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The use and misuse of 'biological aging' in health research

By M. Arfan Ikram

Biological aging clocks are flawed concepts in understanding disease.

'There is no such thing as aging,' wrote Peto and Doll in 1997, arguing that old age is merely associated with disease, but does not cause it[1]. Fast forward 27 years and there has never been more interest in understanding individual aging as a driving cause of disease, in part enabled by emerging -omics technologies. This interest originates from the observation that among people with the same calendar age, some may have more age-related diseases than others. An explanation for this discrepancy is that calendar age and biological age may be two distinct entities.

A plethora of aging clocks has been developed that claim to capture this 'biological aging' process with names such as MethylAge, MetaboAge or BrainAge that reflect the -omics data they are based on. Aging clocks share a similar conceptual framework: a prediction model for calendar age is trained on -omics data and then applied on a new dataset to calculate predicted age. This predicted age, often termed the biological age, is contrasted against calendar age in subsequent analyses and is thought to reflect biological aging. However, I argue that there are several underappreciated pitfalls in the proper interpretation of these clocks.

The value of aging clocks to capture biological age depends on the accuracy of the prediction model[2]. For instance, there is a strong association between age and Alzheimer's disease. If an algorithm perfectly predicts calendar age, then the biological age will equal calendar age and thus have no added value for prediction of Alzheimer's disease. In the other extreme, if the prediction algorithm simply generates random numbers, the biological age again will have no added value. It seems that biological clocks only provide information if their underlying prediction model contains noise and is thus imperfect. How this noise can be distinguished from any possible biological information remains unclear.

A more fundamental question relates to the concept of aging itself. Calendar age can be seen as a single snapshot within the ongoing passage of time. But is aging, measured either by the calendar age or using aging clocks, itself a cause of disease? Interestingly, theoretical models of causality typically do not consider passage of time as a cause of disease, but instead as a separate underlying process, upon which causes and effects are connected to each other and thereby gain meaning[3]. In line with this interpretation, recent work has shown that a reliable aging clock can be constructed by simply counting the number of randomly generated stochastic variations that have accumulated over a given period[2]. Here too, aging (the passage of time) does not contain any biological information per se and is therefore not a cause but is merely a summary measure that reflects the number of variations accumulated up until that point.

From a clinical perspective, this means that older people do not have a higher risk of age-related diseases, such as Alzheimer's disease, simply because they are old, but instead because they have accumulated more real causes of disease, as compared with younger people, who have had less passage of time to accumulate a similar number of causes.

The same reasoning also holds for other disease, such as more accumulation of DNA-damage in old age and higher risk of cancer or accumulating vascular damage and risk of heart disease.

Calendar age is best comparable to a propensity score, a summary measure of several confounders, which can be used in regression models when it is impractical to adjust for every confounder separately. As with propensity scores, calendar age should not be studied as a primary exposure of interest in etiological studies, because neither allows for proper causal interpretation. Instead, calendar age is ideal for confounding control.

Notably, clocks based on stochastic variation correlate strongly with clocks based on variations in biologically meaningful -omics data[2]. This suggests that, even though specific individual -omics variations may be actual causes of specific diseases, the summary measure of these -omics variations (the biological aging clock) does not contain any more information than stochastic variation. Therefore, biological aging clocks should also be treated as propensity scores, a tool for confounding control, but should not be used as primary exposure of interest or be interpreted within a causal framework.

Practically speaking, my recommendation is that studies aimed at understanding causes and mechanisms of age-related diseases should not focus on constructing new and more accurate biological aging clocks, but instead should investigate the proper underlying causes of such diseases. If at all, the biological aging clock may be used in such studies for confounding control, when adjusting for calendar age is insufficient. It seems the recommendation by Peto and Doll was correct after all, namely when studying mechanisms of disease to avoid 'careless use of such an undefined physical concept as the "aging" of … an individual'[1].

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Competing interests
The author declares no conflicts of interest.