AGING &CARDIOMETABOLIC DISEASE

News & Views

Biological ageing as a predictor of cardiometabolic multimorbidity

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Standfirst

Biological ageing impairs functional and structural properties of cells and tissues, rendering individuals more susceptible to various diseases. Based on recent analyses of observational data involving 340,000 UK Biobank participants, individuals with a biological age higher than that of their same-aged peers have an elevated risk of developing cardiometabolic diseases. In contrast, the ability of accelerated biological ageing to predict multimorbidity progression is relatively limited.

The burden of chronic conditions increases with population ageing, but age-standardised rates have decreased over time. The declining trend has been particularly significant for cardiovascular diseases, such as ischaemic heart disease and stroke. A preventive approach that identifies at-risk groups long before clinical disease has been one of the key contributors to this achievement. It has enabled timely intervention and subclinical prevention. [1] For decades, the multifactorial Framingham score has served as a valuable tool in this regard. The prediction algorithm, incorporating age, gender, diabetes, blood pressure, total

cholesterol, HDL-cholesterol, and smoking data, estimates an individual's absolute 10-year disease risk. A corresponding risk algorithm calibrated for European populations is SCORE2.

However, as modern medicine, technology, and public health practices have advanced, more people are surviving long enough to develop multiple long-term health conditions, known as multimorbidity.[2] Cardiometabolic multimorbidity, for example, includes conditions like type 2 diabetes, in addition to cardiovascular disease. Research conducted by the Emerging Risk Factors Collaboration has shown that the increase in mortality rates with combinations of cardiometabolic diseases is multiplicative.[3] This emphasizes the need to broaden the scope of research on predictive algorithms beyond individual disease endpoints.

In this edition of *Nature Cardiovascular Research*, Jiang and colleagues report a study investigating prediction of cardiometabolic multimorbidity.[4] Such inquiries face at least three major challenges. First, as cardiometabolic multimorbidity includes diseases with only partially overlapping causes, it is crucial to identify shared risk predictors or create a multifactorial algorithm with strong non-shared predictors for each individual disease. Second, risk predictors should be applicable at each health transition, spanning from a healthy state to an individual disease and eventually to multimorbidity. Given that the most effective predictors may change during the disease aetiology and progression, the task of predicting multimorbidity presents greater difficulty than predicting a single disease. Third, adding a further layer of complexity, in cardiometabolic multimorbidity, conditions may not follow a specific sequential order. Thus, the predictive performance of a risk predictor may vary depending on the sequence in which metabolic and cardiovascular diseases develop. Obesity, for instance, is a strong predictor of diabetes leading to cardiovascular disease, but

it is a much weaker predictor for cardiovascular disease progressing into diabetes, reflecting differential underlying mechanisms and heterogeneity in cardiometabolic multimorbidity. [5]

To tackle these challenges, Jiang et al. centered their approach on biological ageing, considering it a unifying major risk factor across different cardiometabolic diseases and health transitions. Biological ageing significantly impairs the functional and structural properties of cells, rendering individuals more susceptible to various diseases (**Fig. 1**). [6] Importantly, several mechanisms of ageing at the cellular level are shared among type 2 diabetes, ischaemic heart disease, and stroke, making biological ageing a promising candidate for predicting cardiometabolic multimorbidity. These include, for instance, telomere attrition, deregulated nutrient sensing, stem cell exhaustion and altered intercellular communication. [7]

The study, based on over 340,000 participants of UK Biobank, measured biological ageing using two validated multifactorial algorithms: the Klemera-Doubal method biological age (KDM-BA, including lung function, systolic blood pressure, and 7 blood biomarker) and PhenoAge (chronological age plus 9 blood biomarkers). Although these measures correlated rather weakly with each other (correlation coefficient = 0.14), both indicators showed associations with all health transitions, indicating their potential as predictors.

Jiang and colleagues then employed C-statistics to assess and compare the predictive efficacy of biological age with that of established risk predictors such as the Framingham algorithm and SCORE2. [4] C-statistics, in this context, measures the probability that a randomly selected individual who experiences cardiometabolic disease or multimorbidity possesses a higher biological age score than a randomly selected individual who does not experience those outcomes. A C-statistics value of 0.50 signifies a predictor with no capacity

to differentiate between low- and high-risk individuals, while a score of 1.00 indicates flawless discrimination between these two groups.

For KDM-BA and PhenoAge, the C-statistics were 0.70 and 0.71, respectively, when predicting the initial cardiometabolic disease but decreased to 0.59 and 0.61 for predicting the transition to cardiometabolic multimorbidity. Interestingly, established risk scores like the Framingham score and SCORE2 also had low C-statistics when predicting cardiometabolic multimorbidity (both 0.58). This suggests that predicting multimorbidity is inherently challenging, possibly in part due to the influence of disease-modifying treatments. [8]

While the study by Jiang et al. holds promise, [4] caution should be exercised when drawing conclusions about its clinical utility. For a prediction model to guide clinical decisions, a threshold for high risk must be defined. Furthermore, measures such as the detection rate, false positive rate, and the ratio of true-to-false positives should be evaluated, in addition to C-statistics. Finding the right balance between detection and false-positive rates is crucial. Maximising detection is the aim when considering effective low-cost interventions with a known lack of negative side effects. Conversely, a low false-positive rate becomes the priority when dealing with expensive or novel interventions that may have harmful side effects or less comprehensive evidence on safety profiles.

Future research avenues should explore more accurate ageing measures linked specifically to cardiometabolic diseases and their progression to multimorbidity. The two measures of ageing used by Jian et al are aggregates of several biomarkers; it would be interesting to see the components of these measures analysed separately as predictors of health transitions. Furthermore, recent advancements in proteomics present exciting opportunities, allowing for a quick and minimally invasive quantification of thousands of

proteins in single blood samples. [9 10] This innovation opens the door to identifying accelerated ageing in individual vital organs, including liver, kidneys, heart, arteries and other organs critical for cardiometabolic health, thereby providing potentially more accurate predictors of cardiometabolic multimorbidity. [11] Biological ageing does not only vary between individuals, but also between organs within an individual. This deeper understanding could pave the way for better strategies to identify at-risk groups, delay progression to multimorbidity, and enhance treatment options. The study by Jiang and colleagues represents a significant step forward, [4] but further investigation is needed to fully harness the potential of biological age in predicting cardiometabolic multimorbidity and improving patient outcomes.

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Fig 1 | **Biological ageing and the development of cardiometabolic multimorbidity**. In addition to genetic, environmental and behavioural factors, and comorbidities, cellular mechanisms of biological ageing significantly contribute to the transition from a healthy state to a clinical cardiovascular or metabolic disease. Subsequent disease complications and multiorgan deterioration caused by advancing atherosclerosis increase the risk of progressing to cardiometabolic multimorbidity. Due to disease-modifying therapies and other factors, biological ageing is a weaker predictor of multimorbidity than the development of initial cardiovascular or metabolic disease. In addition, there is a reciprocal association between biological ageing and cardiometabolic health, suggesting that the disease process and disease-modifying treatments may affect the pace of ageing.

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Competing interests

The authors do not declare any conflict of interest.