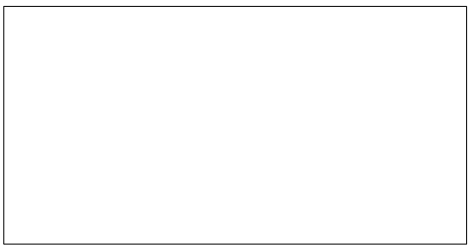

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Review

Digital twin paradigm in diabetes prediction and management

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ABSTRACT

Traditional diabetes management employs reactive strategies with therapeutic adjustments after adverse glycaemic events rather than proactive prevention, resulting in suboptimal control and increased complications. Digital twin (DT) technology creates virtual replicas through computational modelling and real time data integration as a transformative approach. However, questions remain regarding clinical validation, implementation feasibility, and generalisability. This review examines current applications, challenges, and future potential of digital twin technology in diabetes prediction and management. PubMed, Scopus, Web of Science, and IEEE Xplore databases were searched for peer reviewed articles (2015–2024) on DT applications in diabetes care, predictive modelling, and therapeutic optimisation. Critical synthesis compared methodological approaches, performance metrics, and implementation challenges. DT demonstrate variable but promising potential through glucose prediction, personalised insulin dosing, dietary optimisation, and complication risk assessment, integrating continuous glucose monitoring, wearable sensors, and machine learning algorithms. Evidence quality varies substantially, with most studies representing proof-of-concept or pilot implementations. Implementation faces data privacy concerns, validation requirements, and integration complexities. Critical gaps exist in long-term effectiveness, algorithmic bias mitigation, and generalisability to underserved populations. DT technology represents an evolving paradigm towards precision diabetes care. However, rigorous clinical validation, addressing equity concerns, and establishing sustainable implementation frameworks remain essential for widespread adoption.

1. Introduction

Diabetes mellitus has evolved from a relatively uncommon condition to one of the most pressing public health challenges of the 21st century [1]. The International Diabetes Federation reports that approximately 537 million adults aged 20 to 79 years were living with diabetes in 2021, with this figure projected to rise to 643 million by 2030 and 783 million by 2045 [2]. This exponential growth trajectory, coupled with the substantial economic burden estimated at USD 966 billion in global healthcare expenditure annually, necessitates innovative approaches to diabetes prevention, prediction, and management [3]. The disease's multifaceted nature, characterised by complex metabolic interactions and significant inter individual variability in treatment response, presents substantial challenges to conventional one size fits all therapeutic strategies.

The landscape of diabetes care has undergone remarkable transformation over recent decades, transitioning from rudimentary urine glucose testing to sophisticated continuous glucose monitoring systems and automated insulin delivery devices. Despite these technological advances, significant gaps persist in achieving optimal glycaemia control across patient populations [4,5]. Studies across multiple health systems indicate that a substantial proportion of individuals with

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diabetes fail to achieve recommended clinical targets, with optimal attainment often below 50 % in routine practice, underscoring the limitations of current management paradigms [6–8]. The reactive nature of traditional diabetes care, where therapeutic adjustments occur in response to adverse events or suboptimal outcomes rather than anticipating them, contributes to this suboptimal control and the subsequent development of debilitating microvascular and macrovascular complications [9,10].

Digital twin technology, originally developed in aerospace and manufacturing industries for predictive maintenance and system optimisation, has emerged as a potentially transformative approach in healthcare [11]. Digital twins are conceptually distinct from but related to several established approaches in computational medicine [12]. While virtual patient models typically represent population-level physiological responses and in silico simulations focus on specific biological processes or drug interactions, digital twins uniquely combine these elements with continuous real-time data integration to create dynamic, individualised representations that evolve throughout a patient's disease trajectory [13,14]. Unlike conventional clinical decision support systems that primarily provide rule-based recommendations, digital twins employ sophisticated computational modelling to simulate future states and predict outcomes under different scenarios before clinical implementation. A digital twin is defined as a dynamic virtual representation of a physical entity or system that spans its lifecycle, updated from real time data, and uses simulation, machine learning, and reasoning to support decision making [15]. In the context of diabetes, digital twins create individualised computational models that mirror a patient's unique physiological responses to various factors, including food intake, physical activity, medication, stress, and circadian rhythms [16]. However, the term “patient-specific digital twin” refers to a computational replica calibrated to an individual patient's unique metabolic parameters, treatment responses, and disease progression patterns, distinguishing it from generalised population models [17]. These virtual representations enable clinicians and patients to simulate different scenarios, predict outcomes, and optimise therapeutic interventions before implementing them in the real world.

The convergence of several technological advances has catalysed the development of diabetes focused digital twins [17]. Continuous glucose monitoring devices now provide glucose readings every few minutes, generating rich longitudinal datasets that capture glycaemic patterns with unprecedented granularity [18]. Wearable sensors track physical activity, heart rate variability, sleep patterns, and other physiological parameters that influence glucose metabolism [19,20]. Smartphone applications facilitate dietary logging and medication adherence tracking, whilst cloud computing infrastructure enables the storage and processing of massive datasets [17]. Artificial intelligence and machine learning algorithms can identify complex patterns within these multidimensional data streams, learning individual specific relationships between inputs and glycaemic outcomes [21]. Together, these technologies provide the foundation for creating sophisticated, personalised digital twins that hold promise for revolutionising diabetes care pending rigorous validation.

Importantly, behavioural, psychological, and social dimensions fundamentally influence diabetes management outcomes alongside biological factors. Medication adherence, dietary choices, physical activity, stress management, and healthcare engagement profoundly impact glycaemic control [22,23]. Comprehensive digital twin frameworks must therefore integrate these dimensions to achieve clinically meaningful personalization.

However, despite the promise of digital twin technology in diabetes, several critical gaps warrant comprehensive examination [24,25]. The problem lies in the fragmented understanding of how digital twin applications can be effectively implemented across the diabetes care continuum, from early prediction of disease onset to optimisation of long-term management strategies. Additionally, most published evidence represents early-stage research with limited clinical validation, raising questions about real-world effectiveness, safety, and scalability [16,24,25]. The rationale for this review stems from the need to critically synthesise emerging evidence, evaluate methodological quality, identify current capabilities and limitations, and establish a roadmap for future development. The novelty of this work resides in its comprehensive examination of digital twin applications spanning both prediction and management domains, addressing technical, clinical, and implementation perspectives with critical appraisal of evidence quality and generalisability that have not been collectively analysed in existing literature. The aim of this review is to critically evaluate the current state of digital twin technology in diabetes prediction and management, examining its methodological foundations, clinical applications, challenges, and future directions. The specific objectives are to: (1) elucidate the fundamental principles and technical architectures of digital twin systems in diabetes care; (2) analyse current applications in diabetes risk prediction and early detection with critical comparison of methodological approaches and performance metrics; (3) evaluate digital twin implementations in glucose prediction and management optimisation distinguishing between proof-of-concept studies, pilot implementations, and clinically validated systems; (4) identify challenges and barriers to widespread adoption including model limitations, dataset biases, and failure modes; and (5) propose evidence-based future research directions to advance the field. As illustrated in Fig. 1, digital twin technology integrates multimodal data streams to create a dynamic virtual replica of each patient for predictive and personalised diabetes management.

The figure illustrates how multimodal data from continuous glucose monitoring, wearable sensors, and clinical records are integrated into computational models that form patient specific digital twins. These virtual representations enable real time simulation, prediction, and therapeutic optimisation through iterative feedback between patient and clinician interfaces. Also, the figure represents an idealised framework; actual implementations vary substantially in data sources, model complexity, and validation status.

2. Methods

This narrative review was undertaken to provide a comprehensive and critical synthesis of current knowledge regarding digital twin technology applications in diabetes prediction and management. Unlike systematic reviews that aim for exhaustive literature coverage with predefined protocols, narrative reviews offer flexibility to explore complex, multifaceted topics through critical analysis and thematic synthesis. This approach was deemed appropriate given the emerging and rapidly evolving nature of digital twin technology in healthcare, where the landscape encompasses diverse methodological approaches, technological platforms, and clinical applications that benefit from integrative analysis rather than purely quantitative synthesis. However, this methodological choice introduces inherent limitations including potential selection bias and lack of quantitative *meta*-analysis, as discussed in Section 7.

2.1. Literature search and selection

A broad literature search was conducted across multiple databases including PubMed, Scopus, Web of Science, and IEEE Xplore to identify relevant publications from January 2015 to December 2024. This timeframe was selected to capture the contemporary development of digital twin applications in diabetes care whilst acknowledging that the conceptual foundations extend further back. The search strategy employed the following combinations of terms using Boolean operators:

Primary search string: (“digital twin” OR “virtual patient” OR “in silico model*” OR “computational model*”) AND (“diabetes mellitus” OR “type 1 diabetes” OR “type 2 diabetes” OR “glucose” OR “glyc?emic control” OR “glyc?aemic control”) AND (“prediction” OR “forecasting” OR “management” OR “therapy” OR “treatment optim*”)**.

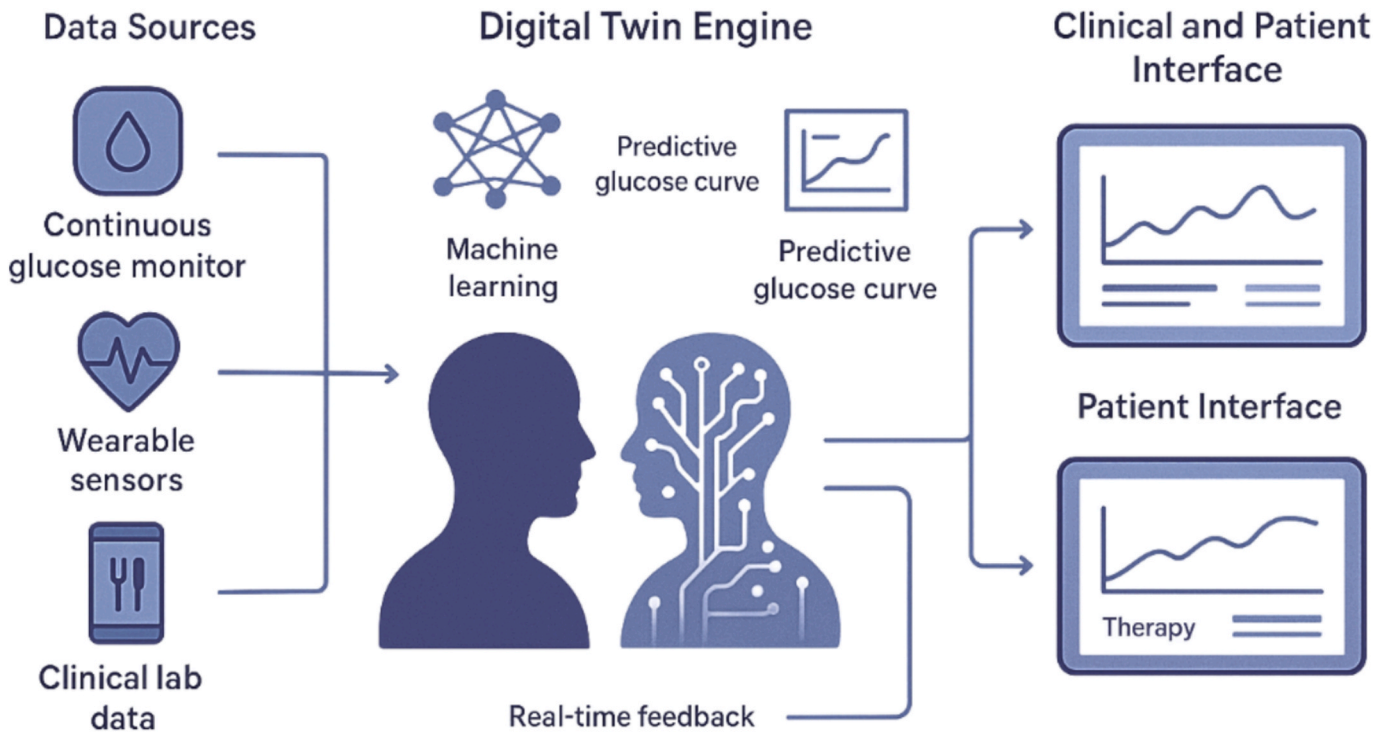

Fig. 1. Conceptual framework of digital twin technology in diabetes prediction and management.

Secondary searches incorporated technology-specific terms: ("continuous glucose monitor" OR "CGM") AND ("digital twin" OR "predictive model*"); ("artificial pancreas" OR "closed loop") AND ("digital twin*" OR "virtual patient*"); ("machine learning" OR "deep learning" OR "artificial intelligence") AND ("diabetes" OR "glucose") AND ("digital twin*" OR "computational model*").

The search strategy was deliberately inclusive rather than restrictive, reflecting the narrative review approach of casting a wide net to capture the breadth of the field. After removing duplicates and screening for relevance, a substantial body of peer-reviewed literature formed the evidence base for detailed analysis.

Literature selection prioritised peer-reviewed journal articles, conference proceedings from major scientific meetings, and technical reports from recognised institutions and regulatory agencies. Publications were included if they: described digital twin, virtual patient, or in silico modelling approaches specifically applied to diabetes prediction or management; presented original empirical data, systematic reviews, or substantive technical/methodological descriptions; were published in English; and provided sufficient methodological detail for critical evaluation. Publications were excluded if they: focused solely on other chronic diseases without diabetes-specific applications; provided only abstract-level descriptions without methodological substance; or represented commentary or opinion pieces without empirical foundation. Both empirical studies reporting original data and conceptual papers providing theoretical frameworks were included to ensure comprehensive coverage. The review emphasised recent publications whilst incorporating seminal earlier works that established foundational concepts. Reference lists of retrieved articles were examined to identify additional relevant sources through snowball sampling, and forward citation searching was employed to locate more recent work building on key publications. Expert knowledge of the field guided identification of important contributions that might not surface through database searching alone, including emerging preprints and conference presentations representing cutting edge developments.

2.2. Thematic analysis and synthesis

The synthesis approach employed thematic analysis to organise the diverse literature into coherent conceptual domains. Initial reading of included publications identified recurring themes, which were iteratively refined through constant comparison and discussion to develop the review's organisational framework. The final thematic structure encompasses fundamental concepts and architectures of digital twin technology; applications in diabetes prediction including risk stratification and early detection; applications in diabetes management spanning glucose prediction, therapy optimisation, and lifestyle personalisation; challenges and barriers to implementation; and future directions and emerging opportunities. This structure was designed to guide readers from foundational understanding through current applications to critical analysis of limitations and forward-looking perspectives.

Within each thematic domain, the synthesis prioritised critically identifying patterns, contrasts, methodological strengths and weaknesses, and gaps in the literature rather than attempting comprehensive enumeration of all published studies. For each application area, we systematically compared: modelling approaches and their theoretical foundations; data sources and quality; validation methods and evidence quality; reported performance metrics and their clinical significance; study populations and generalisability; and acknowledged limitations and potential biases. The narrative approach enabled critical interpretation of findings, contextualisation within the broader diabetes care landscape, and integration of insights from adjacent fields such as systems biology, artificial intelligence, and implementation science. Where quantitative data were reported across multiple studies, ranges or representative values are presented to illustrate typical performance characteristics without formal *meta*-analysis. Evidence quality was assessed using considerations of study design (e.g., prospective vs retrospective, controlled vs observational), sample size, validation approach (e.g., internal vs external validation, in silico vs clinical), follow-up duration, and acknowledgment of limitations. The synthesis deliberately highlights areas of uncertainty, inconsistency, or controversy to inform future research priorities rather than presenting an

artificially unified picture of the field.

This narrative review methodology acknowledges inherent limitations including potential author bias in literature selection and interpretation, lack of formal quality assessment of included studies, and absence of quantitative effect size synthesis. These limitations are particularly relevant in the context of digital twin research, where rapid technological evolution, heterogeneous methodologies, and limited long-term clinical validation create challenges for evidence synthesis. Publication bias favouring positive results may lead to overestimation of digital twin effectiveness, while proprietary commercial developments may not be adequately represented in peer-reviewed literature. However, these limitations are balanced by strengths including flexibility to address complex multidisciplinary topics, ability to incorporate diverse evidence types, and capacity for critical analysis that extends beyond what individual studies report to generate novel insights and frameworks. The resulting review aims to provide readers with a comprehensive yet accessible overview of digital twin technology in diabetes that serves both as an introduction for those new to the field and a critical synthesis for domain experts.

3. Applications of digital twin technology in diabetes prediction

3.1. Early detection and risk stratification

Digital twin technology offers substantial potential for enhancing diabetes prediction and risk stratification at both population and individual levels [26,27]. However, most applications remain in early development stages with limited prospective clinical validation [17,28]. Population based digital twins aggregate data from large cohorts to identify patterns and risk factors associated with diabetes development, enabling targeted screening and prevention strategies [29]. These systems integrate demographic data, genetic information, lifestyle factors, biomarkers, and social determinants of health to generate risk scores with reported superior accuracy compared to traditional risk calculators [30,31]. However, direct comparison studies between digital twin approaches and established risk scores are limited. Studies have demonstrated that machine learning enhanced risk models can achieve area under receiver operating characteristic curves of 0.84 to 0.92 for predicting type 2 diabetes onset within 5 to 10 years, compared to AUC values of approximately 0.74–0.78 for the Finnish Diabetes Risk Score and 0.72–0.76 for the Framingham Offspring Study model, significantly outperforming conventional tools in retrospective validation studies [32–36]. Critical limitations include: most models are validated only on single cohorts from high-income countries; performance in diverse ethnic and socioeconomic groups remains inadequately characterised; prospective implementation studies demonstrating clinical utility are lacking; and cost-effectiveness compared to existing screening approaches has not been established.

Individual-focused digital twins take prediction a step further by creating personalised models that evolve as new data become available [37]. This represents a conceptual advance over static risk calculators, though evidence for clinical superiority remains preliminary. For individuals identified as high risk, continuous monitoring through wearable devices and periodic biomarker assessments feed into digital twin models that refine risk estimates over time [38]. These systems can detect subtle deviations from normal glucose homeostasis that precede overt diabetes, such as progressive postprandial hyperglycaemia or declining first phase insulin secretion [17,39]. Evidence suggests that incorporating Continuous Glucose Monitoring (CGM) data into predictive models can enhance the accuracy of forecasting diabetes progression by capturing glycemic variability missed by standard metrics. In particular, longitudinal studies of high-risk populations—such as individuals with islet autoantibodies, have demonstrated that specific CGM-derived markers (e.g., time spent above 140 mg/dL) can predict the onset of clinical diabetes with positive predictive values (PPV) exceeding 75 % [40,41]. However, these findings are based primarily on retrospective analyses with limited follow-up periods. Key methodological concerns include: CGM-based prediction models require expensive continuous monitoring that may not be cost-effective for population screening; definitions of "progression" vary across studies, complicating comparisons; the incremental benefit over simpler approaches (e.g., periodic HbA1c testing) has not been rigorously quantified; and adherence to continuous monitoring in real-world settings may be substantially lower than in research contexts. This enhanced prediction capability potentially enables implementation of intensive prevention strategies precisely when they are most likely to be effective, though clinical trials demonstrating improved prevention outcomes are needed.

3.2. Gestational diabetes prediction

Gestational Diabetes Mellitus (GDM) affects approximately 14 % of pregnancies globally. Emerging research indicates that digital twin technology, specifically through machine learning-integrated physiological modeling, demonstrates potential for enhancing early risk stratification and personalizing glycemic interventions in this population [42]. The physiological changes of pregnancy, characterised by progressive insulin resistance and increased metabolic demands, create a dynamic system well suited to digital twin modelling [24]. Predictive models incorporating maternal characteristics, first trimester biomarkers, genetic risk scores, and early pregnancy glucose measurements can identify women at high risk for gestational diabetes well before the standard screening at 24 to 28 weeks gestation [43,44]. Early identification could potentially enable implementation of dietary modifications, physical activity programmes, and close monitoring that may prevent or delay gestational diabetes onset. Studies evaluating predictive models in early pregnancy have reported good discriminatory performance, though digital twin-specific sensitivities require further validation [45], and specificities of 75 to 90 percent for predicting gestational diabetes in the first trimester, substantially earlier than conventional screening methods [43,46]. However, critical evaluation reveals several limitations: most studies are retrospective case-control designs rather than prospective cohort validations; prediction performance varies substantially across populations, with lower accuracy in ethnically diverse cohorts; whether early prediction translates to improved pregnancy outcomes through early intervention remains unproven; false positive rates of 10–25 % could lead to unnecessary interventions and maternal anxiety; and cost-effectiveness analyses comparing early digital twin-based screening to standard care are lacking [47,48].

3.3. Complication risk prediction

Beyond predicting diabetes onset, digital twins have been proposed for forecasting the development and progression of diabetes related complications [31]. Microvascular complications including diabetic retinopathy, nephropathy, and neuropathy, as well as macrovascular complications such as cardiovascular disease, cerebrovascular disease, and peripheral arterial disease, result from cumulative metabolic injury over years to decades [49]. Digital twins that integrate longitudinal glycaemic data, blood pressure, lipid profiles, medication adherence, lifestyle factors, and genetic susceptibility have demonstrated individual complication risks with greater accuracy than existing risk equations in validation studies [39,50]. For instance, models predicting cardiovascular events in people with diabetes have achieved C statistics of 0.78 to 0.83, comparing favorably to C statistics of 0.72–0.76 for established risk calculators such as the UKPDS Risk Engine and the Framingham Risk Score [51]. However, several critical gaps limit clinical translation: most models are trained and validated on historical cohort data, potentially limiting applicability to contemporary treatment paradigms; algorithm performance may degrade over time as treatment patterns evolve; whether model-based risk stratification actually improves clinical decision-making and patient outcomes has not been rigorously

tested; many models perform poorly in underrepresented populations due to training data limitations; and the clinical utility of marginal improvements in C statistics (0.06–0.11) for guiding treatment intensification remains unclear [39,52]. This enhanced prediction could potentially enable risk stratified management approaches, directing intensive interventions to those at highest risk whilst avoiding overtreatment in lower risk individuals, though prospective intervention studies are needed to validate this hypothesis.

Table 1 summarises key digital twin applications in diabetes prediction, highlighting their methodologies and reported performance metrics. It is important to note that performance metrics represent findings from validation studies and may not generalise to diverse clinical populations. Most applications remain at proof-of-concept or early pilot stages.

4. Applications of digital twin technology in diabetes management

4.1. Glucose prediction and monitoring Enhancement

Real time glucose prediction represents one of the most mature and clinically impactful applications of digital twin technology in diabetes management [17,28]. This application area includes both commercially available systems with regulatory approval and research prototypes, requiring careful distinction. Short term forecasting (30 to 120 min) enables proactive interventions to prevent hypo and hyperglycaemia by integrating continuous glucose monitoring data with insulin dosing, carbohydrate intake, and physical activity [58]. Advanced models provide confidence intervals alongside point predictions, achieving mean absolute relative differences of 10 to 15 percent for 30 min ahead predictions and 15 to 25 percent for 60 min ahead predictions in type 1 diabetes, performance considered clinically useful for therapeutic decision making [16,59]. However, performance varies substantially across studies depending on: prediction horizon, with accuracy degrading significantly beyond 60 min; glycemic range, with lower accuracy during rapid transitions; patient characteristics, including diabetes duration and glycemic variability; and data quality, with sensor errors and missing data compromising predictions. Critical methodological limitations include: most validation studies use retrospective data rather than prospective real-time implementation; performance metrics often exclude periods of sensor dropout or calibration, inflating apparent accuracy; clinical impact depends not only on prediction accuracy but also on patient/clinician response to alerts; and algorithm failures during critical hypoglycemic episodes could have serious safety implications.

Clinical benefits are substantial for specific commercially available systems with rigorous validation. Predictive low glucose suspend systems, which automatically halt insulin delivery when hypoglycaemia is forecast, have reduced nocturnal hypoglycaemia episodes by 30 to 50 percent without increasing hyperglycaemia or ketoacidosis risk [60,61]. These findings are based on randomised controlled trials of FDA-approved systems, representing the highest level of evidence in this review. Predictive alerts enable preemptive interventions to attenuate glycaemic excursions [62]. User satisfaction is high, with 80 to 90 percent reporting that predictions improve treatment decisions and management confidence, underscoring the value of translating digital twin predictions into actionable insights that empower patients and clinicians [60]. However, real-world effectiveness may differ from trial conditions due to: alert fatigue, with users disabling alerts over time; socioeconomic barriers limiting access to expensive technologies; variable patient numeracy and health literacy affecting interpretation; and limited data on long-term durability of benefits beyond 6–12 month study periods.

4.2. Personalised insulin dosing and therapy optimisation

Digital twin technology enables personalised insulin therapy by modelling individual responses to different dosing regimens [24,63]. For multiple daily injection users, digital twins simulate various basal insulin doses and insulin to carbohydrate ratios to identify optimal parameters maximising time in range whilst minimising hypoglycaemia [64]. However, most such applications remain in research or pilot phases without large-scale clinical validation. For insulin pump therapy, digital twins optimise basal rate profiles, insulin sensitivity factors, and duration of insulin action parameters governing automated delivery algorithms. Studies report time in range increases of 5 to 15 percentage points with digital twin guided dosing compared to standard care, translating to 1 to 3.5 additional hours daily within target glucose levels [63,64]. Critical evaluation reveals important caveats: “standard care” comparators vary widely across studies, from basic insulin pump therapy to sensor-augmented pumps, complicating interpretation; most studies have small sample sizes and short durations; improvement magnitudes are highly variable (5–15 percentage points), suggesting heterogeneous patient benefit; whether personalisation algorithms outperform careful conventional titration by experienced clinicians remains uncertain; and long-term sustainability of improvements and risk of algorithm degradation over time are unknown [28,63].

Closed loop insulin delivery systems (artificial pancreas systems)

Table 1
Digital Twin Applications in Diabetes Prediction.

Application Domain	Data Inputs	Modelling Approaches	Key Outcomes	Reported Performance
Type 2 Diabetes Risk Prediction [53]	Demographics, biomarkers, lifestyle factors, genetic data, social determinants	Machine learning (random forests, neural networks), risk scoring algorithms	5–10-year diabetes onset prediction, identification of high-risk individuals	AUC 0.85–0.92; superior to conventional risk scores
Prediabetes Progression [54]	Continuous glucose monitoring, biomarkers, anthropometrics, lifestyle data	Time series analysis, recurrent neural networks, mechanistic glucose models	Prediction of progression from prediabetes to diabetes	PPV > 75 % for 3-year progression; sensitivity 70–80 %
Gestational Diabetes Prediction [43,55]	First trimester biomarkers, maternal characteristics, genetic risk scores, early glucose measurements	Logistic regression, machine learning, Bayesian models	Early pregnancy prediction of gestational diabetes	Sensitivity 70–85 %, specificity 75–90 % in first trimester
Complication Risk Stratification [56]	Longitudinal glycaemic data, blood pressure, lipids, medication adherence, genetic factors	Cox proportional hazards, machine learning, multi state models	Prediction of microvascular and macrovascular complications	C statistic 0.78–0.83 for cardiovascular events; improved calibration over existing calculators
Hypoglycaemia Prediction [57]	Continuous glucose monitoring, insulin dosing, meals, physical activity	Recurrent neural networks, support vector machines, hybrid models	30–60 min ahead hypoglycaemia prediction	Sensitivity 85–95 %, specificity 80–90 % at 30 min

Note: AUC = Area Under Curve; PPV = Positive Predictive Value. Performance metrics are derived from validation studies, predominantly single-center retrospective analyses. Clinical utility, cost-effectiveness, and performance in diverse populations require further investigation. Evidence quality varies from proof-of-concept (hypoglycemia prediction) to multi-cohort validation (Type 2 diabetes risk prediction).

represent the most clinically mature digital twin applications in diabetes management [65]. These represent the transition from proof-of-concept to commercially available, FDA/CE-approved medical devices with robust clinical evidence. These systems integrate continuous glucose monitoring, insulin pumps, and control algorithms that automatically adjust insulin delivery based on glucose predictions and physiological models [65,66]. The algorithms function as simplified digital twins, continuously updating insulin sensitivity understanding and predicting future requirements to maintain target glucose levels [67]. Commercial hybrid closed loop systems demonstrate substantial glycaemic improvements, with randomized trials and *meta*-analyses reporting time in range increases of approximately 6 to 11 percentage points and haemoglobin A1c reductions of 0.3 to 0.5 percent compared to sensor-augmented pump therapy [68]. These findings represent rigorous evidence from multiple randomised controlled trials, though important limitations include: studies primarily enroll motivated, technology-savvy participants from high-income countries; performance in populations with erratic lifestyles, high glycemic variability, or limited healthcare access is less well characterised; long-term outcomes beyond 6–12 months remain limited; cost-effectiveness compared to conventional intensive therapy has not been definitively established in diverse healthcare systems; and device failures, algorithm errors, and user errors can lead to serious adverse events including severe hypoglycemia and diabetic ketoacidosis [16,39,68]. Fully automated systems under investigation achieve time in range values exceeding 70 percent across diverse populations including children, adolescents, adults, and pregnant women [69]. However, "fully automated" systems still require meal announcements and user oversight, and their performance deteriorates with non-compliance or device malfunctions.

4.3. Dietary and lifestyle optimisation

Digital twins extend beyond medication to encompass dietary and lifestyle interventions, areas that substantially affect glycaemic control but are highly individualised and challenging to optimise [17,70]. Personalised nutrition models predict postprandial glucose responses to specific foods based on individual metabolic characteristics, gut microbiome composition, and dietary patterns [70]. This represents an emerging application area with predominantly proof-of-concept evidence rather than validated clinical systems. The Personalised Nutrition Project demonstrated remarkable inter individual variability, with some people showing greater glucose excursions to bananas than cookies whilst others showed the opposite pattern [71]. Digital twins using machine learning trained on continuous glucose monitoring and dietary data predict postprandial responses with mean absolute errors of 15 to 25 mg/dL, potentially enabling personalised recommendations that optimise glycaemic control without restrictive elimination diets (which refer to complete avoidance of multiple food categories, potentially leading to nutritional inadequacy) [17,71,72]. However, critical methodological concerns include several key limitations. Prediction accuracy of 15 to 25 mg/dL may be insufficient for precise dietary guidance given normal postprandial excursions of 50 to 100 mg/dL [16,73]. Models trained on free-living populations may conflate effects of food composition with eating context, timing, and physical activity. While personalized nutrition approaches show potential, evidence regarding their superior efficacy for long-term glycemic control compared to standard dietary guidelines remains heterogeneous and inconclusive in systematic reviews. Furthermore, the clinical utility of such interventions is frequently limited by sub-optimal adherence, particularly when algorithm-driven recommendations lack concordance with an individual's gustatory preferences or sociocultural food norms [74]. Additionally, the cost of CGM monitoring required for personalisation may not be justified by clinical benefits.

Physical activity represents another critical factor amenable to digital twin optimisation. Exercise effects on glucose metabolism are complex, influenced by type, intensity, duration, timing relative to meals and insulin, and fitness level [17]. Digital twins incorporating wearable sensor data predict exercise related glucose changes and recommend insulin adjustments or carbohydrate supplementation to prevent hypoglycaemia whilst preserving long term activity benefits [75]. Studies report approximately 10 to 25 percent reductions in exercise-associated hypoglycaemia and improvements in physical activity engagement, helping to address a major barrier to optimal diabetes management [76–78]. However, evidence quality is limited by several factors. Most studies are small single-center trials with limited sample sizes. Exercise is often controlled or supervised rather than free-living, limiting real-world applicability [78]. Long-term adherence to digital twin recommendations for activity management remains unknown. Algorithms may fail during high-intensity or unpredictable activities. Whether exercise-related improvements translate to better long-term outcomes requires investigation.

4.4. Clinical decision support and care Coordination

Digital twins serve as clinical decision support tools, synthesising complex data into actionable insights for clinicians [17,79]. These applications range from research prototypes to pilot implementations, with limited evidence of widespread clinical adoption. Rather than reviewing extensive glucose downloads and insulin records, clinicians interrogate digital twin interfaces that highlight patterns, identify problems, and suggest therapeutic modifications [17,25]. These systems detect issues such as persistent postprandial hyperglycaemia indicating inadequate mealtime insulin, recurrent nocturnal hypoglycaemia suggesting excessive basal insulin, or unexplained glucose variability reflecting illness, stress, or medication nonadherence [80]. Digital twin recommendations with appropriate clinical context may enhance clinician efficiency and decision quality. Evidence from decision-support and digital-twin–style tools suggests meaningful reductions in data review burden and improvements in clinically actionable pattern detection compared with manual review, although exact figures vary by study and setting [80,81]. However, these findings come from small feasibility studies in controlled settings with important gaps remaining. Whether automated pattern detection actually improves patient outcomes beyond expert clinical review has not been demonstrated. Algorithm errors or false alerts could lead to inappropriate treatment changes. Clinician trust and acceptance of algorithmic recommendations varies widely [79,82]. Liability concerns when following erroneous algorithmic advice remain unresolved. Integration with existing electronic health record workflows presents substantial technical and administrative barriers.

Beyond individual management, digital twins have been proposed for facilitating population health management by identifying cohorts requiring intervention, predicting healthcare resource utilisation, and evaluating policy or programme changes before implementation [30,82]. This represents a largely theoretical application with minimal empirical validation. Health systems could potentially deploy digital twins to simulate different care delivery models, staffing configurations, or technology deployment strategies, optimising resource allocation and efficiency [30,83]. These applications extend digital twin benefits from individual patients to healthcare systems, supporting value based care initiatives and population health goals [84]. However, population-level digital twin applications face substantial challenges. Data quality and completeness vary substantially across diverse patient populations. Model validation for system-level predictions is complex and rarely attempted. Unintended consequences of system changes may not be captured by models. Ethical concerns about algorithmic allocation of scarce healthcare resources require careful consideration.

5. Challenges and opportunities in digital twin implementation

Table 2 outlines major challenges in digital twin implementation alongside potential strategies to address them. Solution status in the

Table 2
Challenges and Solutions in Digital Twin Implementation for Diabetes Care.

Challenge Domain	Specific Issues	Impact on Implementation	Potential Solutions	Status of Solutions
Data Integration [31,39]	Lack of interoperability, proprietary formats, data silos	Incomplete patient representations, reduced digital twin accuracy	FHIR standards adoption, universal APIs, vendor cooperation mandates	Partial implementation; ongoing development
Data Quality [82]	Sensor inaccuracies, missing data, inconsistent reporting	Compromised predictions, reduced clinical utility	Improved sensor technology, automated data validation, imputation methods	Incrementally improving; requires continued advancement
Model Validation [16,39]	Lack of standardised frameworks, difficulty validating adaptive models	Regulatory uncertainty, limited clinical trust	Regulatory guidance development, prospective clinical trials, validation databases	Early stage; frameworks emerging
Clinical Trust [17,28]	Black box algorithms, liability concerns, insufficient training	Low adoption rates, reluctance to follow recommendations	Explainable AI, comprehensive training programmes, clinical decision support integration	Moderate progress; significant work remaining
Privacy and Security [79,85]	Data breach risks, surveillance concerns, re identification potential	Patient reluctance, regulatory barriers	Strong encryption, federated learning, privacy preserving technologies	Established technologies; implementation inconsistent
Equity and Fairness [82,86]	Algorithm bias, digital divide, disparate performance across groups	Health disparities, limited benefit for underserved populations	Diverse training data, fairness audits, inclusive design	Early attention; requires sustained focus
Cost and Reimbursement [16]	High development costs, unclear payment models	Limited commercial viability, restricted access	Value based care models, health economics studies, tiered solutions	Emerging models; significant uncertainty
Infrastructure [87]	Limited technology access, inadequate internet connectivity	Excludes populations most in need	Low bandwidth solutions, offline capabilities, community technology hubs	Variable by region; ongoing challenge

Note: FHIR = Fast Healthcare Interoperability Resources; AI = Artificial Intelligence. Challenges and solutions represent synthesis across diverse healthcare contexts. Implementation success varies substantially by geographic region, healthcare system structure, and resource availability. Evidence for solution effectiveness is predominantly observational or expert opinion rather than controlled evaluation. Critical gaps exist in addressing equity and fairness concerns, particularly regarding algorithmic bias in underrepresented populations.

table represents author assessment based on current literature; actual implementation varies substantially across contexts.

5.1. Data Quality, Integration, and interoperability

Digital twin effectiveness depends critically on data quality, completeness, and integration. Despite proliferating digital health technologies, substantial challenges persist in aggregating data from disparate sources [88]. Continuous glucose monitors, insulin pumps, activity trackers, food logging applications, and electronic health records often operate as isolated silos with incompatible formats, proprietary interfaces, and limited interoperability [82]. Integration success rates for multi-device data into unified platforms remain low approximately 30 % across digital health applications, with technical barriers, poor user experience, and lack of universal standards as major obstacles [89–91]. This fragmentation represents a fundamental barrier to digital twin implementation, as comprehensive patient representations require multi-source integration. Critical consequences include: incomplete or biased patient profiles that compromise model accuracy; substantial patient burden in managing multiple incompatible systems; widening digital divides as only technologically sophisticated users achieve integration; and proprietary vendor lock-in preventing patients from switching systems [39,82,89]. Even with technical integration, data quality issues including sensor inaccuracies, missing data from device removal or malfunction, and inconsistent patient reporting compromise digital twin performance [85]. Sensor accuracy claims (e.g., MARD < 10 %) are typically derived from controlled validation studies and may not reflect real-world performance during rapid glycemic excursions. Furthermore, missing data patterns are often non-random (e.g., signal loss due to water interference, adhesive failure during exercise, or compression artifacts), introducing systematic biases that standard predictive models may not account for [92,93].

Data heterogeneity presents additional analytical challenges. Structured data (laboratory results, medication lists) coexist with unstructured data (clinical notes, patient reported outcomes, virtual assistant inputs). Temporal misalignment, where data elements are recorded at different frequencies and time points, requires sophisticated synchronisation methods. Naive approaches to data fusion (e.g., simple interpolation of missing values) may introduce artifacts and spurious correlations that compromise model validity [94–96]. Addressing these challenges necessitates advances in data standards, interoperability frameworks, and analytical techniques. Fast Healthcare Interoperability Resources standards and international consensus on diabetes data representation offer promise for improving integration. However, widespread implementation remains inconsistent, particularly in resource limited settings with less developed technology infrastructure. Economic incentives often favour proprietary systems over open interoperability, creating fundamental conflicts between vendor interests and patient welfare. Regulatory mandates for data portability (e.g., 21st Century Cures Act in the US) have not yet achieved meaningful interoperability in practice [97].

5.2. Model validation and clinical trust

Establishing trust requires rigorous validation through multiple lenses: analytical validation confirming model accuracy against gold standards, clinical validation demonstrating improved patient outcomes, and practical validation ensuring usability and workflow integration [29,98]. The dynamic, personalised nature of digital twins complicates validation compared to static diagnostic tests or medications. Traditional regulatory frameworks assume static, population-level performance characteristics that may not apply to continuously adapting individual models. Critical validation challenges include: continuously learning algorithms may drift over time, requiring ongoing validation; individual model performance may vary substantially from population metrics; failure modes are difficult to characterise comprehensively; adversarial inputs or edge cases may cause unpredictable behaviour; and model updates could degrade performance without proper oversight [82,99]. Traditional validation frameworks for in vitro diagnostic devices may not adequately address continuously adapting digital twin characteristics [86]. Regulatory agencies including the FDA and European Medicines Agency are developing frameworks for evaluating software as a medical device and artificial intelligence-based tools, but consensus on appropriate digital twin validation standards remains

incomplete [100–102]. Current regulatory approaches struggle to balance innovation with safety, leading to either overly restrictive requirements that stifle development or insufficient oversight that risks patient harm.

Clinician acceptance represents another critical dimension. Surveys reveal that whilst 70 to 80 percent of healthcare providers express interest in digital twin technology, only 30 to 40 percent feel confident interpreting and acting on recommendations without additional training [82,103]. This confidence gap represents a major implementation barrier that technical solutions alone cannot address. Concerns include black box machine learning models, liability when following algorithmic recommendations leading to adverse outcomes, and balancing algorithmic guidance with clinical judgment [103]. Legal frameworks assigning liability for AI-generated recommendations remain unclear in most jurisdictions [104,105]. Questions include: Who is responsible when a digital twin recommendation leads to patient harm, the clinician who followed it, the software developer, the healthcare institution, or the algorithm itself? This uncertainty creates substantial barriers to clinical adoption. Transparency in model development, clear uncertainty communication, explainable artificial intelligence techniques illuminating recommendation reasoning, and incorporation of clinician feedback into iterative refinement can build trust. However, true explainability may be fundamentally incompatible with complex machine learning models, requiring tradeoffs between performance and interpretability. Demonstrating clinical effectiveness through well designed prospective studies with patient centred outcomes is essential for widespread adoption. Currently, such evidence is limited, with most studies focusing on technical performance metrics rather than patient-important outcomes.

5.3. Privacy, Security, and ethical considerations

Digital twins process highly sensitive health information, raising substantial privacy and security concerns. Continuous data collection, information granularity, and re identification potential amplify concerns beyond traditional medical records [14]. Wearable sensors and applications track health metrics, location, activity patterns, and behavioural data revealing intimate details. Data breach risks with consequences including discrimination, social stigma, or identity theft create patient apprehension [106]. The potential for re-identification from supposedly anonymized data has been demonstrated repeatedly, with researchers re-identifying individuals from combinations of seemingly innocuous data points. Digital twin data, being longitudinal and high-dimensional, may be particularly vulnerable to such attacks.

Regulatory frameworks including the General Data Protection Regulation and Health Insurance Portability and Accountability Act provide baseline protections, but gaps remain. Questions about data ownership, consent for secondary uses, algorithmic decision explanation rights, and cross border data flows require clarification [107]. Current regulatory frameworks were designed for static medical records rather than continuously generated personal data, leaving critical questions unresolved. For example: Do patients "own" their digital twin? Can they demand deletion? Can data be used to train commercial algorithms without explicit consent? What rights do they have to understand algorithmic decisions affecting their care? Ethical considerations extend beyond privacy to equity and fairness. Algorithms trained predominantly on well-resourced population data may perform poorly for underserved groups, exacerbating disparities [108]. Studies document lower glucose prediction accuracy in racial and ethnic minorities and lower socioeconomic populations [109]. This algorithmic bias represents a critical threat to health equity. Mechanisms include: underrepresentation in training data leading to poor model calibration; differential data quality (e.g., sensor accuracy may vary across skin tones); socioeconomic differences in device access and usage patterns; and failure to account for structural determinants of health. Simply including more diverse training data is insufficient if underlying healthcare disparities remain unaddressed. Diverse training data, fairness audits, and inclusive design are essential to prevent widening inequities. However, achieving algorithmic fairness is technically complex, as optimising for one fairness metric (e.g., equal sensitivity across groups) may worsen others (e.g., equal positive predictive value). Moreover, fairness interventions may reduce overall model performance, creating ethical dilemmas about acceptable tradeoffs [110,111].

5.4. Economic considerations and healthcare system integration

The economic viability of digital twin technology in diabetes care remains under active investigation. Development costs for sophisticated platforms are substantial, encompassing data infrastructure, algorithm development, regulatory compliance, clinical validation, and ongoing maintenance [39,82]. Commercial solutions typically require subscription fees ranging from several hundred to several thousand dollars annually per patient, costs often not covered by payers without demonstrated cost effectiveness [25]. These costs potentially limit access to affluent populations, exacerbating existing health inequities. Whilst pilot studies show promising results, comprehensive health economic analyses examining long term costs, complication prevention savings, and healthcare resource impacts are limited [64,108]. Critical economic questions remain unanswered: What is the incremental cost-effectiveness ratio compared to conventional care? Who captures the economic benefits, patients, healthcare systems, or technology vendors? How should value be assessed, traditional QALYs, time in range, patient-reported outcomes? What is the budget impact of widespread adoption on healthcare systems? How should costs be allocated between prevention/detection and management applications?

Successful healthcare system integration requires addressing multiple dimensions beyond functionality. Clinical workflow integration must ensure digital twin interactions fit seamlessly into existing care patterns without excessive burden [112]. Current digital twin systems often require substantial additional clinician time for data review, algorithm supervision, and patient education, potentially worsening clinician burnout rather than alleviating it [113]. Interoperability with electronic health records, enabling bidirectional data flow and documentation of recommendations within legal medical records, remains technically and administratively challenging [114,115]. Lack of standardised documentation formats for digital twin recommendations creates legal and quality assurance problems. How should AI-generated recommendations be recorded? Who verifies their appropriateness? How are deviations from recommendations justified? Care team education and training require time and resource investment to provide clinicians with skills to effectively utilise digital twin insights. Current medical and nursing education curricula rarely include substantive training in AI-based clinical decision support, creating a knowledge gap that will take years to address. Reimbursement mechanisms recognising digital twin enabled care value and appropriately compensating healthcare organisations are necessary for financial sustainability [116]. Some health systems have implemented bundled payment models or capitated arrangements incentivising improved outcomes rather than service volume, creating financial alignment for digital twin adoption. However, fee for service payment models, which still predominate in many regions, provide limited incentive for preventive, technology enabled care innovations [82]. The current reimbursement landscape creates a fundamental misalignment: digital twins primarily generate value through complication prevention and efficiency gains, but fee-for-service systems reward volume of acute interventions. This misalignment may prevent adoption even when technologies are clinically effective and cost-effective from a societal perspective.

6. Future directions and emerging opportunities

6.1. Integration of multi omics and systems biology

The next frontier involves integrating multi omics data (genomics, transcriptomics, proteomics, metabolomics, microbiomics) to create comprehensive systems biology models. Genomic data identifies individuals at high risk for diabetes or complications based on genetic predisposition, enabling targeted prevention [117]. Proteomic and metabolomic profiles provide real-time metabolic state snapshots, capturing perturbations preceding clinical disease progression. Gut microbiome composition influences glucose metabolism, insulin sensitivity, and dietary response, with emerging evidence suggesting microbiome modulation through probiotics, prebiotics, or diet may improve glycaemic control [118]. Digital twins incorporating these multidimensional datasets could achieve unprecedented personalisation, potentially predicting glucose responses and identifying optimal therapeutic targets tailored to individual biology [119]. However, several critical challenges temper enthusiasm for near-term clinical implementation. Multi-omics profiling remains expensive and technically complex, limiting accessibility beyond research settings. Integration of heterogeneous data types including discrete genomic variants, continuous metabolite levels, and compositional microbiome data presents substantial analytical challenges. Biological mechanisms linking omics signatures to clinical outcomes are often poorly understood, limiting causal inference and therapeutic targeting [120,121]. Temporal stability of omics profiles, particularly microbiome composition, raises questions about how frequently assessment must be repeated for accurate digital twin calibration. The incremental clinical benefit of multi-omics integration over simpler approaches combining clinical and basic laboratory data has not been established through comparative effectiveness studies.

Technical advances in sensor technology, high throughput sequencing, and computational biology are making multi-omics digital twins increasingly feasible. Minimally invasive biosensors continuously monitoring multiple metabolites beyond glucose (lactate, ketones, biomarkers) are under development [122]. However, such sensors remain largely in early research stages, with significant technical hurdles including biocompatibility challenges, calibration stability over extended periods, and regulatory approval pathways that remain unclear. Artificial intelligence, particularly deep learning for integrating heterogeneous data, shows promise for extracting insights from complex multi omics datasets. However, interpretability challenges intensify substantially with multi-omics models, potentially creating opaque systems that clinicians cannot understand or validate, raising safety and liability concerns. As these technologies mature and costs decrease, multi-omics digital twins may transition from research tools to clinical reality, offering precision diabetes care [14]. Realistic timelines for clinical implementation likely extend beyond a decade, requiring sustained research investment across multiple disciplines, development of appropriate regulatory frameworks for complex multi-omics devices, and generation of robust evidence demonstrating clinical utility and cost-effectiveness in diverse populations.

6.2. Expansion to type 2 diabetes and broader populations

Digital twin applications focus predominantly on type 1 diabetes, where intensive insulin therapy and continuous glucose monitoring are standard. However, type 2 diabetes, accounting for 90 to 95 percent of cases, represents a far larger opportunity. Its pathophysiology, characterised by progressive insulin resistance and beta cell dysfunction with substantial heterogeneity, presents unique challenges and opportunities [123]. Extending to type 2 diabetes requires addressing different therapeutic paradigms: diverse pharmacological agents beyond insulin, greater lifestyle modification emphasis, and multiple comorbidity management [124]. Critical differences from type 1 diabetes complicate direct translation of existing digital twin approaches. Oral medications and non-insulin injectables require different pharmacokinetic and pharmacodynamic modelling frameworks not yet well developed. Lifestyle factors including diet, exercise, and weight management play more central therapeutic roles, requiring sophisticated behavioural modelling beyond current capabilities. Multimorbidity management involving hypertension, dyslipidemia, and cardiovascular disease requires integrated models spanning multiple organ systems rather than diabetes-specific approaches [16,31]. Disease heterogeneity with distinct phenotypic subtypes and highly variable progression patterns complicates development of standardised digital twin architectures. Simplified solutions leveraging periodic glucose measurements, patient reported outcomes, and population models rather than continuous monitoring may be more practical and scalable. However, whether simplified approaches retain sufficient personalisation to justify digital twin terminology versus conventional population-based clinical decision support remains debatable. The value proposition for expensive digital twin technology may be substantially lower in type 2 diabetes without intensive insulin therapy, where conventional care already achieves reasonable outcomes in many patients through medication titration and lifestyle counselling [25,80].

Geographic and socioeconomic expansion represents another critical frontier. Most digital twin development has occurred in high income countries with advanced infrastructure and technology [14]. Low and middle income countries bear a disproportionate diabetes burden whilst facing limited technology access, constrained resources, and different cultural contexts. Tailored solutions emphasising low-cost sensors, smartphone platforms, task sharing models, and community health worker integration could potentially democratise precision care and address global equity concerns [125,126]. However, substantial barriers impede implementation in resource-limited settings. Infrastructure limitations including unreliable electricity and limited internet connectivity constrain technology deployment in many regions. Low health literacy and digital literacy among target populations limit effective engagement with sophisticated systems. Lack of trained healthcare workforce to support technology implementation and provide backup when systems fail represents a critical bottleneck. Cultural appropriateness of algorithms developed in Western contexts for diverse global populations remains largely unexplored. Financial sustainability when healthcare resources are already severely constrained raises fundamental questions about opportunity costs [127–129]. Simply adapting high-income country technologies may be insufficient; fundamentally different approaches designed specifically for resource-limited settings may be necessary to achieve meaningful impact.

6.3. Behavioural integration and patient engagement

Effective diabetes management depends on biological, behavioural, psychological, and social dimensions. Medication adherence, diet, physical activity, stress management, and healthcare engagement profoundly influence outcomes [17,25]. Digital twins should incorporate behavioural science principles and psychological models to predict adherence challenges, identify barriers, and deliver personalised behaviour change interventions. Currently, most digital twin systems focus predominantly on biological and physiological modelling with limited integration of behavioural dimensions. This represents a critical gap, as behavioural factors often contribute more to glycaemic variability than biological heterogeneity alone, particularly in type 2 diabetes and non-intensive insulin regimens [27]. Integrating cognitive behavioural therapy, motivational interviewing, and positive reinforcement could potentially enhance engagement and sustained modification. Social determinants (food insecurity, housing instability, transportation barriers, social isolation) impact management capacity and should be incorporated into holistic models [130]. However, operationalising these concepts faces significant challenges across multiple dimensions. Behavioural and social determinants are difficult to measure objectively and continuously using available sensors or self-report

mechanisms. Causal relationships between social factors and health outcomes are complex and confounded by numerous unmeasured variables [27]. Algorithmic recommendations addressing social determinants such as obtaining stable housing may be ineffectual without resources to act on them. Privacy concerns intensify substantially when systems track behavioural patterns and social circumstances beyond traditional medical data.

Gamification, social support, and personalised goal setting have been proposed to enhance patient engagement. Gamified interventions may improve adherence and outcomes, particularly among younger populations though evidence is mixed and long-term effectiveness uncertain. Social features enabling peer connection through communities or programmes may enhance motivation and reduce isolation [130]. However, concerns about privacy protection, potential for harmful peer pressure, and risks of unhelpful social comparisons require careful attention in system design. Systems adapting communication style, interaction frequency, and intervention intensity to individual preferences could potentially optimise adherence and prevent abandonment, a common digital health challenge. However, personalisation of engagement strategies remains largely theoretical, with limited empirical evidence demonstrating superiority over well-designed standardised approaches. Digital intervention abandonment rates frequently exceeding 50 to 80 percent within 6 months remain common across diverse platforms, suggesting that current engagement strategies, whether personalised or standardised, are often ineffective at maintaining long-term user engagement [25].

6.4. *Artificial intelligence advances and explainability*

Advances in artificial intelligence, particularly transformer models, graph neural networks, and reinforcement learning, may enhance digital twin capabilities. Transformer models could potentially model complex temporal sequences such as extended glucose patterns [115,131]. However, these remain largely research applications without clinical validation demonstrating superiority over simpler approaches. Graph neural networks could represent interconnected physiological systems, capturing relationships between glucose metabolism, cardiovascular function, inflammatory processes, and organ systems. However, biological network structures are incompletely characterised, and whether graph-based representations improve predictions over conventional approaches remains empirically unproven. Reinforcement learning could theoretically optimise sequential decision making, such as insulin dosing strategies maximising long term outcomes rather than immediate control, offering superior therapeutic recommendations [132]. However, reinforcement learning in healthcare faces substantial challenges limiting near-term clinical deployment. Reward functions must balance multiple competing objectives including glycaemic control, hypoglycaemia prevention, and treatment burden without clear methods for appropriate weighting. Safety constraints are difficult to encode comprehensively, risking unexpected dangerous behaviours. Exploration in clinical settings raises ethical concerns about exposing patients to potentially suboptimal treatments during algorithm learning phases. Real-world deployment of reinforcement learning systems could lead to unexpected behaviours in novel situations not encountered during training, creating potentially serious safety risks [25,27,39].

As models become more complex, ensuring explainability becomes increasingly critical. Clinicians and patients need to understand recommendations and their rationale, enabling trust, error identification, and integration of algorithmic guidance with human judgment and experience [27,39]. Explainable artificial intelligence techniques including attention mechanisms highlighting influential input features, counterfactual explanations showing alternative scenario outcomes, and local interpretable model agnostic explanations approximating complex behaviour with simpler models attempt to bridge the gap between sophistication and comprehension [133]. However, current explainable AI techniques face significant limitations in practice. Explanations may be technically accurate but clinically unintuitive, failing to provide actionable insights for non-technical users. Fidelity-interpretability tradeoffs mean simpler explanatory models may systematically misrepresent complex model behaviour, providing misleading rather than clarifying information. Different stakeholders including clinicians, patients, and regulators require fundamentally different types of explanations that may be difficult to provide simultaneously [134]. Post-hoc explanations may not accurately reflect actual model decision processes, particularly for complex neural networks. Fundamentally, there may be inherent tension between model performance and interpretability that cannot be fully resolved through technical approaches alone. Research on communicating uncertainty, visualising predictions with confidence intervals, and presenting recommendations clearly will be essential as digital twins advance. However, effectively communicating uncertainty to clinical audiences with variable statistical literacy remains an unsolved challenge across healthcare informatics. Oversimplified communication risks misinterpretation and inappropriate confidence, while comprehensive uncertainty quantification may overwhelm users and paradoxically reduce rather than enhance decision quality.

As depicted in Fig. 2, multiple technical, clinical, and ethical challenges remain, but emerging frameworks and technologies provide pathways toward scalable and trustworthy digital twin integration.

Note: Proposed solutions in the figure represent current research directions and expert recommendations rather than validated approaches. Implementation feasibility and effectiveness vary substantially across healthcare contexts. Critical evidence gaps exist for most proposed solutions, particularly regarding equity and fairness interventions.

7. Limitations of the review

This narrative review, whilst comprehensive in scope, has several limitations that warrant acknowledgment. First, the narrative review methodology, whilst enabling breadth of coverage and thematic synthesis, does not employ the systematic, structured approach of systematic reviews with *meta*-analysis. Unlike systematic reviews following PRISMA guidelines, this narrative review did not pre-register a protocol, did not conduct duplicate independent screening, and did not perform formal quality assessment using standardised tools. We did not create a formal PRISMA flow diagram documenting screening decisions at each stage, as narrative reviews prioritise thematic synthesis over quantitative enumeration. This limitation introduces potential for selection bias in included studies and precludes quantitative synthesis of effect sizes across studies. The heterogeneity of digital twin implementations, outcome measures, and study designs further complicates direct comparisons and evidence synthesis. Our thematic synthesis approach, while enabling integration of diverse evidence types, is inherently more susceptible to author bias than quantitative *meta*-analysis. Readers should interpret our critical assessments as informed expert opinion rather than objective quantification of evidence quality. Second, the rapidly evolving nature of digital twin technology means that some emerging developments, particularly those in early research stages or proprietary commercial systems without published peer reviewed data, may not be fully represented. The lag between technological innovation and peer reviewed publication creates an inherent temporal limitation in the literature base. Published literature may overrepresent academic research prototypes while underrepresenting commercially deployed systems, creating a potentially distorted picture of clinical reality.

Third, the majority of published research on digital twin applications in diabetes originates from high income countries with advanced healthcare infrastructure, particularly the United States, United Kingdom, and select European nations. This geographic concentration limits generalisability of findings to diverse healthcare contexts, particularly resource limited settings where the burden of diabetes is growing most rapidly. Moreover, study populations within high-income

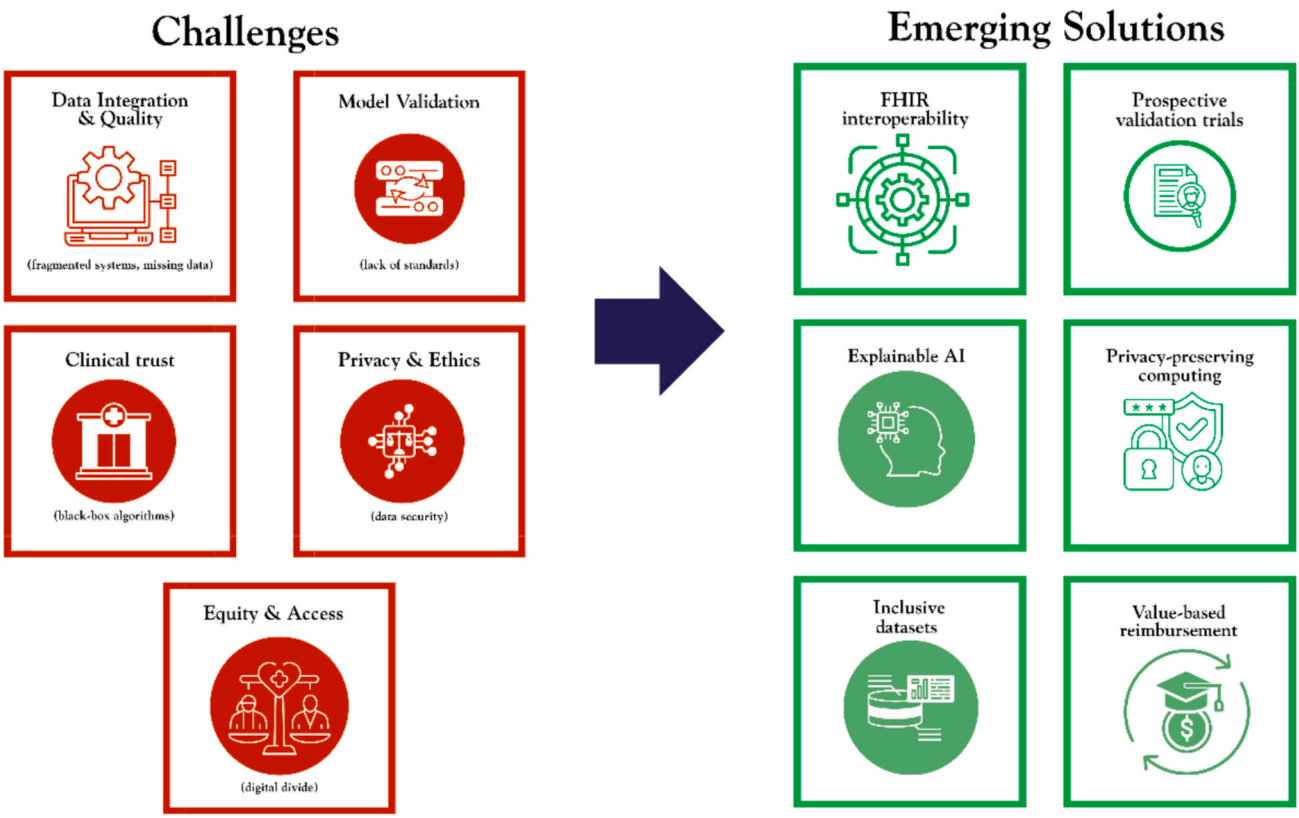

Fig. 2. Major challenges and emerging solutions in implementing digital twin technology for diabetes care. The figure summarises key technical, clinical, ethical, and economic barriers alongside corresponding mitigation strategies. Addressing these interlinked domains is essential for translating digital twin innovation into scalable, equitable, and sustainable clinical practice.

countries often overrepresent affluent, well-educated, technologically savvy individuals willing to participate in research, further limiting generalisability to broader populations. Fourth, many studies examining digital twin performance and clinical impact are relatively short term, spanning weeks to months rather than years. Long term effectiveness, durability of benefits, and evolution of system performance over extended time periods remain inadequately characterised. Algorithm degradation over time due to changing treatment patterns, device updates, or patient characteristics represents a largely unexamined threat to sustainability of digital twin systems. Fifth, publication bias favouring positive results may lead to overestimation of digital twin effectiveness if studies demonstrating limited benefits or implementation challenges are less likely to be published. We attempted to identify negative or null findings through comprehensive searching, but likely underrepresent implementation failures and abandoned projects that never reached publication.

Sixth, this review focuses predominantly on technological and clinical dimensions of digital twin applications, with limited attention to important implementation science considerations including change management, organisational factors influencing adoption, and strategies for scaling successful pilot implementations to routine care. These "soft" factors often determine implementation success or failure more than technical performance, representing a critical gap in our analysis. Seventh, whilst ethical considerations are discussed, comprehensive analysis of complex ethical issues such as algorithmic bias, data governance, and patient autonomy in the context of increasingly sophisticated decision support tools extends beyond the scope of this review. Ethical frameworks for AI in healthcare remain underdeveloped, and many questions lack clear answers in current philosophical or regulatory discourse. Finally, the review does not address in detail the technical specifications of different modelling approaches, machine learning architectures, or validation methodologies, areas that would benefit from dedicated technical reviews aimed at computational and engineering audiences. Our critical synthesis attempts to evaluate model quality and limitations, but readers with deep technical expertise may find our assessments insufficiently granular for computational validation.

Additional specific limitations include several important considerations. Our search was limited to English-language publications, potentially missing important work published in other languages particularly from non-English speaking countries. Grey literature including conference abstracts, white papers, and technical reports received limited systematic attention despite potentially containing important unpublished findings. Our assessment of clinical maturity distinguishing proof-of-concept from commercially available systems relied on author judgment rather than formal criteria, introducing subjectivity.

8. Conclusion

Digital twin technology represents an evolving paradigm in diabetes prediction and management, offering potential opportunities for personalisation, proactive intervention, and precision care. Through continuous integration of diverse data streams with sophisticated computational models, digital twins create dynamic virtual representations of individuals that can predict glucose trajectories, optimise therapeutic regimens, and forecast complication risks with varying degrees of accuracy depending on application and population. Current applications demonstrate promising though variable clinical benefits, including improved glycaemic control, reduced hypoglycaemia, enhanced patient engagement, and more efficient use of healthcare resources in selected populations and controlled settings. The maturation of enabling technologies, including continuous glucose monitoring, wearable sensors, artificial intelligence, and cloud computing infrastructure, has established a foundation for exploring widespread digital

twin implementation in diabetes care. However, significant gaps separate current proof-of-concept demonstrations from validated, equitably accessible clinical systems.

Realising the potential of digital twin technology requires addressing significant challenges spanning technical, clinical, ethical, and economic domains. Data integration and interoperability barriers limit the creation of comprehensive patient representations. Current proprietary systems create data silos that fundamentally undermine the comprehensive integration digital twins require. Model validation frameworks appropriate for dynamic, adaptive systems remain under development. Regulatory pathways for continuously learning algorithms are evolving but incomplete, creating uncertainty for developers and clinicians. Building trust among clinicians and patients necessitates transparency, explainability, and demonstrated clinical effectiveness through rigorous prospective studies. Current evidence consists predominantly of retrospective analyses, small pilot studies, and proof-of-concept demonstrations rather than large-scale randomised trials with patient-important outcomes. Privacy and security concerns must be addressed through robust technical safeguards and clear governance frameworks. However, technical solutions cannot fully mitigate risks inherent in continuous collection of intimate personal data. Equity considerations demand attention to ensure that digital twin benefits extend to diverse populations rather than exacerbating existing health disparities. Evidence of algorithmic bias and differential performance across demographic groups raises serious concerns that cannot be addressed through technical fixes alone but require fundamental attention to healthcare inequities. Economic sustainability depends on demonstrating cost effectiveness and developing reimbursement models that appropriately value technology enabled care. However, current fee-for-service payment structures create misaligned incentives that may prevent adoption of cost-effective preventive technologies.

Looking forward, the integration of multi omics data, expansion to type 2 diabetes and global populations, incorporation of behavioural science, and continued artificial intelligence advances may enhance digital twin capabilities further. However, these future directions face substantial technical, regulatory, economic, and ethical challenges that will require years to decades to address. Realistic expectations are essential; digital twins are not imminent panaceas but rather long-term research priorities requiring sustained investment and rigorous evaluation. The vision of comprehensive, whole body digital twins that predict, prevent, and manage not only diabetes but multiple interconnected chronic conditions remains largely aspirational, achievable potentially within the coming decade with sustained research investment and successful navigation of multiple challenges. Collaboration among technologists, clinicians, researchers, patients, policymakers, and industry stakeholders will be essential to navigate the complex pathway from promising technology to routine clinical practice. This collaboration must prioritise patient benefit and equity over commercial interests, requiring careful governance and regulatory oversight. With sustained effort and appropriate investment, digital twin technology has the potential to contribute to fundamentally reshaping diabetes care, transforming it from reactive disease management to proactive health optimisation though not achieving the ambitious goal of preventing and curing diabetes altogether in the near term. Critical success factors include: rigorous clinical validation demonstrating patient-important outcomes; equitable access ensuring benefits reach underserved populations; transparent governance addressing privacy and algorithmic fairness; sustainable business models aligning incentives for all stakeholders; and realistic expectations balancing enthusiasm with evidence-based caution.

CRediT authorship contribution statement

David B. Olawade: Conceptualization, Project Administration, Supervision, Writing – review & editing, Writing – original draft, Methodology, Investigation, Formal analysis. **Rita Chikeru Owhonda:** Writing – review & editing, Writing – original draft, Methodology, Investigation, Formal analysis. **John Oluwatosin Alabi:** Writing – review & editing, Visualization, Methodology, Investigation. **Eghosasere Egbon:** Writing – review & editing, Visualization, Methodology. **Raphael Igbarumah Ayo Daniel:** Writing – review & editing, Writing – original draft, Investigation. **Oluwakemi Jumoke Bello:** Writing – review & editing, Writing – original draft, Methodology, Investigation.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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