npj | aging

Perspective

Published in partnership with the Japanese Society of Anti-Aging Medicine

https://doi.org/10.1038/s41514-025-00211-6

Optimizing metabolic health with digital twins

Check for updates

Chengxun Su[1,2,7], Peter Wang[1,2,3,7], Nigel Foo[1,2,3] & Dean Ho[1,2,3,4,5,6]

A hallmark of subclinical metabolic decline is impaired metabolic flexibility, which refers to the ability to switch fuel utilization between glucose and fat according to energy demand and substrate availability. Herein, we propose optimizing metabolic health with digital twins that model an individual's metabolic flexibility profile to gamify the process of health optimization and predict long-term health outcomes. We explore key characteristics of this approach from technological and socioeconomical perspectives, with the objective of reducing the burden from metabolic disorders through driving behavior change and early detection of metabolic decline.

Public health burden and challenges in managing and preventing cardiometabolic diseases

Aging, unhealthy diets, and sedentary lifestyles are key risk factors of cardiometabolic diseases (CMDs), which include metabolic syndrome (MetS), type 2 diabetes mellitus (T2DM), and cardiovascular diseases (CVDs)[1–3]. MetS is a cluster of metabolic disorders including obesity, hypertension, escalated blood glucose lipid, which could progress to T2DM and CVDs if not managed effectively[2–4]. Globally, there is a high prevalence of poor cardiometabolic health (Table 1), with CVDs causing 20.5 million deaths in 2021 (approximately one-third of all global deaths)[4,5]. Overall, the prevalence of metabolic disorder increases with age. However, there has been a notable rise in youth-onset obesity and T2DM, driven by factors such as increased consumption of calorie-dense foods, more sedentary behavior, structural racism, and other social determinants of health[6,7]. Since 1990, adult obesity rates worldwide have more than doubled, while adolescent obesity rates have quadrupled[8]. In the US, the prevalence of youth-onset T2DM among children aged 10–19 years nearly doubled from 2001 to 2017[9], with the most pronounced increase occurring in racial and ethnic minority groups[6,9,10]. In 2023, a consensus recommendation from the American Heart Association Presidential Advisory and the American Academy of Pediatrics called for annual obesity screening and blood pressure assessment from 3 years of age[7].

Notably, early-stage metabolic disorders can often be reversed through lifestyle modification and medication, and small habit changes may be more effective than medication alone[3,11,12]. Key challenges of disease management and prevention may be attributed to low adherence to healthy lifestyle and the lack of early detection of asymptomatic metabolic abnormalities[7,13,14], which highlight the critical need for effective methods to facilitate personalized care plan to drive long-term adherence to lifestyle changes in decentralized settings, as well as early detection of metabolic decline across diverse populations including those who are generally healthy.

From a socioeconomic perspective, the potential to use early metabolic health biomarkers for identifying subclinical metabolic decline is strengthened by a growing public interest in self-monitoring health biomarkers and tuning lifestyle habits to achieve optimal health[15]. This trend can be attributed to multiple factors. First, there is an increased awareness of the adverse effects of unhealthy diets and physical inactivity on the risk of metabolic disorders. Second, policy initiatives aimed at fostering environments that facilitate healthy lifestyle choices while rendering unhealthy options less attractive have gained traction. For instance, the sugary drink tax, advocated by the WHO, has been implemented in over 100 countries to deter consumption[16]. Similarly, Singapore has implemented "Nutri-Grade," ranging from A to D, to provide guidance on sugar and saturated fat levels in beverages. Additionally, many countries have launched national public health campaigns to promote healthy lifestyle at the societal level, such as the "Active People, Healthy Nation" initiative in the US[17], "LumiHealth" in Singapore[18], and "LiveLighter" in Australia[19]. Lastly, the advent of digital health technologies and wearables has enabled continuous monitoring of various health-related metrics during daily activities.

Optimizing metabolic health with a metabolic flexibility-based digital twin

Unlike at-risk individuals who are screened for cardiometabolic risk factors, professional athletes undergo a distinct set of comprehensive examinations

[1]The Institute for Digital Medicine (WisDM), National University of Singapore, Singapore, Singapore. [2]The N.1 Institute for Health (N.1), National University of Singapore, Singapore, Singapore. [3]Department of Biomedical Engineering, College of Design and Engineering, National University of Singapore, Singapore, Singapore. [4]Department of Pharmacology, Yong Loo Lin School of Medicine, National University of Singapore, Singapore, Singapore. [5]The Bia-Echo Asia Centre for Reproductive Longevity and Equality (ACRLE), National University of Singapore, Singapore, Singapore. [6]Singapore's Health District @ Queenstown, Yong Loo Lin School of Medicine, National University of Singapore, Singapore, Singapore. [7]These authors contributed equally: Chengxun Su, Peter Wang.
e-mail: biedh@nus.edu.sg

Table 1 | Global prevalence and management of common metabolic disorders

Type of metabolic disorders	Prevalence (%)	Management of the disorder[7]	Challenges in disease management and prevention[7,13,14]
Obesity	1 in 8 (World Health Organization (WHO), 2022)[8]	• Lifestyle modification (achieving and maintaining a healthy weight with behavior change, healthy diet, recommended physical activity level) • Use of medications as needed • Procedures or surgeries as needed	• Low adherence to lifestyle changes • Difficulty in personalizing health regimens that maximize weight loss efficiency
Raised total cholesterol	39% (WHO, 2008)[95]	• Lifestyle modification • Use of medications as needed	• Low adherence to lifestyle changes • Early detection of the disease • Tracking cholesterol over time
Hypertension	32% in women, 34% in men (2019)[96]	• Lifestyle modification • Adoption of a balanced, low-sodium diet • Use of medications as needed	• Low adherence to lifestyle changes • Early detection of the disease
T2DM	10.5% (IDF, 2021)[97]	• Lifestyle modification • Using medications that lower the risk of CVDs • Achieving targets for control of HbA1c, blood pressure and cholesterol	• Low adherence to lifestyle changes • Managing multiple treatment targets • Early detection of the disease • Early detection of complications • Personalized care
CVDs	More than half a billion (World Heart Report, 2023)[98]	• Lifestyle modification • Medications • Procedures or surgeries • Management of other metabolic disorders (co-morbidities) • Additional components such as stress management, healthy sleep and not smoking	• Low adherence to lifestyle changes • Early detection of CVDs risk factors • Long-term care adherence

for their metabolic health. These evaluations focus on assessing the metabolic dynamics in response to exercise, aiming to optimize performance during intense physical activity. Metabolic flexibility, the ability to switch fuel utilization between glucose and fat to maintain homeostasis, is a key indicator of metabolic health as it reflects how adaptive the body is throughout physiologic challenges[20–22]. Studies have shown that professional athletes exhibit a greater level of metabolic flexibility compared to moderately active individuals and those with MetS[23–25]. The enhanced flexibility allows athletes to readily switch between utilizing glucose and fat in response to energy demand and substrate availability. Conversely, individuals with impaired metabolic function, particularly the elderly and individuals with metabolic disorders, have declined metabolic flexibility[21,22,26–29], making them less adaptive to nutritional changes and disturbance in energy balance.

MetS patients and professional athletes represent the extreme ends of the spectrum of metabolic health. For individuals who are non-athletes and free of metabolic disorders, there also exists a varying degree of metabolic flexibility due to interindividual biological differences such as genetic characteristics and overall health and fitness level[25,28,30–33]. Indeed, many studies have shown that evaluating metabolic flexibility could improve risk stratification and enable early detection of metabolic dysfunction even in seemingly healthy individuals[20,30,32–34]. For instance, in a study that investigated the metabolic response to an acute high-fat overload, substantial variability in the ability to switch fuel to lipids was observed among healthy adults. Notably, this degree of flexibility is indicative of the propensity for future weight gain[32]. Conversely, another study found that within the obese group, some individuals exhibited a transcriptional profile that was similar to the normal weight group, suggesting they had retained a degree of metabolic flexibility[33]. This highlights that metabolic flexibility could be independent of body size, and not all obese individuals experience the same degree of metabolic impairment. Taken together, metabolic flexibility could serve as an early biomarker of metabolic abnormalities, in order to (1) differentiate metabolic health status within the generally healthy population. (2) reflect the level of metabolic health at an individual level, which evolves over time as a result of lifestyle choices and health management strategies (diet, intermittent fasting, physical activity, sleep, etc).

One of the decentralized health solutions emerging as a transformative paradigm for personalized metabolic disease management is the digital twin technology[35], defined as an evolving digital entity designed to accurately reflect the object or process it represents[35,36]. The emergence of the digital twin technologies may potentially transform healthcare and, importantly, has led to personalized health management, biomarker predictions, visualization of health data, and many other features[35]. In a study led by Rad et al., the team integrated digital twins with personal health knowledge graphs (PHKGs) and harnessed diverse health data sources to enhance diabetes management[37]. For example, this patient-specific digital twin enables real-time, personalized care including glucose level predictions and insulin dose optimization. In a similar study, Zhang et al. developed a digital twin framework using multi-omic data, mechanistic models, and knowledge graphs coupled with machine learning (ML) to enhance clinical decision support for T2DM patients[38]. Furthermore, a study leveraged generalized metabolic fluxes (GMF) to build a digital twin model that predicts and identifies chronic kidney diseases among T2DM patients[39]. Of note, human digital twin initiatives, such as the EDITH program[40], have been funded by the European Commission to build a roadmap toward an ecosystem for virtual human twins. Taken together, digital twin technologies present a promising approach to personalize treatment strategies with tailored interventions especially for metabolic diseases, which often require longitudinal monitoring[35].

In this perspective, we introduce the concept of a metabolic flexibility-based digital twin model designed to drive adherence to lifestyle changes, enable personalized health management and early detection of subclinical metabolic decline. Two key modules of the proposed digital twin are, (1) the gamification module based on longitudinal monitoring of fuel switching and metabolic flexibility trends, (2) the artificial intelligence (AI)-powered integrated digital twin module for analyzing and predicting long-term health outcomes associated with sustained adherence to health regimen and metabolic flexibility assessment. Importantly, we discuss the technical feasibility of constructing the proposed digital twin, the challenges in its development and implementation, along with the associated socioeconomic perspectives that need to be taken into consideration to realize improvement in metabolic health on a population level (Fig. 1).

Gamification module of the digital twin—promoting adherence to health regimen through fuel switching monitoring

Metabolic flexibility is conventionally determined by measuring the respiratory quotient (RQ), which is defined as the ratio of carbon dioxide produced (VCO_2) and oxygen consumed (VO_2) (VCO_2/VO_2) from rest to exercise, or from fasting to feeding using the indirect calorimetry technique[20,30,41]. The RQ generally ranges from 0.7 during pure fat

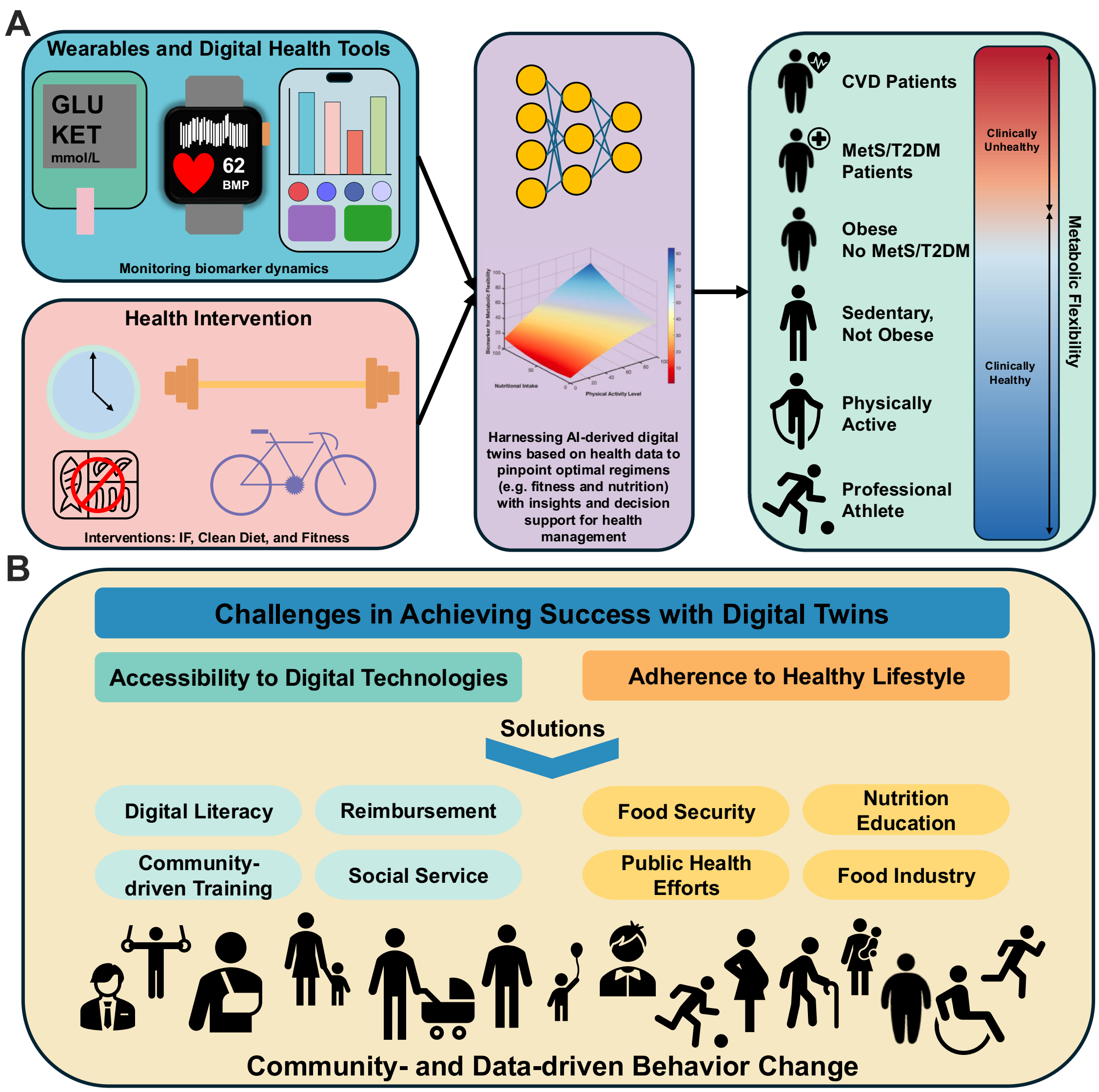

Fig. 1 | Schematic overview of optimizing metabolic health with digital twins. **A** The proposed workflow including employing digital health tools and managing health interventions to generate digital twin models that gamify adherence to improve metabolic flexibility. **B** A summary of challenges pertaining to achieving success with digital twins. IF intermittent fasting, GLU blood glucose, KET ketone bodies.

metabolism to 1.0 during pure carbohydrate metabolism[42]. Past computational models of metabolic flexibility are primarily based on mechanistic simulation of energy expenditure and metabolic fluxes at tissue level or whole-body level using a system biology approach. In one study, genome-scale metabolic models were employed to compute the RQ of computational model of skeletal muscle[42], accounting for energy expenditure and enabling the simulation of metabolic flexibility in response to varying energy demands. Another notable study developed a computational model of human metabolism to predict changes in RQ in lean and obese men, using differential equations to represent nutrient uptake and ATP production[43]. These approaches were implemented in in silico testing or retrospective analysis. In this perspective, we introduce an alternative approach to assess metabolic flexibility by tracking the dynamic changes in blood glucose and ketone bodies (KBs) during health interventions, with the aim to implement this as a digital twin solution to support decentralized metabolic health management in real-world scenarios."

In a glycogen-depleted state, adipose tissues release free fatty acids that further break down into ketone bodies (KBs), such as β-hydroxybutyrate, acetoacetate and acetone, to serve as energy substrates in place of glucose[44,45]. KBs have received tremendous attention as a biomarker of elevated fat metabolism in the context of metabolic disease prediction[46], diabetic ketoacidosis (DKA) detection[47], dietary therapy[48,49], and health optimization[50]. In a recent work, self-monitoring of metabolic dynamics for a healthy subject based on serial measurements of blood KBs and blood glucose (fingerstick- and wearable-based) was reported[50]. Notably, a specific glucose and KBs trajectory indicative of fuel switching (also known as ketosis) was observed after 1–5 days of a sustained regimen of fitness and dietary interventions[50]. This important work indicated the possibility of evaluating metabolic flexibility by monitoring the ease and rapidity to reach fuel switching under fixed health regimen. Interestingly, the knowledge that the implemented health regimen successfully induced ketosis motivated the subject to consistently adhere to the regimen. More importantly, visualizing the dynamics of the biomarkers, especially the ketosis-driven KBs trajectory, also motivated the subject to sustain the regimens, which are essential toward achieving fuel switching[50]. This adherence persisted throughout the study and beyond its completion, even in challenging situations like traveling. Similarly, gamification strategies have also been implemented in clinical trials for disease prevention. For example, physical activity was significantly increased among families with game-based intervention in a clinical trial[51] (NCT02531763). Furthermore, gamification interventions

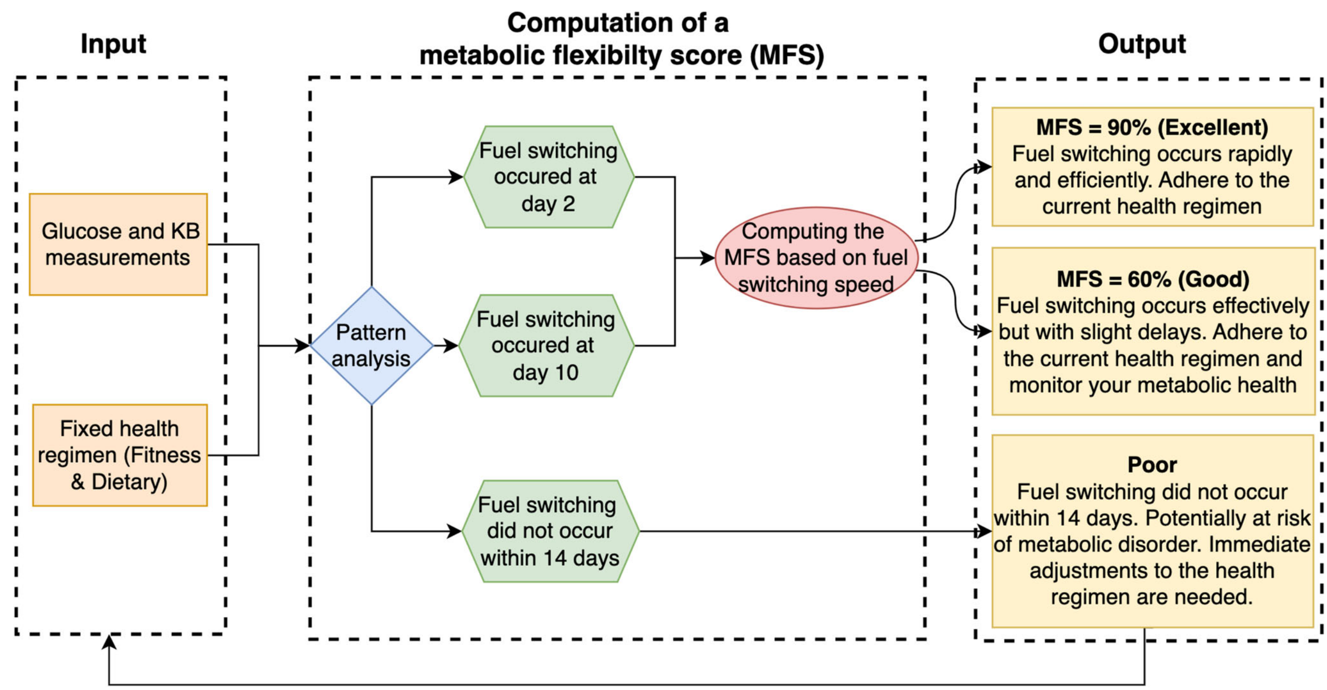

Fig. 2 | Workflow to compute the metabolic flexibility score (MFS). Simplified representation of the workflow for the gamification module within the proposed digital twin that monitors fuel switching to compute a MFS. The score gamifies adherence to healthy behaviors by evaluating fuel switching speed and providing real-time feedback as the reward mechanism.

were deployed to incentivize physical activity for patients who may be at risk with CVDs and T2DM, and the participants engaged in more physical activities in the trials[52,53] (NCT02961192; NCT03749473). In summary, these demonstrated the successful application of gamification strategies in promoting and sustaining adherence to health regimens and potential long-term behavior change.

The module 1 of the proposed digital twin is designed to monitor fuel switching and promote adherence to healthy behaviors (Fig. 2). It begins with input data—glucose and KB measurements and details of a fixed health regimen, followed by pattern analysis to identify the occurrence of fuel switching within a preset period. A Metabolic Flexibility Score (MFS) will be computed based on the fuel switching speed. For instance, an MFS of 90% is assigned if fuel switching occurs rapidly (e.g., day 2), encouraging adherence to the current regimen. If fuel switching occurs with delay (e.g., day 10), an MFS of 60% is given, recommending adherence and continued monitoring. If fuel switching does not occur within 14 days, it will prompt a potential risk of metabolic disorder and immediate adjustments to the health regimen (e.g., reduce carbohydrate intake). The output provides actionable scores to gamify adherence, motivating individuals to optimize metabolic flexibility and healthy behavior.

A key challenge associated with developing the proposed module is the difficulty in obtaining KB measurements due to its invasive nature, as blood fingerstick test strips are currently the gold standard method. Although minimally or non-invasive methods for measuring KBs in human interstitial fluid[54], sweat[55], urine[56], and breath[57,58] have been reported, their accuracy and reliability remain uncertain. An accurate and non-invasive KB monitoring method may eventually become available with further technological advancements. For example, a recent study reported a stretchable wearable sensor for measuring solid-state epidermal biomarkers, showing strong correlation with blood biomarkers and dynamic correlation with physiological activities[59]. Alternatively, considering the convenience of using continuous glucose monitoring (CGM) to collect glucose data and the partially inverse correlation between glucose and KB, it is worthwhile to investigate if KB level or fuel switching occurrence could be estimated using CGM data. ML pipelines like neural networks have been applied to train models using CGM data for accurate and timely forecasting of future blood glucose levels[31,60]. In selected diabetes clinical trials, blood KBs were measured during hyperglycemia for early identification of DKA[61]. Using such datasets, Cichosz et al. utilized a supervised binary classification ML approach to train a model using labeled data, enabling it to predict elevated KB level based on CGM data obtained from patients with type 1 diabetes for the first time[47]. Based on the retrospective CGM data collected for 4 h before the KB measurements, the authors obtained an acceptable prediction accuracy. While further studies are warranted to validate the results in other cohorts and comparing different ML algorithms, this work underscores the possibility to correlate CGM patterns indicative of ketosis.

Harnessing AI for predicting long-term health outcomes with the digital twin

The gamification module provides real-time feedback and a reward mechanism that gamifies adherence to health regimen, empowering users to adopt interventions that most effectively induce and maintain a beneficial state of ketosis. Another critical feature to be integrated into the digital twin is the predictive analytics for evaluation of long-term health outcome resulting from sustained fuel switching (Fig. 3). Frequent post-intervention checkpoints could include self-trackable measurements like body weight, BMI, blood pressure, and body fat composition. Additionally, a panel of metabolic health and aging biomarkers such as Apolipoprotein A (ApoA), Apolipoprotein B (ApoB), Hemoglobin A1c (HbA1C), Interleukin-6 (IL-6), C-reactive Protein (CRP), and blood lipids could be measured as baseline and final health outcome. The relationship between fuel switching occurrence, longitudinal trends of MFS, and changes in health metrics and biomarkers will then be mapped using AI-powered models.

Existing health management technologies like the "January AI" application have leveraged ML pipelines to learn an individual's physiology and provide personalized recommendations based on predicted blood glucose response to specific behavior patterns[31,62]. Excitingly, generative AI (GenAI) models offer significant potential to speed up the development of digital twins[63], as well as enhance the predictive accuracy and user engagement of digital twin platforms. First, GenAI model could

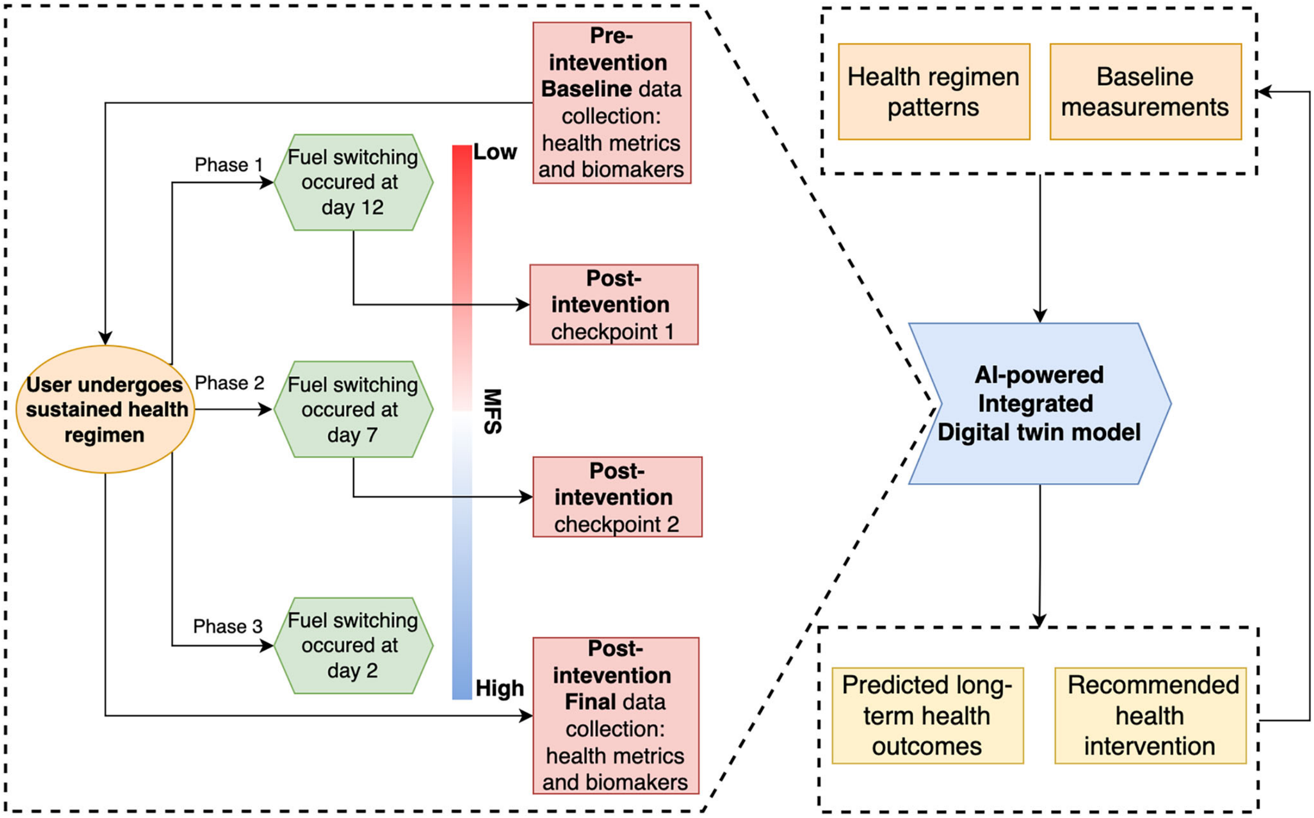

Fig. 3 | Workflow to generate the digital twin model. Simplified representation of the workflow for the proposed digital twin model that integrates health regimen adherence, baseline and post-intervention health data collection, and metabolic flexibility assessment. The AI-powered module links health regimens with long-term health outcomes to provide predictive insights and personalized health interventions.

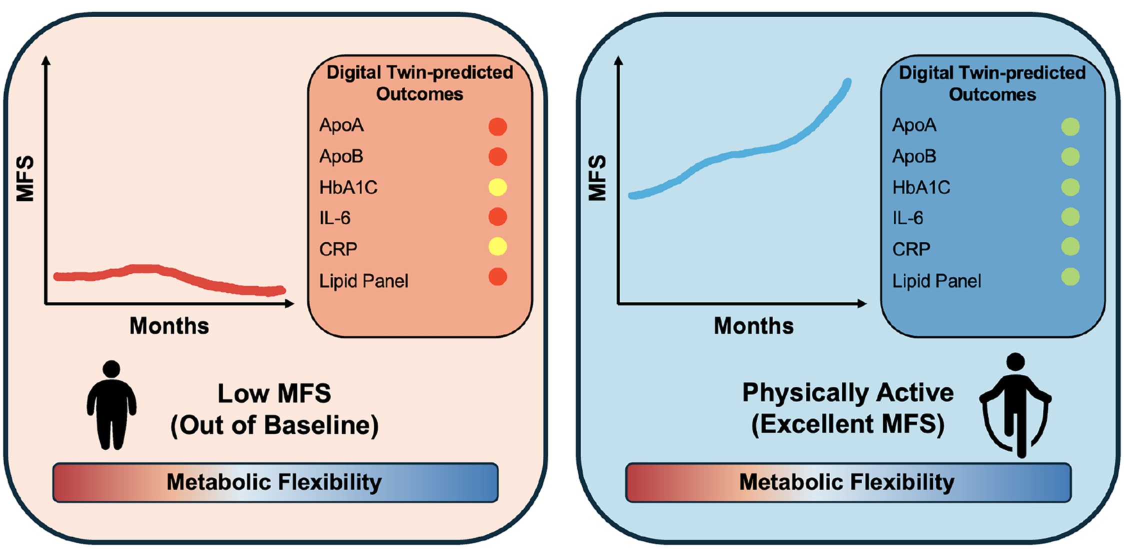

Fig. 4 | User interface of digital twins. The user interface of a sample digital twin that enables proactive health management by providing actionable insights and fostering engagement. In the left panel, a subject with declining MFS over a period of a few months receives poor digital-twin predicted outcomes (red/yellow remarks for biomarkers) for an array of biomarkers. In contrast, digital twin predicts optimal (green remarks for biomarkers) relevant biomarkers for a physically active subject with excellent MFS. MFS metabolic flexibility score, ApoA apolipoprotein A, ApoB apolipoprotein B, HbA1C hemoglobin A1C, IL-6 interleukin-6, CRP C-reactive protein.

be evaluated together with traditional ML models for the simulation of long-term health outcomes based on implemented interventions, potentially outperforming conventional ML approaches. Second, GenAI can generate synthetic data for unmeasured biomarkers to aid in health trajectory forecasting[64] and minimize the need for invasive testing. Lastly, conversational GenAI tools powered by large language models (LLMs) can be integrated into digital twin platforms to provide real-time coaching and motivational feedback to users. An example user interface of the digital twin includes longitudinal trends of MFS and predicted long-term biomarker changes (Fig. 4).

GenAI solutions have the potential to improve the performance of digital twin models for health management. However, addressing challenges related to data privacy and security, trustworthiness and explainability, and bias in GenAI is crucial to ensure its safe and effective integration into wearables and digital health technologies[65–67]. Developing AI risk assessment protocols and formulating specific metrics including inscrutability and trustworthiness, and ongoing model monitoring can help detect and mitigate risks associated with GenAI health technologies[67]. Potential strategies to overcome data privacy and security challenges include the implementation of advanced encryption and anonymization techniques before feeding data into generative models. Additionally, federated learning allows models to be trained across multiple devices or servers holding local data samples without exchanging them, thus enhancing privacy.

Challenges in implementing and achieving success with digital twin solutions

Although there is significant potential for digital twin technologies to improve health management and patient outcomes, their widespread implementation and successful utilization have been hindered by various social factors, (1) disparities in the accessibility of digital health tools, (2) socioeconomical challenges in adopting and adhering to a healthy lifestyle, particularly healthy dietary patterns. For instance, studies from the US and Europe have found that digital health tools are more frequently used in urban areas, while usage is lower among ethnic minorities and individuals with language barriers[68,69]. Furthermore, younger populations, as well as those with more advanced education levels and higher economic status, tend to use these tools more extensively. In other words, people with poor health are among those facing the greatest challenges in accessing digital health tools. These challenges primarily stem from the digital divide that exists between different countries, ethnicities, and communities, with significant disparities in digital infrastructure and inclusiveness, which encompasses accessibility, affordability, digital literacy, and attitudes—such as trust and enthusiasm—toward digital technologies[68,70]. The number of people who have access to the Internet has been steadily increasing over the years. As of 2023, approximately 67% of the global population has internet access, nearly double the figure from ten years ago[71]. Notably, Singapore ranks first in digital inclusiveness among 82 countries in 2020[72], primarily due to initiatives like free public WiFi and financial support for digital skills training. In contrast, other Southeast Asian countries fell below the global average mainly due to substantial low-income populations.

Alongside tackling the digital divide to boost the adoption of digital health technologies, it is crucial to develop effective strategies to overcome access barriers for disadvantaged groups who currently lack any form of healthcare. For instance, training programs could be deployed for community health workers who will provide education and facilitate access to services in underserved communities. Languages and culturally tailored platforms could be developed to help bridge gaps for ethnic minorities and non-native speakers. Furthermore, it is important to recognize that the effective use of digital health does not always demand continuous or sustained use. One potential strategy to reduce the healthcare burden of CMDs could involve a system-wide, short-term implementation of remote monitoring technologies (e.g., CGM) to identify pre-diabetic or diabetic populations. Following this, longitudinal monitoring could be introduced for individuals undergoing lifestyle modification. This approach may necessitate a redesign of healthcare systems that begins with clearly defined goals and rapidly collects data to assess the current landscape[73,74].

Second, the adoption and adherence to healthy dietary patterns is a key challenge that needs to be addressed for achieving successful outcome from digital twin technologies, as a balanced and nutritious diet is the cornerstone of metabolic health management. This challenge could be addressed by improving nutrition education and food security. In the US, fewer than 1 in 10 adolescents and adults consume enough fruits or vegetables and too much sodium[75]. In many countries, clinicians are recommended to provide nutrition care to patients, yet most feel their nutrition training was inadequate. A study from the UK found that over 70% of medical students and doctors reported receiving less than 2 h of nutrition training in medical school[76]. A systematic review indicated that nutrition is insufficiently incorporated into medical education, regardless of country, setting, or year of medical education[77]. Among the general population, many consumers lack a clear understanding of what constitutes healthy carbohydrates. A survey conducted in Australia indicated that 50% of participants did not know precisely what constitutes a whole grain[78]. Moreover, a study in Singapore revealed that while most respondents were able to identify hidden sources of sodium in food like instant noodles and processed meats, only 4 in 10 were aware that sweeter-tasting dipping sauces and foods are higher in sodium[79]. Taken together, it is essential to improve nutrition education for healthcare providers, as well as public awareness campaigns for the general population, to promote healthy eating.

Furthermore, similar to the varying levels of access to digital health tools, access to nutritious food also varies widely across different populations. Food security is one of the key social determinants of health for CMD risk[7,80,81]; however, more than 1 in 10 children and adults report food insecurity in the US, indicating that this issue extends beyond low-income regions[82,83]. The roles of various stakeholders—including insurers, healthcare providers, the food industry, and public health organizations—are critical within this ecosystem[14,84]. Insurers influence access to nutritional services and resources, while healthcare providers are key in referring patients to nutrition programs. The food industry must prioritize the production and marketing of healthy food options. Public health initiatives are essential for addressing food equity and security, recognizing that these factors are interconnected and vital for improving population health outcomes. Notably, the American Heart Association recently launched a new Food Is Medicine research initiative[14], which provides free or subsidized healthy foods to at-risk individuals. This program aims to generate evidence to convince insurers to cover such programs for specific groups and to drive system-level changes that facilitate healthy eating for at-risk populations[84].

Broader ecosystem perspectives on improving community metabolic health

Improving accessibility to healthcare resources and driving behavior change toward a healthy lifestyle are critical groundwork that may potentially prevent CMDs and other diseases. These challenges are also crucial to the eventual adoption as well as the implementation of the proposed digital twin-enabled workflow, which may be a promising tool for metabolic flexibility improvement. However, broader ecosystem considerations, including socioeconomic issues, should be prioritized prior to the implementation of advanced healthcare technologies, such as digital twins. From a broader perspective, considerations across the ecosystem, including gig workers and health of all age groups, should also be carefully addressed. The emergence of the gig economy in Southeast Asia and other parts of the world has created substantial job opportunities. However, gig workers experience significant inequalities in the context of accessing healthcare resources through insurance and protection[85]. For example, in Singapore, gig workers, including hail ride drivers and food delivery riders, only receive insurance depending on the "goodwill" of service providers and coverages vary substantially from different employers[85]. With a new law in effect later in 2024, all gig workers will be covered under standardized insurance similar to employees of other sectors. In other parts of Southeast Asia, gig workers are considered independent contractors who do not enjoy the full benefits of typical employees, such as insurance coverage[86]. Therefore, it is evident that gig workers experience substantial vulnerabilities in the broad ecosystem, and their accessibility to healthcare resources should be addressed[87].

Moreover, gender disparities in health, especially CMDs, may potentially lead to unsatisfactory treatment outcomes[88]. Sex should be considered as a biological variable when studying disease mechanisms, as some diseases may require sex-specific treatment strategies[89,90]. Notably, chronic diseases in women are on the rise, and the National Institutes of Health (NIH) of the US has also developed a framework to account for sex differences for chronic conditions in women[89]. This framework specifically categorizes women-specific chronic conditions into: (1) female-specific, (2) more common in women, (3) potentially understudied in women, and (4) high morbidity for women. For example, around one in three women have hypertension globally, and this condition is considered one of the most important risk factors for women[91]. Conventionally, hypertension is more prevalent in men under 50 years of age, whereas women after the age of 65 (menopause) have higher chances of developing hypertension[92]. Similarly, women tend to experience stroke at a much lower blood pressure than men[91]. It is evident that sex-specific treatment strategies should also be implemented to address potential chronic diseases. Harnessing digital platforms powered by AI may pinpoint trends and patterns in relevant biomarkers for early detection.

In addition, in the context of birth rates in Asia, substantial declines in countries including Korea, Singapore, and China are observed. In contrast, the prevalence of chronic medical conditions is increasing, with approximately 10–30% of youth diagnosed with a condition[93]. Youth and adolescents age between 10 to 24 years old may be one of the most digitally literate group, and they may be more prepared to harness digital health devices to longitudinally monitor their health conditions. However, driving their adherence to treatment and healthy lifestyle may be challenging. For example, a study found that youth are less likely to use CGMs consistently for glucose monitoring when compared to adults[94]. For downstream implementation, gamification strategies should be carefully designed and considered and implemented into health optimization for all age groups.

The challenges discussed above are not siloed to health and healthcare. Harnessing digital health approaches may not solve these broader issues in the ecosystem. Community efforts that involve all stakeholders spanning from pharmaceutical companies, food industry, to government agencies to address challenges including agriculture, sustainability, energy, housing, economy, work, transportation, community planning, and healthcare will lay the groundwork for the success of health optimization via digital platforms.

Concluding remarks and future perspectives

Innovative methods are needed to enable early detection and management of metabolic decline prior to the onset of cardiometabolic diseases. In the absence of metabolic disorders, metabolic flexibility could serve as the differentiating factor of metabolic health among traditionally defined healthy individuals and guide health optimization at an individual level. Recent literature has demonstrated the feasibility of digitally monitoring the process of metabolic switching in a decentralized setting, targeting the favorable switch to fat oxidation as the end point. Key unresolved questions for future research include (1) Is there significant individual variability in the ease and rapidity to reach metabolic switching under a standardized health regimen? (2) Does the magnitude of the ketosis response vary based on different intensities of interventions? Additionally, AI models including digital twins could be leveraged to (1) identify glucose patterns associated with the onset of ketosis during health interventions and (2) simulate the relationship between health regimen, metabolic flexibility trends, and long-term health outcomes. It is important to note that the proposed digital twin approach is not merely a recapitulation of biological processes for observational or fundamental studies; it has the potential to inform the development of proactive, pre-emptive interventions tailored to steer each individual's metabolic health in a more favorable direction. Furthermore, this participatory health approach empowers people to actively take ownership of learning how to improve their health experientially and ethically, fostering both personal responsibility and informed decision-making in their health journeys. Lastly, it is essential to consider broader factors within the healthcare ecosystem, including accessibility, nutrition education, health disparities, and sex differences. Public health initiatives, in conjunction with the emergence of digital health technologies, may help address the aforementioned challenges and accelerate the path toward metabolic health optimization and healthy aging.

Data availability

No datasets were generated or analyzed during the current study.

Received: 19 November 2024; Accepted: 7 March 2025;
Published online: 24 March 2025

References

1. Saunders, T. J., Chaput, J.-P. & Tremblay, M. S. Sedentary behaviour as an emerging risk factor for cardiometabolic diseases in children and youth. *Can. J. Diab.* **38**, 53–61 (2014).
2. Sattar, N., Gill, J. M. R. & Alazawi, W. Improving prevention strategies for cardiometabolic disease. *Nat. Med.* **26**, 320–325 (2020).
3. Diabetes Prevention Program Research Group. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *N. Engl. J. Med.* **346**, 393–403 (2002).
4. World Health Organization. *Cardiovascular Diseases (CVDs)*. https://www.who.int/news-room/fact-sheets/detail/cardiovascular-diseases-(cvds) (2021).
5. Lindstrom, M. et al. Global burden of cardiovascular diseases and risks collaboration, 1990–2021. *J. Am. Coll. Cardiol.* **80**, 2372–2425 (2022).
6. Bjornstad, P. et al. Youth-onset type 2 diabetes mellitus: an urgent challenge. *Nat. Rev. Nephrol.***19**, 168–184 (2022).
7. Ndumele, C. E. et al. Cardiovascular-kidney-metabolic health: a presidential advisory from the American Heart Association. *Circulation* **148**, 1606–1635 (2023).
8. World Health Organization. *Obesity and Overweight*. https://www.who.int/news-room/fact-sheets/detail/obesity-and-overweight (2024).
9. Rodriquez, I. M. & O'Sullivan, K. L. Youth-onset type 2 diabetes: burden of complications and socioeconomic cost. *Curr. Diab. Rep.* **23**, 59 (2023).
10. Perng, W., Conway, R., Mayer-Davis, E. & Dabelea, D. Youth-onset type 2 diabetes: the epidemiology of an awakening epidemic. *Diab. Care* **46**, 490–499 (2023).
11. Li, G. et al. The long-term effect of lifestyle interventions to prevent diabetes in the China Da Qing Diabetes Prevention Study: a 20-year follow-up study. *Lancet* **371**, 1783–1789 (2008).
12. Diabetes Prevention Program Research Group. Long-term effects of lifestyle intervention or metformin on diabetes development and microvascular complications over 15-year follow-up: the Diabetes Prevention Program Outcomes Study. *Lancet Diabetes Endocrinol.* **3**, 866–875 (2015).
13. Miranda, J. J. et al. Understanding the rise of cardiometabolic diseases in low- and middle-income countries. *Nat. Med.* **25**, 1667–1679 (2019).
14. Volpp, K. G. et al. Food is medicine: a presidential advisory from the American Heart Association. *Circulation* **148**, 1417–1439 (2023).
15. Jarvis, P. R. E., Cardin, J. L., Nisevich-Bede, P. M. & McCarter, J. P. Continuous glucose monitoring in a healthy population: understanding the post-prandial glycemic response in individuals without diabetes mellitus. *Metabolism* **146**, 155640 (2023).
16. World Health Organization. *WHO Calls on Countries to Increase Taxes on Alcohol and Sugary Sweetened Beverages*. https://www.who.int/news/item/05-12-2023-who-calls-on-countries-to-increase-taxes-on-alcohol-and-sugary-sweetened-beverages (2023).
17. Centers for Disease Control and Prevention. *Active People, Healthy Nation*[SM]. https://www.cdc.gov/active-people-healthy-nation/php/about/index.html (2024).

18. Singapore's Health Promotion Board. LumiHealth: Your Way to a Healthier Everyday. https://www.lumihealth.sg/ (2025).
19. Government of West Australia Department of Health. LiveLighter: Helping You Lead A Healthier Lifestyle. https://livelighter.com.au/ (2025).
20. Goodpaster, B. H. & Sparks, L. M. Metabolic flexibility in health and disease. *Cell Metab.* **25**, 1027–1036 (2017).
21. Zhou, Q., Yu, L., Cook, J. R., Qiang, L. & Sun, L. Deciphering the decline of metabolic elasticity in aging and obesity. *Cell Metab.* **35**, 1661–1671.e6 (2023).
22. Storlien, L., Oakes, N. D. & Kelley, D. E. Metabolic flexibility. *Proc. Nutr. Soc.* **63**, 363–368 (2004).
23. Bergman, B. C. et al. Evaluation of exercise and training on muscle lipid metabolism. *Am. J. Physiol. Endocrinol. Metab.* **276**, E106–E117 (1999).
24. Bergman, B. C. et al. Muscle net glucose uptake and glucose kinetics after endurance training in men. *Am. J. Physiol. Endocrinol. Metab.* **277**, E81–E92 (1999).
25. San-Millán, I. & Brooks, G. A. Assessment of metabolic flexibility by means of measuring blood lactate, fat, and carbohydrate oxidation responses to exercise in professional endurance athletes and less-fit individuals. *Sports Med.* **48**, 467–479 (2018).
26. Kelley, D. E. & Simoneau, J. A. Impaired free fatty acid utilization by skeletal muscle in non-insulin-dependent diabetes mellitus. *J. Clin. Invest.* **94**, 2349–2356 (1994).
27. McGarry, J. D. Banting lecture 2001: dysregulation of fatty acid metabolism in the etiology of type 2 diabetes. *Diabetes* **51**, 7–18 (2002).
28. Kardinaal, A. F. M. et al. Quantifying phenotypic flexibility as the response to a high-fat challenge test in different states of metabolic health. *FASEB J.* **29**, 4600–4613 (2015).
29. Yu, E. A. et al. Metabolomic profiling after a meal shows greater changes and lower metabolic flexibility in cardiometabolic diseases. *J. Endocr. Soc*. **4**, bvaa127 (2020).
30. Yu, E. A., Le, N.-A. & Stein, A. D. Measuring postprandial metabolic flexibility to assess metabolic health and disease. *J. Nutr.* **151**, 3284–3291 (2021).
31. Zahedani, A. D. et al. Digital health application integrating wearable data and behavioral patterns improves metabolic health. *NPJ Digit. Med.* **6**, 216 (2023).
32. Begaye, B. et al. Impaired metabolic flexibility to high-fat overfeeding predicts future weight gain in healthy adults. *Diabetes* **69**, 181–192 (2020).
33. Gille, D. et al. Caloric dose-responsive genes in blood cells differentiate the metabolic status of obese men. *J. Nutr. Biochem.* **43**, 156–165 (2017).
34. Galgani, J. E. & Fernández-Verdejo, R. Pathophysiological role of metabolic flexibility on metabolic health. *Obes. Rev.* **22**, e13131 (2021).
35. Mosquera-Lopez, C. & Jacobs, P. G. Digital twins and artificial intelligence in metabolic disease research. *Trends Endocrinol. Metab.* **35**, 549–557 (2024).
36. Barricelli, B. R., Casiraghi, E. & Fogli, D. A survey on digital twin: definitions, characteristics, applications, and design implications. *IEEE Access* **7**, 167653–167671 (2019).
37. Sarani Rad, F., Hendawi, R., Yang, X. & Li, J. Personalized diabetes management with digital twins: a patient-centric knowledge graph approach. *J. Pers. Med.* **14**, 359 (2024).
38. Zhang, Y. et al. A framework towards digital twins for type 2 diabetes. *Front. Digit. Health* **6**, 1336050 (2024).
39. Surian, N. U. et al. A digital twin model incorporating generalized metabolic fluxes to identify and predict chronic kidney disease in type 2 diabetes mellitus. *NPJ Digit. Med.* **7**, 140 (2024).
40. EDITH. *European Virtual Human Twin*. https://www.edith-csa.eu/ (2022).
41. Lighton, J. R. B. *Measuring Metabolic Rates: A Manual for Scientists* 2nd edn. (Oxford University Press, 2018).
42. Cabbia, A., Hilbers, P. A. J. & van Riel, N. A. W. Simulating metabolic flexibility in low energy expenditure conditions using genome-scale metabolic models. *Metabolites* **11**, 695 (2021).
43. Rossow, H. A. & Calvert, C. C. Computer modeling of obesity links theoretical energetic measures with experimental measures of fuel use for lean and obese men. *J. Nutr.* **144**, 1650–1657 (2014).
44. Anton, S. D. et al. Flipping the metabolic switch: understanding and applying the health benefits of fasting. *Obesity* **26**, 254–268 (2018).
45. Mattson, M. P., Moehl, K., Ghena, N., Schmaedick, M. & Cheng, A. Intermittent metabolic switching, neuroplasticity and brain health. *Nat. Rev. Neurosci.* **19**, 81–94 (2018).
46. Szili-Torok, T. et al. Fasting ketone bodies and incident type 2 diabetes in the general population. *Diabetes* **72**, 1187–1192 (2023).
47. Lebech Cichosz, S. & Bender, C. Development of machine learning models for the identification of elevated ketone bodies during hyperglycemia in patients with type 1 diabetes. *Diab. Technol. Ther.* **26**, 403–410 (2024).
48. Seyfried, T. N., Sanderson, T. M., El-Abbadi, M. M., McGowan, R. & Mukherjee, P. Role of glucose and ketone bodies in the metabolic control of experimental brain cancer. *Br. J. Cancer* **89**, 1375–1382 (2003).
49. Schoeler, N. E. et al. An examination of biochemical parameters and their association with response to ketogenic dietary therapies. *Epilepsia* **58**, 893–900 (2017).
50. Wang, P. et al. N-of-1 health optimization: digital monitoring of biomarker dynamics to gamify adherence to metabolic switching. *PNAS Nexus* **3**, pgae214 (2024).
51. Patel, M. S. et al. Effect of a game-based intervention designed to enhance social incentives to increase physical activity among families. *JAMA Intern. Med.* **177**, 1586 (2017).
52. Patel, M. S. et al. Effect of behaviorally designed gamification with social incentives on lifestyle modification among adults with uncontrolled diabetes. *JAMA Netw. Open* **4**, e2110255 (2021).
53. Patel, M. S. et al. Effect of goal-setting approaches within a gamification intervention to increase physical activity among economically disadvantaged adults at elevated risk for major adverse cardiovascular events. *JAMA Cardiol.* **6**, 1387 (2021).
54. Moonla, C. et al. Continuous ketone monitoring via wearable microneedle patch platform. *ACS Sens.* **9**, 1004–1013 (2024).
55. Moon, J. M. et al. Self-testing of ketone bodies, along with glucose, using touch-based sweat analysis. *ACS Sens*. **7**, 3973–3981 (2023).
56. Go, A. et al. Highly sensitive electrochemical sensor for diagnosis of diabetic ketoacidosis (DKA) by measuring ketone bodies in urine. *Sensors* **21**, 4902 (2021).
57. Musa-Veloso, K., Likhodii, S. S. & Cunnane, S. C. Breath acetone is a reliable indicator of ketosis in adults consuming ketogenic meals. *Am. J. Clin. Nutr.* **76**, 65–70 (2002).
58. Alkedeh, O. & Priefer, R. The ketogenic diet: breath acetone sensing technology. *Biosensors* **11**, 26 (2021).
59. Arwani, R. T. et al. Stretchable ionic–electronic bilayer hydrogel electronics enable in situ detection of solid-state epidermal biomarkers. *Nat. Mater.* **23**, 1115–1122 (2024).
60. Cichosz, S. L., Jensen, M. H. & Hejlesen, O. Short-term prediction of future continuous glucose monitoring readings in type 1 diabetes: development and validation of a neural network regression model. *Int. J. Med. Inf.* **151**, 104472 (2021).
61. Brown, S. A. et al. Six-month randomized, multicenter trial of closed-loop control in type 1 diabetes. *N. Engl. J. Med.* **381**, 1707–1717 (2019).
62. Dehghani Zahedani, A. et al. Improvement in glucose regulation using a digital tracker and continuous glucose monitoring in healthy adults and those with type 2 diabetes. *Diab. Ther.* **12**, 1871–1886 (2021).
63. Alam, N. et al. Digital twin generators for disease modeling. Preprint at https://arxiv.org/abs/2405.01488 (2024).
64. An, G. & Cockrell, C. Generating synthetic multi-dimensional molecular-mediator time series data for artificial intelligence-based

disease trajectory forecasting and drug development digital twins: considerations. *Front. Syst. Biol*. **3**, 1188009 (2023).
65. Ferrara, E. GenAI against humanity: nefarious applications of generative artificial intelligence and large language models. *J. Comput. Soc. Sci.* **7**, 549–569 (2024).
66. Schramowski, P., Turan, C., Andersen, N., Rothkopf, C. A. & Kersting, K. Large pre-trained language models contain human-like biases of what is right and wrong to do. *Nat. Mach. Intell.* **4**, 258–268 (2022).
67. Chen, Y. & Esmaeilzadeh, P. Generative AI in medical practice: in-depth exploration of privacy and security challenges. *J. Med. Internet Res.* **26**, e53008 (2024).
68. World Health Organization. *Digital Health Not Accessible by Everyone Equally, New Study Finds*. https://www.who.int/europe/news/item/21-12-2022-digital-health-not-accessible-by-everyone-equally-new-study-finds (2022).
69. Chandrasekaran, R., Katthula, V. & Moustakas, E. Patterns of use and key predictors for the use of wearable health care devices by US Adults: insights from a national survey. *J. Med. Internet Res.* **22**, e22443 (2020).
70. Roland Berger. *Bridging the Digital Divide*. https://www.rolandberger.com/en/Insights/Publications/Bridging-the-digital-divide.html (2021).
71. ITU. *Facts and Figures 2023—Internet use*. https://www.itu.int/itu-d/reports/statistics/2023/10/10/ff23-internet-use/ (2023).
72. The Business Times. *Singapore Ranks 1st in Digital Inclusiveness, but South-east Asia Lags: Report*. https://www.businesstimes.com.sg/international/asean/singapore-ranks-1st-in-digital-inclusiveness-but-south-east-asia-lags-report (2021).
73. Fore, D., Goldenhar, L. M., Margolis, P. A. & Seid, M. Using goal-directed design to create a novel system for improving chronic illness care. *JMIR Res. Protoc.* **2**, e43 (2013).
74. Halfon, N. et al. Applying a 3.0 transformation framework to guide large-scale health system reform. *Health Aff*. **33**, 2003–2011 (2014).
75. CDC. *Poor Nutrition*. https://web.archive.org/web/20240418182842/https://www.cdc.gov/chronicdisease/resources/publications/factsheets/nutrition.htm (2022).
76. Macaninch, E. et al. Time for nutrition in medical education. *BMJ Nutr. Prev. Health* **3**, 40 (2020).
77. Crowley, J., Ball, L. & Hiddink, G. J. Nutrition in medical education: a systematic review. *Lancet Planet. Health* **3**, e379–e389 (2019).
78. Foster, S., Beck, E., Hughes, J. & Grafenauer, S. Whole grains and consumer understanding: investigating consumers' identification, knowledge and attitudes to whole grains. *Nutrients* **12**, 2170 (2020).
79. Chan, C. M. J., Dickens, B. S. L. & Chong, M. F. F. Understanding knowledge, attitudes and behaviours related to dietary sodium intake in a multi-ethnic population in Singapore. *Public Health Nutr.* **26**, 2802–2814 (2023).
80. Brandt, E. J., Mozaffarian, D., Leung, C. W., Berkowitz, S. A. & Murthy, V. L. Diet and food and nutrition insecurity and cardiometabolic disease. *Circ. Res.* **132**, 1692–1706 (2023).
81. Thorndike, A. N. et al. Strengthening US food policies and programs to promote equity in nutrition security: a policy statement from the American Heart Association. *Circulation* **145**, E1077–E1093 (2022).
82. USDA ERS. *Food Security and Nutrition Assistance*. https://www.ers.usda.gov/data-products/ag-and-food-statistics-charting-the-essentials/food-security-and-nutrition-assistance/ (2025).
83. Wang, P. et al. WisDM Green: harnessing artificial intelligence to design and prioritize compound combinations in peat moss for sustainable farming applications. *Adv. Intell. Syst.* **4**, 2200095 (2022).
84. Volpp, K. G. & Lamberton, C. Behavioral economics to enhance food is medicine programs. *JAMA Health Forum* **5**, e241586–e241586 (2024).
85. The Straits Times. *Gig Workers in Singapore to Get Basic Protection including Insurance and CPF from as early as 2024*. https://www.straitstimes.com/singapore/platform-workers-to-be-insured-against-workplace-injuries-get-cpf-payments (2022).
86. Eco-Business. *Exploited and Unprotected: Life as a Gig Worker*. https://www.eco-business.com/opinion/exploited-and-unprotected-life-as-a-gig-worker/ (2023).
87. Wang, S., Li, L. Z. & Coutts, A. National survey of mental health and life satisfaction of gig workers: the role of loneliness and financial precarity. *BMJ Open* **12**, 66389 (2022).
88. Vlassoff, C. Gender differences in determinants and consequences of health and illness. *J. Health Popul. Nutr.* **25**, 47 (2007).
89. Temkin, S. M. et al. Chronic conditions in women: the development of a National Institutes of Health framework. *BMC Womens Health* **23**, 162 (2023).
90. Vogt, B. J. et al. Determining sex differences in drug combinations targeting aortic valve myofibroblast activation using an artificial intelligence derived platform. Preprint at https://doi.org/10.1101/2024.10.02.615251 (2024).
91. Gerdts, E. et al. Sex differences in arterial hypertension. *Eur. Heart J.* **43**, 4777–4788 (2022).
92. European Society of Cardiology. *High Blood Pressure is the Most Deadly Risk Factor for Women Worldwide*. https://www.escardio.org/The-ESC/Press-Office/Press-releases/high-blood-pressure-is-the-most-deadly-risk-factor-for-women-worldwide (2023).
93. Russo, K. Assessment and treatment of adolescents with chronic medical conditions. *J. Health Serv. Psychol.* **48**, 69–78 (2022).
94. Miller, V. A., Xiao, R., Slick, N., Feudtner, C. & Willi, S. M. Youth involvement in the decision to start CGM predicts subsequent CGM use. *Diab. Care* **43**, 2355 (2020).
95. Global Health Observatory. *Raised Cholesterol*. https://www.who.int/data/gho/indicator-metadata-registry/imr-details/3236 (2025)
96. Zhou, B. et al. Worldwide trends in hypertension prevalence and progress in treatment and control from 1990 to 2019: a pooled analysis of 1201 population-representative studies with 104 million participants. *Lancet* **398**, 957–980 (2021).
97. International Diabetes Federation. *Diabetes Facts and Figures*. https://idf.org/about-diabetes/diabetes-facts-figures/ (2021).
98. World Heart Federation. *World Heart Report 2023: Confronting the World's Number One Killer* (World Heart Federation, 2023).

Acknowledgements
D.H. gratefully acknowledges funding from the Institute for Digital Medicine Translational Research Programme (grant number A-0001319-00-00) at the Yong Loo Lin School of Medicine, The N.1 Institute for Health, and the College of Design and Engineering at the National University of Singapore.

Author contributions
All authors contributed to concept of the manuscript. C.S. and P.W. drafted and revised the manuscript, N.F. and D.H. reviewed the manuscript. All authors read and approved the final manuscript.

Competing interests
D.H. is one of the inventors of previously filed pending patents on artificial intelligence-based therapy development. D.H. is a co-founder and shareholder of KYAN Therapeutics, which is commercializing intellectual property pertaining to AI-based personalized medicine. The remaining authors declare no competing interests.

Additional information
Correspondence and requests for materials should be addressed to Dean Ho.