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Letter to the Editor

RESPONSE TO DR. MITNITSKI'S AND DR. ROCKWOOD'S LETTER TO THE EDITOR: BIOLOGICAL AGE REVISITED

Morgan E. Levine

Davis School of Gerontology, University of Southern California, Los Angeles.

Address correspondence to Morgan E. Levine, BA, Davis School of Gerontology, University of Southern California, Los Angeles, CA 90089-0191. Email: canon@usc.edu

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I thank Dr. Mitnitski and Dr. Rockwood for their comments about my study in the Journal of Gerontology: Biological Sciences (1), and the opportunity to clarify some points. The study compared how well two of the most commonly used techniques for estimating biological age—multiple linear regression (MLR) and principal component analysis (PCA)—and a newly proposed method (2), predict mortality in contrast to using information on chronological age alone. Results showed that the biological age algorithms did a better job at predicting mortality than did chronological age, and overall the newer method—based on an algorithm by Klemera and Doubal—seemed to perform the best (1). In their letter, Mitnitski and Rockwood state, "The results showed relatively good performance in term of the AUC of all models (superior to [chronological age] but with no significant difference between most algorithms)." Although the paper did only provide p values for the comparison of the various biological age algorithms with chronological age, compared with one another, the Klemera and Doubal method (KDM) did predict mortality significantly better ($p < .05$) than both MLR and PCA.

There are a number of other methods that have been proposed for estimating biological age—one of which is the frailty index, developed and advocated by Mitnitski and Rockwood (3). The exclusion of this method from my original paper was based on a number of factors. First, the algorithms selected were all calculated using the same set of continuously measured biomarkers. This was done to ensure that the methods used to calculate biological age, rather than the measures being used, were what was driving results. Overall, the biomarkers being used were carefully selected using information from previously published work looking at biomarkers of aging, as well as quantitative techniques.

On the other hand, the frailty index as described by Mitnitski and Rockwood cannot be calculated using such continuous measures, given that it relies on counts of self-reported conditions (3). The use of dichotomous measures do not make as much theoretical sense for estimating biological age, since aging is a continuous process and not merely the accumulation of conditions. Rather, cumulative deficits may (in the best scenarios) serve only as a proxy for the progressive deterioration and dysregulation, which accompanies the aging process. Furthermore, Mitnitski and Rockwood point to the assertion I made that such methods "may not be useful in examining young- or middle-aged adults." However, the reason is not "because [biological age] had been derived in an older population (age 65+ years)," but rather physiological changes associated with accelerated aging may be present in younger adults; however they may not have contributed as of yet to a condition and therefore would not be detectible using a deficit accumulation approach.

The frailty index typically relies on deficits such as disability (activities of daily living and instrumental activities of daily living, cognitive problems, hearing problems, vision problems), chronic conditions (asthma, cancer, migraines, heart disease, cataracts, glaucoma), and psychosocial/mental health conditions (depression, feelings of hopelessness, unhappiness) (4), which in a population younger than 40 years, may represent something other than age-related decline. Although the frailty index may detect at-risk individuals in younger populations (4), this may not be "aging," but rather a result of non-aging-related genetic or environmental factors. For this reason, it may be useful to see if the distributions of deficits that contribute to persons being classified as "frail" or "most frail" differ by age. For instance, do "frail" individuals in their 80s share the same deficits as "frail" individuals in their 20s and 30s? Finally, measures such as the frailty index, which rely on current conditions, may not be useful for future studies interested in predicting disease incidence in a relatively healthy population, and therefore, methods that utilize continuous physiological measures may be needed.

Mitnitski and Rockwood also argue that, "For now, how the methods for estimating [biological age] presented by Levine will perform in other databases is not clear. What should be evident, however, is that their application in other datasets will require recalculation of the weights which they employ; this level of precision is unlikely to be generalizable, even for biomarkers." Although this may be true, the authors state that the calculation of the frailty index is also data dependent and estimated using regression techniques—suggesting that the equations for both the frailty index and KDM would have to be recalculated for different samples. Finally, given that the equation and weights for KDM were calculated using a large nationally representative sample (1), there is little reason to believe that they will be any less consistent across databases than is the frailty index.

Lastly, Mitnitski and Rockwood suggest that biological age and other estimates of individual health status should incorporate a systems biology approach beyond the mere application of statistical algorithms. The biomarker measures that I selected to include in the various calculations of biological age were derived from multiple biological systems described in my article as follows: "The 21 biomarkers considered in our analysis can be classified into seven domains: (1) Metabolic Function—glycated hemoglobin, total cholesterol, and high-density lipoprotein; (2) Cardiac Function—systolic blood pressure, diastolic blood pressure, and pulse; (3) Lung Function—forced expiratory volume; (4) Kidney Function—serum creatinine and serum urea nitrogen; (5) Liver Function—serum alkaline phosphatase and serum albumin; (6) Immune Function and Inflammation: C-reactive protein, cytomegalovirus optical density, lymphocyte percent, mononuclear percent, and granulocyte percent; and (7) Cell Blood Count—white blood cell count, red blood cell count, platelet count, hemoglobin, and hematocrit" (1). I agree with Mitnitski and Rockwood that a systems biology approach is important, and in moving forward, algorithms need to incorporate interactions between various systems/levels, which may rely on more advanced computational techniques—such as machine learning. Furthermore, with the introduction of new and improved biomarkers, along with a more specific and agreed upon definition of "biomarkers of aging," our ability to measure biological age should improve over time. Nevertheless, biological age measures that incorporate continuous physiological measures and their associations with one another are more in line with systems biology than those that utilize counts of self-reported conditions.

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References

1. Levine ME. Modeling the rate of senescence: can estimated biological age predict mortality more accurately than chronological age? *J Gerontol A Biol Sci Med Sci*. 2013;68:667–674.
2. Klemera P, Doubal S. A new approach to the concept and computation of biological age. *Mech Ageing Dev*. 2006;127:240–248.
3. Mitnitski AB, Mogilner AJ, Rockwood K. Accumulation of deficits as a proxy measure of aging. *ScientificWorldJournal*. 2001;1:323–336.
4. Rockwood K, Song X, Mitnitski A. Changes in relative fitness and frailty across the adult lifespan: evidence from the Canadian National Population Health Survey. *CMAJ*. 2011;183:E487–E494.