, dean and DeLamar Professor of Public Health at the Columbia University Mailman School of Public Health and lead author. She adds, "It further suggests that therapeutic replacement of any one deficient system, such as testosterone, estrogen, or growth hormone, is unlikely to ameliorate or prevent frailty, unless it improves multiple physiologic systems. This may explainthe public health import of remaining physically active as we get older, since activity improves many aspects of biology and health."

Given that many of the physiological systems evaluated affect or regulate each other, alteration of one may not be independent of another. These data suggest that acceleration of the likelihood of frailty may occur as the number of abnormal systems escalates, and suggests that

there could be a threshold beyond which there is an adverse downward spiraling nature to the progression of frailty and its consequences. "The systems studied here have numerous physiological interconnections with each other," says Dr. Fried, "which would be consistent with the concept of 'majority rules' in systems biology—that past a critical level of dysregulation in physiological systems, the impaired systems may adversely affect other systems functioning at a normal level and bring the whole system to a more dysregulated state, with frailty as an outcome of a dysregulated complex system."

"This research provides evidence of the interaction of a number of factors that contribute to frailty in older people," said Richard Suzman, PhD, director of the Division of Behavioral and Social Research at the National Institute on Aging, which funded the research. "It emphasizes the importance of considering frailty holistically."

The number of chronic diseases was also a predictor of frailty, independent of the number of physiological systems at abnormal levels. This supports frailty as a final common pathway of multiple causes and that the burden of disease is a factor as well as aging-related physiological dysregulation.

More information: *J Gerontol A Biol Sci Med Sci*. doi:10.1093/gerona/glp076.

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