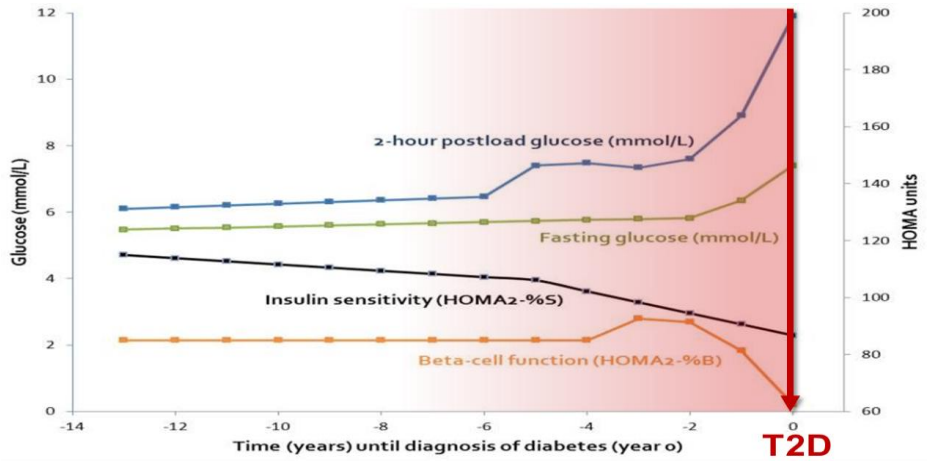
# Pre-Type 2 Diabetes





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**ATTD Asia 2024**
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# Disclosures

- Honoraria from Medtronic, Insulet, Abbott, Novo and Sanofi
- Research Support from Medtronic, Insulet, Dexcom, Roche, GlySense, BioCapillary, and Endogenex
- Advisory Boards for Medtronic, Insulet, Abbott, Ypsomed, Novo, and Sanofi

# Pre-Type 2 Diabetes

- Overweight / Obesity
- Sedentary lifestyle
- Smoking / Pollution
- Hypertension, Fatty Liver, and Dyslipidaemia
- Family History
- Ethnicity
  - Pacific Islander
  - Indigenous Australian
  - South Asian
- Increasing age
- History of GDM

## Pre-T2D

- **HbA1c 5.7 – 6.4% (39 – 47 mmol/mol)**
- **IFG / IGT with 75g OGTT:**

**- Fasting plasma glucose 5.6 – 6.9 mmol/L (100 - 125 mg/dL)**

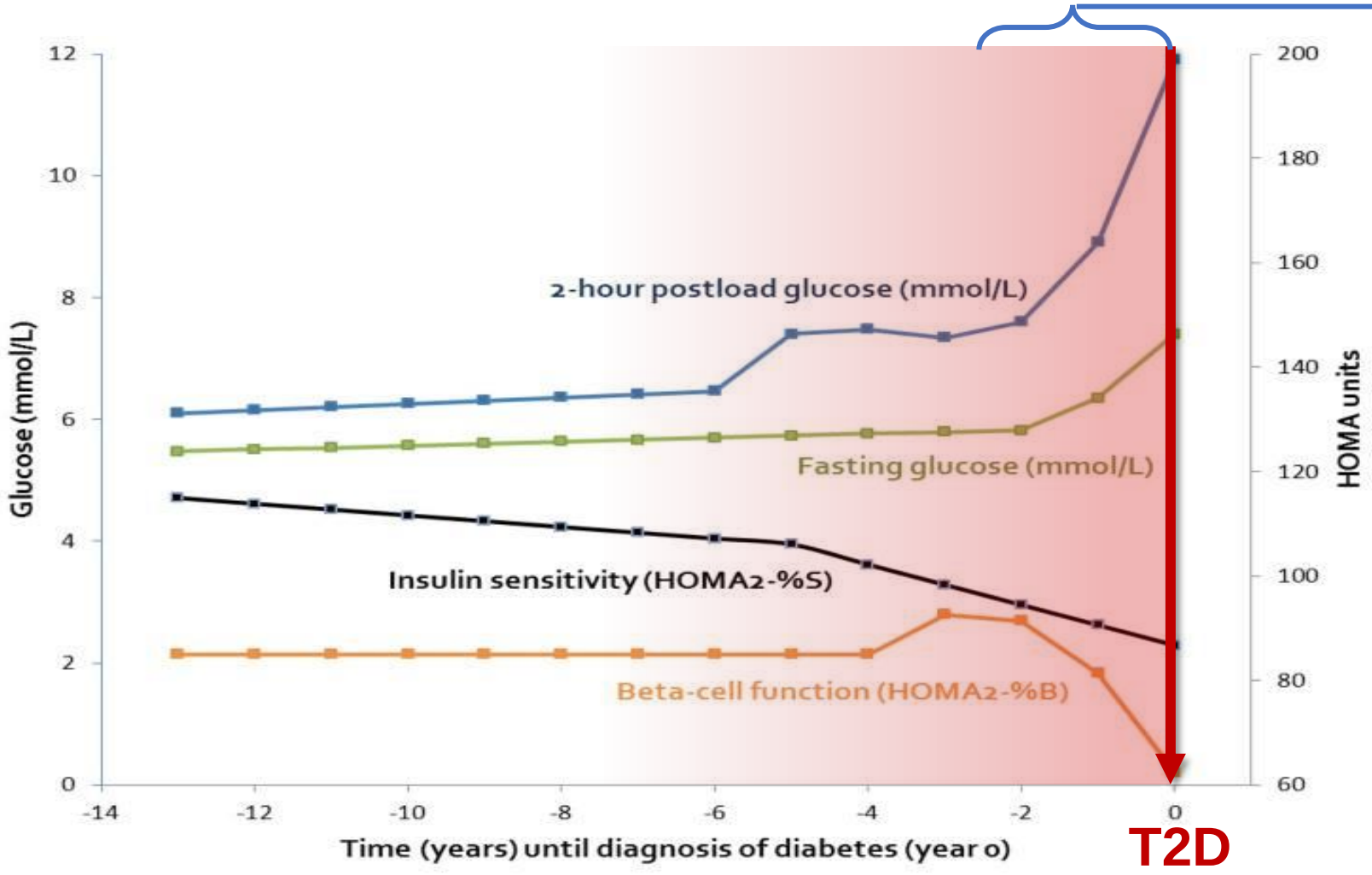
**OR**

**- 2-hour plasma glucose 7.8 – 11.0 mmol/L (140 – 199 mg/dL)**

Chan JCN et al. JAMA. 2009

*ADA Standards of Diabetes Care. Diabetes Care* 2023

# The Evolution of Type 2 Diabetes




- Glucotoxicity
- Lipotoxicity
- Oxidative Stress
- Inflammation
- Amyloid deposition

**β-Cell compromise**
**(50% of function lost)**

*Tabak AG et al.* Lancet 2009; Butler AE et al Diabetes 2003

# Pre-Type 2 Diabetes

## Current Diagnostic Tools

**HbA1c:** (5.7 - 6.4% [39 - 47 mmol/mol])

- Inexpensive and easy to perform
- Glucose exposure over 3 months
- Indirect measure of glucose
- Does not relate lifestyle to glucose
- 25-38% 5-Y progression T2D[1]

**75g OGTT**: (Fasting 5.6 - 6.9 mmol/L [100 -125 mg/dL ] / 2 hr 7.8 - 11.0 mmol/L [140 -199 mg/dL])

- 'Stress test'
- Single snap-shot
- Complex to perform
- Unpleasant
- Non-physiological
- 18 - 26% IFG, 5-Y progression T2D[1]
- 50% IFG + IGT 5-Y progression T2D[1]

## Importance

- 2021, >298 million people worldwide[2]
- Most are unaware of their condition
- Not benign: CVD / CCF / renal disease / dementia[3,4]
- Flags those at risk of progression to T2D[1]
- Opportunity to intervene 'early':
  - Halt / reverse progression to T2D[5]
  - Pre-emptively address CVD risk factors


[1]Richter B et al. Cochrane Database of Systematic Reviews 2018;
[2]Rooney MR et al. Diabetes Care 2023;
[3]Pan Y et al. J Stroke Cerebrovasc Dis. 2019;
[4]Cai X et al. Diabetes Obes Metab. 2021;
[5]Galaviz KI et al. Diabetes Care. 2018

# Preventing Progression From Pre-T2D to T2D

ORIGINAL ARTICLE

## Tirzepatide for Obesity Treatment and Diabetes Prevention

**Authors**: Ania M. Jastreboff, M.D., Ph.D., Carel W. le Roux, F.R.C.P., Ph.D., Adam Stefanski, M.D., Ph.D., Louis J. Aronne, M.D., Bruno Halpern, M.D., Ph.D., Sean Wharton, M.D., Pharm.D., John P.H. Wilding, D.M., +6, for the SURMOUNT-1 Investigators* Author Info & Affiliations

Published November 13, 2024 | DOI: 10.1056/NEJMoa2410819 | Copyright © 2024

- N = 1032 with obesity and prediabetes
- **New Dx T2D 1.3 vs 13.3% @176 weeks**
- **One new case of diabetes prevented for every nine patients treated**

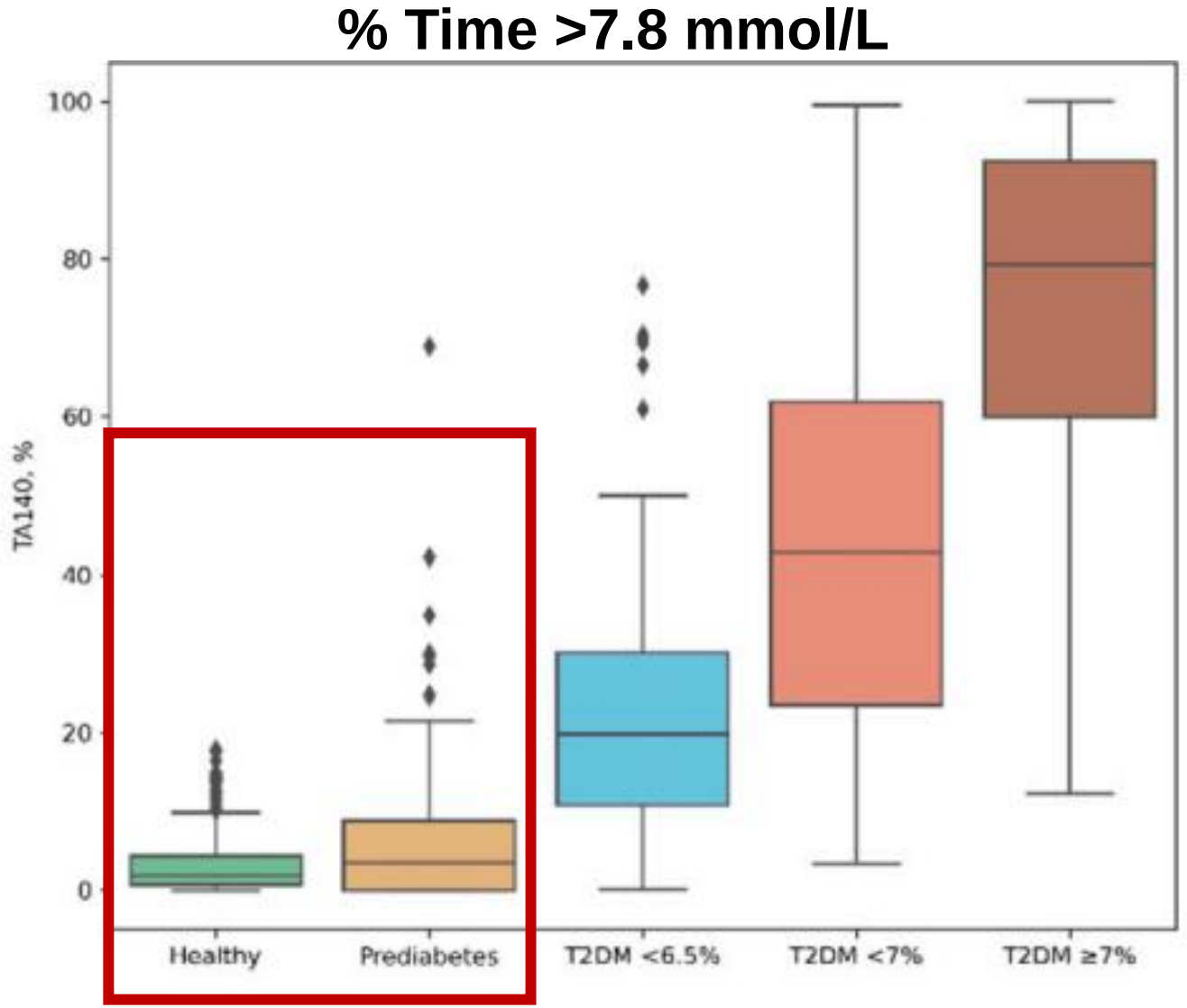
# The Dysglycaemia Spectrum: Consensus CGM Metrics

| | Healthy[1] | At-Risk[2] * | Pre-T2D[2] | T2D[2] |
|---|---|---|---|---|
| (N) | 153 | 32 | 40 | 28 |
| Sensor | Dexcom G6 (Blinded) | Abbott Libre Pro | Abbott Libre Pro | Abbott Libre Pro |
| HbA1c (%) | 4.2 – 5.6 | <5.7 | 5.7 – 6.4 | >6.4 |
| Mean Glucose (mmol/L) | 5.5 (0.4) | 5.5 (5.1, 5.8) | 5.8 (5.3, 6.1) | 7.6 (6.8, 9.1) |
| CV (%) | 17 (3) | 16 (13, 18) | 18 (16, 20) | 23 (20, 28) |
| **%Time 3.9 -7.8 mmol/L** | **96 (93–98)** | **95 (92, 97)** | **92 (85, 94)** | 60 (32, 74) |
| %Time 3.9 – 10.0 mmol/L | 99 (96-99) | 98 (96, 99) | 98 (96, 99) | 87 (68, 92) |
| %Time <3.9mmol/L | 1.1 (0.3, 2.9) | 2·0 (0·3, 4·4) | 1·6 (0·5, 4·0) | 0·2 (0, 1·1) |
| Time >10.0mmol/L | 0.0 (0.0, 0.2) | 0.0 (0.0, 0.0) | 0·2 (0.0, 0·6) | 11.4 (4·6, 28·6) |

*At Risk determined by ADA diabetes risk assessment tool

*[1]Shah V et al JCEM 2019; [2]Barua S et al. eClinical Medicine 2021*

# The Dysglycaemia Spectrum: CGM Metrics




Cichosz LS *et al Diabetes Technology and Therapeutics 2024*

# CGM as a Tool for Predicting T2D (Pre-T2D)

**ADVANTAGES:**

- Direct measure of glucose vs.HbA1c
- More rapid response to interventions vs. HbA1c
- Easier to implement / more acceptable vs. OGTT
- Reflects ‘real life’ vs OGTT
- May provide information in addition to HbA1c in predicting T2D[1]

**DISADVANTAGES:**

- Improvement over HbA1c on its own probably incremental
- More expensive
- Evidence based standardised cut-offs need to be defined

  -? Impact of sensor configuration

[1]Marco A et al. Frontiers in Public Health 2022

# CGM as an Intervention in Pre-T2D

Abstract citation ID: bvac150.724

**Diabetes & Glucose Metabolism**

***OR03-3***

***Impact of Continuous Glucose Monitoring (CGM) on Lifestyle Modifications in Individuals with Prediabetes***

*Shanzay Khan, Chalak Muhammad, Kashif Munir, Alpa Patel, Amani Patel, Elham Rabiei-Flori, Rashmi Reddy, and Hisham Farhan*

- N = 57; Pre-T2D randomised 1:1 to 3 Months CGM + Edu vs. Edu alone
- Findings:
  - -Unhealthy food choices reduced in both arms
  - -CGM + Edu more (vigorous) physical activity
  - -HbA1c: CGM + Edu 5.9 to 5.7% vs Edu 5.9 to 5.8%
  - -CGM + Edu more weight reduction and systolic bp
  - -1/3 in both groups reversed pre-T2D
  - -CGM + Edu group: 56% stated CGM more helpful than education

Khan S et al. Journal of the Endocrine Society 2022. A 348-A349

# Type 2 Diabetes Remission: A New Mission in Diabetes Care

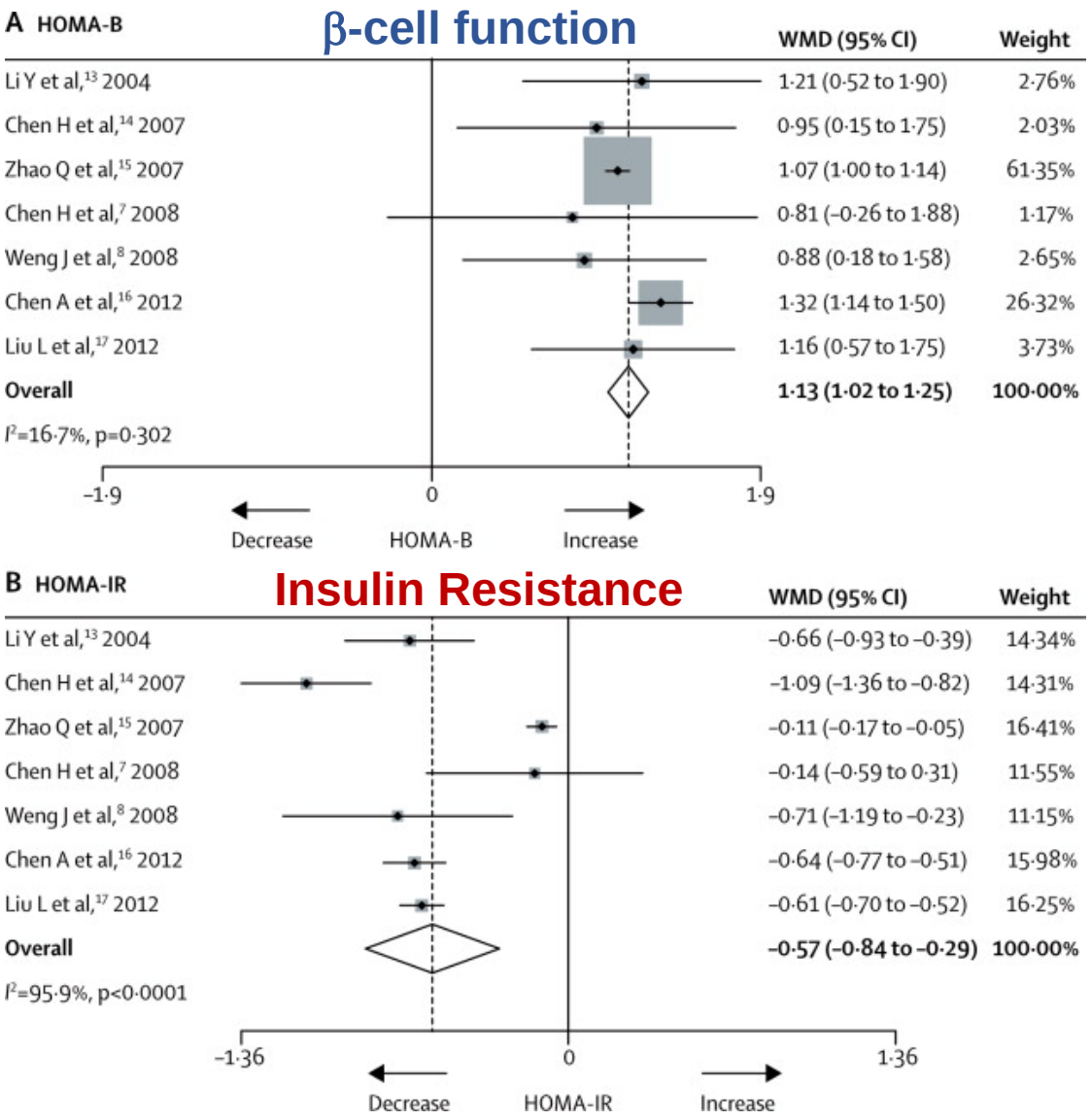
*Shahrad Taheri*

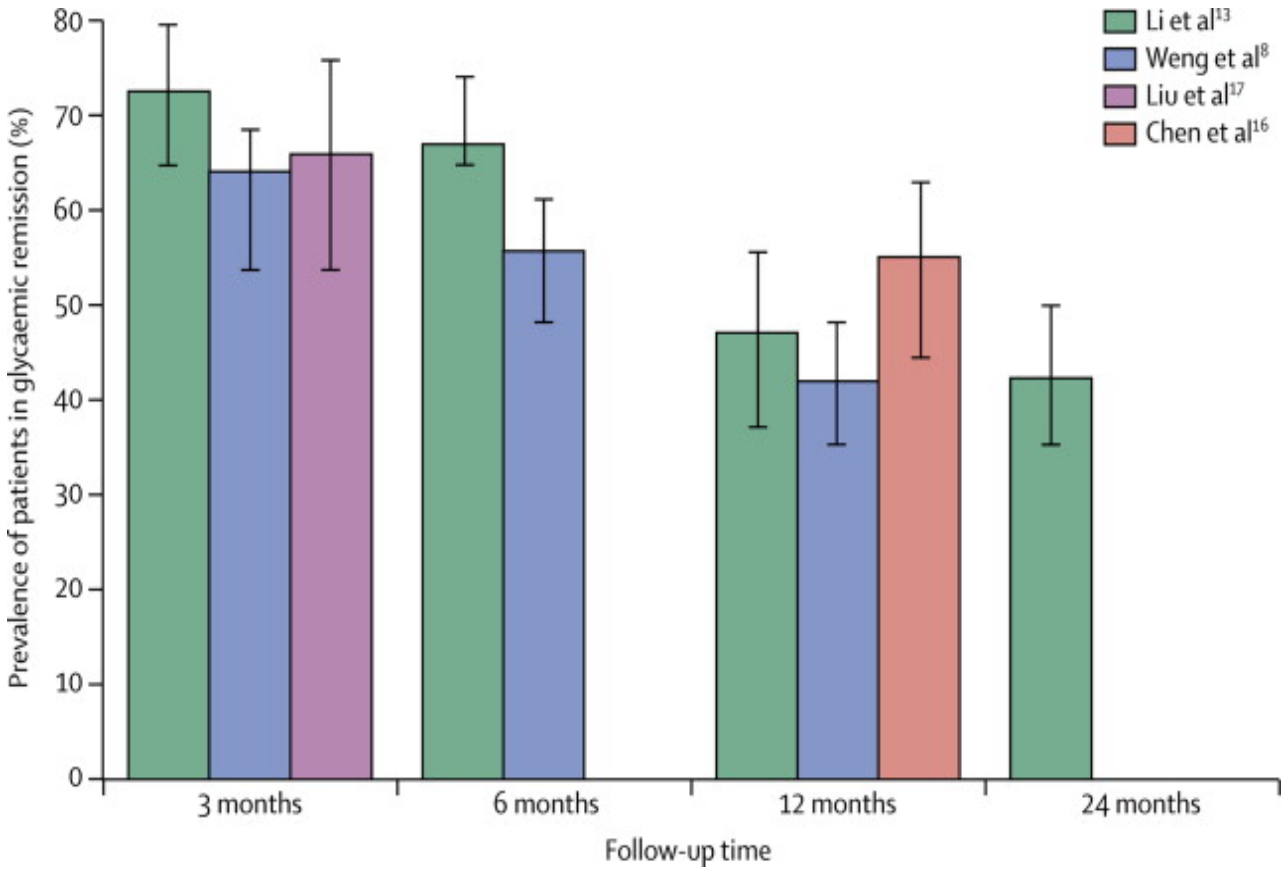
*Diabetes Care 2024;47:47–49 | https://doi.org/10.2337/dci23-0062*

- Remission = HbA1c <6.5% [48mmol/mol] and at least 3 months without glucose lowering therapies.[1]
- Approx 1.7% of T2D achieve remission.[2,3]
- Increased chance of remission
    - <2 Y from diagnosis higher (4.6%) chance of remission.[2]
    - >10% BMI reduction 3.5 odds of remission.[3]
    - Early intensive insulin therapy increases remission.[4]

[1]Riddle MC et al. Diabetes Care 2022; [2]karter AJ et al. Diabetes Care 2014; [3]Holman N et al Diabetes care 2022;
[4] Kramer CJ et al. Lancet 2013

# Short-Term Early Intensive Insulin Therapy and Remission in Type 2 Diabetes

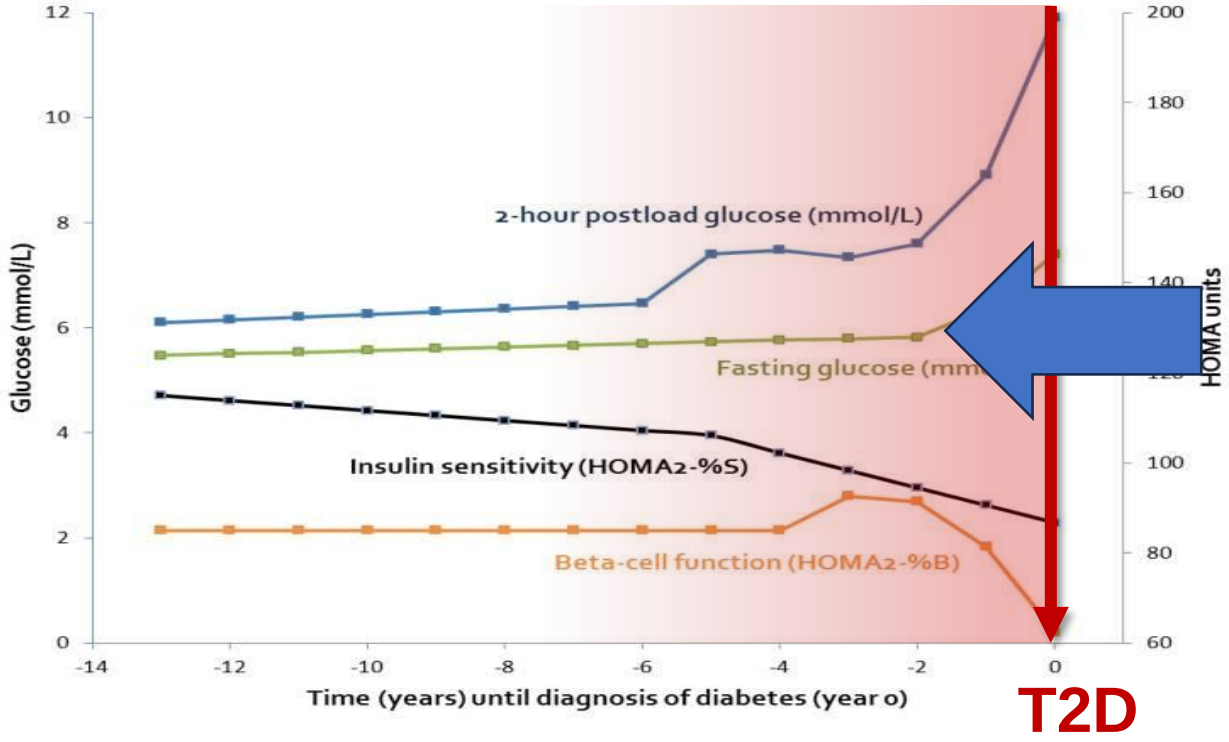



Kramer CJ et al. Lancet 2013

# Achieving T2D Remission

- Resource and effort intensive
- Not attainable in all
- Reverting to Pre-T2D does not eliminate risk
- Adverse outcomes may already be present




Adapted from Tabak AG et al. Lancet 2009; Butler AE et al Diabetes 2003

# The Case to Intervene Earlier

Significant glucose excursions are a late phenomenon in the evolution of T2D

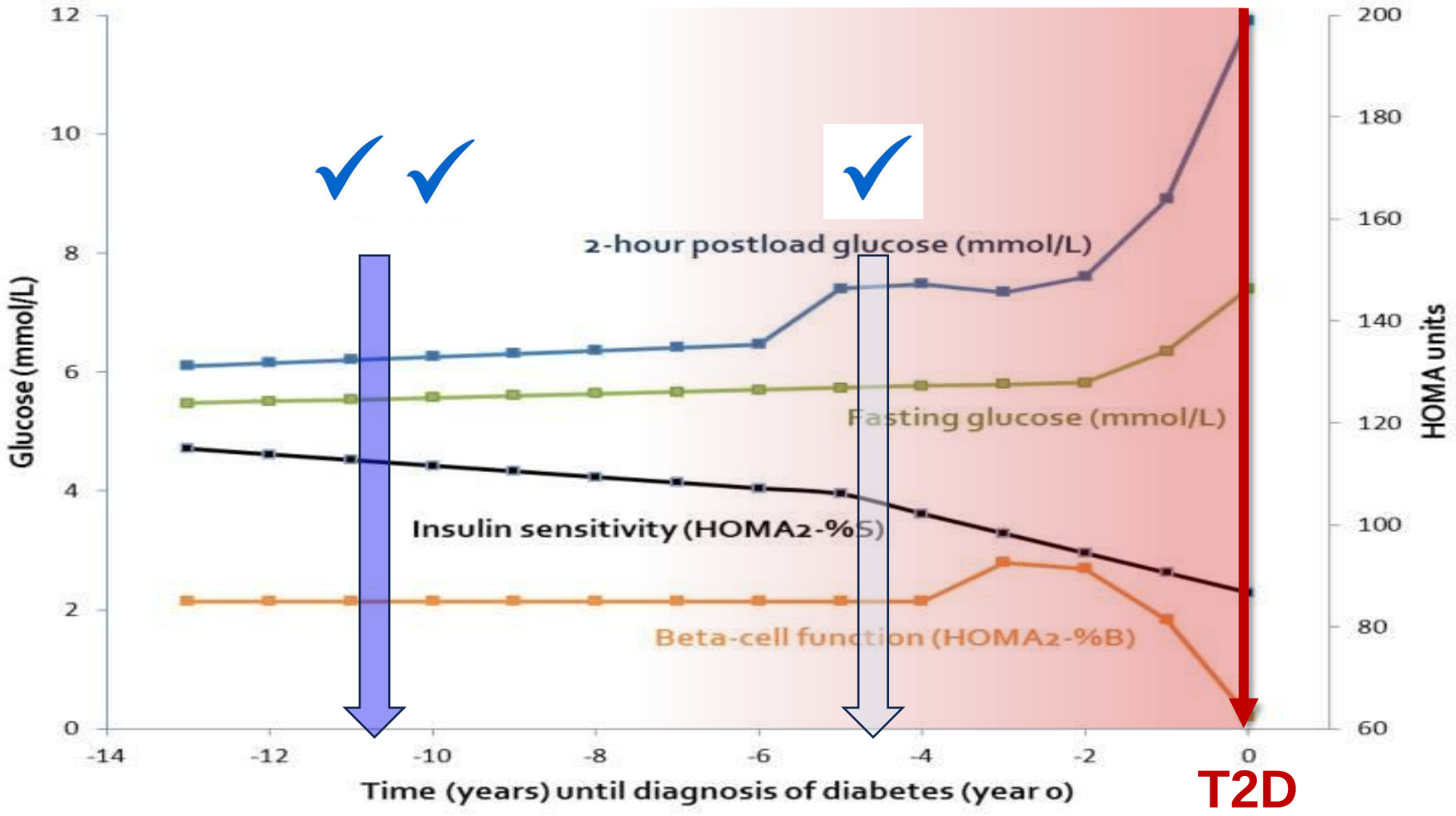
Pre-T2D (glucose definition) is still associated with increased risk

Glucose alone may not comprehensively assess metabolic risk

Earlier identification of those at risk = more effective intervention

We should aim to prevent / reverse Pre-T2D

# Most Effective Time to Intervene: Before Glucose Rises Significantly




*Tabak AG et al.*Lancet 2009; Butler AE et al Diabetes 2003

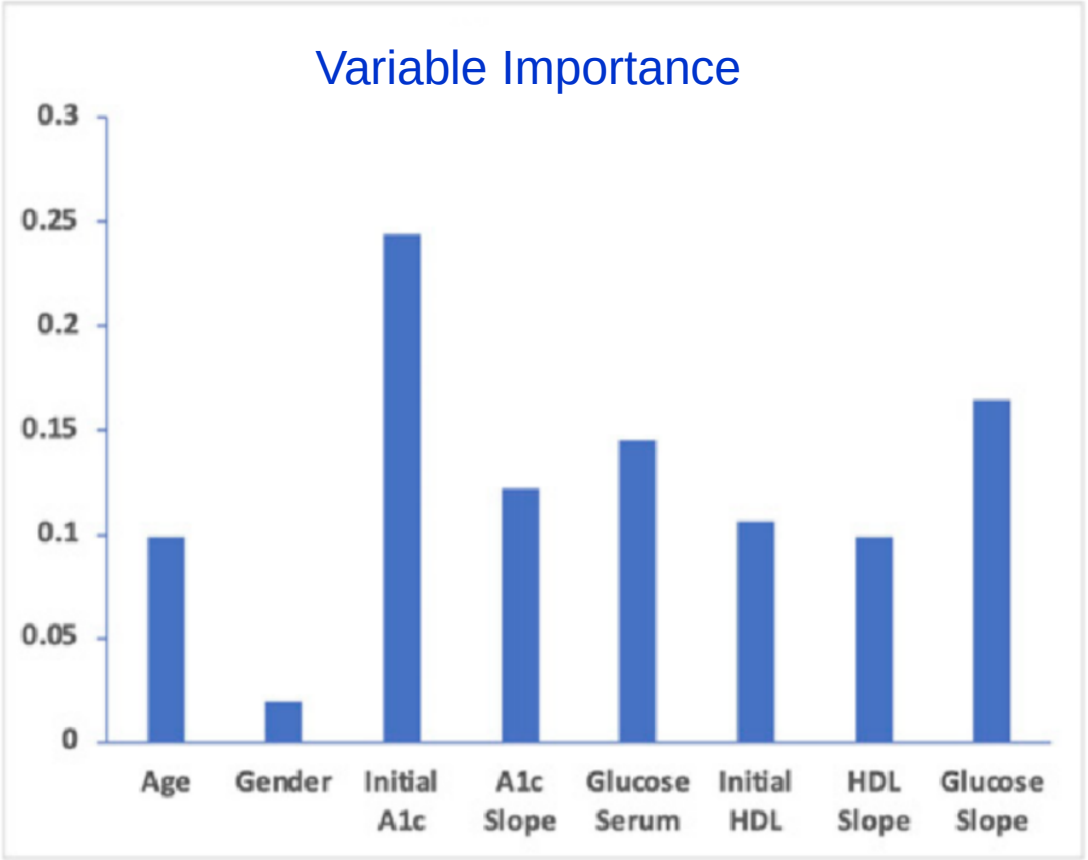
# Machine Learning and a Multi-Faceted Approach
## (Model predicting 5-Y transition from Pre-T2D to T2D)

**>15,000 people with HbA1c 5.0 - 6.5%**

| | *Training set* | *Test set* |
|---|---|---|
| Patient demographics | | |
| Number of unique individuals | 12,023 | 3006 |
| Age, median (IQR) | 62 (15) | 62 (15) |
| Male (%) | 49.2 | 48.9 |
| Laboratory values | | |
| Serum glucose, mg/dL, initial, median (IQR) | 98 (17) | 98 (18) |
| A1C, %, initial, median (IQR) | 5.8 (0.5) | 5.8 (0.5) |
| Serum HDL, g/dL, initial, median (IQR) | 50 (20) | 50 (19) |
| Endpoint, A1C ≥6.5% | | |
| Events (%) | 1703 (14.2%) | 426 (14.2%) |
| Progression time, months (IQR) | 27.9 (18) | 26.0 (18) |
| Observation time, months (IQR) | 30.7 (21.6) | 29.8 (22.6) |

Progression time is defined as the average number of months identified for hemoglobin A1C values ≥6.5% from initial value. Observation time is defined as the average number of months of laboratory data procured for the cohort.
IQR, interquartile range.

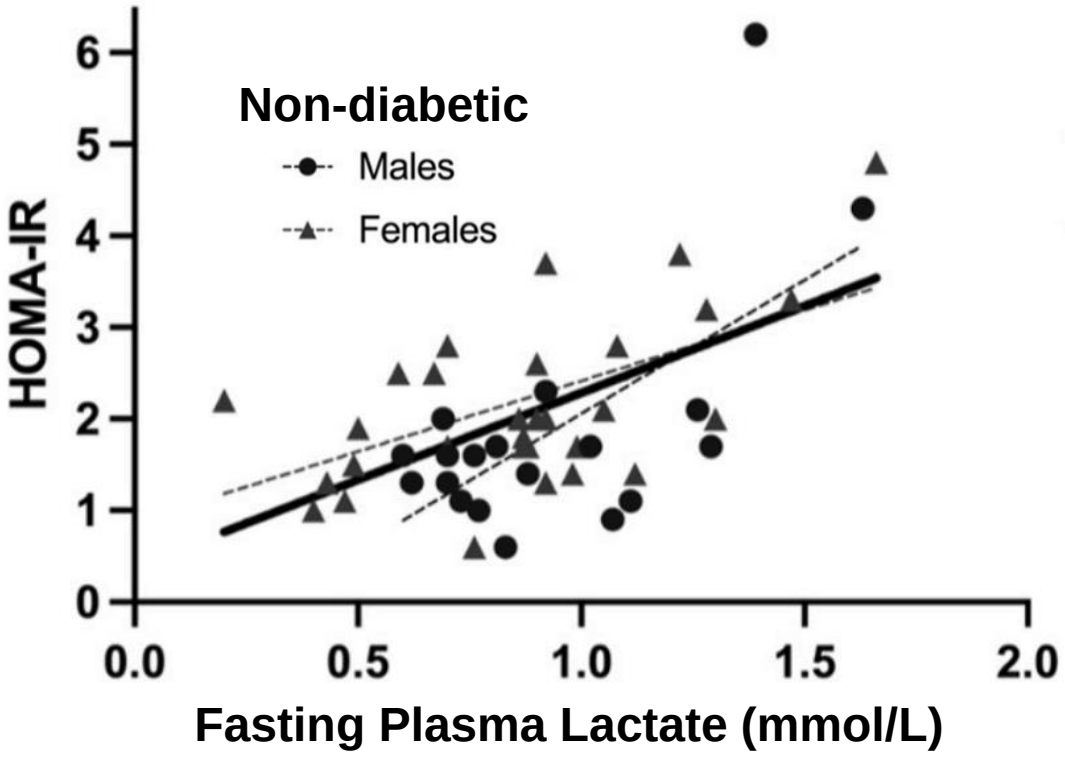
**Positive Predictive Value 0.91**
**Negative Predictive Value 0.89**




*Aoki J et al Diabetes Technology and Therapeutics 2024*

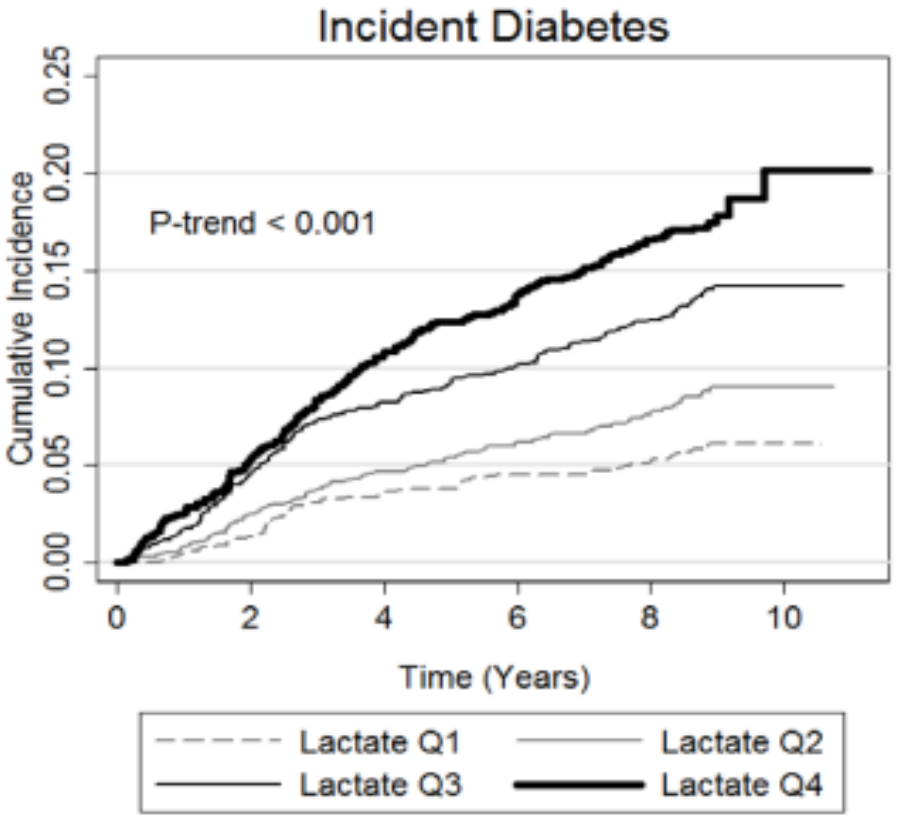
# Fasting Lactate Reflects Impaired Mitochondrial Oxidation: Marker of Future T2D Risk?

**N= 50**
**r = 0.53; p <0.0001**



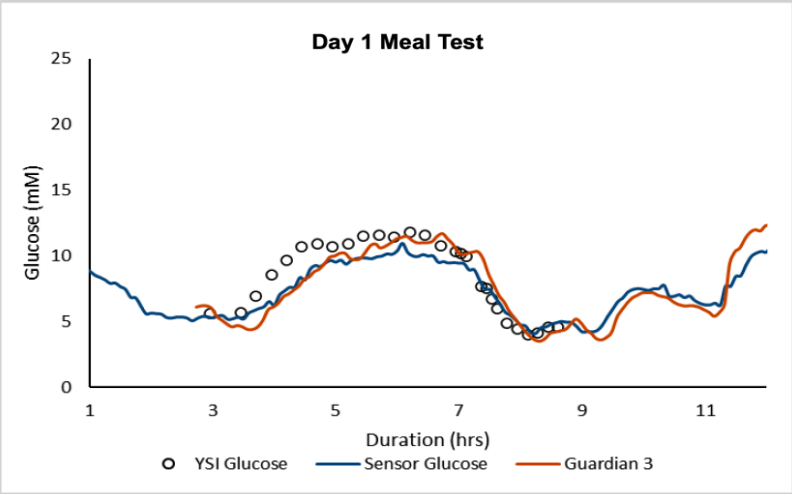

*Broski NT et al Clinical Research & Reviews 2024*

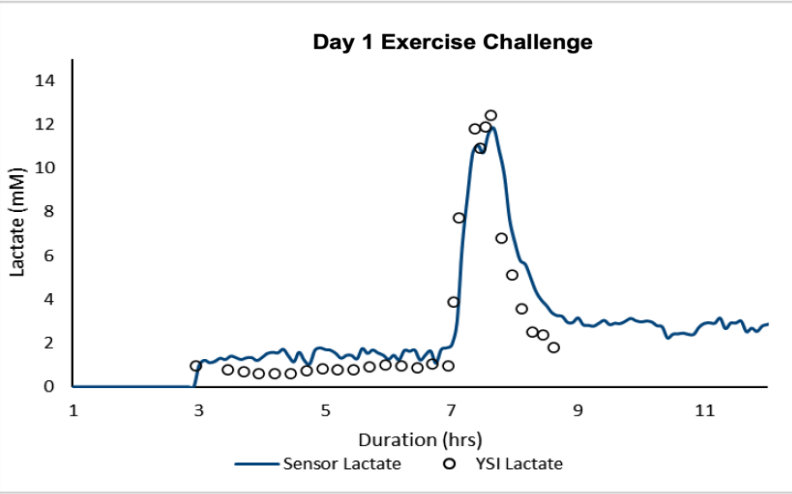
**Prospective cohort study (n = 15,792)**
**Case (n = 552 ) Control (n = 637 )**

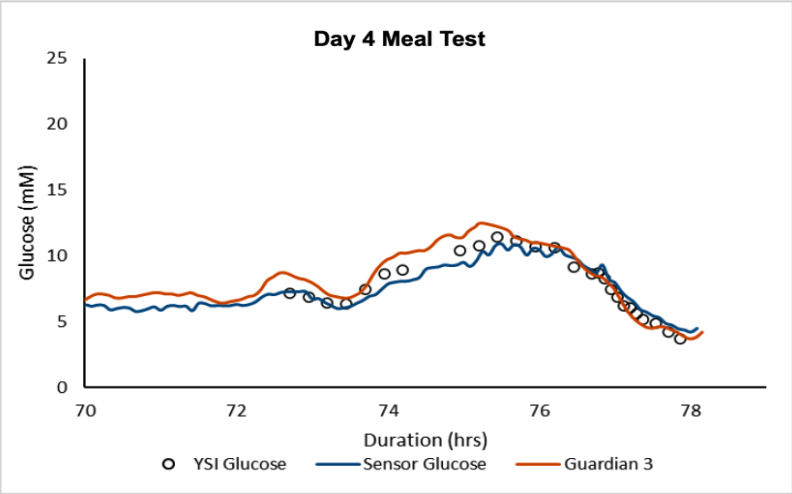


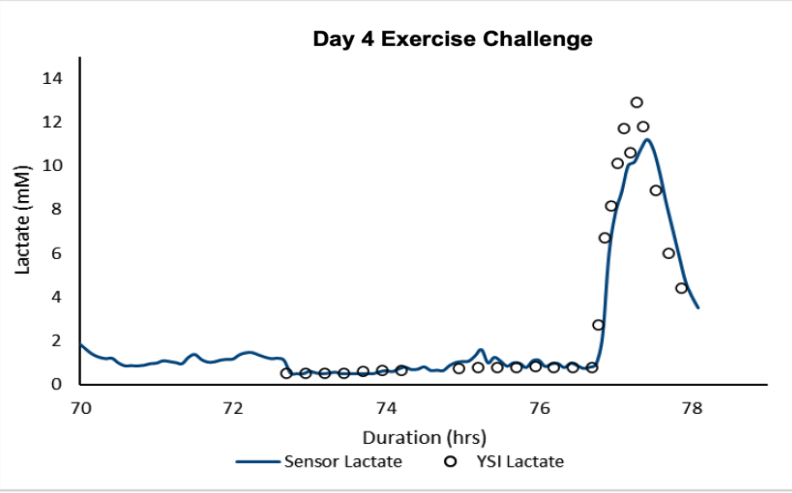

*Juraschek SP et al PLOS 1 2013*

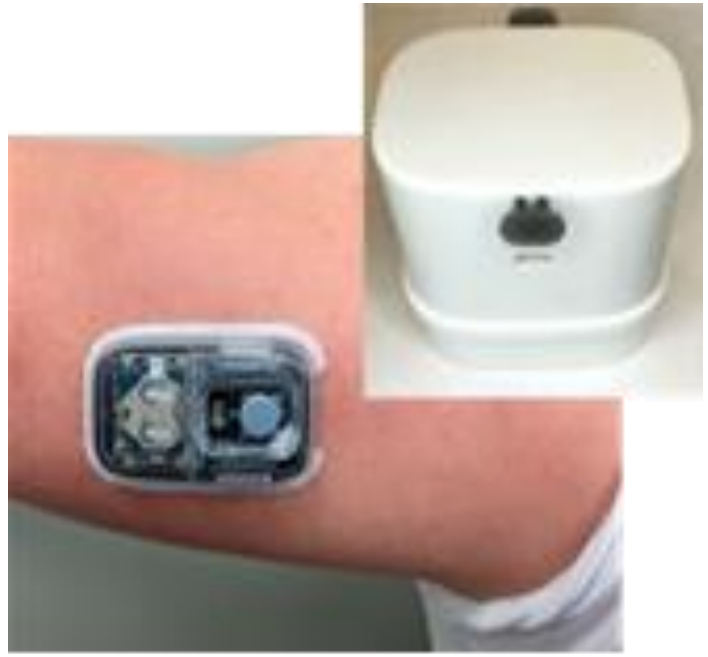
# Proof of Concept:
# Glucose and Lactate Continuous Monitor



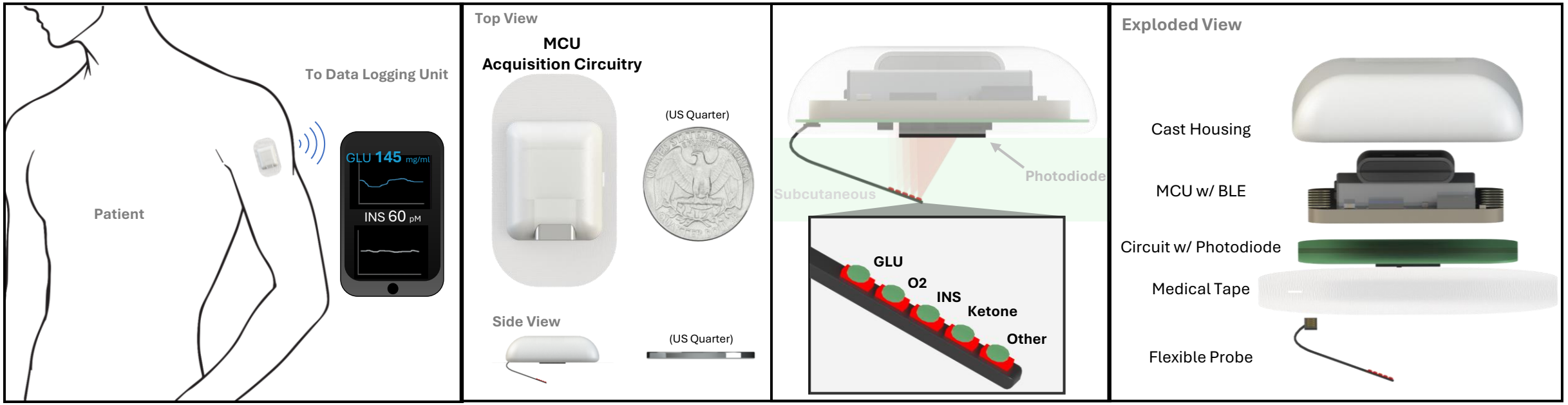



PercuSense

*Lu JC et al Journal of Diabetes Science, and Technology 2024*

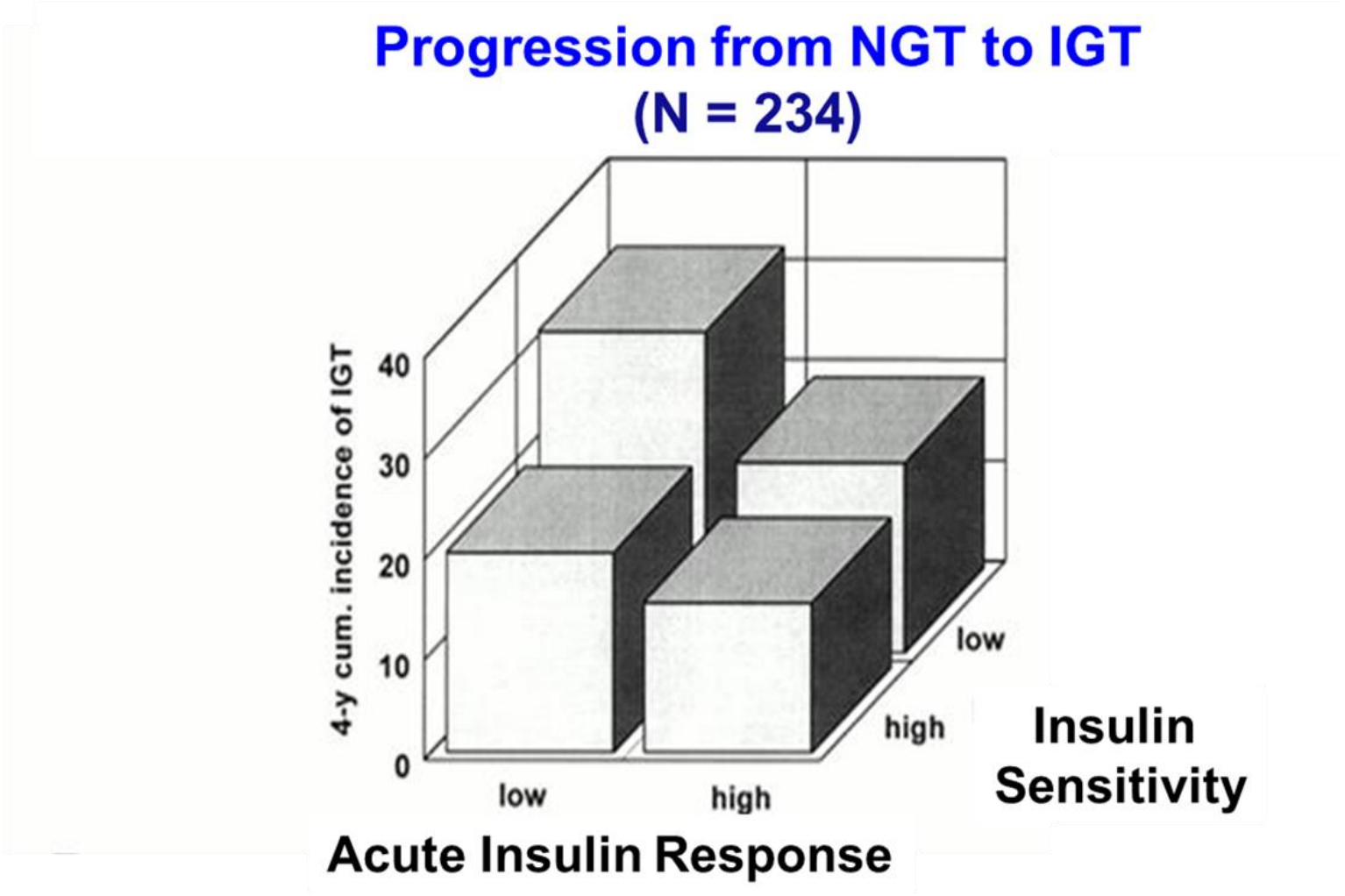
# Combined Interstitial Fluid Continuous Glucose / Ketone / Insulin Monitor




UCI Beckman Laser Institute & Medical Clinic

*Slide courtesy of Professor Elliot Botvinick 2024*

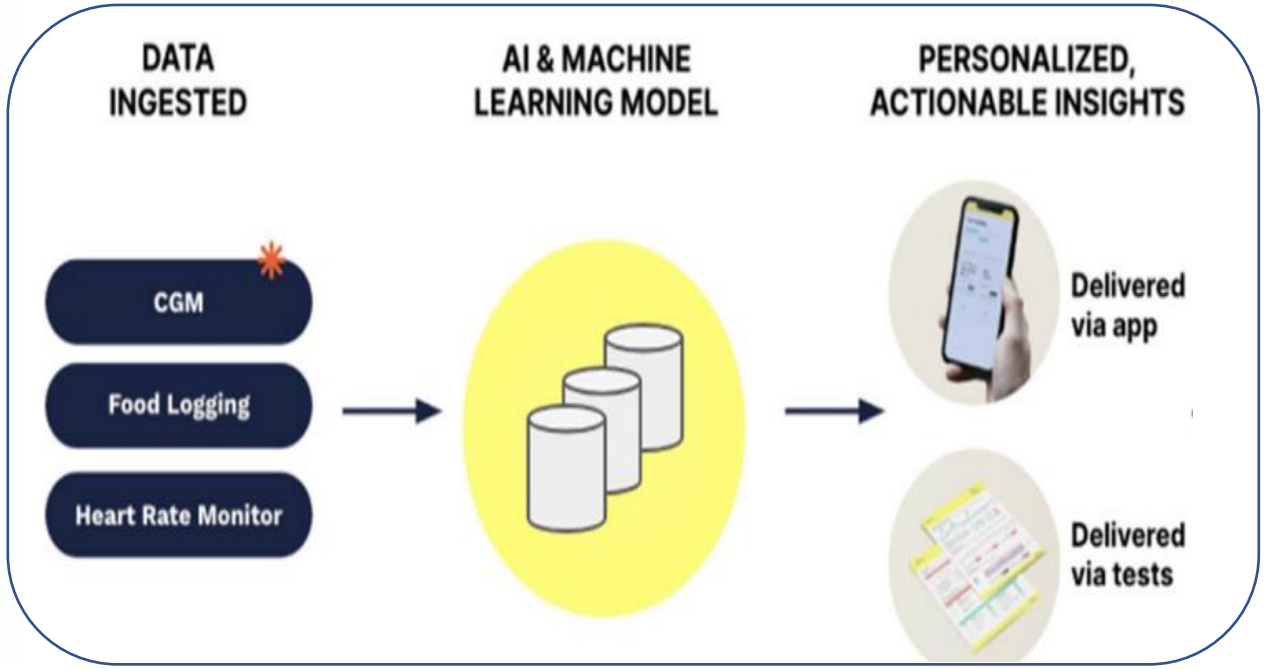
# Changes in Insulin Secretion and Sensitivity and Future Pre-T2D Risk

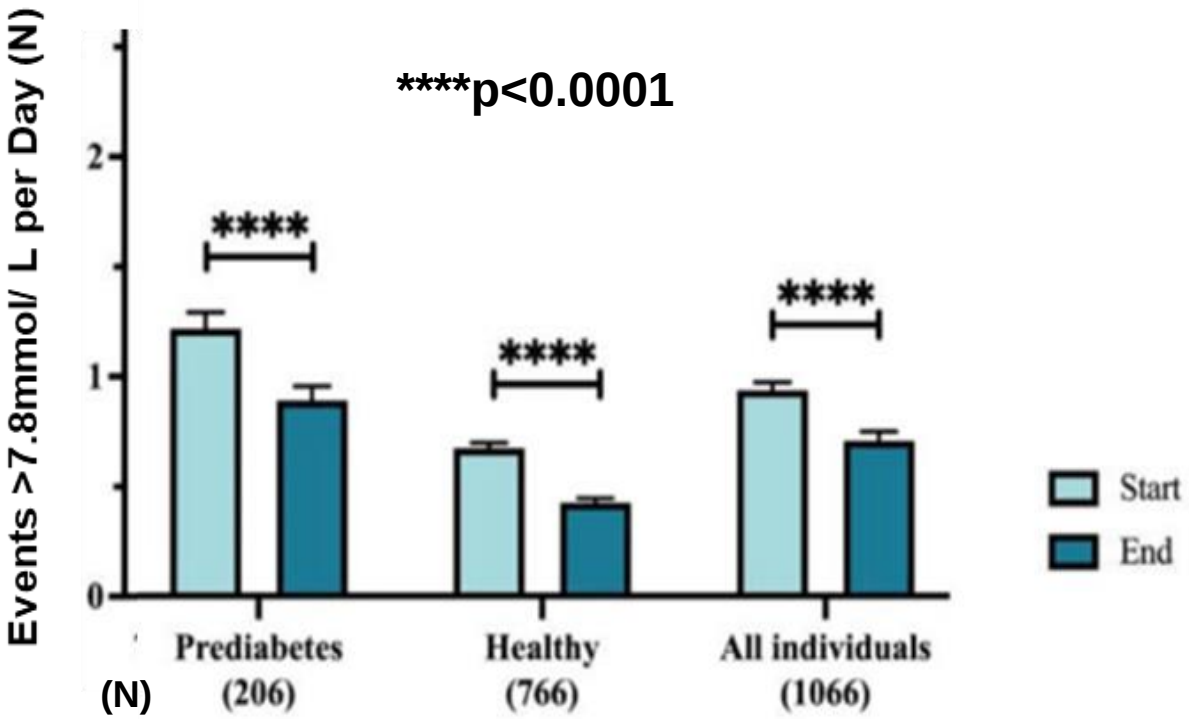



*Weyer C et al Diabetes Care 2000*

# Preventing T2D with CGM, Wearables, and AI

- 28 Days: Freestyle CGM + Apple Watch / Fitbit + January AI App
- App integrated user CGM + HR + Diet + Activity data and gave AI-based personalised recommendations to optimise glucose[3]




Zahedani et al. npj Digital Medicine, 2023

# LumosFit leverage's GenAI to enable realistic and lasting behavior change

Make healthful eating low burden

Improve individual decision making

Adapt suggestions with user's life

**AI:** Please provide your ZIP code to get started.

**User:** My zip code is 48109

**AI:** Great! Now please provide your weekly budget for groceries.

**User:** my weekly budget is $62

**AI:** Here are two stores with a focus on nutritional value:

1. **Plum Market**
   - **Address:** 3601 Plymouth Rd, Ann Arbor
   - **Distance:** 1.11 miles
2. **Whole Foods Market**
   - **Address:** 3135 Washtenaw Ave, Ann Arbor
   - **Distance:** 3.59 miles

## Recommendation:

I recommend **Plum Market**. It is closer in distance, which may save you time and transportation costs. Additionally, Plum Market is known for its emphasis on fresh, organic, and locally sourced products, making it a great choice for health-conscious shopping. With a budget of $62.00, you should be able to find a variety of nutritious options that align with your health priorities.

Here are the details on where to find the selected items within **Plum Market** at 3601 Plymouth Rd, Ann Arbor:

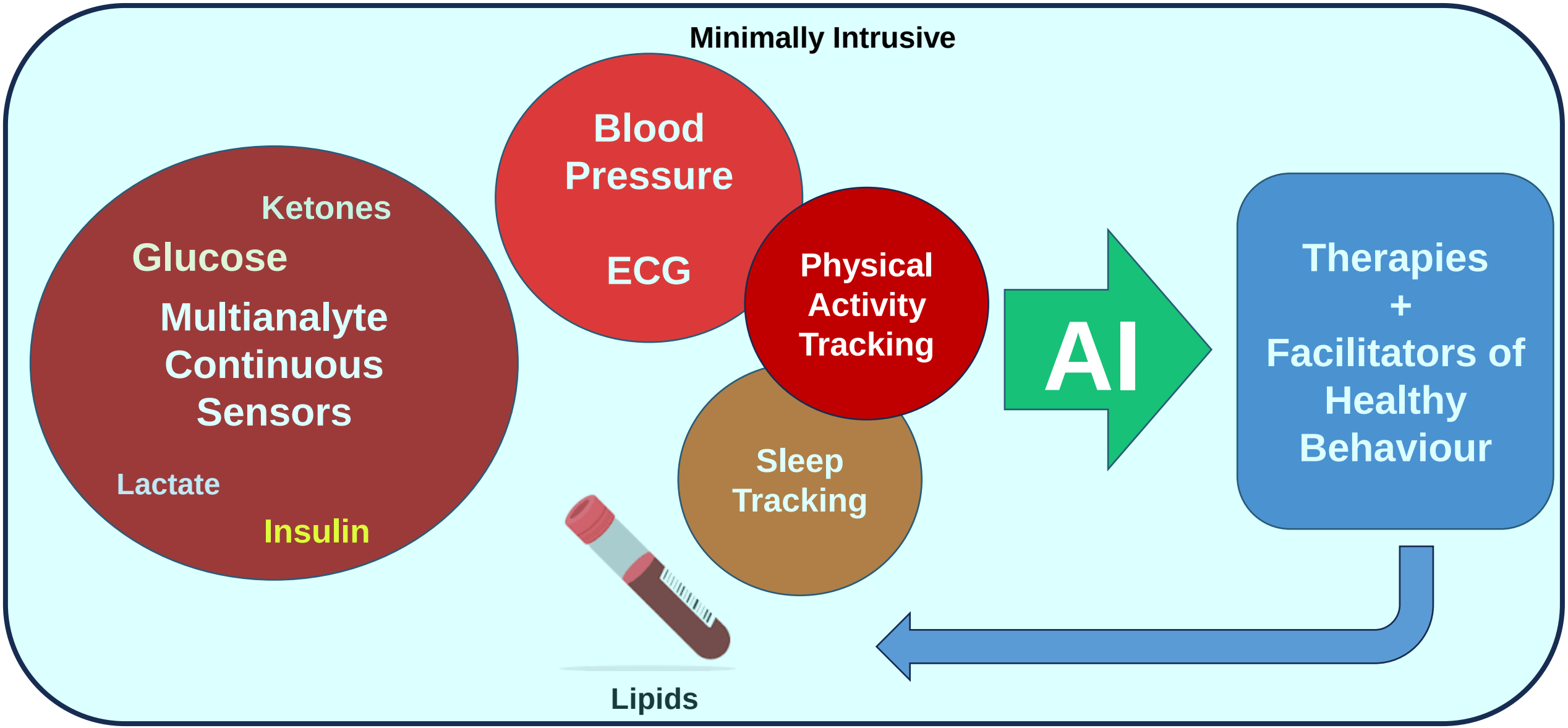
1. **Organic Spinach (1 lb)** - $2.99
   **Location:** Produce Section (leafy greens area)
2. **Quinoa** - $3.49
   **Location:** Produce Section (near other fruits)
3. **Almonds (Raw)** - $6.99
   **Location:** Nuts and Dried Fruits Section
4. **Organic Chicken Breast (1 lb)** - $7.99
   **Location:** Meat Department (refrigerated section)
5. **Chickpeas (1 lb)** - $1.29
   **Location:** Canned Goods Aisle (or Dry Beans Section)
6. **Avocado** - $1.50
   **Location:** Produce Section (near other fruits)
7. **Brown Rice** - $2.49
   **Location:** Grains and Pasta Aisle
8. **Greek Yogurt (Plain)** - $4.49
   **Location:** Dairy Aisle (yogurt section)
9. **Sweet Potatoes** - $0.99
   **Location:** Produce Section (root vegetables area)
10. **Salmon (Fresh)** - $12.99
    **Location:** Seafood Department (fresh fish section)
11. **Blueberries (Fresh)** - $3.99
    **Location:** Produce Section (berries area)
12. **Organic Eggs (Dozen)** - $4.99
    **Location:** Dairy Aisle (egg section)
13. **Broccoli (Fresh)** - $1.99
    **Location:** Produce Section (cruciferous vegetables area)
14. **Hummus (8 oz)** - $3.49
    **Location:** Deli Section (refrigerated dips area)
15. **Lentils (1 lb)** - $1.99
    **Location:** Dry Beans Section or Grains Aisle

Total cost: $61.66

*AI agent example*: Grocery recommendation for a user in a low-income neighborhood on a thrifty weekly budget of US$ 62.

Slide courtesy of Hema Mandlekar 2024

# Technology Ecosystem for Preventing T2D



# Summary

- CGM provides a rich dataset under ‘real life’ conditions
- Glucose is a core signal but clear changes occur late
- Early identification = more effective intervention
- Metabolic thumbprint ? Better than glucose alone:

  -Additional Signals: Physical activity, HDL, lactate, insulin…

- Trajectory of **multiple signals over time** processed by AI may enhance identification of those at risk of **Pre-T2D**
- Aspirations for Technology:

  - **IDENTIFY** individuals before CVD etc risk is increased significantly
  - **MOTIVATE AND FACILITATE** healthy behaviour
  - **PERSONALISE PHARMACOTHERAPY** in a timely manner
  - **ASSESS RESPONSES** to interventions and modify strategies accordingly

# Acknowledging Our Team

D.T.R.G
Diabetes Technology Research Group

***To improve the lives of people with diabetes through exceptional research that drives advancement in innovative technologies***

## Endocrinologists
David O'Neal MD
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Glenn Ward PhD
Melissa Lee PhD
Barb Paldus PhD
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Jean Lu (PhD student)

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Declan Hennessy PhD

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## Project Lead
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Katerina Kiburg PhD

## Administrative Support
Lachlan Christian (BA)
Amanda Coleman (BSc)

# Thank You

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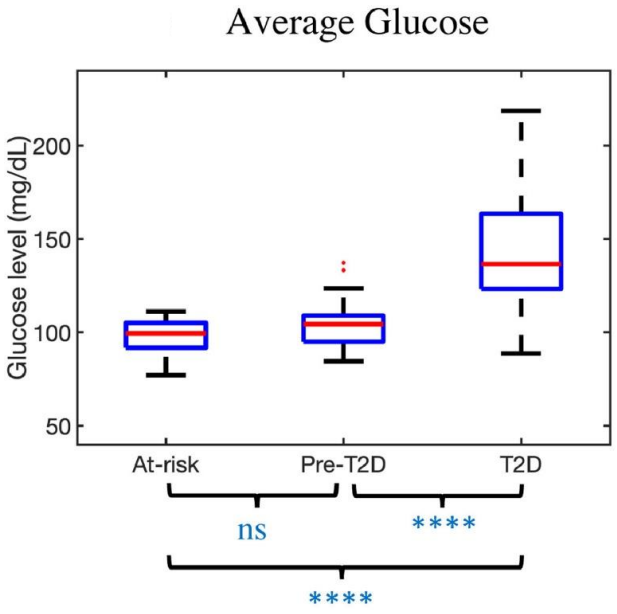
# A Mathematical Model Screening for Impaired Glucose Homeostasis with CGM

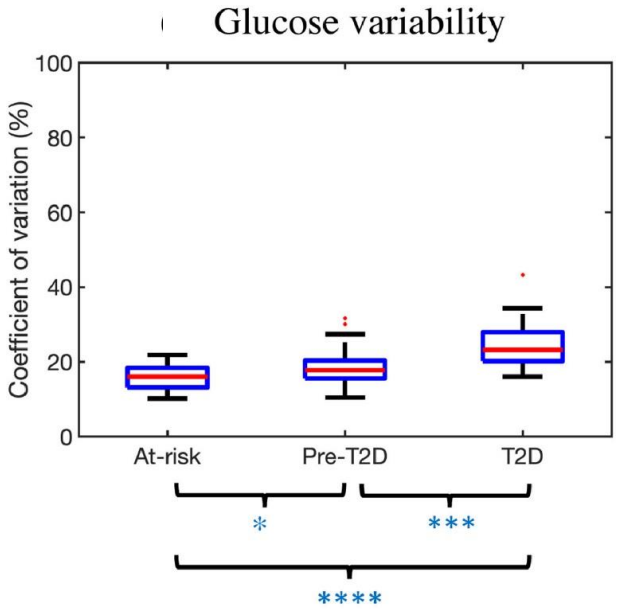
- Functional homeostatic glucose mathematical model (FLAG) based on CGM glucose excursions
- Calibration study followed by a validation study on a different population (India)
- Participants classified based on CGM data as:
  - Effective Glucose Homeostasis (EGH) or;
  - Impaired Glucose Homeostasis (IGH)
- Benchmarked against ADA classification

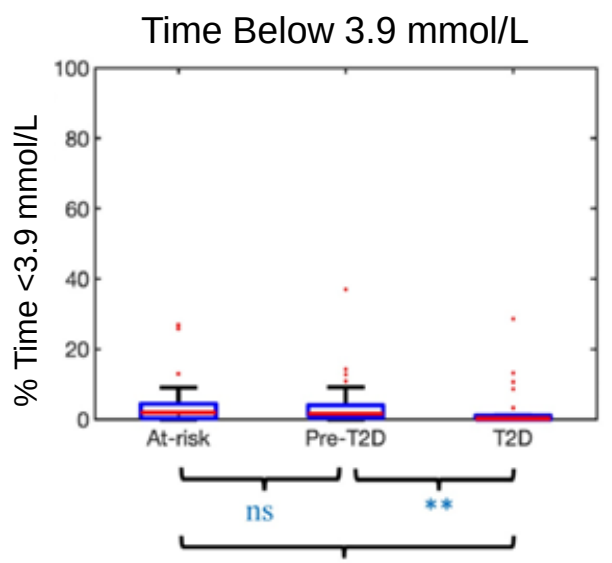
| Glycemic variability metric across diabetic status | Non-Diabetic (ADA) | | Pre-T2D (ADA) | |
|---|---|---|---|---|
| | EGH | IGH | EGH | IGH |
| All participants<br>Number of participants | **N = 145** | **N = 50** | **N = 15** | **N = 84** |
| AUC (mmol minutes/L) | 552.84±461.72[a*,c*,d*] | 701.84±724.88[a*,e*,f*,g*] | 505.48±380[e*,h*,j*] | 811.16±767.28[c*,f*, |
| AUCm (mmol minutes/L) | 618.68±482.28[a*,c*,d*] | 798.56±778.68[a*,e*,f*,g*] | 574±401.96[e*,h*,j*] | 924.96±809.8[c*,f*,h |
| Max glucose (mmol/L) | 5.98±0.78[a*,c*,d*] | 6.38±1.11[a*,e*,f*,g*] | 5.98±0.71[e*,h*,i*] | 6.89±1.26[c*,f*,h*,j |
| Max deviation (mmol/L) | 1.94±0.77[a*,c*,d*] | 2.19±1.03[a*,e*,f*,g*] | 1.9±0.72[e*,h*,i*] | 2.4±1.19[c*,f*,h*,j |
| Peak length (minutes) | 152.99±71.42[a*,c*,d*] | 162.49±79.37[a*,e*,f*,g*] | 147.14±64.82[e*,h*,j*] | 170.47±80.06[c*,f*,h |
| Mean glucose (mmol/L) | 4.49±0.5[a*,c*,d*] | 4.83±0.74[a*,e,f,g*] | 4.52±0.4[e,h*,j*] | 5.24±0.64[c*,f,h*,j* |
| Glucose SD (mmol/L) | 0.86±0.16[a*,c*,d*] | 1.12±0.42[a*,e*,f,g*] | 0.85±0.14[e*,h*,i*] | 1.21±0.27[c*,f,h*,j* |
| TIR proportion | 0.61±0.23[a,c*] | 0.73±0.18[a,f] | 0.62±0.25[h] | 0.84±0.16[c*,f,h,j] |
| TAR proportion | 0.0±0.0[a*,c*,d*] | 0.004±0.015[a*,g*] | 0.0±0.0[h,i*] | 0.004±0.011[c*,h,j* |
| TBR proportion | 0.39±0.23[a,c*,d*] | 0.27±0.19[a,f*,g*] | 0.38±0.25[h,i*] | 0.16±0.16[c*,f*,h,j* |

*Kaufman JM et al. Mayo Proceedings Digital Health 2023*

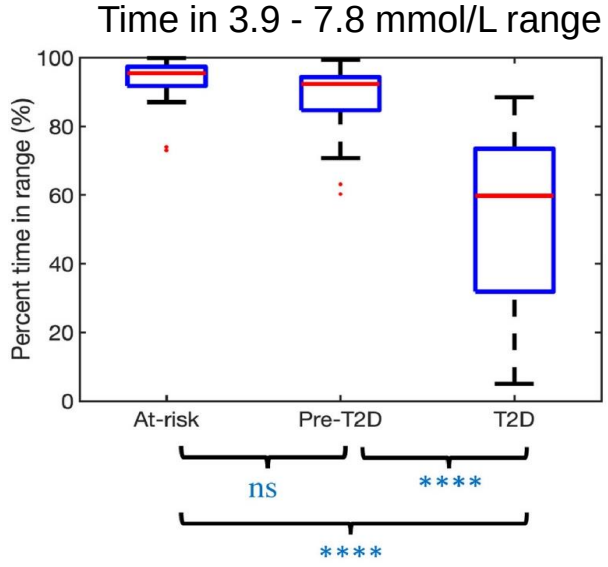
# CGM Metrics: 'At-Risk', Pre-T2D, and T2D

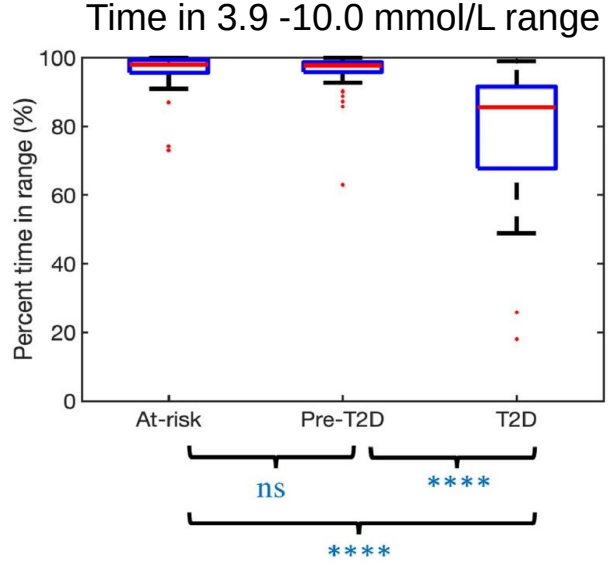


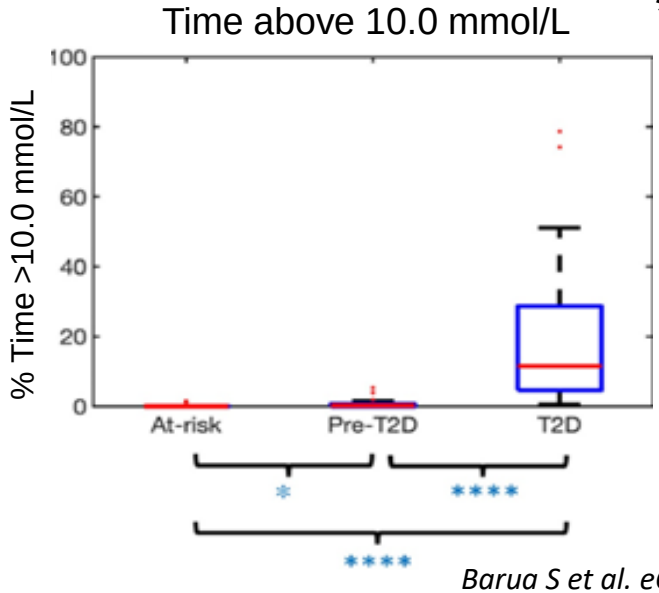




, *:p<0.05
**p<0.01
***p<0.001
****p<0.0001



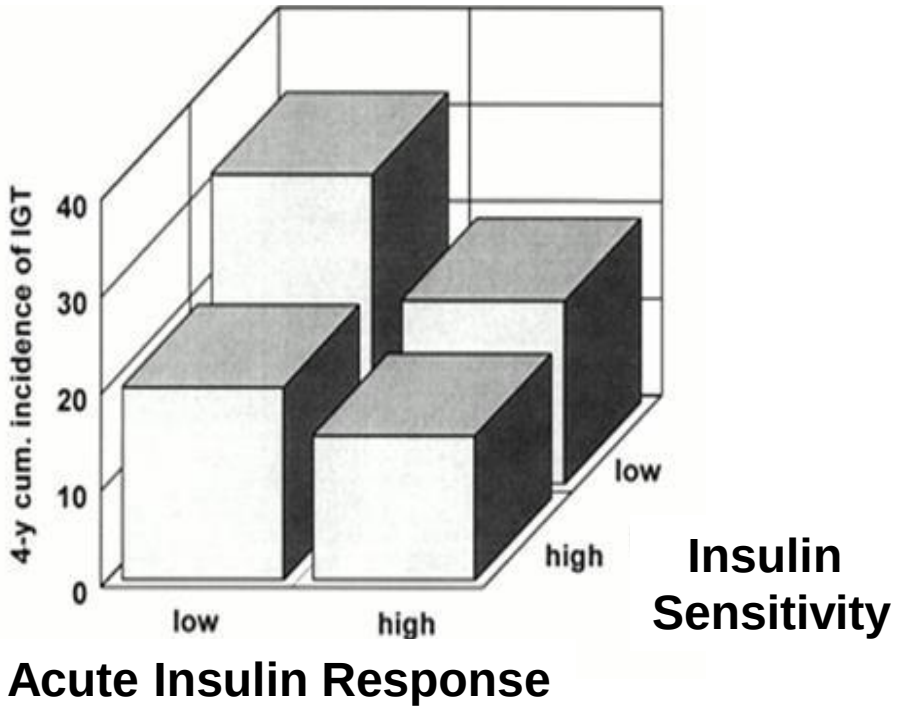



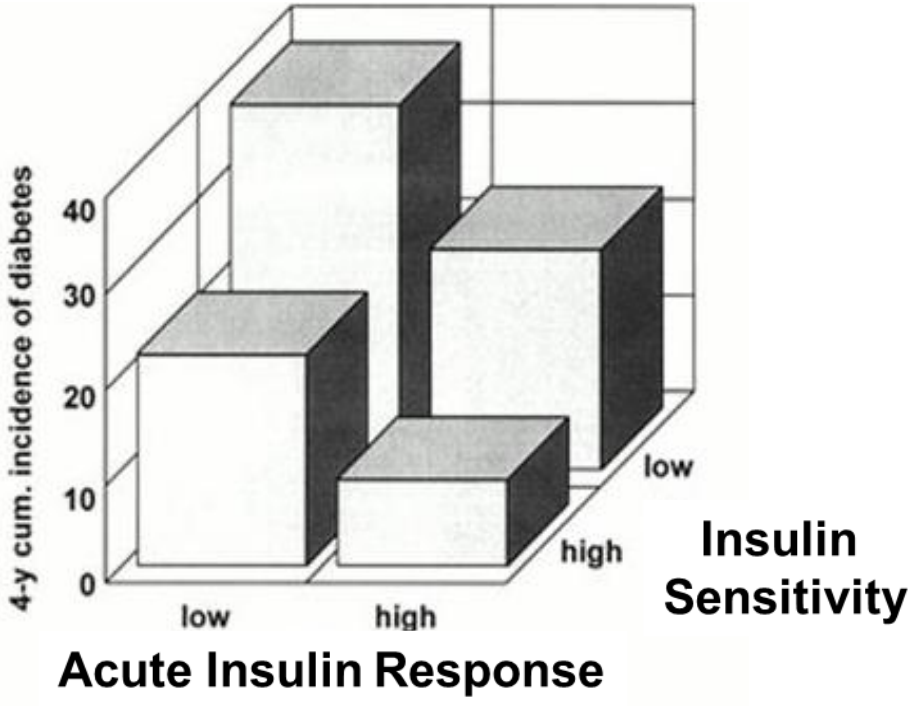

*Barua S et al. eClinical Medicine 2021*

# Changes in Insulin Secretion and Sensitivity and Future T2D Risk?

**Progression from NGT to IGT**
**(N = 234)**



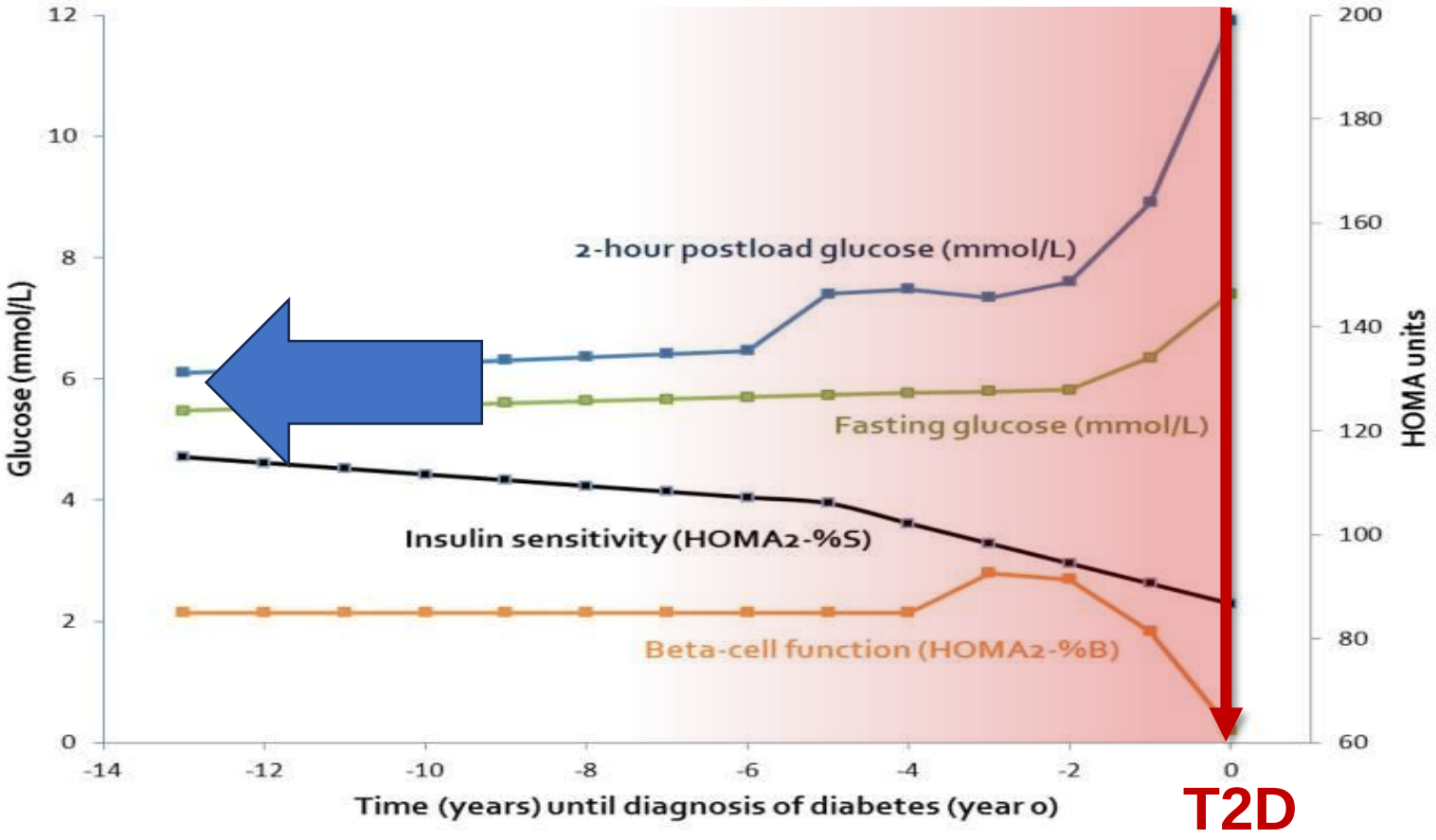

**Progression from IGT to T2D**
**(N = 145)**




*Weyer C et al Diabetes Care 2000*

# Achieving Pre-T2D Remission…

**“It is suspected that the risk of diabetes and macrovascular complications begin to develop at glucose levels below the current cut-off levels for pre-diabetes.”**




Adapted from Tabak AG et al. Lancet 2009