# Causal Mediation Pathways in Continuous Postprandial Glucose Monitoring for Type 1 Diabetes Patients

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# Type 1 Diabetes: Treatment Challenges

- Type 1 Diabetes (T1DM): autoimmune destruction of pancreatic $\beta$-cells $\Rightarrow$ absolute insulin deficiency
- Patients must coordinate exogenous insulin with carbohydrate intake at every meal to keep glucose within safe limits (70–180 mg/dL)
- Dosing relies on **carb-to-insulin ratios**
- These ratios are typically estimated from population averages and applied uniformly across meals, times of day, and subjects

# Why Pooled Analysis Fails

**Postprandial glucose depends on more than insulin:**

- Many factors beyond insulin affect postprandial glucose (pre-meal physiology, circadian variation, physical activity)
- Insulin is on the **causal pathway**, not merely a confounder

**Heterogeneity across the day:**

- A patient well-compensated at breakfast may be under-dosed at dinner
- Pooling averages over opposing patterns ⇒ **null mean effects**

⇒ **Meal-type-stratified mediation analysis** can disentangle the insulin pathway and detect where dosing fails.

# OhioT1DM Dataset Overview

**Data Source:** OhioT1DM 2018 and 2020 cohorts (12 adults with T1D, 8 weeks each)

**Train/test split:** The original study defines a temporal boundary per subject (~80/20 by CGM observations). We assign each meal window to train or test based on whether the meal event falls before or after this boundary:

| | Train meals | Test meals | Total |
|---|---|---|---|
| 2018 Cohort (6 subjects) | 488 | 117 | 605 |
| 2020 Cohort (6 subjects) | 289 | 82 | 371 |
| **Combined** | **777** | **199** | **976** |

**Test set by meal type:** Breakfast $n = 51$, Lunch $n = 58$, Dinner $n = 42$, Snack $n = 39$

# Treatment and Mediator Heterogeneity by Meal Type

**Table 1.** Data characteristics by cohort and meal type. N = meal observations; SD = standard deviation; % Zero Bolus = meals with no insulin bolus.

| | | | Carbs (g) | | Bolus (U) | | % Zero | Glucose (mg/dL) |
|---|---|---|---|---|---|---|---|---|
| Cohort | Meal Type | N | Mean | SD | Mean | SD | Bolus | Mean $\pm$ SD |
| 2018 | Breakfast | 160 | 46.5 | 40.4 | 8.10 | 7.05 | 3.8 | 171.7 $\pm$ 63.0 |
| | Lunch | 183 | 56.5 | 37.5 | 8.40 | 6.20 | 7.1 | 146.9 $\pm$ 52.5 |
| | Dinner | 124 | 62.8 | 44.0 | 10.86 | 7.11 | 7.3 | 157.7 $\pm$ 52.3 |
| | Snack | 138 | 26.6 | 14.7 | 3.88 | 3.52 | 19.6 | 140.2 $\pm$ 58.8 |
| 2020 | Breakfast | 87 | 47.3 | 24.3 | 5.80 | 4.44 | 14.9 | 143.3 $\pm$ 40.3 |
| | Lunch | 97 | 79.2 | 31.9 | 9.61 | 5.45 | 11.3 | 134.7 $\pm$ 45.3 |
| | Dinner | 114 | 63.8 | 30.0 | 8.33 | 6.45 | 16.7 | 151.1 $\pm$ 55.3 |
| | Snack | 73 | 27.5 | 18.0 | 4.73 | 4.38 | 21.9 | 149.7 $\pm$ 54.2 |

# Postprandial Glucose Trajectories by Meal Type

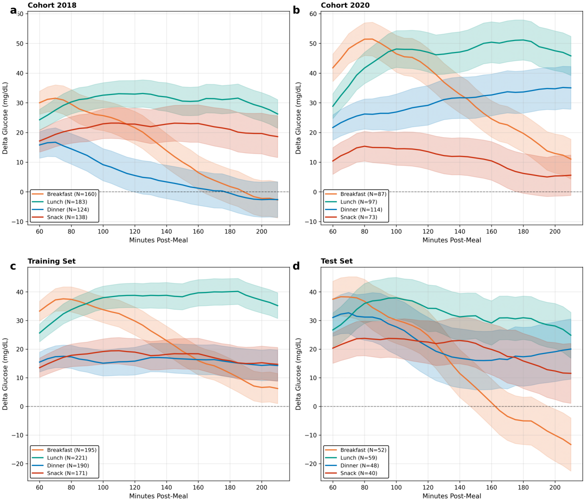
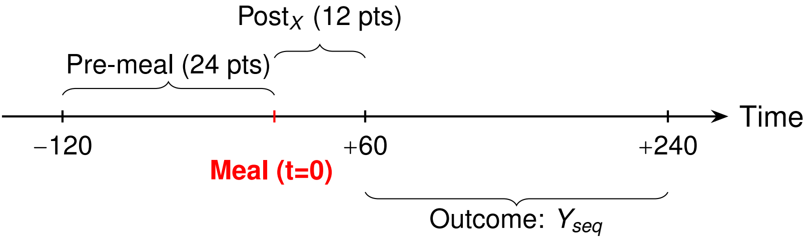



**Figure 1.** Mean ± 1 SE glucose excursion ($\Delta G$) from 60 to 210 min post-meal. (a, b) Stratified by cohort; (c, d) stratified by train/test.

# Meal Window Structure

**Each meal creates a temporal window:**




**Key Variables:**

- **X**: Pre-meal CGM trajectory (24 timepoints × 6 features)
- $A$: Meal carbohydrate content (grams)
- $M$: Insulin bolus taken (units)
- $Y_t$: $\Delta$Glucose at time $t$ = $\text{Glucose}_t - \text{Glucose}_{\text{meal}}$

# Causal Structure and Estimands

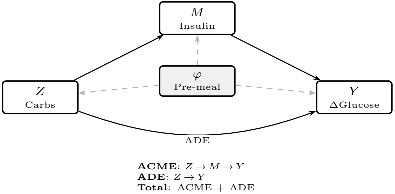


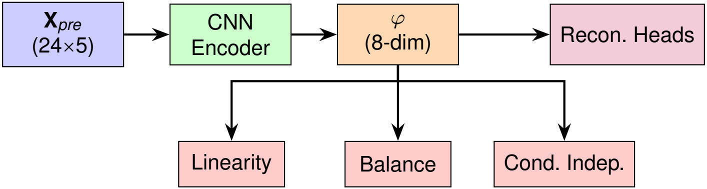

**Figure 2.** $Z$ = carbs, $M$ = insulin, $Y = \Delta G$. Covariates $\varphi$ learned from pre-meal CGM adjust for confounding (dashed).

**Causal effects (+30 g contrast):**

- **ACME**: $Z \to M \to Y$ (expected **negative**)
- **ADE**: $Z \to Y$ (expected **positive**)
- **Total**: ACME + ADE

**Key insight:**
When |ADE| ≈ |ACME|, insulin compensation is adequate and Total ≈ 0.

# Causally-Constrained Linear Autoencoder (CLAE)




*Causal Constraint Penalties*

**Four penalties** enforce causal assumptions during training:

- **Linearity:** $E[Y \mid \varphi]$ linear in $\varphi$
- **Balance:** $\varphi \mid Z_{\text{high}} \approx \varphi \mid Z_{\text{low}}$
- **Cond. Indep.:** $Z \perp M \mid \varphi$
- **Stability:** Robust to resampling

# Outcome Models and Causal Effect Estimation

**Mediator model** (Tobit, left-censored at 0 for ~12% zero-bolus obs.):

$$M_i = \gamma_0 + \gamma_1 Z_i + \boldsymbol{\gamma}_2^\top \varphi_i + \gamma_3 G_0 + \epsilon_i$$

**Outcome model 1: LMER** (random effect for subject):

$$Y_i = \beta_0 + \beta_1 Z_i + \beta_2 M_i + \boldsymbol{\beta}_3^\top \varphi_i + \beta_4 G_0 + v_{j[i]} + \eta_i$$

**Outcome model 2: Quantile regression** ($\tau \in \{0.25, 0.50, 0.75\}$):

$$Q_\tau(Y_i) = \beta_0^\tau + \beta_1^\tau Z_i + \beta_2^\tau M_i + \boldsymbol{\beta}_3^{\tau\top} \varphi_i + \beta_4^\tau G_0$$

**Estimation:** Treatment contrasts at +15/+30/+45 g above meal-type-specific median. ACME, ADE, and Total via quasi-Bayesian simulation (1000 draws). All models weighted by npCBPS. Analyses run pooled and stratified by meal type.

# Causal Mediation Effects by Meal Type and Outcome Model

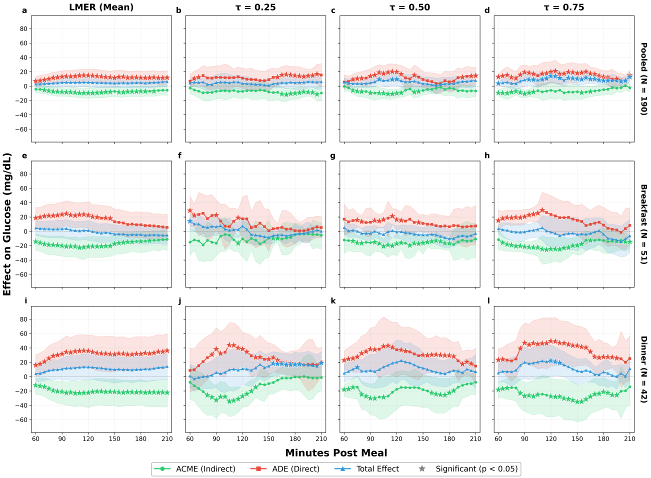



**Figure 3.** +30 g contrast. Columns: LMER and QR at $\tau \in \{0.25, 0.50, 0.75\}$. Rows: pooled, breakfast, dinner. Stars = $p < 0.05$.

# LMER and QR Causal Effects at 120 Minutes (+30 g contrast)

**Table 2.** Point estimates (mg/dL) and *p*-values for ADE, ACME, and Total at three quantiles. LMER included for comparison. Bold = $p < 0.05$.

| | | ADE | | ACME | | Total | |
|---|---|---|---|---|---|---|---|
| **Meal** | **Model** | Est. | *p* | Est. | *p* | Est. | *p* |
| Pooled | LMER | **14.81** | **<0.001** | **-9.64** | **0.01** | 5.17 | 0.13 |
| | $\tau = 0.25$ | 10.95 | 0.15 | -7.34 | 0.13 | 3.61 | 0.52 |
| | $\tau = 0.50$ | **19.71** | **<0.001** | **-10.06** | **<0.001** | **9.66** | **0.04** |
| | $\tau = 0.75$ | **19.73** | **0.02** | -5.79 | 0.31 | **13.95** | **0.006** |
| Breakfast | LMER | **22.38** | **0.02** | **-21.15** | **0.004** | 1.23 | 0.85 |
| | $\tau = 0.25$ | 17.53 | 0.24 | -10.28 | 0.38 | 7.25 | 0.23 |
| | $\tau = 0.50$ | **16.40** | **0.03** | **-17.21** | **0.02** | -0.81 | 0.88 |
| | $\tau = 0.75$ | 23.58 | 0.09 | **-24.58** | **<0.001** | -1.00 | 0.96 |
| Dinner | LMER | **35.73** | **0.006** | **-22.56** | **0.01** | 13.17 | 0.14 |
| | $\tau = 0.25$ | **38.28** | **0.004** | **-27.49** | **<0.001** | 10.79 | 0.35 |
| | $\tau = 0.50$ | 37.44 | 0.06 | -17.49 | 0.18 | 19.95 | 0.17 |
| | $\tau = 0.75$ | **49.46** | **0.008** | **-27.43** | **0.04** | **22.03** | **0.04** |

# Pooled Quantile Regression Mediation Effects

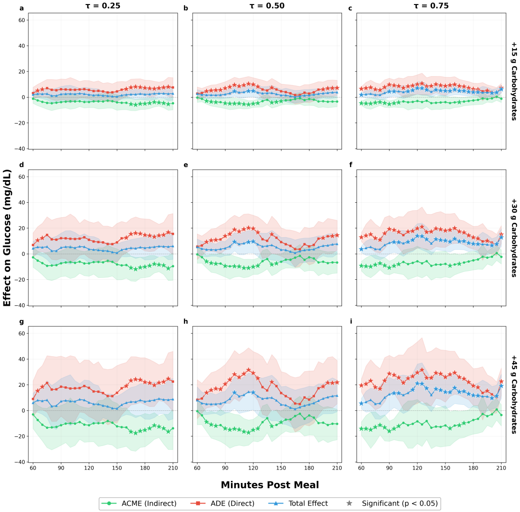



**Figure 4.** QR mediation effects, pooled (all meals). Rows: treatment contrasts (+15, +30, +45 g). Columns: $\tau \in \{0.25, 0.50, 0.75\}$.

# Pooled QR Detailed Results (+30 g contrast)

**Table 3.** Pooled ($N$ = 190) QR mediation effects across timepoints and quantiles. Bold = $p < 0.05$.

| | | ACME | | | ADE | | | Total | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Time | Quantile | Est. | 95% CI | $p$ | Est. | 95% CI | $p$ | Est. | 95% CI | $p$ |
| 60 min | $\tau = 0.25$ | -2.65 | (-10.45, 5.09) | 0.50 | 6.84 | (-2.62, 16.26) | 0.16 | 4.20 | (-1.17, 9.75) | 0.11 |
| | $\tau = 0.50$ | -0.38 | (-7.28, 7.15) | 0.88 | 5.66 | (-4.38, 15.52) | 0.26 | 5.28 | (-0.98, 11.55) | 0.09 |
| | $\tau = 0.75$ | **-9.30** | **(-13.24, -5.79)** | **<0.001** | **12.93** | **(9.67, 16.42)** | **<0.001** | **3.63** | **(0.97, 6.17)** | **0.01** |
| 90 min | $\tau = 0.25$ | -7.33 | (-17.65, 2.36) | 0.15 | 12.17 | (-3.44, 28.29) | 0.14 | 4.84 | (-6.40, 16.09) | 0.43 |
| | $\tau = 0.50$ | **-9.46** | **(-18.00, -0.91)** | **0.04** | **13.83** | **(3.12, 23.97)** | **0.01** | 4.36 | (-1.19, 9.57) | 0.11 |
| | $\tau = 0.75$ | **-10.81** | **(-16.24, -5.69)** | **<0.001** | **19.33** | **(9.02, 29.75)** | **<0.001** | 8.52 | (-0.06, 17.82) | 0.05 |
| 120 min | $\tau = 0.25$ | -7.34 | (-17.41, 2.75) | 0.13 | 10.95 | (-3.10, 25.01) | 0.15 | 3.61 | (-6.89, 13.65) | 0.52 |
| | $\tau = 0.50$ | **-10.06** | **(-15.99, -4.36)** | **<0.001** | **19.71** | **(9.24, 30.03)** | **<0.001** | **9.66** | **(0.68, 18.36)** | **0.04** |
| | $\tau = 0.75$ | -5.79 | (-17.21, 5.98) | 0.31 | **19.73** | **(4.43, 33.85)** | **0.02** | **13.95** | **(4.82, 23.47)** | **0.006** |
| 150 min | $\tau = 0.25$ | -8.19 | (-20.17, 3.92) | 0.19 | 8.93 | (-6.89, 23.68) | 0.28 | 0.74 | (-5.95, 7.44) | 0.85 |
| | $\tau = 0.50$ | -6.06 | (-12.34, 0.06) | 0.05 | 9.20 | (-1.69, 20.24) | 0.10 | 3.14 | (-6.59, 12.74) | 0.50 |
| | $\tau = 0.75$ | -7.79 | (-17.77, 2.15) | 0.12 | **18.09** | **(5.07, 31.07)** | **0.006** | **10.29** | **(2.14, 18.90)** | **0.02** |
| 180 min | $\tau = 0.25$ | **-10.08** | **(-18.43, -2.52)** | **0.008** | **14.69** | **(2.26, 27.18)** | **0.02** | 4.62 | (-4.70, 13.08) | 0.28 |
| | $\tau = 0.50$ | -2.62 | (-12.88, 6.87) | 0.61 | 5.85 | (-8.56, 20.02) | 0.43 | 3.22 | (-5.82, 12.35) | 0.48 |
| | $\tau = 0.75$ | -5.00 | (-12.49, 2.03) | 0.17 | **12.82** | **(3.75, 21.39)** | **0.004** | **7.82** | **(2.58, 13.31)** | **0.002** |
| 210 min | $\tau = 0.25$ | -9.53 | (-20.58, 0.78) | 0.08 | 15.50 | (-0.63, 31.36) | 0.07 | 5.97 | (-4.23, 16.25) | 0.26 |
| | $\tau = 0.50$ | -6.73 | (-14.95, 1.70) | 0.10 | **14.44** | **(2.95, 26.07)** | **0.01** | 7.71 | (-0.18, 15.70) | 0.06 |
| | $\tau = 0.75$ | -2.33 | (-7.84, 2.99) | 0.41 | **15.12** | **(8.20, 21.95)** | **<0.001** | **12.79** | **(5.77, 19.41)** | **<0.001** |

# Dinner Quantile Regression Mediation Effects

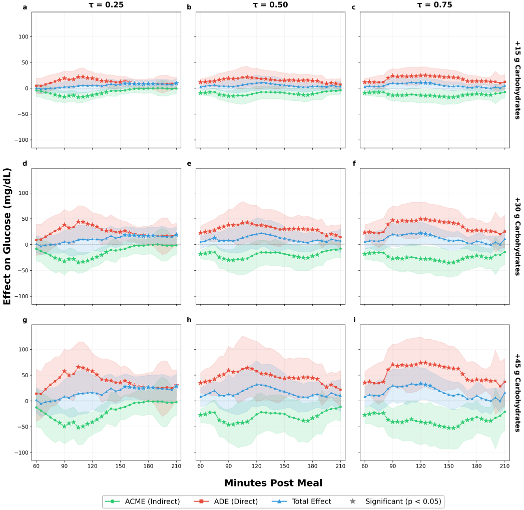



**Figure 5.** QR mediation effects, dinner. Rows: treatment contrasts (+15, +30, +45 g). Columns: $\tau \in \{0.25, 0.50, 0.75\}$.

# Dinner QR Detailed Results (+30 g contrast)

**Table 4.** Dinner ($N$ = 42) QR mediation effects across timepoints and quantiles. Bold = $p < 0.05$.

| | | ACME | | | ADE | | | Total | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Time | Quantile | Est. | 95% CI | $p$ | Est. | 95% CI | $p$ | Est. | 95% CI | $p$ |
| 60 min | $\tau = 0.25$ | -7.86 | (-31.91, 15.55) | 0.50 | 8.70 | (-21.36, 39.89) | 0.61 | 0.84 | (-15.26, 17.59) | 0.93 |
| | $\tau = 0.50$ | **-18.12** | **(-27.15, -10.52)** | **<0.001** | **22.82** | **(9.24, 35.70)** | **<0.001** | 4.70 | (-7.89, 17.05) | 0.45 |
| | $\tau = 0.75$ | **-18.37** | **(-29.94, -7.95)** | **<0.001** | **23.39** | **(7.11, 38.56)** | **0.004** | 5.02 | (-8.10, 18.96) | 0.45 |
| 90 min | $\tau = 0.25$ | **-32.78** | **(-58.22, -11.84)** | **0.002** | **38.30** | **(7.65, 67.99)** | **0.01** | 5.52 | (-15.12, 27.33) | 0.61 |
| | $\tau = 0.50$ | **-30.07** | **(-53.28, -10.24)** | **<0.001** | **38.28** | **(6.73, 67.83)** | **0.02** | 8.21 | (-14.99, 31.48) | 0.47 |
| | $\tau = 0.75$ | **-27.16** | **(-48.46, -8.29)** | **0.004** | **46.98** | **(20.79, 74.66)** | **<0.001** | 19.81 | (-2.78, 41.60) | 0.07 |
| 120 min | $\tau = 0.25$ | **-27.49** | **(-42.78, -14.81)** | **<0.001** | **38.28** | **(14.79, 61.82)** | **0.004** | 10.79 | (-11.23, 33.41) | 0.35 |
| | $\tau = 0.50$ | -17.49 | (-45.49, 7.49) | 0.18 | 37.44 | (-0.23, 76.00) | 0.06 | 19.95 | (-10.44, 50.84) | 0.17 |
| | $\tau = 0.75$ | **-27.43** | **(-56.25, -1.94)** | **0.04** | **49.46** | **(14.69, 82.08)** | **0.008** | **22.03** | **(0.59, 44.31)** | **0.04** |
| 150 min | $\tau = 0.25$ | -9.75 | (-24.50, 4.03) | 0.18 | **24.20** | **(2.00, 46.73)** | **0.03** | 14.46 | (-2.78, 32.24) | 0.11 |
| | $\tau = 0.50$ | -18.20 | (-43.49, 2.84) | 0.10 | **30.02** | **(2.31, 57.77)** | **0.04** | 11.82 | (-10.06, 34.02) | 0.34 |
| | $\tau = 0.75$ | **-35.24** | **(-63.25, -12.01)** | **0.002** | **43.09** | **(14.87, 70.75)** | **0.004** | 7.85 | (-10.87, 25.14) | 0.38 |
| 180 min | $\tau = 0.25$ | -0.38 | (-18.20, 16.98) | 0.94 | 17.24 | (-1.76, 36.14) | 0.09 | **16.87** | **(0.52, 34.38)** | **0.05** |
| | $\tau = 0.50$ | **-22.59** | **(-45.66, -2.41)** | **0.03** | **29.31** | **(6.19, 51.10)** | **0.02** | 6.72 | (-12.69, 24.93) | 0.46 |
| | $\tau = 0.75$ | **-21.27** | **(-44.04, -1.24)** | **0.03** | **27.59** | **(8.42, 47.55)** | **0.008** | 6.32 | (-12.42, 22.17) | 0.46 |
| 210 min | $\tau = 0.25$ | -1.30 | (-19.24, 16.20) | 0.89 | 20.38 | (-0.06, 41.00) | 0.06 | **19.09** | **(2.99, 34.61)** | **0.01** |
| | $\tau = 0.50$ | -7.85 | (-25.38, 8.65) | 0.34 | 14.67 | (-9.80, 39.06) | 0.24 | 6.83 | (-15.96, 30.70) | 0.57 |
| | $\tau = 0.75$ | -14.16 | (-38.36, 8.80) | 0.20 | 25.21 | (-5.42, 56.73) | 0.13 | 11.05 | (-8.33, 31.60) | 0.27 |

# Meal-Type Mediation Structure

| | ADE | ACME | Total, $\tau = 0.75$ (120 min) |
|---|---|---|---|
| **Dinner** | Large (+) | Large (−), but smaller | **22.03 mg/dL** ($p = 0.04$) |
| **Breakfast** | Large (+) | Large (−), near-equal | −1.00 mg/dL ($p = 0.96$) |

**Dinner:** ADE exceeds ACME at every quantile ⇒ insulin compensation is **incomplete**

- At 120 min, the total effect increases from 10.79 mg/dL ($\tau = 0.25$) to 19.95 ($\tau = 0.50$) to 22.03 mg/dL ($\tau = 0.75$)

**Breakfast:** ADE and ACME are individually large but cancel ⇒ bolusing is **well-calibrated**

- Both effects roughly double the pooled estimates, consistent with morning insulin resistance

# Clinical Implications

**Mean-level analysis misses the signal:**

| Model | Total effect (120 min) | $p$ |
|---|---|---|
| Pooled LMER (mean) | 5.17 mg/dL | 0.13 |
| Pooled QR ($\tau = 0.75$) | 13.95 mg/dL | 0.006 |
| Dinner QR ($\tau = 0.75$) | 22.03 mg/dL | 0.04 |

$\tau = 0.75$ corresponds to individuals at the 75th percentile of the glucose response distribution: those who experience larger postprandial excursions than typical, conditional on the same meal size and pre-meal state.

**The strongest effects emerge at dinner in the upper tail of the glucose distribution**

$\Rightarrow$ Fixed carb-insulin ratios systematically undertreat upper-quartile dinner responders. Quantile-aware, meal-type-specific dosing adjustments could improve outcomes for this subpopulation.

# Limitations and Future Directions

**Limitations:**

- 12 subjects; per-stratum test sizes of 42–58 meals
- Sequential ignorability is untestable
- Single dataset (OhioT1DM)

**Future directions:**

- Transfer learning: pre-train CLAE on external CGM data, fine-tune per patient
- Quantile-focused autoencoder training for the clinical tails
- Validation on larger multi-site CGM datasets

# Summary

**How do meals affect glucose in Type 1 Diabetes?**

1. **Challenge:** High-dimensional confounding + insulin on the causal pathway
2. **Solution:** CLAE learns $\varphi(\mathbf{X})$ satisfying mediation assumptions
3. **Method:** LMER + QR for time-varying, meal-type-stratified mediation
4. **Finding:** Dinner bolusing is consistently miscalibrated; breakfast is well-tuned; mean-level analyses miss it

**Thank you! Questions?**

# Appendix: Autoencoder Loss Function

**Total Loss:**

$$\mathcal{L} = \mathcal{L}_{\text{recon}} + \alpha\mathcal{L}_{\text{linear}} + \gamma\mathcal{L}_{\text{balance}} + \lambda_1\mathcal{L}_{\text{CI}} + \lambda_2\mathcal{L}_{\text{stability}}$$

where:

- $\mathcal{L}_{\text{recon}}$: MSE for trajectory reconstruction (4 prediction heads)
- $\mathcal{L}_{\text{linear}}$: MSE for linear outcome prediction from $\varphi$
- $\mathcal{L}_{\text{balance}}$: Moment matching between treatment groups
- $\mathcal{L}_{\text{CI}}$: Correlation between residualized $Z$ and $M$
- $\mathcal{L}_{\text{stability}}$: Frobenius norm of bootstrap covariance difference