Digital biomarkers of ageing for monitoring physiological systems in community-dwelling adults

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Digital health technologies are transforming health care and personal health management by providing quantifiable data on physiological, behavioural, and environmental health parameters using digital biomarkers. This narrative review classified, characterised, and evaluated digital biomarkers of ageing across ten physiological systems to explore the applications of these biomarkers in research and clinical practice. The systematic search identified minimally invasive or non-invasively measured digital biomarkers suitable for longitudinal studies and practical use by community-dwelling adults. The digital biomarkers were classified according to their physiological system, characterised by their capture methods, and evaluated based on the following criteria: validity (age-associated, function-associated, and mortality-associated), generalisability, responsiveness to interventions, associations with clinical outcomes, and cost-effectiveness in large-scale settings. Digital biomarkers of ageing were found across eight physiological systems. Registered clinical trials that used these digital biomarkers as outcomes were also identified. Continued research and technological advancements are crucial for maximising the potential of digital biomarkers in promoting healthy ageing and longevity.

Introduction

The Biomarkers of Aging Consortium defines biomarkers of ageing as quantitative parameters in an organism that can predict biological age.[1] Biological age refers to the extent of ageing-related molecular and cellular damage that has occurred in an individual (as opposed to chronological age, which indicates the passage of time since birth). Ideally, biomarkers of ageing also feature the ability to track changes in biological age in response to interventions promoting healthy ageing and longevity.[1] Biomarkers of ageing can be categorised as molecular (eg, specific molecules or omics),[1,2] physiological (eg, functional performance or physical characteristics),[3,4] or digital (derived from wearable or non-wearable technologies).[5] The Biomarkers of Aging Consortium has developed a framework for characterising and classifying biomarkers of ageing, which can be used as predictive or prognostic biomarkers, response biomarkers, surrogate endpoints, or discovery biomarkers in clinical trials on anti-ageing and longevity.[1] Among such biomarkers, molecular[2] and physiological[3,4] biomarkers of ageing have been extensively studied; however, digital biomarkers of ageing have received considerably less attention. Thus, an in-depth exploration is necessary to completely understand the potential and applications of digital biomarkers in the context of ageing, longevity interventions, and precision geromedicine.[6]

Technological advancements have driven the rise of digital health technologies, including biosensors and telemedicine platforms.[7] Innovations, such as wearable fitness trackers and health-data collection apps, have not only enhanced patient outcomes[8] but also provided valuable insights for research[9] and helped individuals better understand their health status, which might in turn prompt them to seek professional care for continuous health management.[10] Digital phenotyping refers to the generation of data by digital health technologies.[11] When digital phenotypes are associated with health outcomes, they are identified as digital biomarkers: objective, quantifiable indicators[12] of physiological, behavioural, and environmental parameters relevant to health, disease progression, and responses to interventions.[5] Digital biomarkers offer unique advantages by supplementing traditional in-clinic assessments with continuous, real-world monitoring, capturing day-to-day variations in natural settings over time.[13] Such advantages are especially valuable for community-dwelling adults, as digital biomarkers enable the monitoring of ageing trajectories in non-clinical environments, in which most ageing-related changes occur and ongoing clinical oversight might be low. Continuous tracking is crucial for measuring changes associated with ageing, thus helping individuals to optimise health and extend their health span. However, the utility of digital biomarkers can be constrained by issues of validation, standardisation, and data integrity, as well as ethical and data privacy concerns that require careful consideration. Addressing these limitations, including potential biases, and ensuring equitable access, are crucial for the successful and responsible integration of digital biomarkers of ageing into routine clinical practice. This narrative review aims to classify, characterise, and evaluate digital biomarkers of ageing by exploring their potential to measure biological age and their applications in clinical trials and health-care practice, including precision geromedicine.

Methods

A systematic search was performed to identify digital biomarkers. The digital biomarkers were classified according to their physiological system, characterised by their capture methods, and evaluated based on the criteria adapted from the framework developed by Biomarkers of Aging Consortium.[1] Subsequently, use cases of existing digital biomarkers of ageing were reviewed, with a focus on

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examples from completed or ongoing registered clinical trials. The full methods with references is presented in the appendix (pp 3–6).

See Online for appendix

Results

Nervous system

As individuals age, the nervous system undergoes various structural and functional changes that can affect cognitive and motor abilities.[14] Several digital biomarkers have been suggested to measure these structural and functional changes, including measures of circadian rhythmicity,[15] cognitive function (eg, memory and executive function),[16] eye lens elasticity and transparency,[17] and sleep (figures 1, 2).[18,19] Circadian rhythm and sleep, such as duration and efficiency, can be measured by wearable devices.[15,18–20] Cognitive function and lens elasticity and transparency can be assessed with non-wearable technological solutions, including human–computer interaction through smartphone usage for cognitive function and deep learning models (eg, the LensAge index) that analyse smartphone photographs of the eye for lens characteristics.[16,17] Deterioration of these four nervous system digital biomarkers has shown association with age, functional decline, and increased mortality risks.[14,15,18,21] These digital biomarkers have shown generalisability across diverse populations, including White and Asian individuals, spanning ages 20 to 96 years.[15–19,22] Circadian rhythm and sleep responded to interventions in clinical studies involving adults with insomnia, Alzheimer's disease,[23] or depression.[24] However, digital biomarkers of cognitive function and lens elasticity and transparency have not yet been used as outcome measures in interventional studies. Owing to variations in study designs and reporting standards, the strength of these responses, such as effect size, sensitivity, or specificity, was not consistently available across studies and is, therefore, not summarised here. References to individual studies and their outcomes is presented in the appendix (pp 7–15). The associations between these digital biomarkers of ageing and health outcomes, such as mental health, the ability to perform activities of daily living, obesity, cardiovascular disease, and diabetes,[14,17,18] highlight their potential as non-invasive tools for monitoring age-related changes in home settings during large-scale, longitudinal clinical studies.

Musculoskeletal system

Musculoskeletal health is closely linked to physical capacity, and various measures of physical function associate with biological age.[25] Digital biomarkers of ageing for the musculoskeletal system can include measures of physical activity[26,27] (eg, daily step count,[28] intensity, frequency), physical performance (eg, gait, walking speed, stride length),[29,30] lactate,[31–34] and skeletal muscle haemoglobin oxygen saturation (figures 1, 2).[35] These biomarkers can be captured using dedicated wearable sensors[26–29,31–35] or accelerometers integrated into smartphones[28,30] and are associated with age, function, and mortality, highlighting their relevance to the ageing process. Specifically, reductions in physical movement and abnormalities in lactate homoeostasis[36] and locomotion (gait) tend to increase with age and are associated with high risks of all-cause mortality and cardiovascular diseases.[37] These changes serve as indicators of an individual's mobility, which is the ability to move and perform physical activities. Digital biomarkers of ageing for the musculoskeletal system have been studied across various age groups, from 18 to older than 85 years, in White populations within Sweden,[31,32] Spain,[34] the UK,[28] and the USA[26,27,33,35] and in populations in China.[30] Although some studies examined digital biomarkers across different age groups, findings varied depending on the biomarker and study designs, with poor consistency in age group stratification and reporting standards. Notably, several digital biomarkers, including physical performance measures and lactate, have shown greater relevance at older chronological ages; however, trends across age groups remain under-reported or inconsistent across studies. Gait analysis from digital biomarkers has been applied in both healthy adults[29] and individuals with cerebral small vessel disease,[30] showing its versatility. Responsiveness to interventions was observed in studies reporting improvements in physical activity levels among adults with chronic obstructive pulmonary disease.[38] Increases in daily step counts were also reported in cardiovascular clinical trials[39] and physical activity interventions.[40] Nonetheless, results are still pending from a phase 4 trial assessing changes in gait among adults aged 40–85 years with knee osteoarthritis pain, an interventional trial measuring changes in skeletal muscle oxygen saturation during resistance exercise, and an early phase 1 trial evaluating active muscle oxygen supply adjustments in postmenopausal women receiving a β1 selective antagonist (appendix p 9). Blood plasma lactate levels (molecular biomarker), but not sweat lactate levels (digital biomarker), have been used as an interventional study outcome; nevertheless, the results are not yet reported (appendix p 9). Mobility encompasses a range of functions that are essential for daily living activities and independence.[41] Owing to the low cost and ease of implementation, accelerometers are ideal for integration into various digital health technologies for use in large-scale clinical trial settings.

Respiratory system

Lung function is a well-established physiological marker of ageing;[42] however, home spirometry devices are typically reserved for medical purposes and spot-checking.[43] In contrast, respiration rate is a practical and accessible surrogate digital biomarker for the respiratory system that can be measured with wearable devices. These wearable devices include strain or motion sensors embedded in patch devices[44] and photoplethysmography sensors on rings or wrist wearables (figures 1, 2).[45] Photoplethysmography sensors estimate respiration rate during sleep by analysing the heart rate and detecting wrist-based body movements.[45] Several

Classification	Characterisation	Evaluation						
		Validity						
Digital biomarkers	Capture method(s)	Age-associated	Function-associated	Mortality-associated	Generalisability	Responsive to interventions	Clinical health outcomes	Costs in large-scale settings
Nervous system								
Circadian rhythm	Wearable-derived circadian patterns	✓*	✓	✓	✓	✓	4	Potentially low
Cognitive function	Smartphone usage (HCI)	✓*	✓	✓	✓	—	2	Potentially low
Eye lens elasticity and transparency	Smartphone eye photographs (DL model)	✓*	✓	✓	✓	—	4	Potentially low
Sleep	Consumer wearable device	✓*	✓	✓	✓	✓	5	Potentially low
Musculoskeletal system								
Physical activity	Accelerometer in wearable device or smartphone	✓	✓	✓	✓	✓	2	Potentially low
Physical performance	Accelerometer in wearable device or smartphone	✓*	✓	✓	✓	Results not yet reported	2	Potentially low
Lactate	Wearable microfluidic patch or continuous lactate monitor	✓*	✓	✓	✓	—	7	Higher costs
Muscle oxygen saturation (StO_2)	Wearable NIRS calf oxygen monitor	✓	✓	✓	✓	Results not yet reported	6	Potentially low
Respiratory system								
Respiratory rate	Wearable patch, ring, or wrist device	✓	✓	✓	✓	No change	7	Potentially low
Cardiovascular system								
Blood pressure	Wearable wrist device or shirt	✓*	✓	✓	✓	✓	2	Potentially low
Heart rate	Wearable device or DL model	✓	✓	✓	✓	✓	1	Potentially low
Heart rate variability	Wearable ring or wrist device	✓	✓	✓	✓	✓	4	Potentially low
Arterial stiffness	Wearable ring or watch or smartphone	✓*	✓	✓	✓	—	5	More research required
Cardiorespiratory fitness (VO_2 max)	DL model: heart rate and step count from wearable device	✓	✓	✓	✓	—	2	Potentially low
Digestive system								
Intestinal microbiota	Gas-sensing capsule	✓	✓	✓	✓	✓	7	Higher costs
Endocrine system								
Cholesterol	Soft contact lens or epidermal patch	✓*	✓	✓	✓	—	1	More research required
Cortisol	Microfluidic wearable epidermal patch	✓*	✓	✓	✓	—	4	More research required
Glucose	Continuous glucose monitor or biosensor on human tooth	✓*	✓	✓	✓	✓	3	Higher costs
Reproductive system								
Finger temperature	Wearable ring or smartphone app	✓	✓	More research required	✓	—	2	Potentially low
Oestradiol	Finger nanobiosensor	✓*	✓	✓	✓	—	2	More research required
Hot flushes	Smart clothing or skin conductance monitor	✓	✓	More research required	⚠	Results not yet reported	3	More research required
Integumentary system								
Advanced glycation end-products AGE	Wearable smartwatch	✓	✓	✓	⚠	✓	2	Potentially low
Facial wrinkles	Photographs of eye corner wrinkles or 3D facial images (CNN)	✓	✓	✓	✓	—	4	Potentially low
Facial temperature	Thermal facial images (CNN)	✓	✓	✓	✓	—	2	Potentially low

Figure 1: **A summary of the classification, characterisation, and evaluation of digital biomarkers of ageing with a focus on biological age and longevity**
The green checkmark indicates that the criterion used to evaluate the suitability of a digital biomarker as a biomarker of ageing, adapted from the framework developed by Biomarkers of Aging Consortium, is satisfied, * indicates a higher relevance at older chronological ages, the yellow caution symbol indicates caution required during interpretation as the finding might not apply broadly, and — indicates that this digital biomarker has not yet been used in interventional studies. CNN=convolutional neural network. DL=deep learning. HCI=human–computer interaction. NIRS=near-infrared spectroscopy. StO_2=muscle oxygen saturation.

studies have used photoplethysmography-based wearable devices to estimate respiration rate, although accuracy varies depending on the device and algorithm used.[43] Respiration rate, a vital sign that decreases slightly with age,[45] is associated with physical fitness and elevated during illness.[45] A high respiration rate is independently associated with an increased risk of all-cause mortality[46] and can be incorporated into broader measures of sleep quality and stress to provide a comprehensive assessment for health and wellbeing.[47,48] Respiration rate was used as an outcome measure in a mindfulness-based intervention for healthcare providers; nonetheless, no significant changes were observed after 8 weeks compared with baseline, highlighting the need for further research.[49] Respiration rate remains a sensitive marker for various pathological conditions[50] and would be valuable for large-scale measurements, as it can be measured at a low cost with existing commercial wearable devices.[45] The widespread adoption of

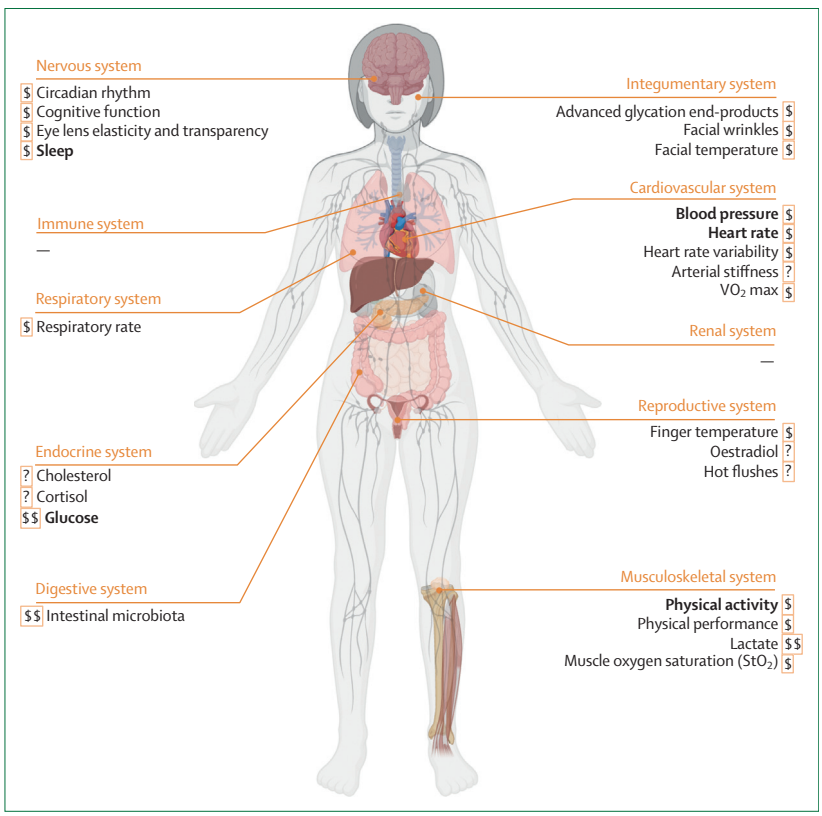

Figure 2: **Digital biomarkers for ageing and longevity**
Each digital biomarker of ageing is categorised into a physiological system. — indicates that no digital biomarker of ageing fulfils the inclusion criteria for that physiological system. Bolded lettering indicates that the digital biomarker was used as an outcome measure in clinical trials. Costs for usage in large-scale settings are indicated inside an orange box by $, potentially low; $$, higher costs; or ?, more research required. Figure created with BioRender.com.

wearable devices highlights their practical feasibility. Therefore, validation of these devices is essential to confirm their accuracy and ensure that they can reliably provide useful insights for users, clinicians, and researchers.

Cardiovascular system

As individuals age, the cardiovascular system undergoes various changes that reduce its efficiency and increase susceptibility to disease.[51] Digital biomarkers for the cardiovascular system encompass several key indicators, including blood pressure (eg, systolic blood pressure and diastolic blood pressure),[52–56] heart rate,[51,57,58] heart rate variability,[59–61] arterial stiffness,[62–65] and cardiorespiratory fitness, a measure of which is maximal oxygen consumption (VO_2 max; figures 1, 2).[66,67] These biomarkers can be effectively measured using advanced wearable sensors on the wrist[51,54,55,57–60,62,63] or body[56] and assessed through deep neural network technologies.[52,53,58,61,64–67] All five examples of cardiovascular digital biomarkers are linked to age, function, and mortality, and declines in these biomarkers are associated with an increased risk of mortality and adverse cardiovascular events as chronological age progresses.[51,66,68–73] Furthermore, cardiorespiratory fitness, a strong predictor of cardiovascular outcomes, is inversely associated with all-cause mortality without an observed upper limit of benefit.[72] Digital biomarkers for the cardiovascular system have been studied across various age groups, from ages 16 to 92 years, in both White and Asian populations.[51–67] However, the findings are heterogeneous, with poor consistency in the reporting of age-related trends. Measures such as blood pressure and arterial stiffness are associated with ageing, particularly in older adults; however, age-stratified results are not consistently reported across studies. Although digital biomarkers of blood pressure, heart rate, and heart rate variability have shown responsiveness to interventions in clinical studies involving both healthy adults[49,74] and individuals with hypertension,[75] digital biomarkers of arterial stiffness and VO_2 max have not yet been widely used as outcome measures in interventional studies. Clinically tested VO_2 max has been used as an interventional study outcome; however, the results are not yet reported (appendix pp 10–12). The strong associations between these cardiovascular biomarkers and clinical health outcomes, such as cardiovascular disease and morbidity, underscore the importance of digital biomarkers for the cardiovascular system.[51,61,65,66] Furthermore, the sensors required to measure these biomarkers are already integrated into many commercially available wearable devices,[76] translating to low-cost monitoring options in large-scale settings. Many of these commercially available wearable devices can be compared to gold-standard devices used in clinical settings.[76]

Digestive system

The digestive system undergoes modest changes with age, although these changes typically do not lead to malnutrition.[42] The composition of the intestinal microbiota is an emerging digital biomarker with potential applications in ageing (figures 1, 2). The intestinal microbiome shows age-related changes, known as age-associated dysbiosis; these changes are associated with physiological decline and cognitive impairment.[42] Specific microbiome signatures (eg, the *Enterobacteriaceae* family) have been associated with an increased risk of all-cause mortality.[77] The use of gas-sensing capsules is being investigated as clinical tools to profile intestinal gases,[78] offering insights into the gut microbiome and taxonomic profiles within the intestines.[79] These gas-sensing capsules can provide information on the site of gas production[80] and have shown potential in revealing improvements in gut health[81–83] during interventional studies. However, gas-sensing capsule technology requires further verification and validation[84] before being adopted widely and effectively on a large scale. The composition of intestinal microbiota is an important potential digital biomarker of ageing, as gut dysbiosis is associated with various health issues, including mental wellness, cardiometabolic diseases, and cancer.[85]

Endocrine system

The endocrine system regulates hormones that are essential for metabolism, growth, and stress. Age-related dysregulation

of the endocrine system contributes to diseases such as diabetes, cardiovascular issues, and inflammaging.[86] Digital biomarkers for the endocrine system include key indicators such as cholesterol,[87,88] cortisol (which reflects stress response),[89,90] and glucose,[91–93] all of which can be measured with portable digital devices (figures 1, 2). Cholesterol and cortisol can be measured with available prototypes of wearable biomolecular sensors for tears[77] and sweat.[88–90] Both cholesterol and cortisol production increases with age, and elevated cholesterol and cortisol levels are associated with impaired physiological function and increased morbidity and mortality risk.[87,94] Glucose, a crucial marker of metabolic health and ageing, is also influenced by age-related insulin resistance and changes in metabolism. Glucose levels can be tracked with advanced technologies such as interstitial continuous glucose monitors,[91] sensors adhered to human teeth,[92] or innovative materials including cellulose acetate–based devices.[93] Glucose is particularly relevant as it is used as an outcome measure in interventions for adults with type 2 diabetes.[95] Digital biomarkers for the endocrine system play a role in regulating metabolism, immune function, and cardiometabolic health[96–98] and are implicated in age-related diseases. Although glucose levels and metabolism are well studied and have been used in clinical interventions, such as measurements with a continuous glucose monitor, similar real-time applications for cholesterol and cortisol are still emerging. Continued advancements in sensor technology for continuous monitoring of glucose, lactate, and other endocrine biomolecules are expected to reduce costs, improve reusability, and increase accessibility for widespread use in ageing research and health care.[99]

Reproductive system

As individuals age, changes in the reproductive system, especially hormonal fluctuations, influence fertility, metabolic health, and the risk of age-related diseases.[100] Examples of digital biomarkers for the reproductive system include body temperature (predicted from finger temperature), oestradiol (measured using a wearable ring sensor[101,102] or a dedicated smartphone app[103]), and hot flushes (vasomotor symptoms, which can be measured with smart clothing[104,105] or a sternal skin conductance monitor[105] figures 1, 2). All these biomarkers are linked to ageing, particularly in females. Body temperature is associated with menstruation and pregnancy,[106] with luteal phase body temperature increasing until around the age of 29 years, stabilising, and then gradually decreasing after age 42.[103] Low body temperature is linked to better physical performance[107] and higher luteal phase body temperature to better cognitive performance;[108] nevertheless, the relationship between body temperature in terms of the reproductive system and mortality remains unclear. Hot flushes and decrease in oestradiol are the most evident symptoms of menopausal transition for females around age 45–55 years.[102,104,109] Despite hot flushes being associated with sleep quality, brain health,[110] and cardiovascular risk factors,[111] the link between hot flushes and mortality is not well established.[112] Higher oestradiol levels are associated with better cognitive function in older females[113] and lower risk of postmenopausal osteoporosis.[109] These digital biomarkers have primarily been studied in females aged 15–60 years across various countries, including China,[104] Finland,[101] Japan,[103] and the USA,[102,105] and conclusions might not apply to males. Although digital biomarkers of body temperature and oestradiol have not yet been used in interventional studies, monitoring hot flushes is an outcome measure in a phase 2 trial for a menopause treatment; however, results are not yet reported (figure 1). Overall, low basal body temperature might be associated with healthy ageing in the absence of excessive adiposity.[107] Body temperature can be easily measured with commercially available wearable devices, making it suitable for large-scale settings at a low cost. Nonetheless, more clinical validation and technological advancements are needed to enhance the use of digital biomarkers for menopause monitoring of oestradiol and hot flushes.[102,104]

Integumentary system

Perceived facial age, characterised by skin changes such as epidermal thinning, decreased dermal elasticity, and diminished subdermal fat, has long been a visible biomarker of ageing.[114] Digital biomarkers such as facial age are assessed using machine learning algorithms that analyse photographs of eye corner wrinkles,[115] 3D facial images,[116] and thermal facial images (figures 1, 2).[117] The algorithms were trained on photographs of White females aged 20–80 years[115] and Han Chinese adults aged 20–88 years.[116,117] Facial ageing is associated with a high chronological age; increased perceived age is also associated with decreased physical and cognitive functions[118] and increased mortality risk.[119] Accumulation of advanced glycation end-products in the skin is another important biomarker of ageing[120] that is linked to cognitive performance[121] and predictive of all-cause mortality.[122] A smartwatch equipped with a UV light sensor was reported to measure the advanced glycation end-product index via skin autofluorescence,[123] although its applicability might be limited in individuals with darker skin tones.[124] Advanced glycation end-product status has been studied in interventional trials investigating the association between vitamin D status and skin autofluorescence in adults with type 2 diabetes and the effects of casein hydrolysate on facial pigmentation and skin autofluorescence in healthy adults (figure 1). Thermal facial ageing marker levels were found to be decreased following jump-rope training, suggesting potential as an anti-ageing intervention.[117] Clinically, features such as wrinkles, ptosis, and skin sagging serve as valuable biomarkers of ageing and show a linear increase with age.[114] The combination of smartphone photography and advanced algorithms offers a scalable, low-cost solution for assessing ageing through the integumentary system. Although these preliminary observations suggest a promising direction, more extensive studies are needed to validate these findings and determine the broader applicability of these ageing biomarkers.

Renal and immune systems

No digital biomarkers of ageing meeting the selection criteria were identified for the renal and immune systems.

Clinical use and applications of digital biomarkers of ageing

Digital biomarkers have been gradually incorporated into clinical studies focused on ageing and longevity interventions, but they are often included as secondary or exploratory outcomes.[125] Despite their potential, few digital biomarkers have undergone verification and validation specifically as biomarkers of ageing.[126] Some studies have included digital biomarkers as secondary outcomes in clinical trials. In a randomised controlled trial investigating the effects of α ketoglutarate supplementation in middle-aged adults aged 40–60 years, physical activity data derived from wearable devices were used as a secondary measure to assess the effect of an anti-ageing intervention on biological age.[127] Similarly, an ongoing anti-ageing intervention trial in older Chinese adults (NCT06432491) uses accelerometer-based physical activity data to monitor the time spent across different activity intensities (table). These examples show growing interest in incorporating digital biomarkers into ageing-related trials, which can provide additional evidence to support the limited formal validation of these measures as biomarkers of ageing. Despite growing interest, the potential of digital biomarkers in ageing and longevity research remains underutilised and warrants more effective utilisation. For example, only one study cited by the Biomarkers of Aging Consortium used a digital device,[1] highlighting the potential underutilisation of digital biomarkers in longevity research. Although daily step counts[26] and physical activity[28] have been proposed as biological age predictors, clinical studies on ageing and longevity should incorporate a broader range of digital biomarkers beyond just steps and physical activity.[129] Thus, the categorisation was limited to digital biomarkers explicitly reported as outcomes in ageing and longevity trials, because sufficient trial-based evidence is lacking for broad application across other identified digital biomarkers. To establish robust associations with clinical endpoints, more extensive validation across diverse populations is necessary. Notably, five of the nine studies were focused on populations older than 50 years, underscoring the need for broader research to encompass a wider age range (table).

Discussion

This Review classified, characterised, and evaluated digital biomarkers of ageing across various physiological systems. Among the ten systems examined, digital biomarkers across eight physiological systems showed potential for monitoring ageing. However, clinical validation of these biomarkers remains scarce, highlighting the need for further research and development of digital biomarkers of ageing.

Digital biomarkers of ageing represent an emerging landscape. The digital biomarkers presented here provide an overview and understanding for future research and clinical practice, suggesting more possibilities for consistent and continuous monitoring of age-related changes. Unlike most molecular and clinical biomarkers, which are difficult or impossible to monitor continuously, digital biomarkers allow continuous monitoring. Digital biomarkers are more established for the nervous, musculoskeletal, respiratory, cardiovascular, digestive, endocrine, reproductive, and integumentary systems, likely owing to the maturity and accessibility of sensor technologies in these domains (eg, accelerometers and microfluidic and optical biosensors). The strong associations of these digital biomarkers with ageing have further supported their incorporation into biological age prediction models. Wearable-derived circadian rhythmicity (CosinorAge[15]), lens elasticity and transparency (LensAge index[17]), activity patterns,[26,27] and daily step counts[28] have been used to develop biological age predictors. Blood pressure alone has not been used as a standalone biological age predictor. However, blood pressure is an important contributor to composite biological age predictors, including physical activity and glucose.[130–132] Several digital biomarkers have been incorporated into biological age predictors; nevertheless, a comprehensive comparison of their predictive performance lies outside the scope of this review and warrants investigation in future work. Relevant studies have been cited in the appendix (pp 7–15) for readers interested in model-specific metrics and outcomes. Digital biomarkers for the renal system remain less developed, as existing technologies such as artificial kidneys[133] and continuous monitoring options for creatinine clearance,[42] cystatin C, and albumin[134] have yet to be adapted for non-invasive monitoring in community-dwelling adults. Current technological limitations also prevent continuous monitoring of immune system biomarkers, such as leucocytes, erythrocytes, thrombocytes, C-reactive protein,[134] and other types of immune risk profiling.[42] Nonetheless, advancements are anticipated. Point-of-care devices such as Hemo-Control can measure blood haemoglobin and haematocrit[135] and next-generation wearable electronics (wearable 2.0) are expanding in both modalities and capabilities,[136] suggesting considerable potential for continuous monitoring in the future.

Despite the promise shown by digital biomarkers in tracking age-related changes, particularly in sleep, physical activity, blood pressure, and heart rate, current applications primarily rely on accelerometer data and heart rate measurements owing to the widespread availability of accelerometers and optical heart rate sensors in consumer devices on the market.[137] Many digital biomarkers and the devices that measure them have not yet undergone rigorous validation in large-scale studies or randomised controlled trials. The accuracy of cardiovascular measurements from consumer-grade devices, compared to gold-standard clinical-grade devices, varies depending on both the device and the type of measurement being assessed.[138] Although some sensors are specific to particular systems, the digital biomarkers that these sensors measure can provide insights across multiple systems and health conditions, such as

	Official study title	Design; N; age range; (m/f)	Primary outcome measure	Biomarker (device)	Biomarker outcome measure	Clinical area; physiological system (application of biomarker*)	Study status
The Association Between Core Temperature and Health (NCT06432491)	Study to explore how core temperature reduction influence health	RCT; 36; 50–65 years	Core body temperature, body weight, height, body mass index, body composition, waist and hip circumference, and brown adipose tissue around the clavicle and its temperature	Physical activity (ActiGraph GT3X)	Secondary	Body composition and ageing; musculoskeletal system (response and monitoring)	Not yet recruiting
PACMan (NCT06100224)	Piloting a healthy aging cohort in Manitoba - PACMan	O; 20; ≥30 years	Physical activity, diet, sleep, stress, cognition, frailty, health history, VO_2 max, blood pressure, heart rate, clinical biochemistry, urinalysis, and body composition	Physical activity and sleep (ActiGraph activity monitor) Blood pressure (ambulatory blood pressure monitor)	Primary	Healthy ageing and wellness; musculoskeletal system (predictive or prognostics and monitoring)	Active, not recruiting
SitLESS (NCT02629666)	Exercise referral schemes enhanced by self-management strategies to battle sedentary behaviour	RCT; 1360; >65 years	Change in sitting time, sedentary behaviour time, and total activity counts per minute	Physical activity (ActiGraph, Axivity, activPAL)	Primary	Biological ageing, frail older adults, and physical function; musculoskeletal system (response and monitoring)	Completed; results not yet reported
Lu et al (2024); based on data from the REStORing health of acutely unwell adulTs (RESORT) cohort observational study[128]	The association between blood biological age at rehabilitation admission and physical activity during rehabilitation in geriatric inpatients: RESORT	O, 111, 70–90 years	Blood biological age of geriatric rehabilitation inpatients	Physical activity (activPAL)	Secondary	Ageing and rehabilitation; musculoskeletal system (predictive or prognostic and monitoring)	Completed; post-hoc analysis: higher biological age associated with higher activity and lower sedentary behaviour
TirolGESUND (NCT05678426)	Baseline-controlled comparison of the effects of fasting dietary intervention or smoking cessation combined with exercise in healthy female Tyrolean volunteers aged 30–60 on epigenetic and multi-omic biomarkers of health, ageing, and disease	BCS; 156; 30–60 years (f)	Epigenetic biomarkers of ageing and disease risk	Physical activity and resting heart rate (unnamed fitness tracker)	Secondary	Healthy lifestyle, smoking cessation, and intermittent fasting; musculoskeletal system (predictive or prognostic, response, and monitoring)	Active; not recruiting
INSPIRE (NCT04224038)	The INSPIRE bio-resource research platform for healthy aging	O; 1000; ≥30 years	Data collection of key variables and biospecimens for research platform	Physical activity and sleep (activPAL)	Secondary	Biological ageing; musculoskeletal system (predictive or prognostic, discovery, and monitoring)	Recruiting
ABLE (NCT05706389)	Does alpha-ketoglutarate supplementation lower biological age in middle-aged adults?	RCT, 120, 40–60	Change in blood DNA methylation status	Physical activity (ActiGraph wGT3X-BT)	Secondary	Ageing; musculoskeletal system (predictive or prognostic, response, and monitoring)	Completed, results not yet reported
Do Ketone Drinks Improve Immune, Metabolic and Cognitive Health in Older Adults? (NCT06068803)	Investigating the immunometabolic and cognitive effects of 4 weeks of ketone supplementation in older adults	RCT; 30; 60–80 years	Change in 24 h average glucose area under the curve	Blood glucose (unnamed continuous glucose monitor); physical activity and heart rate (Actiheart)	Primary and secondary Exploratory	Ageing, metabolic health, inflammation, immune function, and cognitive performance; musculoskeletal system and metabolic health (response and monitoring)	Recruiting
The Effects of Exercise on Sleep and Brain Health (NCT04210882)	The effects of exercise on sleep and brain health	BCS; 26; 50–75 years	Change from baseline in EEG-based brain age (brain age index algorithm) and in cognitive performance	Sleep quality (home sleep monitoring device, Prodigy Sleep System, respiratory sensor, and Airgo)	Secondary	Ageing and sleep disorders; nervous system (response and monitoring)	Completed; results not yet reported

(m/f) indicates whether the study includes only male or only female participants. *Applications of the digital biomarker: predictive/prognostics, response, surrogate endpoint, discovery, or monitoring.[1] BCS=baseline-controlled study. EEG=electroencephalography. O=observational. RCT=randomised controlled trials.

Table: **A list of recently completed or ongoing registered clinical trials or post hoc analyses using digital biomarkers of ageing with a focus on ageing and longevity interventions**

Search strategy and selection criteria

Relevant publications were identified through searches of PubMed and Google Scholar for articles and reviews on digital biomarkers of ageing published between Jan 1, 2010, and Sept 30, 2024. The search strategy combined terms related to digital health and ageing, including ("digital health" OR "digital health technolog*" OR "digital biomarker*" OR "sensor*" OR "wearable" OR "mobile" OR "smartphone" OR "e-health" OR "telehealth" OR "telemedicine" OR "telemonitoring" OR "smart home") AND ("aging" OR "aging" OR "biological age" OR "biological aging" OR "clock" OR "age predict*" OR "longevity") and terms related to specific physiological systems. A physiological system refers to a network of organs and tissues that collaborate to maintain homoeostasis and support life functions. Only articles published in English were included. A biomarker was included if it could be measured using a digital device, which is defined as an electronic device equipped with sensors that are wearable, portable, or suitable for use at home or in free-living environments. Digital devices include devices worn on the body or integrated into clothing and other body-worn accessories (wearables), and non-wearable but portable monitoring technologies, such as implantable devices, ingestible devices, smartphones, smartphone cameras, app-based assessments, or standalone sensors. Large-scale clinical instruments (eg, radiographic or imaging devices) were excluded, as these instruments fall outside the scope of digital biomarkers in this Review. Additionally, potential digital biomarkers of ageing relevant to community-dwelling adults were searched for in the Library of Digital Endpoints by the Digital Health Measurement Collaborative Community and the Digital Medicine Society (accessed Aug 2, 2024). ClinicalTrials.gov registry was searched on Aug 2, 2024, with the same terms applied in database searches to identify clinical trials focused on ageing and longevity that used digital biomarkers as the outcome measures.

To ensure feasibility in conducting this Review and real-world applicability, we included only digital biomarkers that could be measured minimally or non-invasively with digital devices, so that measurements are repeatable for longitudinal analyses and practical for regular use by community-dwelling adults outside clinical settings to capture intraindividual variability. Formal dual-reviewer screening and article count tracking were not conducted, as this is a narrative review with a systematic search. More details on the methods with references are presented in the appendix (pp 3–6).

For more details on **ClinicalTrials.gov**, see https://clinicaltrials.gov

monitoring physical activity, blood pressure, heart rate, oxygen saturation in nephrology,[137] or cardiovascular health.[139] Gait speed and gait assessments, categorised under the musculoskeletal system, can also be used to assess cognitive frailty, which comes under the nervous system,[140] demonstrating the cross-system applicability of these metrics. Novel technologies are also capable of finding out the fractional utilisation of carbohydrates and lipids in metabolism (digestive and endocrine systems) through gas analysis of exhaled carbon dioxide and oxygen (respiratory system).[141]

Emerging smart biosensors capable of non-invasively detecting biomarkers in sweat, saliva, and exhaled breath outside of traditional laboratory and clinical environments represent a promising direction for future research.[142] A wearable device designed for sweat analysis has been proposed to predict biological age.[143] Moreover, wearable devices can collect a wide array of biomolecular and physiological data, with each biomarker providing a piece of information into an individual's health status.[99] Artificial intelligence, and more specifically machine learning, can support the integration and analysis of the complex digital biomarker data, enabling the interpretation and application of data in clinically meaningful ways.[144] Artificial intelligence and machine learning not only help to analyse complex data from individual physiological systems but also have the capability to integrate data across multiple systems, such as activity patterns, cardiovascular signals, and cognitive performance, to generate composite indicators that more accurately reflect the multisystem nature of ageing.[145] System-level analysis can improve the understanding of ageing mechanisms and support the development of more robust digital biomarkers that represent biological age in a more holistic way. However, digital biomarker technologies are still in the early stages of development, with limited verification and clinical validation as digital biomarkers of ageing, which hinders the understanding of how these biomarkers respond to interventions aimed at promoting healthy ageing. Current wearable sensors can use anthropometry, heart rate, and step count data[67] or anthropometry, resting heart rate, and physical activity in a deep learning model[66] to measure cardiorespiratory fitness; nevertheless, these devices are often less accurate than gold-standard measurements. To support practical application, researchers and clinicians should use published frameworks and guides for selecting appropriate digital tools.[146] To completely realise the potential of digital biomarkers, the biomarkers should be incorporated as endpoint and outcome measures in clinical trials focused on ageing and longevity, facilitating more robust validation and application of these tools.[126]

Strengths and limitations

Although composite biomarkers that integrate molecular, physiological, and digital device measurements were not a focus of this review, future research could explore the development and validation of such models to improve predictive power for biological ageing.[132,147] Additionally, incorporating a systematic review method in future studies would enhance the robustness of findings and improve the strength of conclusions. This Review included only digital biomarkers that were applied in studies of ageing and might not have captured digital measures that did not show utility or were not reported owing to negative findings, reflecting a potential publication bias. Despite the existence of a wide

range of digital capture methods, including external cameras, gaming platforms, and non-portable systems, this review focused on digital biomarkers measured using portable or wearable technologies that have been applied in studies related to ageing and longevity. Focusing only on digital biomarkers measured using portable or wearable technologies ensured feasibility and relevance for use in community-dwelling adults but might have excluded emerging modalities not yet translated into ageing and geromedicine research. Broader implementation concerns, such as unequal access to digital technologies, economic burden,[148] digital literacy barriers,[149] and ethical issues related to data ownership and privacy,[150] present challenges to the widespread adoption of digital biomarkers. These implementation concerns fall outside the primary scope of this Review. Nonetheless, these concerns are essential for translating digital biomarker research into real-world health systems and are discussed in related literature focusing on digital health implementation[5] and digital health equity.[151] Finally, although this study did not examine the use of digital biomarkers for diagnostic purposes, an area that has been addressed elsewhere,[152] future studies should integrate these findings to better understand their diagnostic potential.

Future directions

Future research should prioritise incorporating digital biomarkers into geroscience and geromedicine studies to track biological age and ageing-related changes. Key areas for advancement include establishing normative response patterns to interventions and improving validation processes through consistent reporting of response strength using standardised metrics such as effect size, sensitivity, and specificity. As ongoing registered trials begin to report findings, they might provide the necessary evidence base to support broader clinical and real-world implementation of digital biomarkers. Advancements in sensor technology to reduce costs and increase accessibility will be crucial in integrating these tools into clinical practice. Moreover, successful implementation of digital biomarkers will require both consumers and health-care professionals to develop sufficient digital health literacy to interpret and act on these data,[149] a challenge that warrants further investigation in future work. Broadening the applications of digital biomarkers in diverse populations is essential for establishing strong associations with clinical outcomes. Population health studies such as the UK Biobank, US NHANES, Korean NHANES, and Singapore TRUST have incorporated digital biomarker data; however, large cohort studies focused on ageing-related research, such as the Baltimore Longitudinal Aging Study, remain limited in their collection of such data. Although no single digital biomarker of ageing might emerge as the most important, this study highlights several promising digital biomarkers for monitoring age-related changes.

Contributors

JKL, WW, and ABM conceptualised the review and designed the study. JKL curated the data, did the formal analysis, and wrote the original draft. WW, MDAM, JRP, MM, CH, EV, VS, VNG, and ABM wrote, reviewed, and edited the manuscript. WW and ABM supervised the research. All authors had full access to all the data in the study and accept responsibility for the decision to submit for publication.

Declaration of interests

EV is a paid consultant on the WHOOP Scientific Advisory Board. EV, VS, VNG, and ABM are on the Scientific Board of the Biomarkers of Aging Consortium. ABM is the past founding president of the Healthy Longevity Medicine Society (HLMS), council member of the Academy for Health and Lifespan Research, and co-founder of Chi Longevity (healthy longevity medicine clinic).

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