

Frailty as an Outcome in Geriatrics Research: Not Ready for Prime Time?

Frailty, one of the key syndromes of aging, is defined as a state of decreased physiologic reserve and increased vulnerability to stressors, such as acute illness, injury, or surgery. During the past several decades, frailty has been increasingly recognized as a strong predictor of poor outcomes, including acute care use, disability, and death, in older adults (1). For this reason, developing interventions to prevent or delay frailty and its associated adverse outcomes is an emerging area of geriatrics research.

Despite this growing focus, no single, universally accepted definition of frailty exists. Rather, several definitions are commonly used, each of which takes a different approach to capturing the key feature of decreased physiologic reserve (2, 3). Although these definitions differ, each has been shown to have similar predictive power for identifying older adults at highest risk for poor outcomes (1). This tension points to a key issue in frailty research: Although the role of frailty as a predictor is well-established and increasingly used to inform clinical care, its core definition—and by extension, its role as an outcome—is still evolving.

Because the defining feature of frailty is decreased physiologic reserve, physical activity is regarded as one of the most promising interventions for preventing or ameliorating frailty (4). By improving endurance and lean muscle mass, exercise is hypothesized to reduce frailty and, more important, prevent the adverse consequences of frailty, such as loss of independence in activities of daily living and loss of mobility (4). An increasing number of studies have tested this hypothesis by examining whether physical activity prevents disability among frail older adults (5, 6). Findings from these studies are mixed, possibly because they used varying definitions of frailty and did not always define frailty by using validated criteria (5, 6). A smaller number of studies have examined whether physical activity reduces the risk for frailty and also have shown inconsistent findings (7, 8).

In their current *Annals* article, Trombetti and colleagues (9) address some of these previous inconsistencies by using data from the LIFE (Lifestyle Interventions and Independence for Elders) trial. This study was a large, multicenter, single-blind, randomized controlled trial comparing the effect of a long-term physical activity program with that of a health education program on the incidence of major mobility disability (MMD) among sedentary older adults (10). The study's main findings showed that the physical activity intervention reduced MMD during an average follow-up of more than 2.5 years (10). In this secondary analysis of the LIFE data, Trombetti and colleagues asked the following 2 questions: Is the LIFE intervention equally effective in reducing MMD in both frail and nonfrail per-

sons, and is it associated with a lower risk for frailty, defined according to a commonly used frailty index?

For the first question, the authors found that baseline frailty status did not influence the beneficial effect of physical activity on the incidence of MMD. Rather, the LIFE intervention was equally effective in reducing MMD among both frail and nonfrail people. This is an important point for clinicians to take away, because we sometimes have concerns about the safety or efficacy of prescribing exercise for our frail older patients. However, these findings suggest that we should not use frailty as a reason not to prescribe activity but should prescribe physical activity to all of our older patients, regardless of frailty status.

For the second question, the authors found that the effect of the physical activity intervention on preventing or delaying frailty was inconsistent and unconvincing. Although 1 submeasure of the frailty index improved as measured by the full frailty index, the overall risk for frailty did not differ between the physical activity and health education groups. This finding seems surprising given the clear and compelling effect of the LIFE intervention on reducing the risk for MMD. Frailty generally precedes the downstream outcomes of disability and loss of independence in older persons, and frailty, as a measure of physiologic reserve, often is used to identify persons at high risk for adverse outcomes, such as MMD. For most patients, the value of preventing frailty rests on the assumption that preventing this intermediate outcome will prevent or delay disability (1). Of interest, this investigation showing that the LIFE intervention did not prevent frailty was a post hoc analysis conceived after the LIFE study was completed. However, it would have been quite logical for the LIFE team to assess the effect of LIFE on this measure of frailty before committing to the very resource-intensive full study. Yet, this very logical approach of assessing the intermediate outcome of frailty as proof of concept would have been unfortunate, because we would have never learned of the highly beneficial effects of the LIFE intervention in preventing MMD.

These findings raise a key, larger question: Is frailty ready for a role as an intermediate outcome in geriatrics research? The use of frailty as an intermediate outcome has considerable appeal, because studies focused on frailty often require less time and expense than those focused on the more downstream outcome of disability. The frailty measure used in this study represents just one of several commonly used criteria. Yet, the results of smaller, previous studies examining the effect of physical activity on other frailty measures also have shown inconsistent results (7, 8). We know that current measures of frailty are highly effective in predicting the risk for poor outcomes. However, the find-

ings from this and previous trials suggest that as defined, these frailty measures may not yet capture the core feature of decreased physiologic reserve in a way that can be used as a meaningful intermediate outcome.

Our understanding of the basic mechanisms of frailty is continuing to evolve (1). As this understanding grows, frailty may play an increasingly important role as an intermediate outcome that can elucidate the basic mechanisms by which physical activity improves mobility and functioning among older adults. In the meantime, a continued focus on patient-centered outcomes that directly correspond to improved quality of life for patients—such as mobility and function—is warranted. We thus argue that for now, frailty remains a powerful predictor of patient-centered outcomes but is not yet ready for a role as a full-fledged outcome measure in geriatrics research.

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Disclosures: Authors have disclosed no conflicts of interest. Forms can be viewed at www.acponline.org/authors/icmje/ConflictOfInterestForms.do?msNum=M17-3048.

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Ann Intern Med. 2018;168:361-362. doi:10.7326/M17-3048

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