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Frailty as an outcome in geriatrics research: not ready for prime time?

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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. Over the past several decades, frailty has been increasingly recognized as a strong predictor of poor outcomes among older adults including acute care utilization, disability, and death (1). For this reason, developing interventions to prevent or delay frailty and associated adverse outcomes is an emerging area of geriatrics research.

Despite this growing focus on ameliorating frailty, there is still no single universally accepted definition of frailty. Rather, there are several commonly-used ways of defining frailty, each of which uses a different approach to capture the key feature of decreased physiologic reserve (2, 3). Although these definitions differ, each has been shown to have comparable predictive power for identifying older adults at highest risk for poor outcomes (1). This tension points to a key issue in frailty research: while frailty's role 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, it is hypothesized that exercise may improve frailty, and more importantly, prevent the adverse consequences of frailty such as loss of independence in activities of daily living and loss of mobility (4). A growing 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 these studies used varying definitions of frailty, and also did not always define frailty using validated criteria (5, 6). A smaller number of studies have examined whether physical activity reduces the risk of developing frailty, and have also shown inconsistent findings (7, 8).

In this issue, Trombetti and colleagues (9) set out to address some of these previous inconsistencies using data from the Lifestyle Interventions and Independence for Elders (LIFE) trial. The LIFE trial was a large, multicenter, single-blind, randomized controlled trial that compared the effect of a long-term physical activity program with a health education program on the incidence of major mobility disability among sedentary older adults (10). In its main findings, the LIFE intervention was found to reduce major mobility disability over an average follow-up of more than two and a half years (10). In this

secondary analysis of the LIFE data, Trombetti and colleagues ask two questions: Is the LIFE intervention equally effective in reducing major mobility disability in both frail and non-frail people? And is the LIFE intervention associated with a lower risk of frailty, defined using 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 major mobility disability. Rather, the LIFE intervention was equally effective in reducing major mobility disability among both frail and non-frail people. This is an important point for clinicians to take away, because we may 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. Rather, we 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. While one sub-measure of the frailty index improved, the overall risk of frailty as measured by the full frailty index 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 of major mobility disability. Frailty generally precedes the downstream outcomes of disability and loss of independence in older persons, and frailty, as a measure of physiologic reserve, is often used to identify persons at high risk of adverse outcomes such as major mobility disability. For most patients, the value of preventing frailty rests on the assumption that preventing this intermediate outcome will prevent or delay disability (1). Interestingly, this analysis 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 impact of LIFE on this measure of frailty before committing to the very resource-intensive full study. And yet this very logical approach of assessing the intermediate outcome of frailty as proof-of-concept would have been unfortunate, as we would have never learned of the highly beneficial effects of the LIFE intervention in preventing major mobility disability.

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, as studies focused on frailty often require less time and expense than studies focused on the more downstream outcome of disability. The frailty measure used in this study represents just one of several commonly-used measures. Yet the results of smaller previous studies examining the impact of physical activity on other frailty measures have also shown inconsistent results (7, 8). We know that current measures of frailty are highly effective in predicting the risk of poor outcomes. However, the findings from this and previous trials suggest that as currently 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 still not ready for a role as a full-fledged outcome measure in geriatrics research.

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