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A Human Cohort Data Validated Mechanistic Model Linking Psychosocial Stress to Type 2 Diabetes Risk

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Abstract

Psychosocial stress is associated with type 2 diabetes (T2D) related glycemic dysregulation, but quantitatively linking chronic stress to fasting glucose remains challenging. We developed a coupled endocrine metabolic model of stress hormone regulation and glycemic control. Depressive symptoms were quantified using the Center for Epidemiologic Studies Depression Scale (CESD) score, which served as a proxy for sustained stress drive. Using clinical data from the Multi Ethnic Study of Atherosclerosis (MESA) dataset, we identified a single physiologically plausible joint parameter range for glycemic regulation, stress coupling strength, and caloric intake drive. The model performed better for non diabetic individuals, whereas the proportion in the diabetes category was overestimated, most prominently in the depressed group. The findings were consistent on a reserved evaluation subset without refitting.

Introduction

Type 2 diabetes is a complex metabolic disorder characterized by chronic hyperglycemia, impaired insulin secretion, and progressive insulin resistance¹. Its prevalence has more than doubled over the past three decades². Beyond lifestyle risk factors, studies associate stress related factors, including depressive symptoms, with elevated T2D risk^{2,3}. However, chronic stress is not routinely incorporated into prevention and risk stratification guidelines, as the mechanistic pathway from stress exposure to metabolic deterioration remains difficult to quantify³.

A plausible biological link is sustained activation of the hypothalamic pituitary adrenal (HPA) axis, which translates chronic distress into glucocorticoid signaling³. Prolonged cortisol elevation can impair insulin sensitivity, increase hepatic glucose production, and promote visceral adiposity and inflammation⁴⁻⁷. Key questions remain regarding how these processes interact over time and how neuroendocrine dysregulation shapes long term glycemic risk.

Computational modelling can help address these questions by simulating coupled physiology and enabling systematic testing of hypothesized pathways and interventions. Recent models have captured HPA axis regulation⁸ and obesity driven T2D progression with lipotoxicity and inflammation^{9,10}. However, these components have not yet been combined into a single framework that links stress responsive neuroendocrine dynamic to downstream metabolic progression.

Here, we develop and evaluate an endocrine metabolic progression model in which chronic stress, proxied by the Center for Epidemiologic Studies Depression Scale (CESD)¹¹, modulates HPA axis activity and downstream glycemic regulation. We validate population level behavior against clinical data from the MESA dataset using stress stratified simulations under a fixed parameter range.

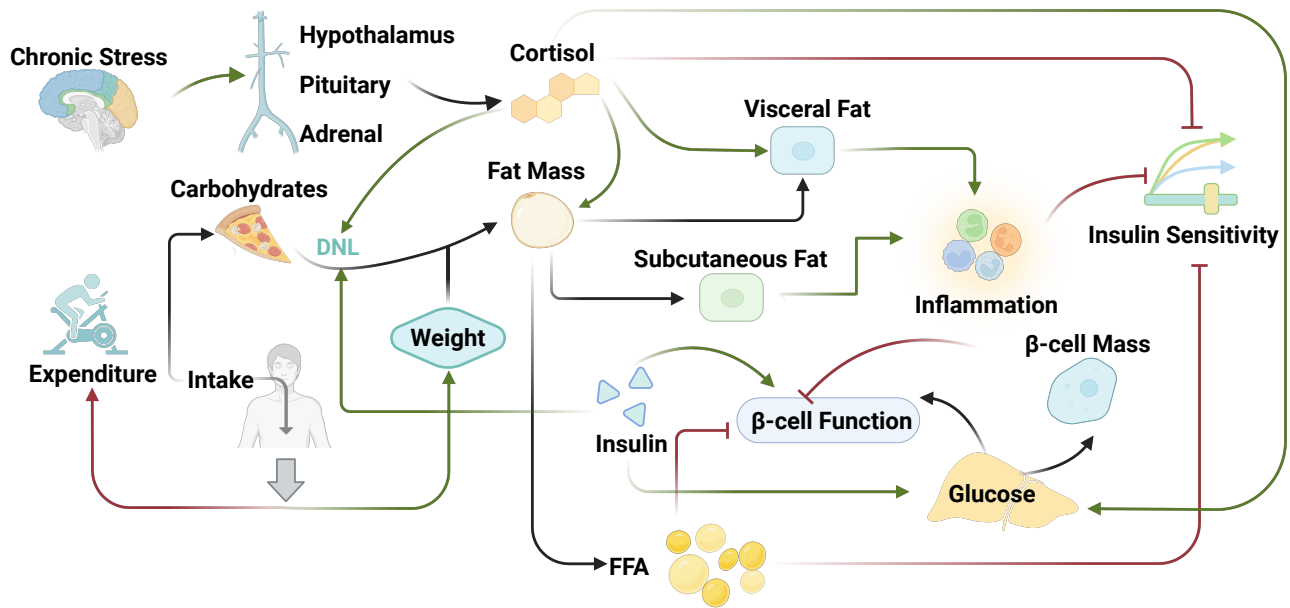


Figure 1: Conceptual model structure and coupling pathways. Arrows denote the primary interactions: stress drives HPA axis activation and cortisol dynamics, which promote visceral fat accumulation and impair insulin sensitivity and β cell function. Visceral adiposity promotes inflammation, further exacerbating metabolic dysfunction. Created with BioRender.com.

Figure 1 provides a schematic overview of the model structure. CESD derived chronic stress acts through HPA axis activation and cortisol dynamics to influence adiposity, inflammation, insulin sensitivity, and long term fasting glucose outcomes^{4,6,7}. The model combines the HPA axis module of Karin et al.⁸ with the metabolic module of Yildirim et al.⁹, extended here by a depression based stress input and cortisol dependent cross module coupling.

Methods

Data Source and Study Population

Validation used data from the Multi-Ethnic Study of Atherosclerosis (MESA), a longitudinal cohort of adults aged 45 to 84 years at baseline comprising four racial and ethnic groups (White, African American, Hispanic, and Chinese American). The original MESA study was approved by the institutional review boards at participating centers, and written informed consent was obtained from all participants. The present study used existing data obtained through the NHLBI BioLINCC repository in accordance with repository access procedures and applicable data use requirements.

We used an analytic sample from Exams 1, 3, 4, and 5 (2000 to 2012), yielding $N = 2394$ participants (52.8% female, mean age 64.4 ± 9.9 years, BMI range 17.6 to 56.0 kg/m^2). For main validation, we used CESD and fasting glucose recorded at the same exam and excluded observations missing either measure (see supplemental information Figure S1). We fixed the anthropometric quantities used to initialize the model (age, height, weight, and BMI) to the mean values of the analytic cohort. Of the included observations, 1803 were used for parameter range tuning and primary CESD stratified validation. The remaining 601 observations from Exams 3 and 4 among participants not included in stress study were reserved for hold out evaluation. For

each individual, the model was simulated over five years under a constant stress input. The final simulated fasting glucose value was compared with the clinical glucose distribution of the corresponding stress group.

Model Framework

The model implements the pathways in Figure 1 as a single coupled ODE system. It combines a published HPA axis module⁸ with a published metabolic progression framework^{9,10}, and extends them with a stress signal derived from depression scale scores and cortisol-dependent coupling terms linking adiposity, inflammation, and insulin sensitivity. For clarity, we present the equations in modular form: (i) stress input derived from CESD scores, (ii) HPA dynamics, (iii) cortisol modulated weight change and fat partitioning between visceral and subcutaneous fat, (iv) adipose induced inflammation, and (v) glucose, insulin, beta cell, and FFA dynamics with systemic insulin sensitivity.

Stress Input Construction

Chronic stress spans psychosocial and socioeconomic (SES) domains¹². We focus on the psychosocial domain because it provides a direct mechanistic drive to the HPA axis via CRH signaling, which is the primary neuroendocrine pathway represented in our system⁴. Psychosocial stress was operationalized as a continuous distress signal derived from validated questionnaires, using the Center for Epidemiologic Studies Depression Scale (CESD) as a continuous proxy of depressive symptom burden relevant to stress physiology¹¹. A continuous input (rather than a binary disease state) is required to couple distress severity quantitatively to HPA drive and downstream metabolic consequences within a dysregulation framework⁴.

Following composite stress measurement practice¹², CESD was normalized to $[0, 1]$:

$$\text{CESD}_{\text{norm}} = \min \left(\frac{\text{CESD}}{\text{CESD}_{\text{max}}}, 1 \right). \quad (1)$$

Stress input was then defined by a saturating Hill function:

$$\text{Stress} = \frac{\text{CESD}_{\text{norm}}^{n_s}}{K_s^{n_s} + \text{CESD}_{\text{norm}}^{n_s}}. \quad (2)$$

Here, K_s is the half maximal constant of the Hill mapping and sets the scale of the stress input, while n_s controls the steepness of the dose response curve.

Emotional social support Index (EMOT), measured in MESA using a 6 item index, was implemented as an optional buffering factor that attenuates effective distress transmitted to the HPA axis¹¹ (Details shown in supplemental information). This extension was not used in the current validation pipeline.

This formulation enables a direct mechanistic coupling between continuous stress input and GR mediated HPA dysregulation⁴. Although SES and neighborhood stressors may capture additional variance in stress exposure¹², we prioritized interpretability and identifiability given the available measures. Future work can incorporate SES stressors in an additional manner, following established composite stress frameworks¹².

HPA Submodel

We model the HPA axis using the gland mass adaptation framework of Karin et al.⁸. State variables include corticotropin releasing hormone (CRH, x_1), adrenocorticotrophic hormone (ACTH,

x_2), cortisol (x_3), and the functional masses of pituitary corticotrophs (C_{pit}) and adrenal cortex (A_{adr}). CRH stimulates ACTH release, ACTH drives cortisol production, and cortisol inhibits CRH synthesis through two receptor mediated pathways. Mineralocorticoid receptor (MR) feedback is inversely proportional to cortisol, while glucocorticoid receptor (GR) feedback is sigmoidal to represent cooperative binding. CRH, ACTH, and the gland mass variables are not measured in MESA and are treated as latent model states. Cortisol is generated by the HPA submodel.

Gland masses evolve on slower timescales in response to upstream stimulation. Elevated CRH promotes pituitary growth, and elevated ACTH increases adrenal mass. Hormone secretion scales linearly with gland mass under the assumption of constant per cell secretory capacity. The resulting nondimensional ODE system is

$$\frac{dx_1}{dt} = \gamma_1 (u(t) MR(x_3) GR(x_3) - x_1), \quad (3)$$

$$\frac{dx_2}{dt} = \gamma_2 (C_{\text{pit}} x_1 - x_2), \quad (4)$$

$$\frac{dx_3}{dt} = \gamma_3 (A_{\text{adr}} x_2 - x_3), \quad (5)$$

$$\frac{dC_{\text{pit}}}{dt} = \gamma_C C_{\text{pit}} (x_1 - 1), \quad (6)$$

$$\frac{dA_{\text{adr}}}{dt} = \gamma_A A_{\text{adr}} (x_2 - 1), \quad (7)$$

with feedback functions

$$MR(x_3) = \frac{1}{x_3}, \quad GR(x_3) = \frac{1}{1 + \left(\frac{x_3}{K_{GR}}\right)^n}. \quad (8)$$

All variables are scaled, so their homeostatic baseline equals 1. Parameters $\gamma_1, \gamma_2, \gamma_3$ are turnover rates for CRH, ACTH, and cortisol, and γ_C, γ_A set the adaptation timescales of C_{pit} and A_{adr} .

The external input $u(t)$ drives CRH secretion and represents net stress. In simulations, $u(t)$ is implemented as a constant step to mimic sustained stress and reproduce canonical HPA dynamics. In clinical applications, $u(t)$ is replaced by an input constructed from CESD. Because stress duration and persistence are not observed, each CESD observation is treated as a proxy for sustained stress drive throughout the simulation.

At baseline, the system remains at steady state. Increasing stress elevates CRH and ACTH rapidly and raises cortisol, and the slow gland mass adaptation yields sustained cortisol elevation and slow recovery even after stress removal, consistent with chronic stress HPA dysregulation⁸.

Body Weight and Fat Partitioning Dynamics

Body weight change was modeled using an energy balance formulation with an additional hormone mediated de novo lipogenesis (DNL) term:

$$\frac{dW}{dt} = \frac{1}{\tau_w} (\text{TDEI } k_w - \text{TDEE } k_w + \phi), \quad (9)$$

where W is body weight (kg), $\tau_w = 1$ day is the adaptation timescale, and $k_w = 1/7700$ (kg/kcal) converts net energy surplus to weight change. Total daily energy intake (TDEI) and expenditure (TDEE) define the baseline surplus term, consistent with standard energy balance principles¹³. Total expenditure was computed as

$$\text{TDEE} = \text{BMR} \times \text{PAL}, \quad (10)$$

with basal metabolic rate (BMR, kcal/day) estimated by age and sex stratified linear equations¹³:

- Men:

- Age from 18 to 30: $\text{BMR} = 15.057 W + 692.2$
- Age from 30 to 60: $\text{BMR} = 11.472 W + 873.1$
- Age ≥ 60 : $\text{BMR} = 11.711 W + 587.7$

- Women:

- Age from 18 to 30: $\text{BMR} = 14.818 W + 486.6$
- Age from 30 to 60: $\text{BMR} = 8.126 W + 845.6$
- Age ≥ 60 : $\text{BMR} = 9.082 W + 658.5$

where W is in kg. Because individual level activity measures were unavailable in MESA, physical activity level was fixed at $\text{PAL} = 1.6$, the modal value for sedentary adults¹⁴.

To capture endogenous fat synthesis beyond direct dietary fat deposition, we added a DNL term ϕ representing hormone dependent conversion of carbohydrate energy to stored fat^{15,16}. DNL is modest under eucaloric conditions but increases under carbohydrate overfeeding, particularly with hyperinsulinemia^{15,17}. Assuming carbohydrate availability sufficient to provide substrate for DNL, we defined

$$\phi = p_{\text{carb}} \times \text{TDEI} \times k_w \times \phi_{\text{insulin}} \times \phi_{\text{cort}}(C), \quad (11)$$

where p_{carb} is the dietary carbohydrate fraction¹⁸, ϕ_{insulin} represents the insulin effect of DNL, and $\phi_{\text{cort}}(C)$ captures cortisol dependent amplification. We threshold gate terms of the form $(x - x_0)$ by using the rectified form $(x - x_0)_+ \equiv \max(x - x_0, 0)$.

Insulin is the principal hormonal driver of DNL under carbohydrate replete conditions, acting through transcriptional activation of lipogenic enzymes^{16,19}. Studies in humans have shown that modest increases in fasting insulin during carbohydrate overfeeding can increase hepatic DNL by more than tenfold¹⁷, demonstrating a steep, threshold dependent dose response relationship¹⁵. The insulin activated DNL component was modeled as a sigmoidal Hill type response:

$$\phi_{\text{insulin}} = \frac{\max_{\text{insulin}} (I - I_{\text{thresh}})^{n_i}}{k_i^{n_i} + (I - I_{\text{thresh}})^{n_i}}, \quad (12)$$

where I is plasma insulin ($\mu\text{U}/\text{mL}$) and the formulation captures nonlinear activation once insulin exceeds a physiological threshold.

Cortisol amplifies the lipogenesis stimulated by insulin. Although cortisol has no direct effect on DNL in the absence of insulin²⁰, under chronic stress with hyperinsulinemia and carbohydrate excess, it can synergistically increase hepatic lipogenic enzyme activity, including acetyl CoA carboxylase and fatty acid synthase²⁰. Regulation of adipocyte DNL is more complex²¹, but the net whole body effect is dominated by the hepatic response. We therefore represented cortisol as a multiplicative amplification term:

$$\phi_{\text{cort}}(C) = 1 + \frac{\max_{\text{cort}} (C - 1)^{n_{\text{cort}}}}{k_{\text{cort}}^{n_{\text{cort}}} + (C - 1)^{n_{\text{cort}}}}, \quad (13)$$

where cortisol C is normalized to baseline ($C = 1$), and $\max_{\text{cort}}$, k_{cort} , n_{cort} determine maximal amplification, sensitivity, and steepness. This construction activates amplification when cortisol is elevated.

Total fat mass accumulation combined direct energy surplus allocation with DNL:

$$\frac{dF_m}{dt} = \frac{1}{\tau_w} (p_{\text{fmass}} (\text{TDEI } k_w - \text{TDEE } k_w) + \phi), \quad (14)$$

Here, p_{fmass} represents the propensity for net energy surplus to be stored as fat mass, informed by MESA associations between macronutrient intake and body composition²². This separates direct dietary fat storage from endogenous synthesis via ϕ under surplus and metabolic stress^{15,16}.

Newly accumulated fat was partitioned into visceral (VF) and subcutaneous (SF) compartments:

$$\frac{dV_F}{dt} = p_{vf}(C) \frac{dF_m}{dt}, \quad (15)$$

$$\frac{dS_F}{dt} = (1 - p_{vf}(C)) \frac{dF_m}{dt}, \quad (16)$$

with a cortisol dependent partition fraction

$$p_{vf}(C) = p_{vf,\text{base}} + p_{vf,\text{amp}} \frac{(C - 1)^{n_p}}{k_p^{n_p} + (C - 1)^{n_p}}. \quad (17)$$

This represents the net depot bias under glucocorticoid exposure without explicitly modeling depot specific pathways, such as lipid uptake/storage and lipolysis re esterification. Study suggests that glucocorticoids can preferentially enhance lipogenic programs in visceral relative to subcutaneous depots²³. In this formulation, $p_{vf}(C)$ captures the aggregate incremental storage induced by cortisol. The model assumes that all additional fat is allocated exclusively to VF and SF, consistent with mass conservation. It also distinguishes baseline cortisol, representing normal adipose function, from elevated cortisol ($C > 1$), which drives preferential visceral accrual. This assumption is consistent with depot specific differences in glucocorticoid receptor expression and responsiveness⁶, as well as with associations between endogenous cortisol production and intra abdominal fat in men⁷.

As an empirical reference for short term weight gain in normal weight adults, newly acquired fat is predominantly stored subcutaneously ($\sim 90\%$) with a smaller visceral fraction ($\sim 10\%$), although inter individual variability is substantial (visceral fraction ranging from -5% to 22%)²⁴.

Inflammation Dynamics

At pharmacological doses, cortisol suppresses inflammation, whereas at physiological to moderate levels it can facilitate inflammatory responses⁵. Under chronic stress, this sustained proinflammatory influence operates predominantly through visceral adipose expansion induced by cortisol, consistent with experimentally observed delayed priming effects⁵. We therefore model inflammation on metabolic timescales as arising primarily through adipose tissue, rather than through direct interactions between cortisol and cytokines.

Adipose tissue is a major source of proinflammatory cytokines in systemic metabolic inflammation. Chronic glucocorticoid elevation preferentially promotes visceral fat accumulation, in part via higher glucocorticoid receptor density in visceral depots²⁵. Visceral adipose tissue also exhibits substantially greater secretion of proinflammatory cytokines (IL 6, IL 8, TNF α) and adipokines (leptin, visfatin, resistin) than subcutaneous fat^{6,25}. This supports its dominant contribution to systemic inflammation and insulin resistance.

Inflammation dynamics are:

$$\frac{d\theta}{dt} = \theta_b + \frac{\theta_{\text{drive}} - \theta}{\tau_\theta} \quad (18)$$

where θ_b represents baseline nonadipose inflammation and τ_θ (days) sets the adjustment timescale.

The adipose derived inflammatory drive is:

$$\theta_{\text{drive}} = \theta_{\text{max},V_F} \frac{V_F^{n_\theta}}{V_F^{n_\theta} + k_\theta^{n_\theta}} + \theta_{\text{max},S_F} \frac{S_F^{n_\theta}}{S_F^{n_\theta} + k_\theta^{n_\theta}} \quad (19)$$

with $\theta_{\max, V_F} + \theta_{\max, S_F} = 1$. assigning visceral fat the larger weight to reflect its higher inflammatory potency. The Hill forms capture saturating relationships between depot mass and cytokine production.

Glucose, Insulin, β Cell, and Free Fatty Acid Submodel

The metabolic submodel captures long timescale interactions among plasma glucose (G), insulin (I), free fatty acids (FFA), insulin sensitivity (S_i), β cell mass (β), and β cell function (σ). We adapted the obesity driven T2D progression model of Yildirim et al.⁹ and extended it to incorporate cortisol mediated regulation of glucose metabolism and insulin sensitivity.

Glucose evolves from the balance of hepatic glucose production (HGP) and peripheral disposal (R_d):

$$\frac{dG}{dt} = H_{GP} - R_d. \quad (20)$$

Glucocorticoids chronically increase hepatic gluconeogenesis and impair peripheral glucose uptake, contributing to hyperglycemia and insulin resistance²⁶. Cortisol activates gluconeogenic enzymes such as PEPCK and G6Pase²⁶ and impairs post receptor insulin signaling in muscle, including IRS 1 and PI3 kinase pathways²⁷. These effects produce rightward shifts in the insulin response curves for both HGP suppression and glucose disposal²⁸. HGP was formulated as

$$H_{GP} = H_{GP, b} + [1 + c_{hgp}(C - 1)] \cdot \frac{H_{GP, \max} \cdot K_{hgp}^n}{K_{hgp}^n + (S_i \cdot I)^n}, \quad (21)$$

where C is cortisol normalized to baseline ($C = 1$), $H_{GP, \text{bas}}$ is basal production, $H_{GP, \max}$ is insulin suppressible capacity, and c_{hgp} captures cortisol amplification. This structure raises HGP and weakens insulin suppression under elevated cortisol, consistent with hypercortisolemic shifts^{26,28}. Peripheral disposal was modified as

$$R_d = \left[E_{G0} + S_{ci} \cdot S_i \cdot I + \frac{[1 - r_{acor1}(C - 1)] \cdot R_{d, \max} \cdot (S_i \cdot I)^n}{[1 - r_{acor}(C - 1)] \cdot K_{crd}^n + (S_i \cdot I)^n} \right] \cdot G, \quad (22)$$

where E_{G0} is basal uptake, $R_{d, \max}$ is maximal insulin stimulated disposal, and r_{acor} and r_{acor1} quantify cortisol antagonism by shifting the insulin response curve rightward and modulating maximal disposal, respectively^{26–28}.

A simple treatment proxy was also introduced to represent average glucose lowering effects. This formulation was motivated by evidence that medications such as metformin and TZDs improve fasting hepatic insulin sensitivity and glucose clearance, whereas peripheral insulin mediated glucose uptake is more clearly enhanced for TZDs than for metformin alone²⁹. Insulin based therapy also acts on both pathways³⁰. Its multiplicative implementation was guided by prior PK PD modeling in which metformin was represented through scaling of hepatic glucose production and peripheral glucose uptake terms³¹.

A glucose dependent activation term was defined as

$$w_{tr}(G) = \frac{G^{n_{tr}}}{K_{tr}^{n_{tr}} + G^{n_{tr}}}, \quad (23)$$

where K_{tr} denotes the half activation glucose level and n_{tr} controls the steepness of treatment activation. The treatment adjusted glucose fluxes were then written as

$$H_{GP}^{tr} = (1 - \alpha_{hgp} w_{tr}(G)) H_{GP}, \quad R_d^{tr} = (1 + \alpha_{rd} w_{tr}(G)) R_d, \quad (24)$$

so that

$$\frac{dG}{dt} = H_{GP}^{tr} - R_d^{tr}. \quad (25)$$

Here α_{hgp} and α_{rd} denote the maximal fractional suppression of hepatic glucose production and enhancement of peripheral glucose disposal, respectively. The current extension was intended to represent average treatment effects at the cohort level rather than to reconstruct drug specific treatment histories.

Insulin follows secretion from β cells and first order clearance:

$$\frac{dI}{dt} = \frac{\beta \cdot ISR}{V} - k \cdot I, \quad (26)$$

where V is plasma volume, k is the clearance rate, and ISR is secretion per unit β cell mass. Following⁹,

$$ISR = \sigma \cdot \frac{M^{K_{ISR}}}{M^{K_{ISR}} + \alpha_{ISR}^{K_{ISR}}}, \quad (27)$$

with glucose driven metabolic demand

$$M = \frac{G^{K_M}}{G^{K_M} + \alpha_M^{K_M}}. \quad (28)$$

Insulin sensitivity evolves with first order kinetics⁹:

$$\frac{dS_i}{dt} = \frac{S_{i,\infty} - S_i}{\tau_{S_i}}, \quad (29)$$

where τ_{S_i} is the adjustment time constant. We extended the original formulation⁹ to include glucocorticoid effects on insulin sensitivity. This mechanism was absent from the baseline formulation and is dose dependent, producing rightward shifts in insulin response curves²⁸. This impairment correlates quantitatively with cortisol production rates⁷, and is mediated by glucocorticoid receptor effects on insulin signaling cascades, including IRS1 downregulation and PI3K/AKT inhibition across insulin sensitive tissues³². The steady state sensitivity combines cortisol, inflammation, and lipotoxicity multiplicatively:

$$S_{i,\infty} = \frac{K_{cortSi}^{n_{Si}}}{K_{cortSi}^{n_{Si}} + (C - 1)^{n_{Si}}} \cdot \frac{K_{Si,\theta}}{K_{Si,\theta} + \theta} \cdot \left(1 - m_{FFA} \cdot \frac{FFA^{n_{FFA}}}{FFA^{n_{FFA}} + K_{Si,FFA}^{n_{FFA}}} \right), \quad (30)$$

where $(C - 1)$ indexes sustained hypercortisolemia²⁸. This multiplicative form assumes that these factors act through distinct pathways to reduce insulin signaling³².

FFA dynamics balance insulin suppressed lipolysis and peripheral uptake⁹:

$$\frac{dFFA}{dt} = FFA_{Ra,max} \cdot \frac{1}{1 + (S_i \cdot I / K_{SiF})^{\alpha_{SiF}}} - c_f \cdot W \cdot FFA, \quad (31)$$

where insulin action ($S_i \cdot I$) suppresses lipolysis via an inhibitory Hill function with half maximal response K_{SiF} and Hill coefficient α_{SiF} . The maximal lipolysis rate $FFA_{Ra,max}$ scales linearly with fat mass⁹, and c_f is the clearance rate per kilogram body weight.

β cell mass includes replication, apoptosis, neogenesis, and logistic constraints⁹:

$$\frac{d\beta}{dt} = \frac{P_{ng} + P(ISR) \cdot \beta - A(M) \cdot \beta - s \cdot \beta^2}{\tau_\beta}, \quad (32)$$

where $P(ISR)$ and $A(M)$ are sigmoidal functions of ISR and M , respectively, P_{ng} is constant neogenesis, and s is the density dependent growth parameter. β cell function σ relaxes to a steady state⁹:

$$\frac{d\sigma}{dt} = \frac{\sigma_{\infty}(G, FFA, \theta) - \sigma}{\tau_{\sigma}}, \quad (33)$$

with

$$\sigma_{\infty}(G, FFA, \theta) = \sigma_b \cdot (\sigma_{gu} - \sigma_{gd} \cdot \sigma_{FFA} - \sigma_{\theta}). \quad (34)$$

Here, σ_{gu} denotes glucose stimulated upregulation, and σ_{gd} , σ_{FFA} , and σ_{θ} represent glucotoxic, lipotoxic, and inflammatory impairments of secretory capacity, respectively.

Simulation Setup and Validation Design

We performed population simulations in which chronic stress derived from CESD scores serves as the upstream input to the HPA axis. Parameters were taken from prior studies^{8,9}, regression based estimates from MESA¹¹, or conservative assumptions when needed (Supplemental Information, Table S1). The CESD to stress mapping was specified in the model formulation, and selected model parameters were further examined through sensitivity analysis. Inter individual heterogeneity was introduced in two ways. selected regulatory/metabolic parameters were sampled by Latin Hypercube Sampling (LHS), and baseline initial conditions, including glucose, insulin, insulin sensitivity, β cell mass, FFA, and inflammation, were pertubated by $\pm 10\%$. Stress input was computed from CESD using a sigmoidal Hill function (Eq. 2). Within each group, CESD values were sampled from the corresponding clinical distribution. All validations were conducted using a common set of parameter ranges and simulation settings.

Simulations and validation analyses were performed on the Snellius HPC system using Python 3.11.3 (module Python/3.11.3 GCCcore 12.3.0) with NumPy 2.4.0, pandas 2.3.3, SciPy 1.16.3, matplotlib 3.10.8, and joblib 1.5.3. The ODE system was solved with `solve_ivp` using LSODA over five years with daily output. Each stratum comprised 30,000 individuals simulated as 30 batches of 1,000. Strata were defined as Unstressed ($CESD \leq 3$), Stressed ($3 < CESD < 16$), and Depressed ($CESD \geq 16$). Here, $CESD \geq 16$ indicates clinically significant depressive symptoms or high depressive symptom burden. $CESD \leq 3$ was an operational choice used to define a near-baseline reference regime, in which the model exhibited less than 1% long-term metabolic variation over 5 years.

Statistical Analysis

Agreement was assessed at the category proportion and distribution summary levels. We computed proportions in standard diagnostic bins (mg/dL): normal ($70 \leq G < 100$), IFG ($100 \leq G < 126$), and diabetes ($G \geq 126$)³³, and the fraction exceeding the clinical stratum median. For consistency across analyses, glycemic categories were harmonized using the current IFG cutoff of 100 mg/dL. Earlier MESA exams may not have applied this threshold in contemporaneous clinical classification and treatment. Across simulation batches, variability is reported as minimum and maximum ranges. Proportion comparisons were evaluated using participant level bootstrap resampling to account for repeated observations across exams. Continuous outcomes were evaluated by comparing simulated batch level distributions with the clinical distributions. All tests were two sided with $\alpha = 0.05$ unless noted otherwise.

Results

We used cross sectional fasting glucose from MESA and stratified participants by CESD into unstressed ($\text{CESD} \leq 3$, $n = 583$), stressed nondepressed ($3 < \text{CESD} < 16$, $n = 900$), and depressed ($\text{CESD} \geq 16$, $n = 307$). Here, $\text{CESD} \geq 16$ indicates clinically significant depressive symptoms or high depressive symptom burden. This group is referred to as depressed throughout.

Median fasting glucose was similar across strata (93.0 [86.0, 103.0], 93.0 [86.0, 102.0], 94.0 [86.5, 105.0] mg/dL, respectively), and a Kruskal Wallis test found no significant evidence of a distributional difference ($p = 3.25 \times 10^{-1}$). This limited cross-sectional separation by fasting glucose alone motivates a stratified validation focused on distributional agreement between simulated and clinical glucose.

Baseline Validation

We first established a healthy reference regime using the unstressed stratum ($\text{CESD} \leq 3$). The model was initialized at a metabolically healthy state and driven by CESD values sampled from the empirical unstressed distribution. Under this condition, the simulated fasting glucose median matched the clinical median (89.00 mg/dL). The resulting unified parameter range was then held fixed for all subsequent CESD-stratified evaluations (see supplemental information Table S2).

Validation across CESD strata

We next evaluated whether the fixed parameter range could reproduce clinical fasting glucose distributions across the three stress groups.

In Figure 2, the model reproduced the main clinical fasting glucose pattern across the non-depressed strata (unstressed and stressed groups) under the same parameter range. In both groups, the central normoglycemic mode was preserved, and the model reproduced the main clinical fasting glucose pattern, with proportion deviations below 10%. In the unstressed group, the simulated distribution closely overlapped with the clinical profile, indicating agreement with the clinical fasting glucose pattern. In the stressed group, simulations reproduced a modest rightward shift in fasting glucose relative to the unstressed group. This difference appeared primarily as mild upper tail expansion rather than displacement of the dominant mode, suggesting a directional stress associated increase in glycemic risk.

Across strata, grouped glucose proportions remained broadly consistent with the clinical references, with error within about 10%. A recurring bias was a slight overestimation of the normal bin with a corresponding underestimation of IFG.

Against this overall agreement, the most prominent residual discrepancy was observed in the distribution shape of the depressed group ($\text{CESD} \geq 16$) (Figure 3). Within this group, the residual distributional mismatch was larger and phenotype specific. The simulated diabetic fraction ($G \geq 126$ mg/dL) was systematically elevated. The excess probability mass did not arise from a uniform rightward shift of the entire distribution. Instead, it concentrated in the upper tail, producing a rise with partial saturation pattern across approximately ~ 130 to 300 mg/dL range (Figure 3D), where the clinical distribution contains substantially less mass. A qualitatively similar tail tendency was also observed in the stressed nondepressed stratum but remains mild. This suggests regime dependent amplification rather than a uniform failure across strata.

We then performed targeted parameter scans guided by a tail focused screening analysis to localize mechanisms underlying the residual upper tail mismatch (see Figure S3 in supplemental information). The glucotoxic impairment gate in the σ_{gd} term was the main focus because it

was highly sensitive to tail behavior and provided the most direct structural explanation for the observed rise and partial saturation pattern. Varying its two Hill parameters produced structured effects on the diabetic range tail. Increasing the exponent sharpened the transition from preserved to impaired regulation and amplified curvature in the tail segment, whereas increasing the half saturation parameter shifted the onset of this transition toward higher glucose values (Figure 3E and F). The combined scan summarizes joint parameter variation as an envelope of attainable tail morphologies (Figure 3G). The clinical tail shape falls within this envelope, and a subset of paired values above the baseline validation setting yields tail densities that lie close to the clinical tail over the 130 to 300 mg/dL range. In an additional diagnostic scan, varying n_{crd} altered mass within the diabetic range tail, but its effect was less systematic than that of the σ_{gd} gate (Supplemental information, Figure S2).

In Figure 4, we grouped the clinical diabetes reference by treatment status to contextualize the diabetes range discrepancy. Treated cases dominated this subset, and the pooled clinical diabetes distribution closely tracked the treated subgroup. This produced a left shift with substantial mass below the diagnostic threshold (126, mg/dL), consistent with treatment associated glycemic control^{1,34}. The pooled clinical diabetes distribution was therefore left shifted relative to the model defined diabetes subset and closely resembled the treated subgroup. Untreated diabetes cases were sparse ($n = 4$), limiting subgroup interpretation. We quantified the distribution mismatch on the model defined diabetes slice ($G \geq 126$, mg/dL) using the Wasserstein 1 distance (W1) and the two sample Kolmogorov Smirnov statistic (KS statistic). Both metrics indicated a discrepancy between the simulated and clinical diabetes distributions in this range. Relative to treated only diabetes, the pooled clinical reference yielded a marginally lower mismatch to simulations (W1: 60.16 vs. 59.64 mg/dL, KS statistic: 0.606 vs. 0.592).

Treatment extension

To explore whether pharmacological glucose control could account for part of the residual mismatch in the depressed group, we introduced a simplified treatment proxy acting on hepatic glucose production and glucose disposal (Figure 5). With this extension, the simulated category proportions agreed with the clinical reference at the category level. The treatment adjusted distribution remained close to the clinical profile around the main mode while preserving a modest right tail.

This supports the interpretation that omission of glucose lowering treatment contributed to part of the diabetic range mismatch in the base model.

Out of sample evaluation subset

Using the unified parameter ranges, we evaluated out sample generalization on a reserved subset ($n=601$) without refitting (Figure 6). Simulations preserved the overall distributional structure in the normoglycemic range while retaining the same diabetes range upper tail mismatch. Category level deviations were also consistent with the primary validation, with slight over allocation to normal, under allocation to IFG, and a compensatory increase in the diabetes fraction. Together, these results support out sample generalization under the same simulation setup and suggest that the residual discrepancy reflects a regime dependent limitation rather than cohort specific tuning.

Discussion

We developed an integrated model of stress, HPA axis activity, and metabolic regulation. Under a common simulation setting with population heterogeneity, the model reproduced the main clinical fasting glucose pattern observed in the nondepressed group. In the model, higher stress burden was associated with a shift toward worse glycemic profiles, most clearly reflected in a heavier upper tail of the glucose distribution. This provides a mechanistic interpretation of how chronic stress may contribute to metabolic dysregulation. The model helps localize where endogenous stress driven dynamics are sufficient and where additional mechanisms are likely required. In the present cohort, however, cross sectional fasting glucose showed only limited separation across CESD strata. Accordingly, the value of the current framework lies less in reproducing a strong empirical CESD glucose association than in clarifying how stress related effects may arise through underlying regulatory dynamics. It may also provide a useful basis for future hypothesis driven analyse, including more comprehensive intervention analyses.

The dominant residual mismatch concentrated in the depressed diabetic subgroup, and this pattern remained evident in the hold out cohort. This pattern argued against a cohort specific artifact and instead suggested a systematic limitation that becomes amplified in higher impairment regimes. The discrepancy was only partly reduced after the addition of the simplified treatment extension. Because depression has been associated with altered HPA axis dynamics and elevated inflammatory cytokines^{35,36}, such subgroup specific mismatch is biologically plausible.

A practical consideration is that the clinical diabetes reference distribution is treatment mixed, whereas the current simulation framework does not explicitly represent glucose lowering therapy. In our data slice, treated diabetes cases dominated, whereas untreated cases were sparse (Figure 4). This pooling can left shift the clinical diabetes distribution and inflate apparent diabetes range mismatch relative to a no treatment simulation. Quantitatively, mismatch metrics on the diabetes slice ($G \geq 126$ mg/dL) were slightly smaller when using the pooled clinical reference than when using treated only diabetes (W1: 60.16→59.64 mg/dL, KS statistic: 0.606→0.592), but the improvement was small, consistent with the limited contribution of rare untreated cases.

Figure 6 further shows that this discrepancy is regime dependent. Because the model encodes untreated endogenous regulation, agreement in the normoglycemic to moderately elevated range is the most informative regime for mechanism based stress to risk mapping. By contrast, the upper tail presents progressive divergence, with simulated quantiles exceeding clinical quantiles. In this regime, empirical fasting glucose is increasingly shaped by processes not represented here. These include clinical treatment, diagnosis related behavior change, and heterogeneity in disease progression, such as inter individual differences in β cell decline trajectories. Thus, the upper tail divergence is best interpreted as a scope limitation of an untreated natural history model rather than a failure of out of sample generalization. To localize the onset of this divergence in a reproducible way, we quantify the Q Q residual pattern using an upper tail changepoint criterion, yielding $x^* \approx 122$ mg/dL. We use this as a data driven reference point for the transition to tail dominated behavior. Below x^* , simulated and clinical quantiles remain relatively closely aligned. Above x^* , the quantile gap widens progressively, consistent with the mechanistic upper tail mismatch observed in simulations. Consequently, quantitative distributional inferences in the diabetic range motivate treatment aware stratification or explicit therapy representation.

Mechanistically, the rise with partial saturation in the upper tail implicates nonlinear gating in the β cell function module. In our formulation, the glucose dependent suppression term σ_{gd} enters $\sigma_{\infty}(G, \text{FFA}, \theta)$ as a multiplicative impairment factor (Eq. 34). The Hill exponent n_{sgkd} controls the steepness of impairment activation, whereas the half saturation scale sets the glycemic range at which impairment transitions from weak to strong^{37,38}.

The targeted scan in Figure 3, panels E and F, shows that this gate strongly shapes local tail morphology and the amount of probability mass in the diabetes range. This is consistent with amplification of between individual variability near a transition region. Figure 3, panel G shows that multiple paired σ_{gd} Hill settings can produce similarly attenuated tails and comparable reductions in tail mass. The depressed stratum tail therefore does not uniquely identify the impairment threshold. Instead, the threshold is better interpreted as an effective phenomenological quantity that may also be influenced by treatment confounding. The improved fit obtained with an upward threshold shift is consistent with the clinical reference distribution being influenced by treatment stabilized glycemia. The simplified treatment extension was also consistent with this interpretation. Although it reduced the depressed group discrepancy, it did not remove it completely. This suggests that treatment related effects are only part of the explanation, and that the remaining mismatch may also reflect structural limitations in how glucotoxic impairment is represented, together with other unmodeled sources of heterogeneity. Such residual error is therefore expected and supports using the model as a framework for future intervention oriented analysis within its current scope.

Conceptually, a delayed onset of glucotoxic impairment corresponds to an extended compensation window. This is consistent with clinical evidence that β cell dysfunction can be partially reversed when hyperglycemia is corrected early and antecedent glucotoxic exposure is shortened³⁹. By constraining sustained glycemia, therapy can reduce the ongoing glucotoxic burden^{39,40}. This may help preserve functional insulin secretion and keep many clinically diabetic trajectories closer to controlled ranges than an untreated natural history reference would imply^{39,40}. In a phenomenological formulation, this appears as a delayed engagement of strong glucose dependent impairment, which in turn reduces excess simulated mass in the lower diabetic range. Supplementary analysis further indicated that the Hill nonlinearity in insulin stimulated peripheral disposal (R_d) can reshape the diabetic range tail (Supplemental information, Figure S2). However, its effect mainly redistributed probability mass, supporting glucotoxic impairment gating as the more direct tail mechanism.

Limitations of the Study

These conclusions are conditioned on both data and model structure constraints. Although validation against fasting glucose distributions and category proportions provides a strong population level validation target, it does not uniquely identify internal pathways in a tightly coupled endocrine metabolic system. Multiple mechanisms can reproduce similar summary statistics under heterogeneity⁴¹. Stress is introduced via a CESD derived phenomenological input, and CESD stratification remains an imperfect proxy for heterogeneous biological stress states. Therefore, fitted parameters should be interpreted as effective quantities rather than fixed physiological constants.

The current validation uses cross sectional data, and CESD is represented as a sustained input across a simulation window of 5 years. Parameter evaluation is performed at population level. The framework is therefore best interpreted as a test of whether stress stratified glycemic patterns can be reproduced at the cohort scale. Finer temporal variation in stress exposure and subject specific metabolic adaptation remain outside the current scope.

Structurally, net fat mass change is allocated only to visceral and subcutaneous compartments, and inflammation is modeled primarily through adipose tissue. Neuroendocrine regulation of intake, including insulin brain feedback⁴², is not represented mechanistically, and endocrine axes beyond the HPA axis, such as growth hormone and incretin effects, are not included as major influences. Missing compensatory controls may contribute to distributional mismatches independently of the pathways included here^{42,43}. The clinical depressed diabetes distribution is

also shaped by factors not fully captured by the current model structure. A simple treatment extension improved agreement in the depressed group, suggesting that treatment may contribute to the residual discrepancy. However, treatment is still represented only coarsely, and more treatment aware stratification or a more explicit therapy module may help distinguish treatment related shifts from intrinsic model behavior⁴⁴. Additionally, historical IFG threshold changes may introduce minor inconsistencies between earlier clinical classification and the harmonized categories used here.

Moreover, the model is deterministic and represents variability through parameter and initial state heterogeneity. Incorporating intrinsic stochasticity would enable a more explicit decomposition of variability into intrinsic and extrinsic sources, rather than absorbing all variability into inter individual heterogeneity⁴⁵.

Conclusion

This study developed a coupled stress, HPA, and metabolic model to examine how psychosocial distress relates to population-level fasting glucose patterns. Within a single physiologically plausible parameter range and a consistent simulation framework, the model reproduced the fasting glucose distribution and glycaemic category proportions of the nondepressed group, with similar qualitative behaviour observed in a reserved evaluation subset without refitting. The main limitation was an overestimation of diabetes prevalence and the upper glucose tail in the depressed group, for which glycemic control treatment appears to be one important explanation. As a result, the model is most reliable for metabolically healthier profiles, whereas inference becomes more uncertain in the diabetic range. Overall, the findings support the usefulness of the mechanistic modelling for linking chronic stress to metabolic outcomes.

Data and Code Availability

- The data used in this study were obtained from the Multi-Ethnic Study of Atherosclerosis (MESA) through the NHLBI BioLINCC repository. Access to these data requires approval from NHLBI and is subject to data use agreements.
- The model code used in this study will be deposited in Zenodo and made publicly available upon publication.
- Any additional information required to reproduce or reanalyze the results reported in this paper is available from the corresponding author upon request.

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Author Contributions

Conceptualization, Q.C., V.Y., M.N., and V.M.S.; Methodology, Q.C., V.Y., M.N., and V.M.S.; Software, Q.C. and V.Y.; Formal analysis, Q.C. and V.M.S.; Validation, Q.C. and V.M.S.; Visualization, Q.C.; Writing - original draft, Q.C.; Writing - review & editing, Q.C., V.Y., M.N., and V.M.S.; Supervision, V.M.S.

Declaration of Interests

The authors declare no competing interests.

Supplemental Information

- Supplemental Information PDF, containing supplemental methods for EMOT buffering in stress input, Tables S1-S2, Figures S1-S4, and supplemental references.

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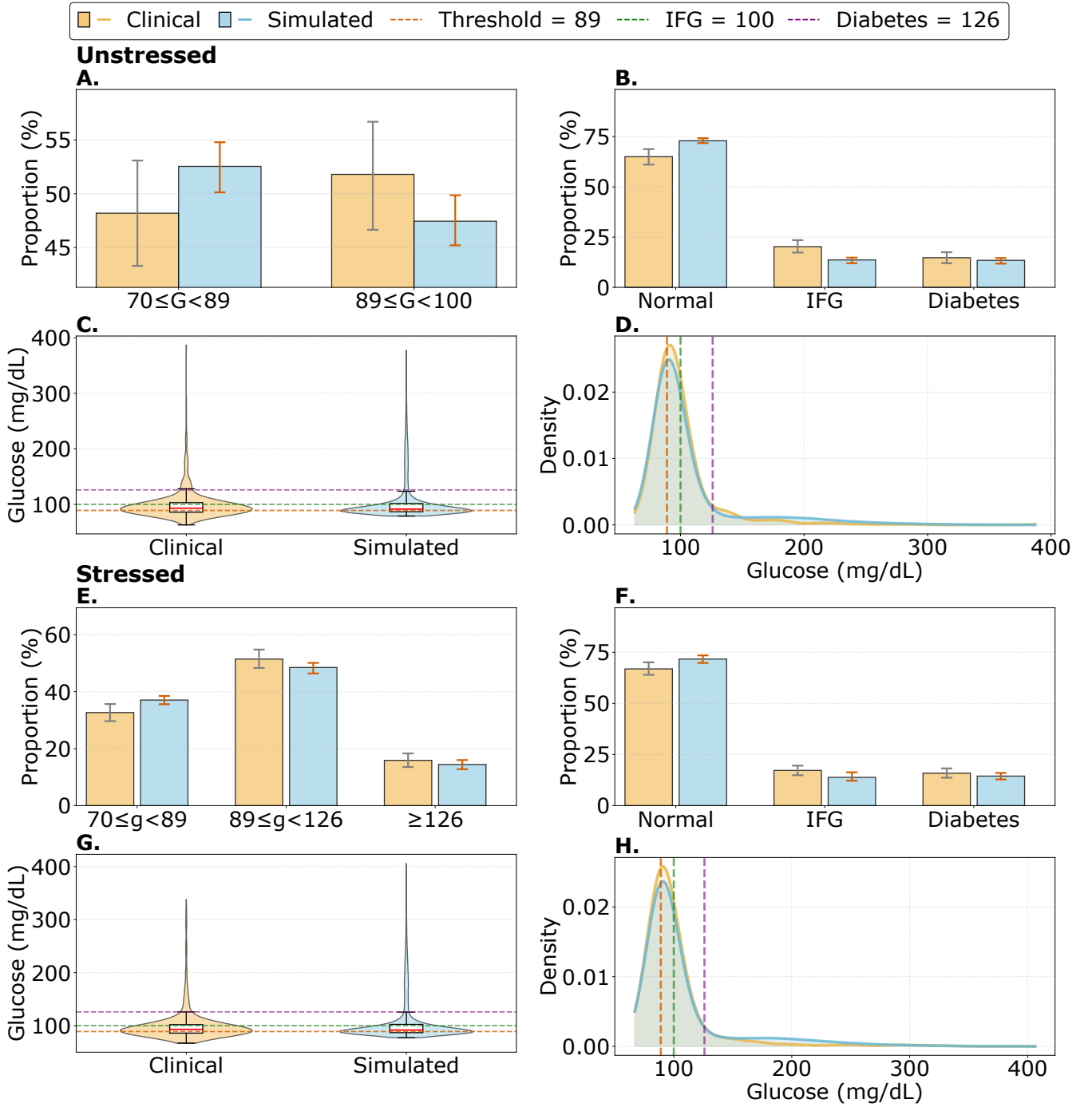


Figure 2: Nondepressed strata (CESD < 16). Panels A to D: unstressed (CESD ≤ 3). Panels E to H: stressed nondepressed (3 < CESD < 16). Bars compare clinical and simulated proportions. Clinical error bars illustrate 95% bootstrap CI. Simulated error bars show the batch minimum to maximum. p values are obtained from participant level bootstrap resampling.

(A) Glucose range proportions, clinical 48.2% and 51.8%, simulated 52.7% [50.5%, 54.6%] and 47.3% [45.4%, 49.5%], $p = 0.1385$. (B) Glycemic categories, clinical 65.0%, 20.2%, 14.8%, simulated 72.6% [70.7%, 74.1%], 13.9% [12.3%, 15.5%], 13.5% [11.2%, 15.3%], $p = 0.0015$. (C) Fasting glucose distribution (violin). (D) Density overlay (KDE).

(E) Glucose range proportions, clinical 32.7%, 51.4%, 15.9%, simulated 37.3% [36.0%, 39.2%], 48.1% [45.8%, 50.8%], 14.6% [13.2%, 16.3%], $p = 0.0420$. (F) Glycemic categories, clinical 66.9%, 17.2%, 15.9%, simulated 71.6% [69.6%, 73.0%], 13.9% [11.4%, 16.2%], 14.6% [13.2%, 16.3%], $p = 0.0190$. (G) Fasting glucose distribution (violin). (H) Density overlay (KDE).

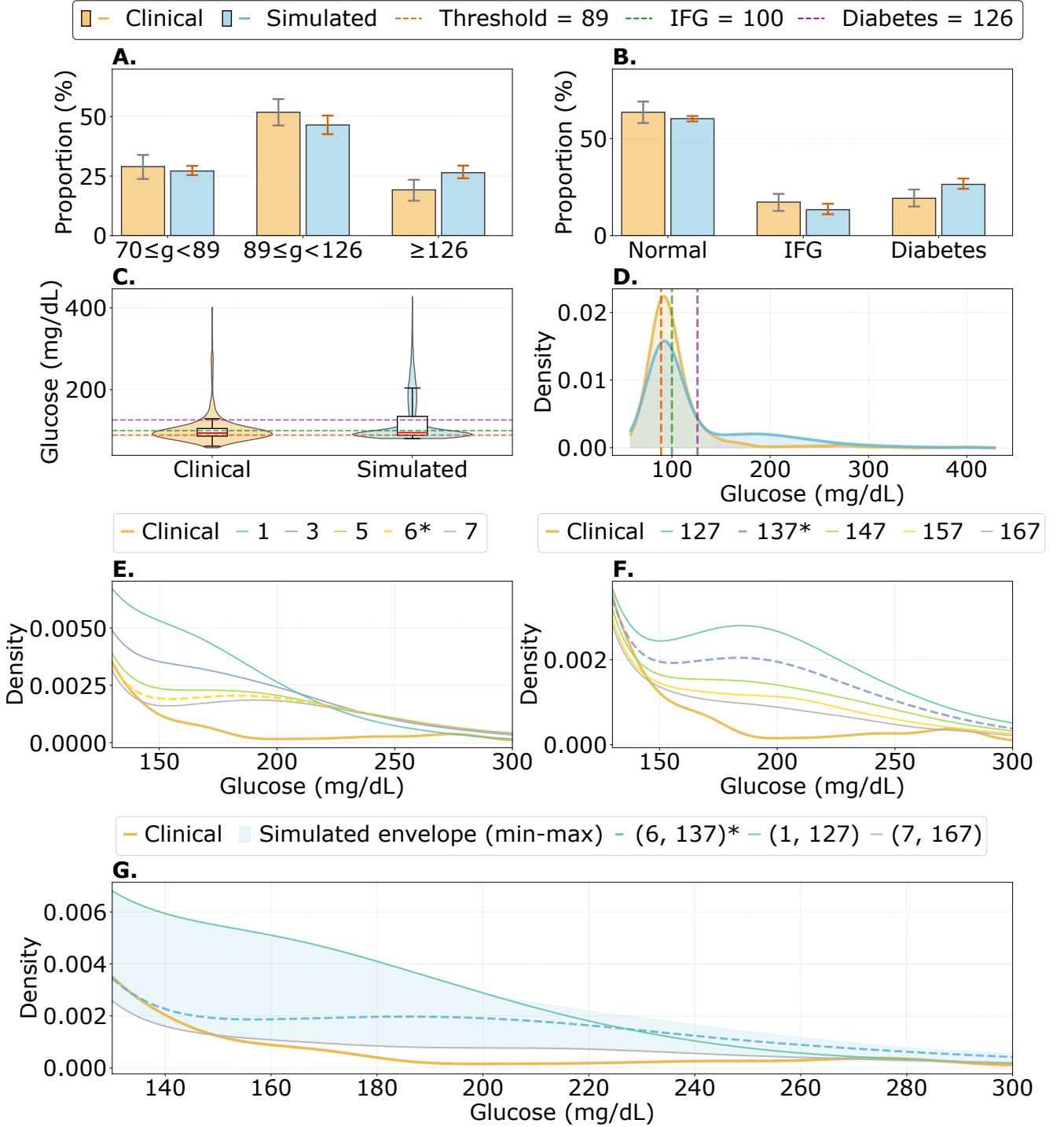


Figure 3: Depressed strata (CESD ≥ 16). Panels A and B compare clinical and simulated proportions. Clinical error bars show 95% bootstrap confidence intervals, and simulated error bars show the batch minimum and maximum. p values are obtained from participant level bootstrap resampling. (A) Glucose ranges ($70 \leq g < 89$, $89 \leq g < 126$, and ≥ 126 mg/dL). $p = 0.0475$. Simulated: 27.36% [26.30, 29.00], 46.14% [43.40, 48.30], 26.51% [25.10, 28.30]. (B) Glycemic categories (Normal: $70 \leq G < 100$, IFG: $100 \leq G < 126$, Diabetes: $G \geq 126$ mg/dL). $p = 0.0315$. Simulated: 60.59% [58.90, 62.30], 12.91% [11.00, 14.80], 26.51% [25.10, 28.30]. (C) Violin plus boxplot. (D) KDE overlay, showing excess simulated upper tail density at approximately 130 to 300 mg/dL. (E) $n_{\sigma d}$ scan. (F) $K_{\sigma d}$ scan. Both scans are centered on the baseline $(n_{\sigma d}, K_{\sigma d}) = (6, 137)$ used throughout the nondepressed strata. (G) Joint scan envelope across parameter pairs, with the baseline curve and anchor settings (1, 127) and (7, 167) overlaid.

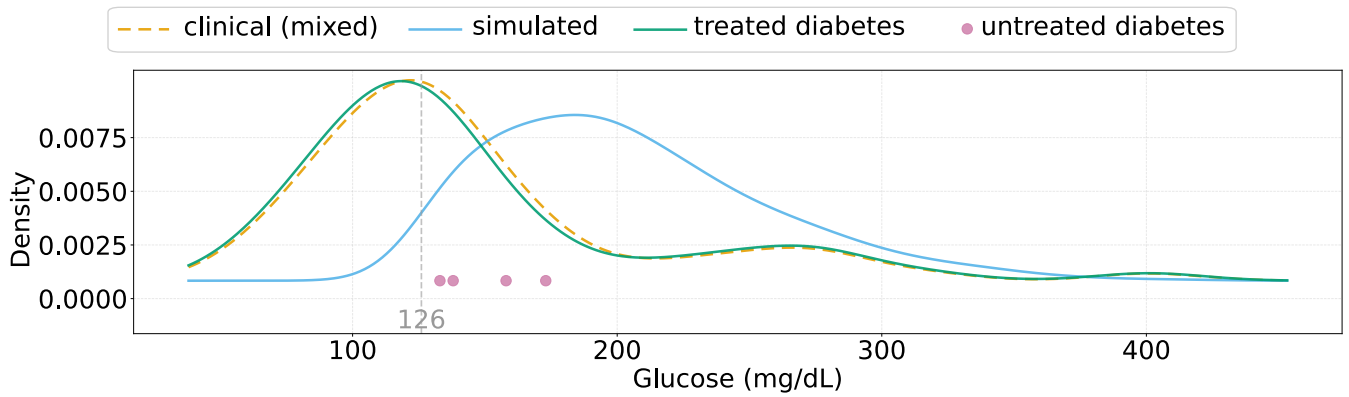


Figure 4: Treatment status stratification of fasting glucose distributions among clinically classified diabetes cases in the depressed group ($\text{CESD} \geq 16$). Kernel density estimates are shown for treated diabetes and the pooled clinical mixture, alongside the model simulated diabetes subset. Untreated diabetes is displayed as individual data points ($n=4$) to avoid small sample KDE artifacts. The pooled clinical distribution closely tracks the treated subgroup and retains substantial mass below the diagnostic threshold (126 mg/dL). Summary statistics (median, P90, mg/dL): Clinical (mixed) (129.0, 249.2), Treated (125.0, 255.6), Simulated (195.5, 276.2).

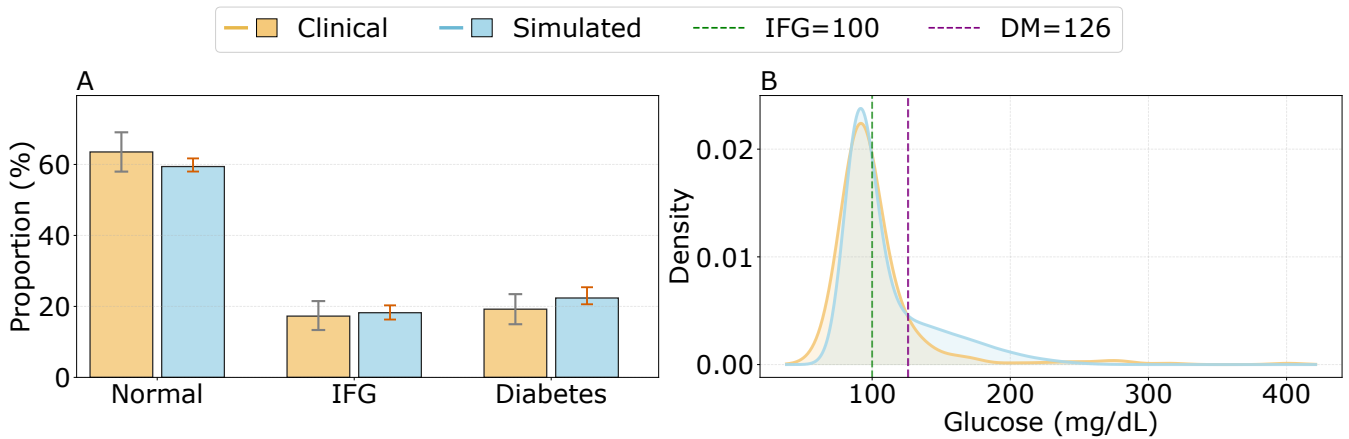


Figure 5: Treatment proxy analysis in the depressed group ($\text{CESD} \geq 16$). Clinical error bars indicate 95% confidence intervals, and simulated error bars indicate batch-to-batch variability across repeated simulations. (A) Comparison of clinical and simulated category proportions ($70 \leq g < 100$, $100 \leq g < 126$, and $g \geq 126$ mg/dL), $p = 0.3338$. Clinical proportions were 63.5% (95% CI: 58.0% to 69.1%), 17.3% (95% CI: 13.3% to 21.5%), and 19.2% (95% CI: 15.0% to 23.5%). Simulated proportions after introducing the treatment proxy were 59.5% (range 56.4% to 60.8%), 18.5% (range 16.4% to 21.3%), and 22.1% (range 19.4% to 24.4%). (B) Density overlay (KDE).

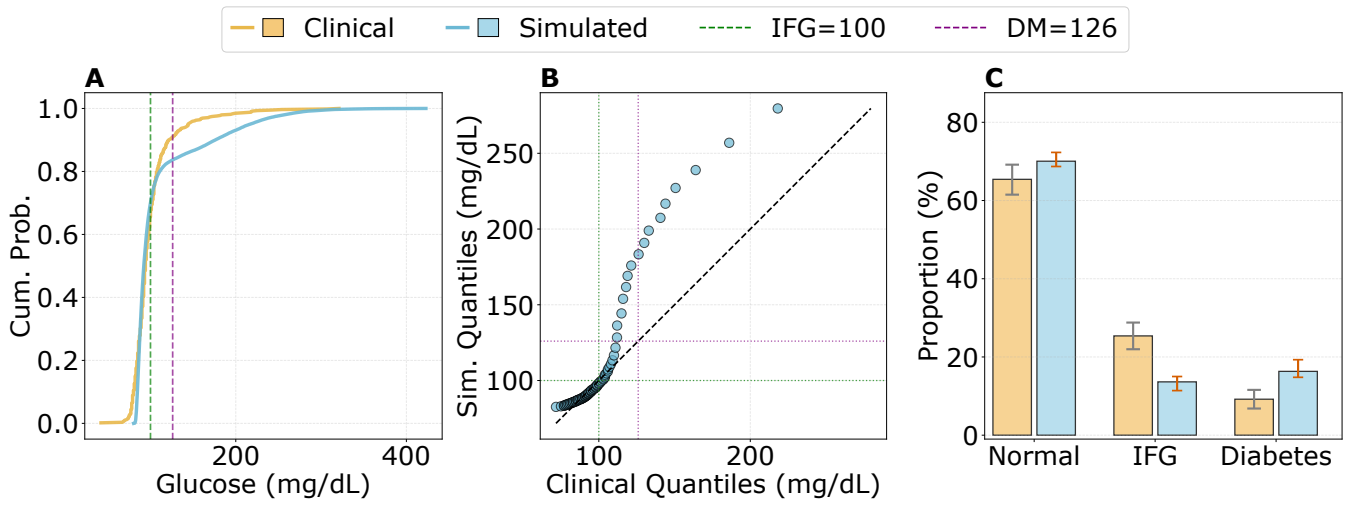


Figure 6: Prediction on a hold out cohort under the same parameter ranges. (A) Empirical cumulative distribution functions of fasting glucose for the hold out clinical cohort (orange) and simulated population (blue). Vertical dashed lines indicate clinical cut points for impaired fasting glucose (IFG, 100 mg/dL) and diabetes (126 mg/dL). (B) Q Q plot comparing clinical and simulated glucose quantiles. Deviations from the diagonal highlight residual upper tail mismatch. (C) Comparison of clinical and simulated proportions in standard glycemic categories. Clinical proportions were normal 65.4%, IFG 25.4%, and diabetes 9.2%. Simulated proportions were normal 70.0% (range 68.7% to 72.3%), IFG 13.6% (range 11.4% to 15.0%), and diabetes 16.3% (range 14.8% to 19.3%). Error bars indicate batch to batch variability across repeated simulation batches.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [SupplementalInformation.pdf](#)