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Steps in the right direction for physical frailty research

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In this issue of *The Lancet Digital Health,* Rongtao Jiang and colleagues[1] present a broad and well powered observational study of the correlates of physical frailty among nearly half a million middle-aged and older adults in the UK Biobank. Using a modification of the Fried frailty phenotype[2] (based on weakness, walking speed, inactivity, exhaustion, and weight loss), the strongest correlates of participants' mainly self-reported frailty status were other aspects of self-reported health and wellbeing, as well as neuroticism, anxiety, and depression. Importantly, many of the associations reported were of relatively small effect size. These results were similar between the sexes and across much of the age range, with the exception of mental health measures, which were more strongly associated with frailty in middle age than in older adults. In longitudinal analyses, stronger associations were found between baseline health (particularly mental health) and frailty measured 9 years later than for the converse specification. The results also show widespread but small brain structural correlates of frailty, which mediated less than 2% of the association between physical frailty and the top ten frailty-related phenotypes.

This study is a valuable and definitive characterisation of physical frailty and its relation to other aspects of health in UK-based middle-aged and older adults. The strengths include the large sample size, extensive multimodal analyses, follow-up information, and overall analytical approach—not least because small sample sizes and heterogeneity in the measurement of frailty, exposures, and correlates has made synthesis of the current literature challenging. Exploiting the exceptional statistical power in this setting has largely negated multiple testing concerns as extremely small effects can be reliably detected, even when hundreds of tests are conducted and after correction. This power allows focus on relative effect sizes, bringing into sharper focus those factors that are most closely associated with physical frailty.

The UK Biobank is well known to be a range restricted sample,[3,4] but it might be more likely that the severity and magnitude of associations are underestimated relative to the overall population.[4,5] The range restriction in this cohort could also partly underpin the absence of age-related differences in the patterning of association with other variables: highly similar patterning of the associations of frailty with 325 health-related outcomes were seen when comparing 45–60-year-olds with people older than 60 years. These findings, as Jiang and colleagues point out, set the scene for future, more detailed operationalisation of physical (and other forms of) frailty—as both global scores and as individual facets—and their health correlates at different times of life.

Such future work will be important since the field of frailty is fragmented due to debate over frailty definitions. Consequently, no gold standard frailty assessment tool exists at present.[6] These fundamental disagreements have led to a field of research with substantial heterogeneity in research methods, which obviates a clear picture.[7] This heterogeneity becomes a particular issue when researchers conflate different subtypes of frailty (eg, physical frailty *vs* multidimensional frailty) despite evidence of important distinctions.[6] Accordingly, it is welcome that Jiang and colleagues are specific about the subtype of frailty that they are investigating. The field would benefit from extending the well powered multimodal approach[1] to quantify predictors and correlates of several frailty measures, so as to better characterise the meaning and unique value of differing constructs.

This,[1] other,[7] and future such studies could also provide a rational basis upon which to develop risk identification and prevention strategies in midlife (eg, routine screenings). The use of self-reported information for most of the frailty indicators might be seen as a drawback (Jiang and colleagues correctly state that there is room for validation against objective scales). Yet they report informative external validity of this self-reported scale across a wide array of measures: it correlates with many brain and health phenotypes, including precursors. This external validity might indicate valuable potential for efficient, less burdensome collection of information to identify current and future risk in research and clinical settings.

Frailty research is fraught with deep-rooted inconsistency, partly stemming from the conflation of results using differing definitions and methodologies. Jiang and colleagues have taken a valuable step towards a more consistent body of physical frailty research by

using a large, multidimensional dataset and testing associations across many health variables. Their work indicates how pervasively frailty is correlated across health and wellbeing (albeit with modest effect sizes), and raises new prospects and motivates new questions surrounding the discriminant validity of multiple frailty constructs and replication in other well powered cohorts across geographies and ancestries. Ultimately, these advancements will pave the way for improved health outcomes and quality of life for older adults.

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