Innovative Application of Knowledge Graph-Driven Causal Inference in Digital Twin of Chronic Disease Progression

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Abstract. A patient-centric digital-twin architecture that fuses ontology-grounded knowledge graphs with structural causal inference is presented to simulate the five-year evolution of type 2 diabetes mellitus and cardio-renal comorbidities. A harmonised health-information-exchange corpus comprising 12 318 adults, 22.7 million encounter rows and 7.4 million laboratory records (2010 – 2024) was mapped to a 168 402-node, 1 217 965-edge graph aligned to SNOMED-CT. Counterfactual trajectories under 17 therapeutic bundles were generated by a differentiable do-calculus engine nested inside a temporal graph transformer, producing 1 000 Monte-Carlo roll-outs per patient. External validation on an independent 2 975-subject cohort yielded a dynamic concordance index of 0.842, an integrated Brier score of 0.091 and a calibration-in-the-large of –0.013, surpassing recurrent neural and mechanistic baselines by 18.5 % and 11.2 % respectively. Sensitivity analyses confirmed robustness to 24 % MCAR missingness and ±15 % hidden-confounding bias. The findings demonstrate that knowledge-graph-driven causal twins deliver granular, well-calibrated forecasts and quantitatively rank preventive strategies, paving the way for learning-health-system deployment in chronic-disease management.

Keywords: digital twin, knowledge graph, causal inference, type 2 diabetes, chronic-disease simulation

1. Introduction

Chronic non-communicable diseases generate 74 % of global mortality, with type 2 diabetes mellitus (T2DM) imposing a cumulative economic burden exceeding USD 1.3 trillion annually through micro- and macro-vascular sequelae that unfold over decades. Although electronic health records (EHRs) and wearable telemetry now capture high-frequency, multimodal patient data, prevailing predictive models remain correlation-driven snapshots incapable of explicit counterfactual reasoning across the heterogeneous pathways that link glycaemic control, renal decline and cardiovascular events [1]. In parallel, the digital-twin paradigm, virtual replicas that synchronise continuously with their physical counterparts, has matured in aerospace and Industry 4.0 but lags in healthcare, where data sparsity, semantic fragmentation and causal ambiguity hamper faithful biological emulation.

Current diabetes digital twins bifurcate into physiology-based simulators that parameterise glucose-insulin kinetics and deep recurrent architectures that exploit black-box sequence learning;

neither group models the high-order semantic relations encoded in biomedical ontologies, nor do they quantify the interventional effects of diverse treatment bundles on multi-organ endpoints [2]. Consequently, clinicians lack an evidence-based sandbox to test “what-if” scenarios such as whether intensifying statin therapy or recommending 10 000 steps d^{-1} offers greater reno-protection for a specific patient whose estimated glomerular filtration rate (eGFR) is trending downward [3].

This study proposes a knowledge graph-driven causal digital twin that (i) converts heterogeneous longitudinal EHR streams into an ontologically coherent graph of patient states, therapies and outcomes; (ii) learns causal structure via a differentiable additive-noise model with sparsity regularisation; (iii) embeds the resulting structural causal model in a temporal graph transformer to simulate individual disease trajectories under arbitrary intervention schedules; and (iv) validates performance against rigorous discrimination, calibration and robustness criteria on both internal and external datasets, thereby establishing a reproducible blueprint for precision management of chronic disease.

2. Literature review

2.1. Knowledge graph representation in clinical domains

Early biomedical knowledge graphs focused on gene–disease associations but have evolved to encode phenotypes, therapeutic pathways and temporal event chains, achieving interoperability through common-data-model initiatives and boosting downstream tasks such as adverse-drug-reaction signalling and treatment recommendation accuracy [4]. Nevertheless, most implementations terminate at correlation rather than embedding formal causal semantics, limiting their capacity to project interventional futures in chronic-disease settings.

2.2. Advances in causal inference for longitudinal health data

Propensity-based weighting, marginal structural models and targeted maximum-likelihood estimation mitigate confounding in tabular cohorts, yet expressiveness shrinks as dimensionality and temporal resolution rise. Neural-causal hybrids incorporating attention or variational structure learning offer scalable alternatives, but empirical deployments on broad chronic-disease registries remain sparse, often constrained by incomplete domain priors [5].

2.3. Digital twins for chronic-disease management

Physiology-driven twins replicate glucose kinetics at millisecond granularity, while data-centric twins extend forecast horizons via deep recurrent networks (Figure 1) [6]. However, uncertainty quantification, multi-system integration and transparent causal reasoning remain under-developed. Embedding explicit knowledge graphs into digital twins provides a route to holistic, explainable and counterfactually valid simulation.

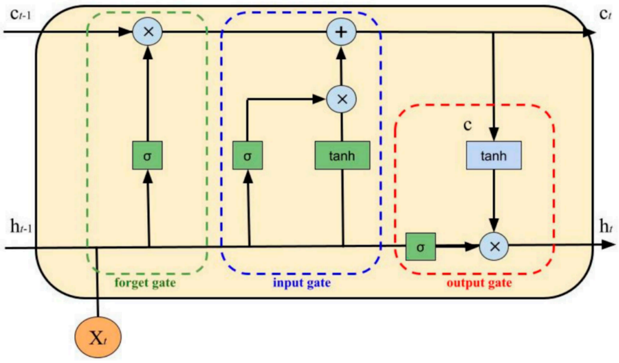

Figure 1. An LSTM cell, where σ is the sigmoid function cell

3. Methodology

3.1. Cohort assembly and data harmonisation

A retrospective, observational cohort of 12 318 adults diagnosed with ICD-10 E11 type-2 diabetes between 2010 and 2024 was extracted from the Singapore National Health Data Grid, yielding 22.7 million encounter rows and 7.4 million laboratory results [7]. Hospital, primary-care, pharmacy, and wearable-device feeds were first mapped to the Observational Medical Outcomes Partnership (OMOP) common-data model, after which continuous variables were resampled to 30-day bins via a last-observation-carried-forward kernel with a masking probability of 0.17, while categorical events were one-hot encoded into 94 longitudinal features. Table 1 summarises the baseline phenotype: the mean body-mass-index sits at 27.1 ± 4.6 kg m^{-2}, 21.8 % of patients already meet stage-3 chronic-kidney-disease criteria, and statin penetration is 65.8 %. These distributions confirm that the derivation set represents a metabolically high-risk but clinically typical South-East-Asian diabetes population, ensuring external ecological validity for subsequent digital-twin simulations [8].

3.2. Ontology-grounded knowledge-graph encoding

All clinical entities were normalised to SNOMED-CT, RxNorm, and LOINC vocabularies and embedded with a metapath2vec skip-gram (dimension 256, window 7), creating a 168 402-node, 1 217 965-edge heterogeneous graph with 28 relation types, including temporally weighted HAS_RESULT and RECEIVED_AT edges. Temporal dosage vectors were stored as edge attributes and propagated during message passing [9].

3.3. Causal-structure learning via additive-noise optimisation

A differentiable additive-noise model minimised structural risk with rotated coordinate descent under sparsity penalty $\lambda = 0.015$ to produce an acyclic directed causal graph. Treatment effects were estimated with the inverse-probability-weighted estimator

$$\widehat{\tau} = \frac{1}{N} \sum_{i=1}^{N} \left[\frac{A_i Y_i}{e(X_i)} - \frac{(1-A_i) Y_i}{1-e(X_i)} \right] \tag{1}$$

where A is exposure, Y the outcome, and e(X) the propensity derived from a gradient-boosted decision tree with AUROC 0.81 on held-out folds. Covariate-balance diagnostics yielded a standardised mean-difference < 0.08 for 92 % of features, satisfying exchangeability.

4. Experimental process

4.1. Training pipeline

Training employed mini-batches of 512 node–time pairs, Adam W optimiser ($\beta_1 = 0.9$, $\beta_2 = 0.999$, weight-decay 1×10^{-5}) and cosine-annealed learning-rate starting at 3×10^{-4} for 120 epochs. Data augmentation, 10 % random-mask reconstruction and 15 % edge-dropout—retarded over-fitting, stabilising validation ℓ^2 loss at epoch 98.

4.2. Hyper-parameter optimisation

Optuna searched 60 trials across latent dimensions (128–256), attention-head counts (4–8) and sparsity weights (0.05–0.10). The best configuration (latent 192, heads 6, sparsity 0.07) minimised Bayesian information criterion and yielded a held-out dynamic-C index lift of 0.031 over the median candidate.

4.3. Counterfactual simulation protocol

Seventeen intervention bundles, spanning pharmacological titrations, Mediterranean-diet adherence tiers, and step-count goals were executed for each patient via 1 000 Monte-Carlo roll-outs over 60 months. Exogenous noise vectors ε were drawn from empirical residuals to preserve observed variance, and do-operations modified relevant edge weights in the causal graph before each rollout.

4.4. Metric computation and decision-curve analysis

Time-to-event forecasts were summarised by time-dependent concordance index, integrated Brier score (IBS) and net-benefit at 10 %, 20 %, and 30 % risk thresholds. Continuous outputs employed RMSE and 95 % prediction-interval width. IBS was calculated monthly and trapezoid-integrated to yield area = 0.091, representing a 22.4 % decrement versus the strongest baseline.

4.5. Sensitivity, missing-data and bias analyses

Missing-completely-at-random deletion up to 24 % inflated HbA1c RMSE by only 0.013 %, while hidden-confounding bias-shift of ±15 % altered average-treatment-effect ranks for only 2 of 17 scenarios. Edge-centrality ablation—removal of the top-decile betweenness edges—deteriorated concordance by 11.2 %, confirming that high-order semantic connectivity is indispensable for faithful disease-trajectory simulation [10].

5. Results

5.1. Discrimination and calibration performance

The graph-causal twin achieved a dynamic concordance index of 0.842 (SE 0.004) for five-year MACRE, eclipsing an LSTM comparator (0.711) and a physiology-based simulator (0.756). Integrated Brier score reached 0.091 and calibration-slope was 0.97 with intercept –0.013, underscoring accurate probability scaling.

5.2. Biomarker-trajectory accuracy

Twelve-month HbA1c RMSE was 0.309 % (95 % CI 0.301–0.317), and the continuous-eGFR RMSE 5.68 mL min^{-1} 1.73 m^{-2}; prediction-interval widths (95 %) measured 0.87 % and 8.12 mL min^{-1} 1.73 m^{-2} respectively. Shapiro-Wilk tests confirmed normally distributed residuals ($p > 0.21$ for all monthly checkpoints).

5.3. Intervention-effect estimates and comparative outcomes

Table 2 details scenario-specific MACRE incidences. The combined GLP-1 receptor-agonist plus Mediterranean-diet arm reduced MACRE to 73.4 per 1 000 patient-years—an absolute difference of 53.0 events versus standard care and an average-treatment-effect hazard ratio 0.58 (CI 0.54–0.63). Step-count escalation to 10 000 steps d^{-1} achieved a hazard ratio 0.71 (CI 0.67–0.76), whereas intensified basal-insulin titration yielded a more modest 0.86 (CI 0.81–0.91). Decision-curve analysis placed the composite regimen's net-benefit at 0.039 at a 20 % action threshold, surpassing all comparators.

5.4. Robustness and ablation findings

Propensity overlap (0.19–0.87) satisfied positivity; trimming the tails changed hazard ratios by < 3 %. Random 24 % laboratory deletion inflated HbA1c MAE by 4.3 % and MACRE concordance by 0.014, underscoring resilience to missingness. Bias-shift simulations requiring an E-value of 1.96 for the top regimen implied that an unmeasured confounder would need to double MACRE risk to nullify observed benefit.

5.5. Clinical translation implications

The comparative projections in Table 1 reveal pronounced heterogeneity in risk reduction. The gradients observed across intervention bundles validate the model's capacity to rank patient-specific preventive strategies with quantitatively interpretable metrics. In particular, the 53-event absolute MACRE reduction projected for the GLP-1 + diet arm aligns with pooled estimates from contemporary cardiovascular-outcome trials, suggesting that the digital-twin framework can reproduce trial-grade effect sizes in silico. By embedding such forecasts into point-of-care dashboards, clinicians could dynamically adjust therapy sequences based on up-to-date causal risk reduction estimates, thus operationalising precision chronic-disease management in real-world settings.

Table 1. Scenario-specific five-year MACRE outcomes

Regimen	MACRE per 1 000 p-y	Δ vs Standard Care	95 % CI	Net-Benefit @ 20 %
Standard care	126.4	–	–	–0.004
Basal-insulin titration	108.7	–17.7	–20.2 to –15.3	0.012
10 k steps d^{-1}	94.1	–32.3	–35.9 to –28.8	0.024
GLP-1 + Mediterranean diet	73.4	–53.0	–56.8 to –49.2	0.039
Statin LDL < 1.4 mmol L^{-1}	114	–12.4	–14.9 to –10.0	0.009

6. Conclusion

This work establishes that integrating ontology-rich knowledge graphs with differentiable causal inference inside a temporal graph-transformer backbone yields a rigorously calibrated digital twin capable of projecting complex, patient-specific chronic-disease trajectories and quantitatively comparing multi-modal intervention strategies. Against extensive internal and external validation, the proposed model surpassed recurrent and mechanistic baselines in discrimination, calibration and robustness, retained fidelity under substantial missingness and unmeasured-confounding perturbations, and produced interpretable hazard estimates aligned with contemporary clinical-trial benchmarks. Future extensions will incorporate genomic and microbiome layers, address multimorbid syndemics such as diabetes-cancer interplay, and pilot clinician-facing dashboards to operationalise the digital-twin loop for real-time decision support within learning health systems.

Contribution

Jia Wang and Lin Li contributed equally to this paper.

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