ATTD Advanced Technologies & Treatments for Diabetes

ATTD-ASIA
18-20 NOVEMBER 2024
SINGAPORE

Unlocking the Potential of Menin Inhibition

Icovamenib and a look into the future of diabetes management

Prof. Juliana CN Chan, MD
Professor of Medicine and Therapeutics
Founding Director. Hong Kong Institute of Diabetes and Obesity
The Chinese University of Hong Kong

Juan Pablo Frías, MD
Chief Medical Officer and Head of Diabetes Biomea Fusion, Inc.

biomea FUSION™ We Aim to Cure™

Professor Juliana CN Chan, MD

- Endocrinologist, clinical pharmacologist, and a diabetes researcher
- Professor of Medicine and Therapeutics, The Chinese University of Hong Kong
- Founding Director of the Hong Kong Institute of Diabetes and Obesity and CEO of the Asia Diabetes Foundation
- Directs the CUHK-PWH International Diabetes Federation (IDF) Centre of Education and Centre of Excellence in Diabetes Care
- Research focuses on the epidemiology, genetics, clinical trials, and data-driven clinical management of diabetes
- Published over 900 articles and 20 book chapters
- Her contributions to diabetes research and care have earned her numerous awards, including the American Diabetes Association's Harold Rifkin Award

Disclosures

- Consultancy, lecture fees and research support: Astra Zeneca, Bayer, Biomea Fusion, Boehringer Ingelheim, Celltrion, Powder Pharmaceuticals, Hua Medicine, Lilly, Merck, MSD, Novo Nordisk, Novartis, Sanofi, Pfizer, Viatris
- Chief Executive Officer (pro-bono), Asia Diabetes Foundation
- Founding director, GemVCare

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AGENDA

17:10 - 17:15	Introduction to Biomea Fusion	Juan P. Frías, MD
17:15 – 17:25	The Role of Menin in Glucose Homeostasis, and Icovamenib a Covalent Menin Inhibitor	Juan P. Frías, MD
17:25 – 17:50	Diabetes: A Focus on Subgroups and Phenotypes	Prof. Juliana CN Chan, MD
17:50 – 18:00	Case Study, Summary & Conclusions	Juan P. Frías, MD
18:00 – 18:10	Q&A	Prof. Juliana CN Chan, MD Juan P. Frías, MD

biomea FUSION™ We Aim to Cure™

Introduction to Biomea Fusion

Juan Pablo Frías, MD
Chief Medical Officer and Head of Diabetes
Biomea Fusion

biomea FUSION™ We Aim to Cure™

A long history of developing successful drugs - together

Thomas Butler
Chairman & CEO

biomea FUSION™
Co-Founder

The FUSION™ SYSTEM
icovamenib*
Co-Inventor

imbruvica® (ibrutinib)
560, 420, 280, 140 mg tablets | 140, 70 mg capsules

Veklury® remdesivir 100 MG FOR INJECTION
Co-Inventor

Ramses Erdtmann
President & COO

biomea FUSION™
Co-Founder

imbruvica® (ibrutinib)
560, 420, 280, 140 mg tablets | 140, 70 mg capsules

Juan Frías, M.D.
Chief Medical Officer

once weekly mounjaro® (tirzepatide) injection 0.5 mL
2.5 mg | 5 mg | 7.5 mg | 10 mg | 12.5 mg | 15 mg

once weekly trulicity® (dulaglutide) injection 0.5 mL
0.75 mg | 1.5 mg | 3.0 mg | 4.5 mg

OZEMPIC® semaglutide injection 0.5 mg, 1 mg, 2 mg

Byetta® (exenatide) injection

ONCE-WEEKLY wegovy® semaglutide injection 2.4 mg

Januvia® sitagliptin

Invokana® (canagliflozin) tablets

Jardiance® (empagliflozin) tablets 10 mg/25 mg

farxiga® (dapagliflozin) 5 mg & 10 mg tablets

Naomi Cretcher
Chief of People

imbruvica® (ibrutinib)
560, 420, 280, 140 mg tablets | 140, 70 mg capsules

Heow Tan
Chief Technical & Quality Officer

ZADAXIN®

imbruvica® (ibrutinib)
560, 420, 280, 140 mg tablets | 140, 70 mg capsules

Xtampza® ER (oxycodone) EXTENDED-RELEASE CAPSULES (II)

PLENAXIS®

HylatopicPlus® Cream

Steve Morris, M.D.
Chief Development Officer

XALKORI® CRIZOTINIB 250 MG CAPSULES

ZYKADIA® ceritinib 150 mg tablets

LORBRENA® LORLATINIB | 100 mg tablets

ALECENSA® alectinib 150 mg capsules

ALUNBRIG™ BRIGATINIB 30mg TABLETS

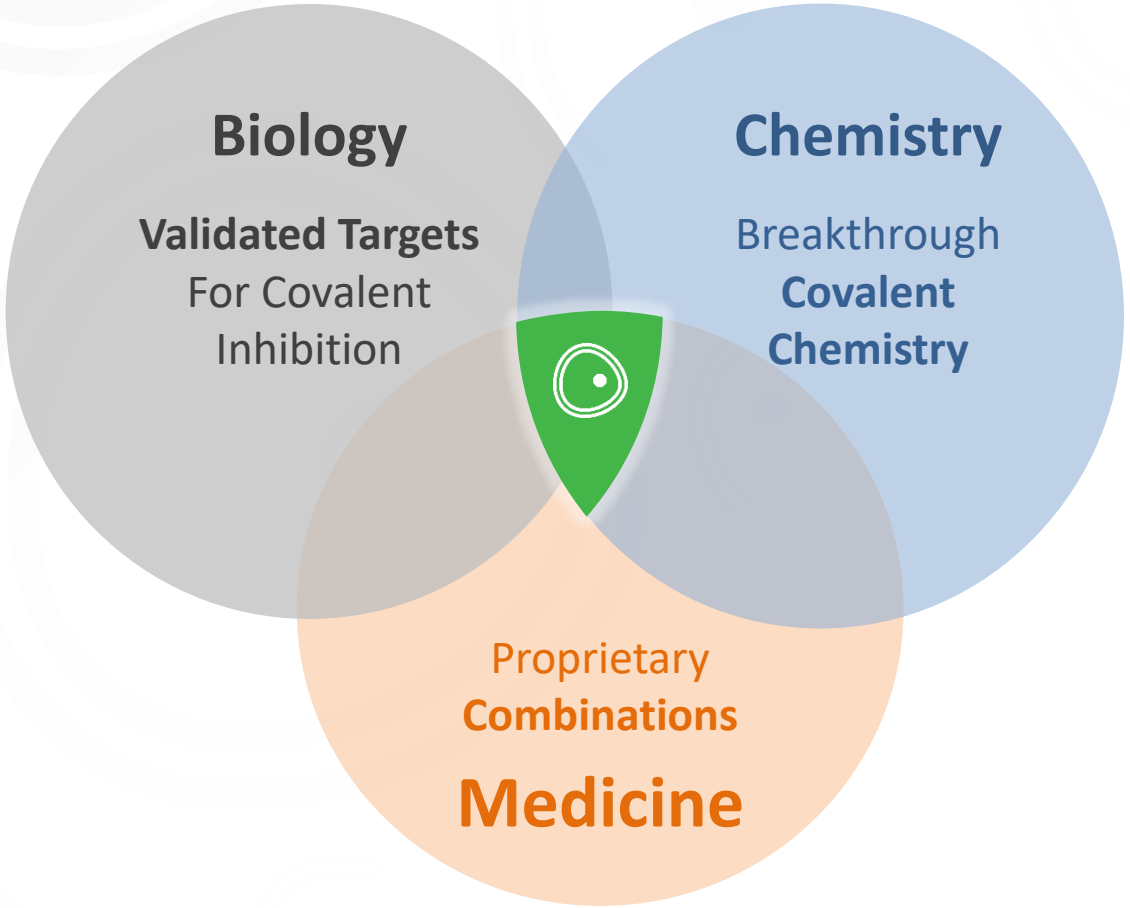
Franco Valle
Chief Financial Officer

imbruvica® (ibrutinib)
560, 420, 280, 140 mg tablets | 140, 70 mg capsules

AMTAGVI™ (lifileucel) Suspension for IV infusion

*Note: icovamenib is an investigational new drug

“We Aim to Cure” by addressing validated targets with breakthrough covalent chemistry in proprietary combinations



Validated Targets

Drugs pursuing **Validated Disease Targets** have a ~2x higher likelihood of approval than molecules pursuing a new mechanism of action

Sources: Nelson et al. (2015) Nat Genet.; Thomas et al. (2016) BIO; In a Landscape of 'Me Too' Drug Development, What Spurs Radical Innovation? HBS Weekly Review (Jun 2018)

Covalent Inhibitors

Covalent Small Molecule Inhibitors provide deep target inactivation and a wider therapeutic window, allowing for longer duration on therapy

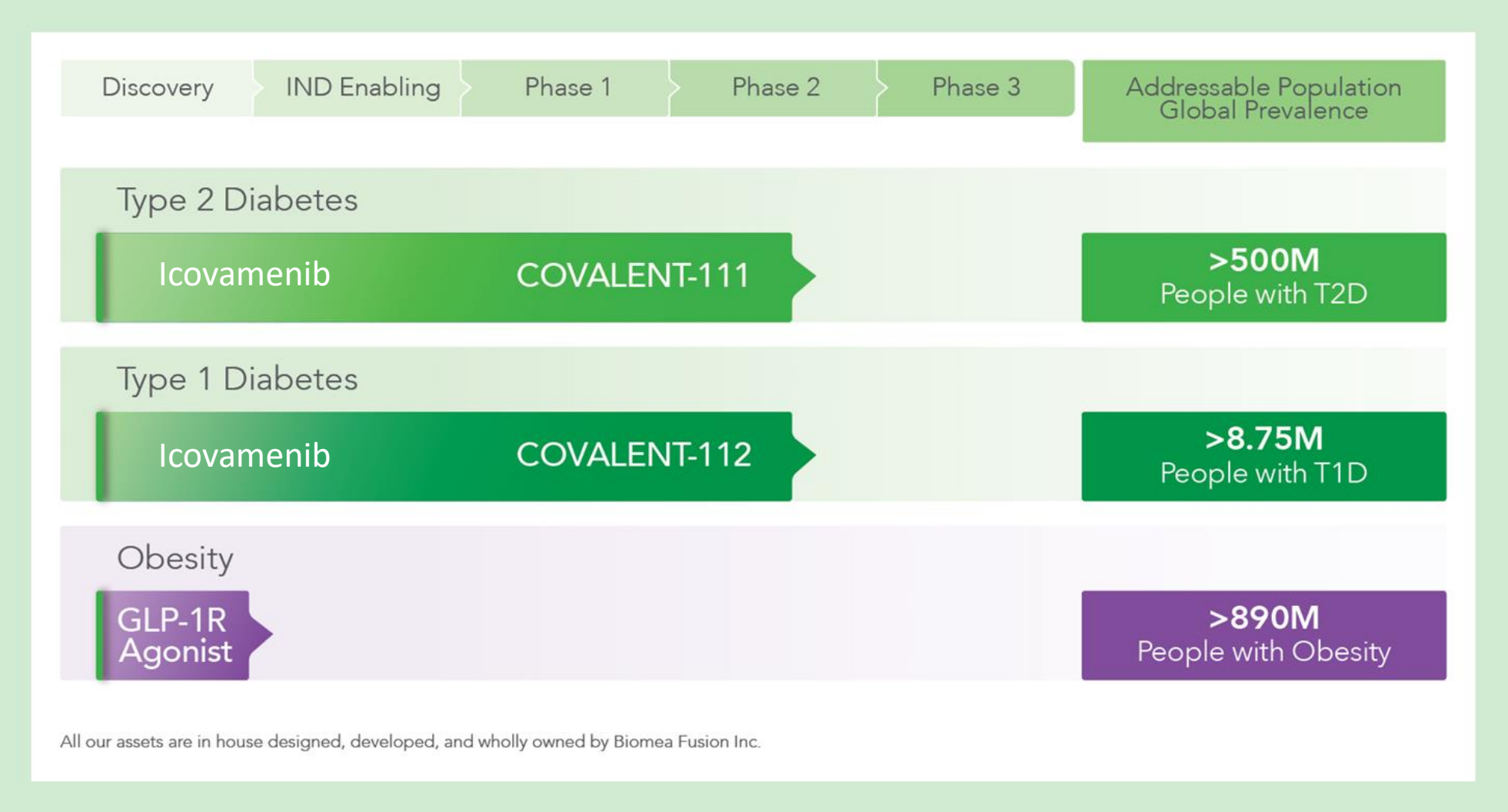
Sources: Singh et al. (2011) Nature Reviews Drug Discovery; Cheng et al. (2020) Journal of Hematology & Oncology; Strelow (2017) SLAS Discovery; Kalgutkar & Dalvie (2012) Expert Opin. Drug Discov.;

Proprietary Combinations

Combination Therapy with non-overlapping resistance mechanisms results in more durable responses and better outcomes

Sources: Palmer et al. (2019) eLife; Mokhtari et al. (2017) Oncotarget

Our product pipeline includes diabetes and obesity



The Role of Menin in Glucose Homeostasis, and Icovamenib a Covalent Menin Inhibitor

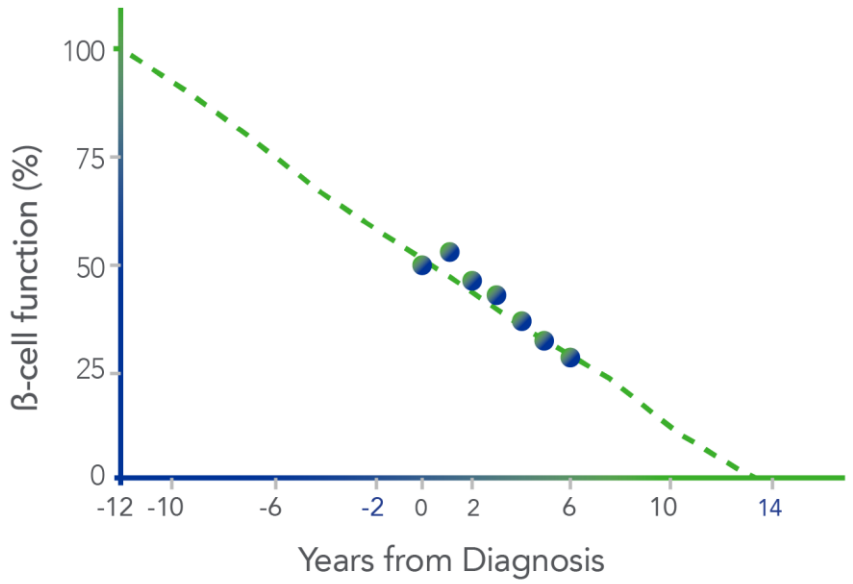
Juan Pablo Frías, MD
Chief Medical Officer and Head of Diabetes
Biomea Fusion

biomea FUSION™ We Aim to Cure™

The progressive decline in beta cell function in diabetes

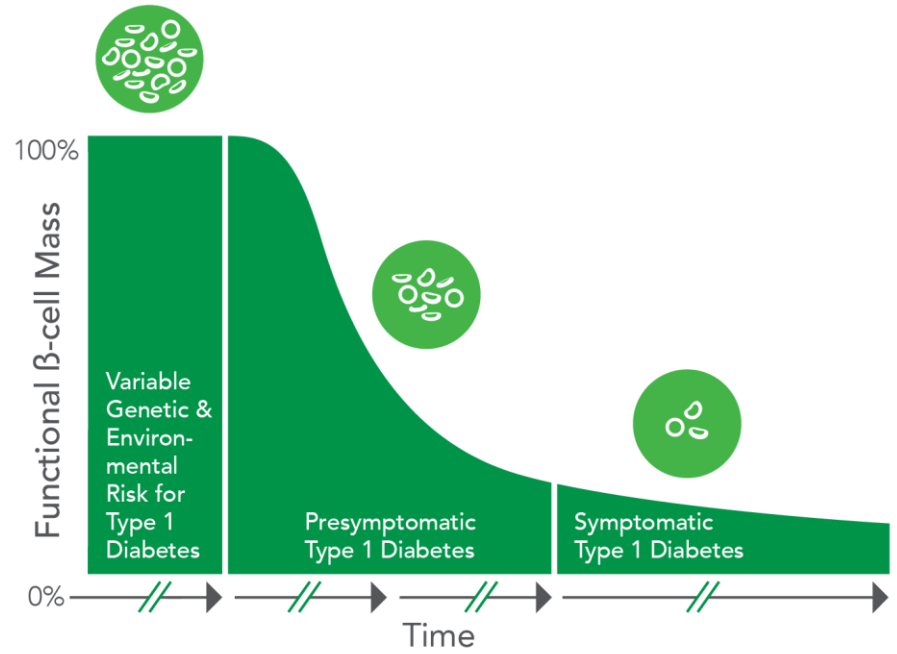
None of today's antidiabetic agents address the root cause of diabetes

Progressive Decline in Beta-cell Function over the Course of T2D



Source: Lebovitz et al. Diabetes Review 1999

Functional Beta Cells Decline over the Course of T1D

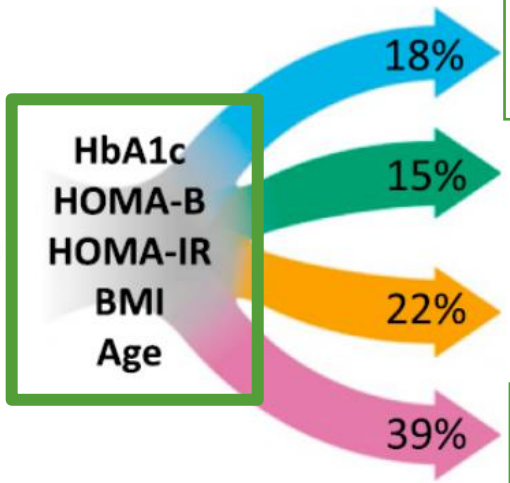


Sources: New advances in type 1 diabetes; BMJ 2024;385:q1224
Insel, et al. (JDRF) Diabetes Care. 2015 Oct; 38(10): 1964–1974
Roep, et al. Nature Reviews Endo. 2020 Dec; 17, pages150–161

“While diabetes is diagnosed on the basis of a single metabolite, glucose, hyperglycemia can arise due to multiple complex etiological processes that can vary between individuals.”[1,2]

Prediabetes

Initial Decline in Glucose Tolerance/Control
Increasing HbA1c, increasing insulin resistance, decreasing beta cell numbers and function



SIDD = Severe Insulin Deficient Diabetes
Low insulin secretion, poor metabolic control, increased risk of retinopathy and neuropathy

SIRD = Severe Insulin Resistant Diabetes
Insulin resistance, obesity, late onset, increased risk of nephropathy and fatty liver

MOD = Mild Obesity-Related Diabetes
Obesity, early onset

MARD = Mild Age-Related Diabetes
Late onset, low risk of complications

T1D

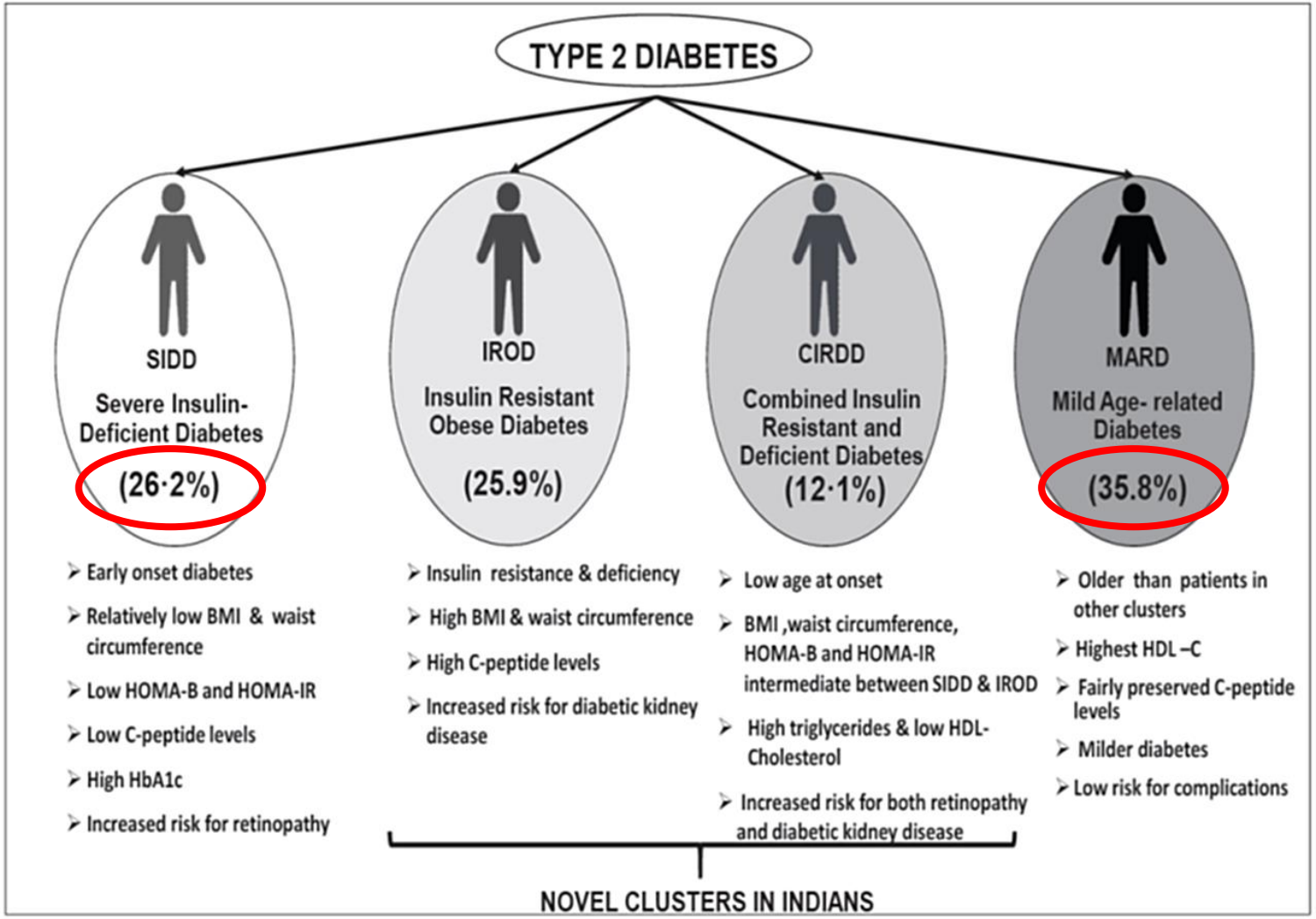
Initial Diagnosis/Disease – Stage 2/Stage 3
Increasing HbA1c, initial reduction in insulin significant decrease in beta cell number and function

SIDD and MARD patients (insulin deficient) represent approximately 50-70% of patients with T2D[3,4], depending on the population, and are characterized by lower BMI, less insulin resistance, and low insulin production/beta-cell deficiency

1. American Diabetes Association. 2. Classification and diagnosis of diabetes: Standards of Medical Care in Diabetes—2019. Diabetes Care 2019;42(Suppl. 1):S13–S28
2. Ahlqvist R, et al. Diabetes 2020;69:2086–2093
3. Ahlqvist E, et al. Lancet Diabetes Endocrinol. 2018;6:361-369
4. Zaghlool SB, et al. Nat Commun. 2022;13:7121

T2D subtyping in Indian revealed approximately 60% SIDD and MARD (insulin deficient)

INSPIRED Study

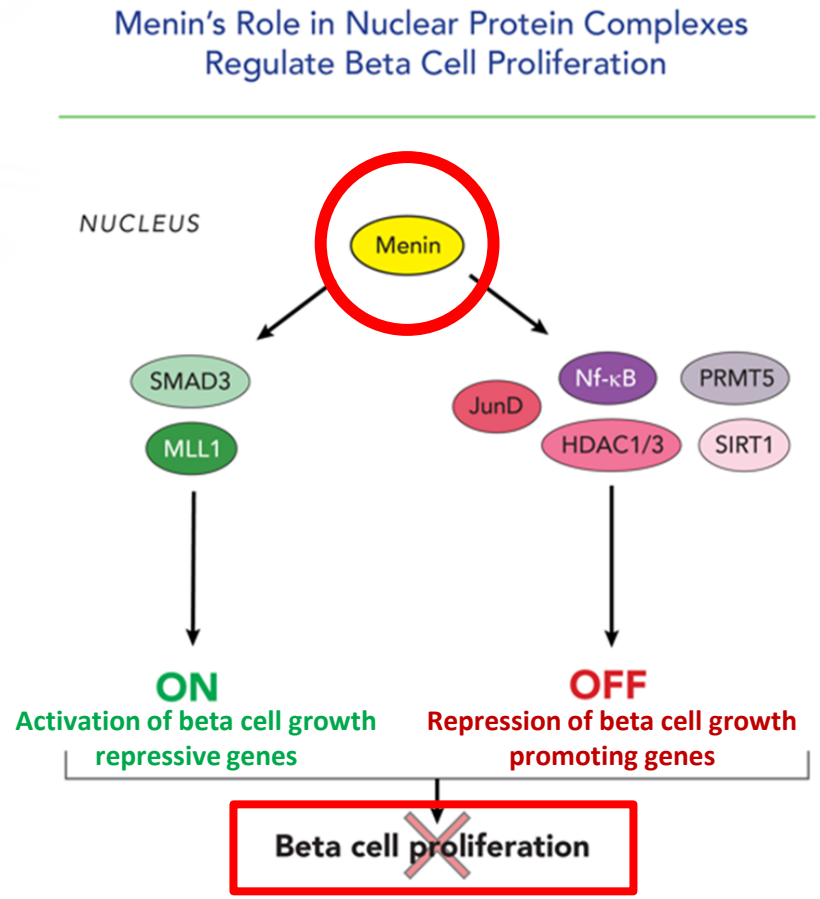


Anjana RM, et al. BMJ Open Diab Res Care 2020;8:e001506. doi:10.1136/bmjdrc-2020-001506
Graphic from: Anjana RM, et al. Journal of the Association of Physicians of India. 2021;68:58-61

- 50 Centers, N=19,084 T2D
- Age at diagnosis, body mass index, waist circumference, HbA1c, serum TG, serum HDL-C, fasting and stimulated C-peptide

Menin's role in beta cell proliferation and glucose homeostasis

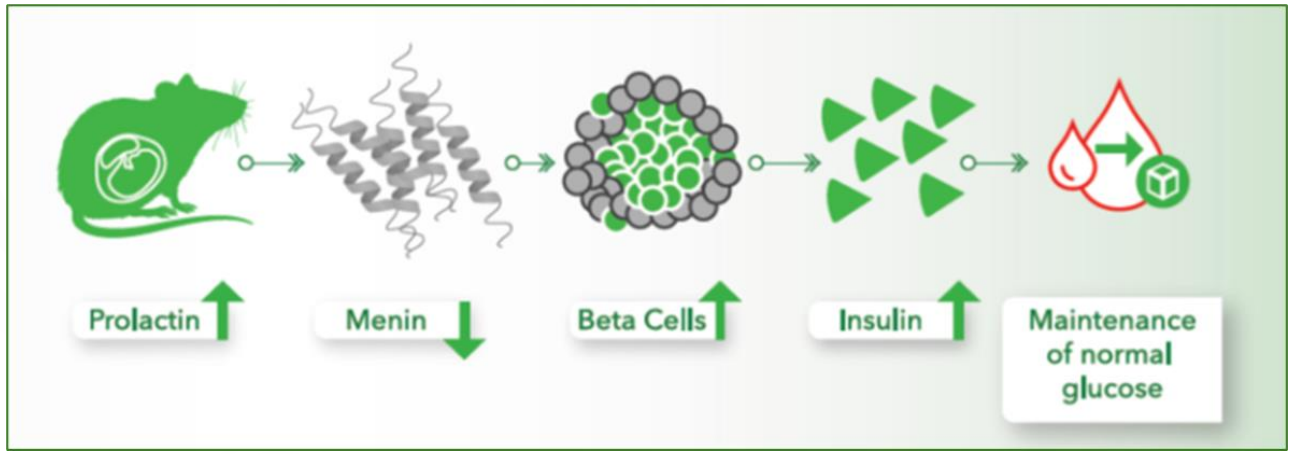
- **Menin is a scaffold protein** with multiple functions, including the **regulation of gene transcription and cellular signaling**
- Through interacting with its binding partners, menin acts as an important regulator of glycemic control, whereby **inhibition of menin activity enhances beta cell proliferation and function**



Physiologic states associated with beta cell regeneration

Menin is downregulated by prolactin during pregnancy allowing for beta cell replication and prevention of gestational diabetes

- In 2007, Stanford University researchers found that menin regulated adaptive islet growth in pregnant mice
- Prolactin, a hormonal regulator of pregnancy, repressed beta cell menin levels and stimulated beta cell proliferation



Science
AAAS

Menin Controls Growth of Pancreatic β-Cells in Pregnant Mice and Promotes Gestational Diabetes Mellitus

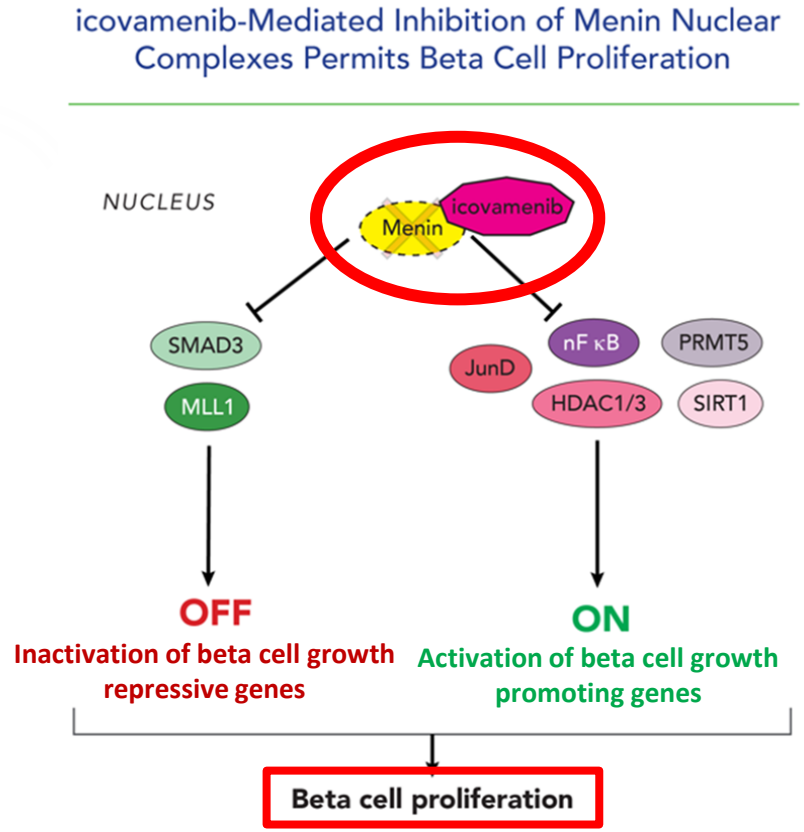
Satyajit K. Karnik,[1] Hainan Chen,[1*] Graeme W. McLean,[1*] Jeremy J. Heit,[1*] Xueying Gu,[1] Andrew Y. Zhang,[1] Magali Fontaine,[2] Michael H. Yen,[1,3] Seung K. Kim[1,3]†

During pregnancy, maternal pancreatic islets grow to match dynamic physiological demands, but the mechanisms regulating adaptive islet growth in this setting are poorly understood. Here we show that menin, a protein previously characterized as an endocrine tumor suppressor and transcriptional regulator, controls islet growth in pregnant mice. Pregnancy stimulated proliferation of maternal pancreatic islet β-cells that was accompanied by reduced islet levels of menin and its targets. Transgenic expression of menin in maternal β-cells prevented islet expansion and led to hyperglycemia and impaired glucose tolerance, hallmark features of gestational diabetes. Prolactin, a hormonal regulator of pregnancy, repressed islet menin levels and stimulated β-cell proliferation. These results expand our understanding of mechanisms underlying diabetes pathogenesis and reveal potential targets for therapy in diabetes.

Karnik SK, et al. Science. 2007;318(5851):806-9.

Icovamenib: A potent and selective covalent menin inhibitor

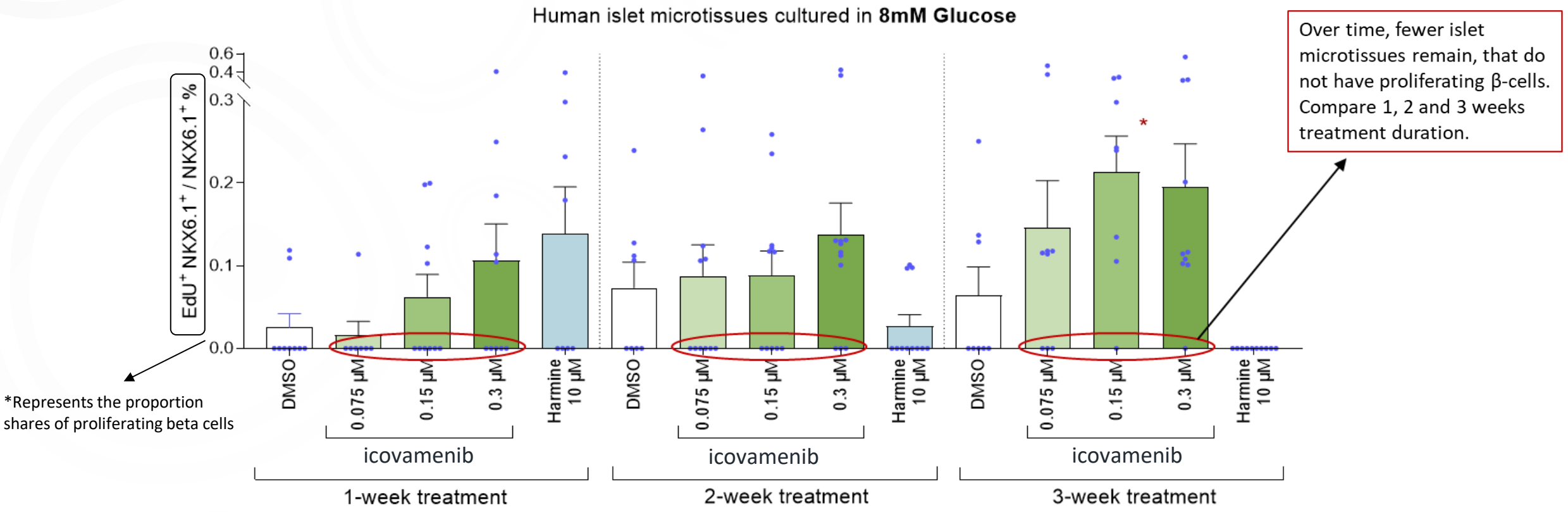
- **Icovamenib is an oral covalent menin inhibitor** in clinical development for the management of T2D and T1D
- In **preclinical models of diabetes**, icovamenib showed durable glycemic control following short-term treatment in ZDF and STZ rat models[1,2]
- In a **multiple ascending dose (MAD) study in persons with T2D**, 4 weeks of daily icovamenib improved glycemic control at Week 26 (22 weeks after the final dose) and was generally safe and well tolerated[3]



1. Butler T. et al. Diabetes. 2022; 71 (Supplement_1): 851–P
2. Somanath P. et al. Diabetes. 2022; 71 (Supplement_1): 113–LB
3. Abitbol A, et al. (ATTD 2024, March 6, 2024)

Longer dosing is predicted to generate an increase in responder rates based on human donor islet experiments

Proliferating beta cells plotted as fraction of total beta cells



Data represent mean ±SEM of 1 donor with n = 9-12 technical replicates.
One-way ANOVA with Dunnett's post hoc test rel. to DMSO control. *p < 0.05, **p < 0.01, ***p < 0.001

Key eligibility criteria and study design (Multiple Ascending Dose Cohort)

Eligibility Criteria

- T2D, age 18-65 yr
- Duration of diabetes 15 yr or less
- HbA_{1c} 7.0 to 10.0%
- BMI 25 to 40 kg/m^2
- Treated with diet/exercise ± up to 3 antihyperglycemic agents (insulin secretagogues and insulin excluded)

Primary Objective

- Safety and tolerability of icovamenib

Key Secondary Objectives

- Impact on glycemic parameters
- Changes in beta-cell function
- PK exposure of Icovamenib

COVALENT-111 T2D MAD Cohorts

50 mg QD, without food
x 4 weeks

100 mg QD, without food
x 4 weeks

100 mg QD, with food
x 4 weeks

200 mg QD, without food
x 4 weeks

200 mg QD, with food
x 4 weeks

Icovamenib (n=10) and placebo (n=2) per cohort*

*200 mg with food cohort enrolled n=2 participants

100 mg BID, without food
x 4 weeks

200 mg QD x 2 weeks	**400 mg QD** x 2 weeks

without food

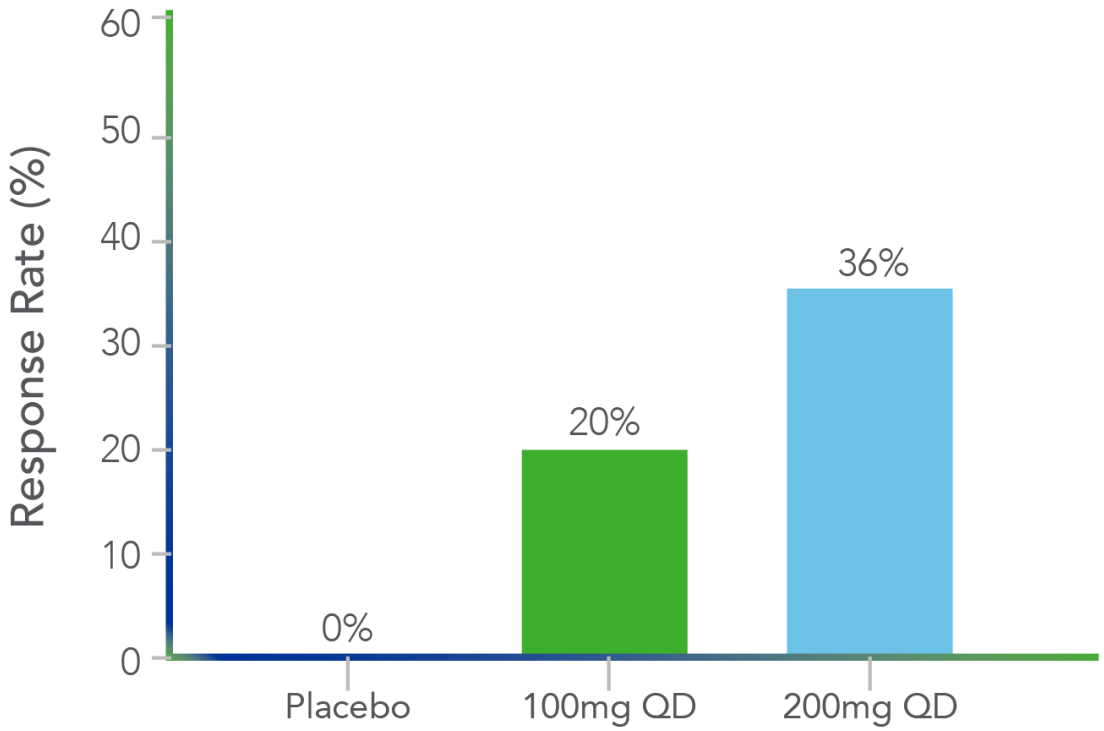
4 weeks dosing + 22 weeks follow-up

https://clinicaltrials.gov/study/NCT05731544

Proportion of patients with ≥1.0% HbA_{1c} reduction at Week 26

Icovamenib demonstrated dose-dependent response

Response Rate, 100mg and 200mg



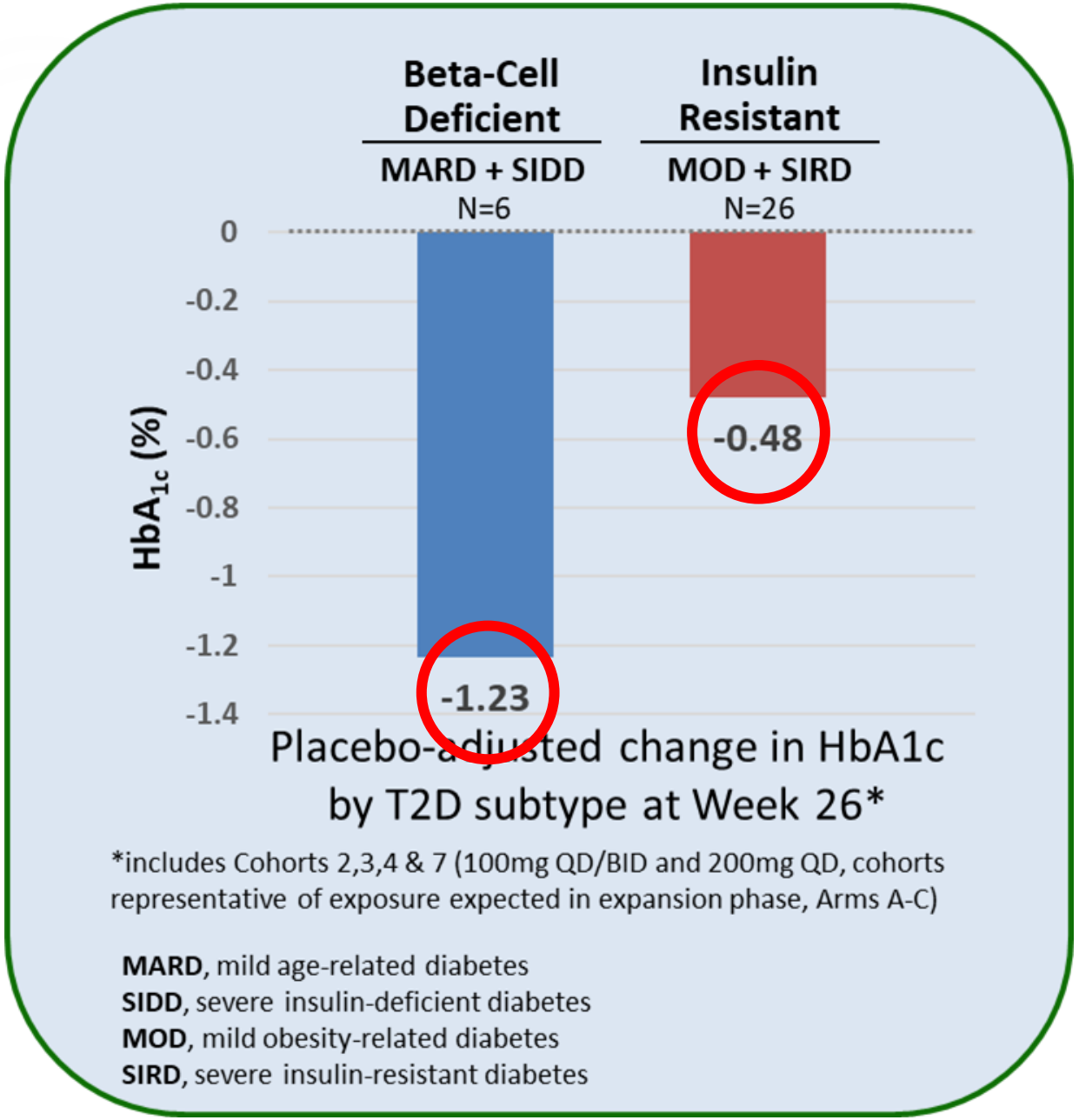
At Week 26 (22 weeks after 4 weeks icovamenib), **≥1.0% HbA_{1c}** reduction in:

- **20%** of patients across **100 mg** cohorts
- **36%** of patients across **200 mg** cohorts
- Across **100 and 200 mg** cohorts (**N=31**)
  - **39%** (12/31) had **≥0.5%** HbA_{1c} reduction at Week 26 (mean HbA_{1c} reduction 1.3%)
  - **26%** (8/31) had **≥1.0%** HbA_{1c} reduction at Week 26 (mean HbA_{1c} reduction 1.5%)

Abitbol A, et al. (ATTD 2024, March 6, 2024)

COVALENT-111 MAD:

HbA1c change at Week 26 by T2D subtype



Frías JP, et al. (ATTD-Asia 2024, November 19, 2024)
Subtyping per Ahlqvist E, et al. Lancet Diabetes Endocrinol. 2018;6:361-369

COVALENT-111 Expansion: Up to 12 weeks icovamenib with 40 weeks of follow-up

COVALENT-111 T2D MAD Cohorts

50 mg QD, without food x 4 weeks
100 mg QD, without food x 4 weeks
100 mg QD, with food x 4 weeks
200 mg QD, without food x 4 weeks
200 mg QD, with food x 4 weeks
100 mg BID, without food x 4 weeks

200 mg QD x 2 weeks	**400 mg QD** x 2 weeks

without food

Part 1: MAD Cohorts
4 weeks dosing + 22 weeks follow-up

COVALENT-111 T2D Dose Expansion

- Adults (18-65 yo) with T2D (<7 yr T2D duration)
- HbA_{1c} 7.0-10.5%; BMI 25-40 kg/m^2
- Treated with up to 3 antidiabetic agents
- N=72 participants per arm (3:1 ratio, Icovamenib:PBO)

Arm A*	**100 mg daily** x 8 weeks	**Placebo** x 4 weeks
Arm B	**100 mg daily** x 12 weeks	
Arm C	**100 mg daily** x 8 weeks	**200 mg daily** x 4 weeks

*Redosing as required at Week 22 for 4 weeks (Arm A only)

Part 2: Dose Expansion
8-12 weeks dosing + 40 weeks follow-up

HbA_{1c}, glycated hemoglobin; MAD, multiple ascending dose; QD, once daily; T2D, type 2 diabetes

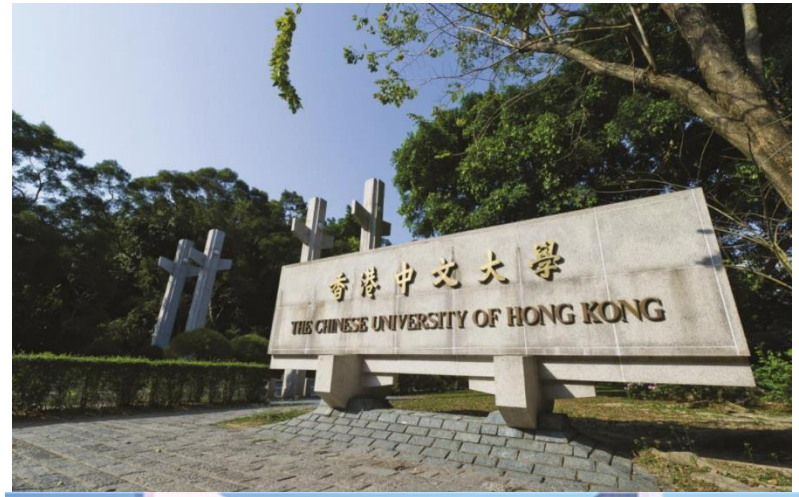
Icovamenib – An investigational agent focusing on beta cell health

Icovamenib: First-in-Class Agent with a Differentiated Profile

- Oral Small Molecule
- Complementary Agent to Available Diabetes Therapies
- Short-Treatment Duration
- Well-Tolerated Profile To Date
- Disease-Modifying Potential Addressing the Root Cause of Diabetes
- Durable Glycemic Control
- Broad Application Across Persons with Diabetes

Diabetes: Focus on subgroups and phenotypes

Juliana Chan
Professor of Medicine and Therapeutics
Hong Kong Institute of Diabetes and Obesity
The Chinese University of Hong Kong



International Diabetes Federation
Centre of Excellence in Diabetes Care
2022-23

Disclosure

- Consultancy, lecture fees and research support from
  - Astra Zeneca, Bayer, Biomea Fusion, Boehringer Ingelheim, Celltrion, Powder Pharmaceuticals, Hua Medicine, Lilly, Merck, MSD, Novo Nordisk, Novartis, Sanofi, Pfizer, Viatris
- CEO (pro-bono), Asia Diabetes Foundation
- Founding director, GemVCare

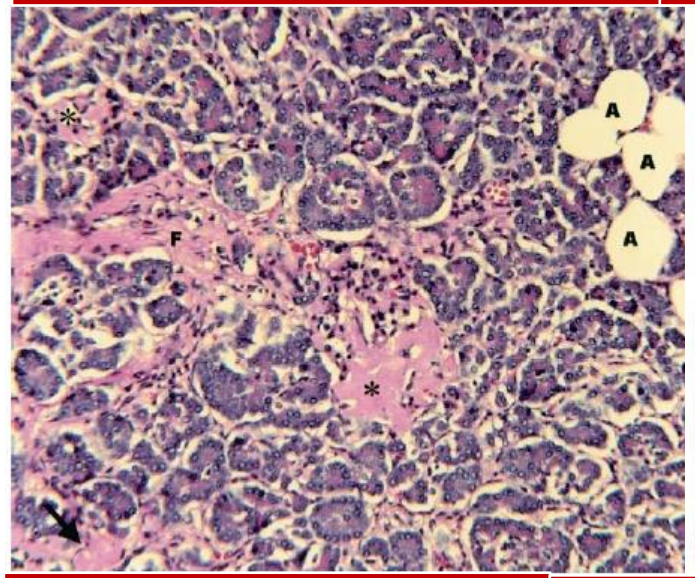
Outline

- Complex aetiologies of type 2 diabetes
- Insulin secretion versus insulin resistance/sensitivity
- Importance of pancreatic islets in diabetes
- Heterogeneity of phenotypes
- Subtypes of diabetes and Inter-ethnic differences
- Early treatment to preserve beta cell function and change disease trajectory

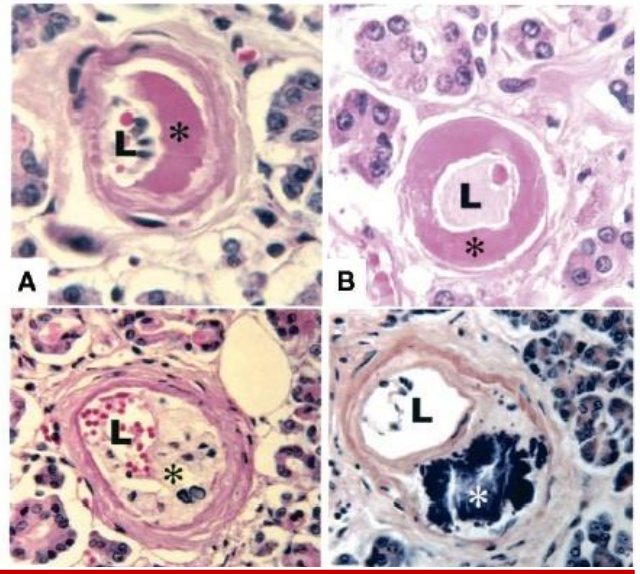
Pancreatic abnormalities in autopsy cases

Insulin is the key hormone for processing energy for utilization or storage (fat or glycogen)

Islet amyloid deposits

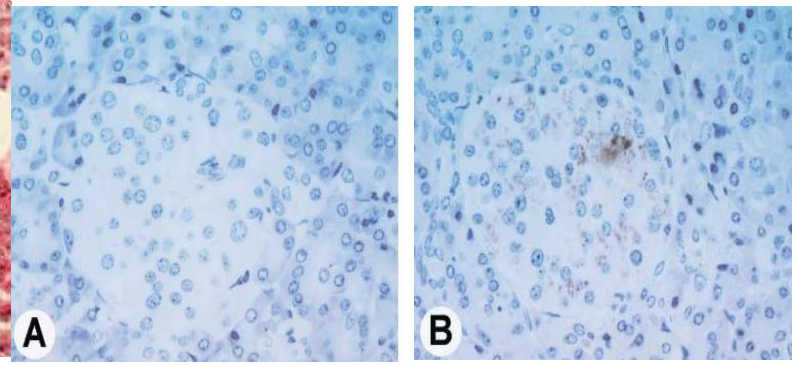


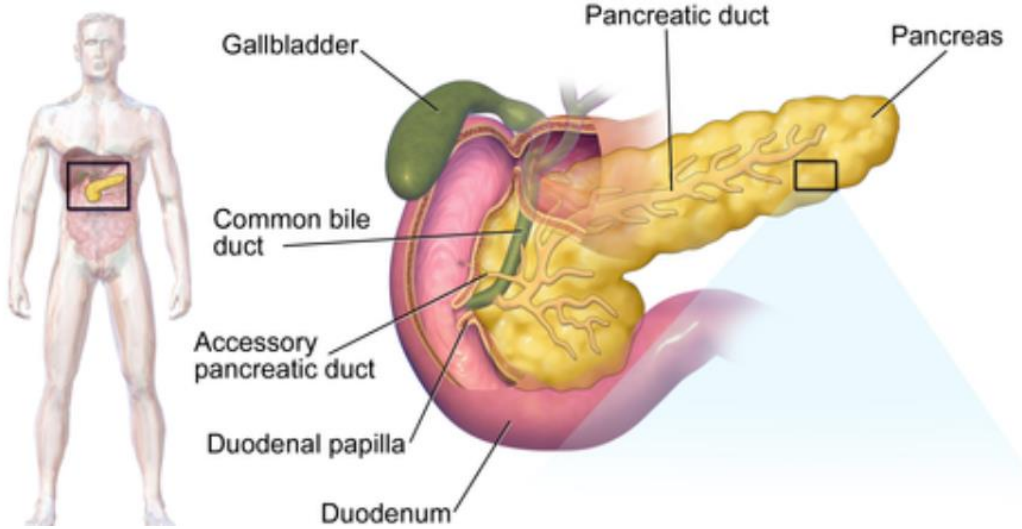
Pancreatic arteriosclerosis

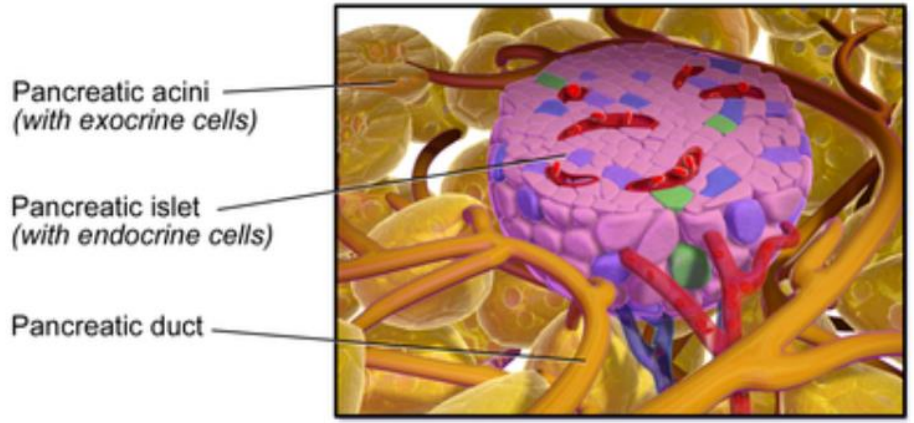


Fat infiltration

Oxidative stress damaged proteins

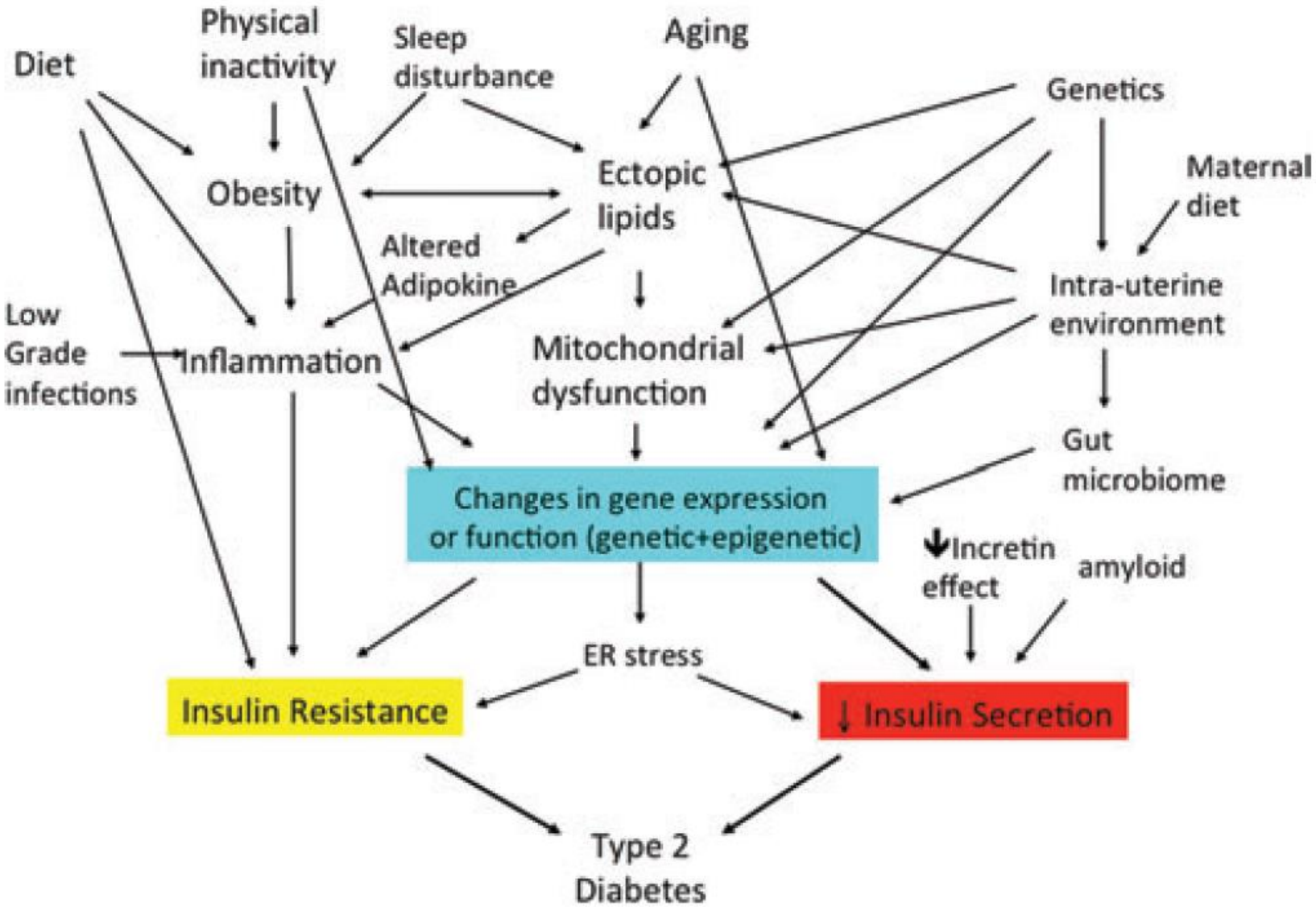






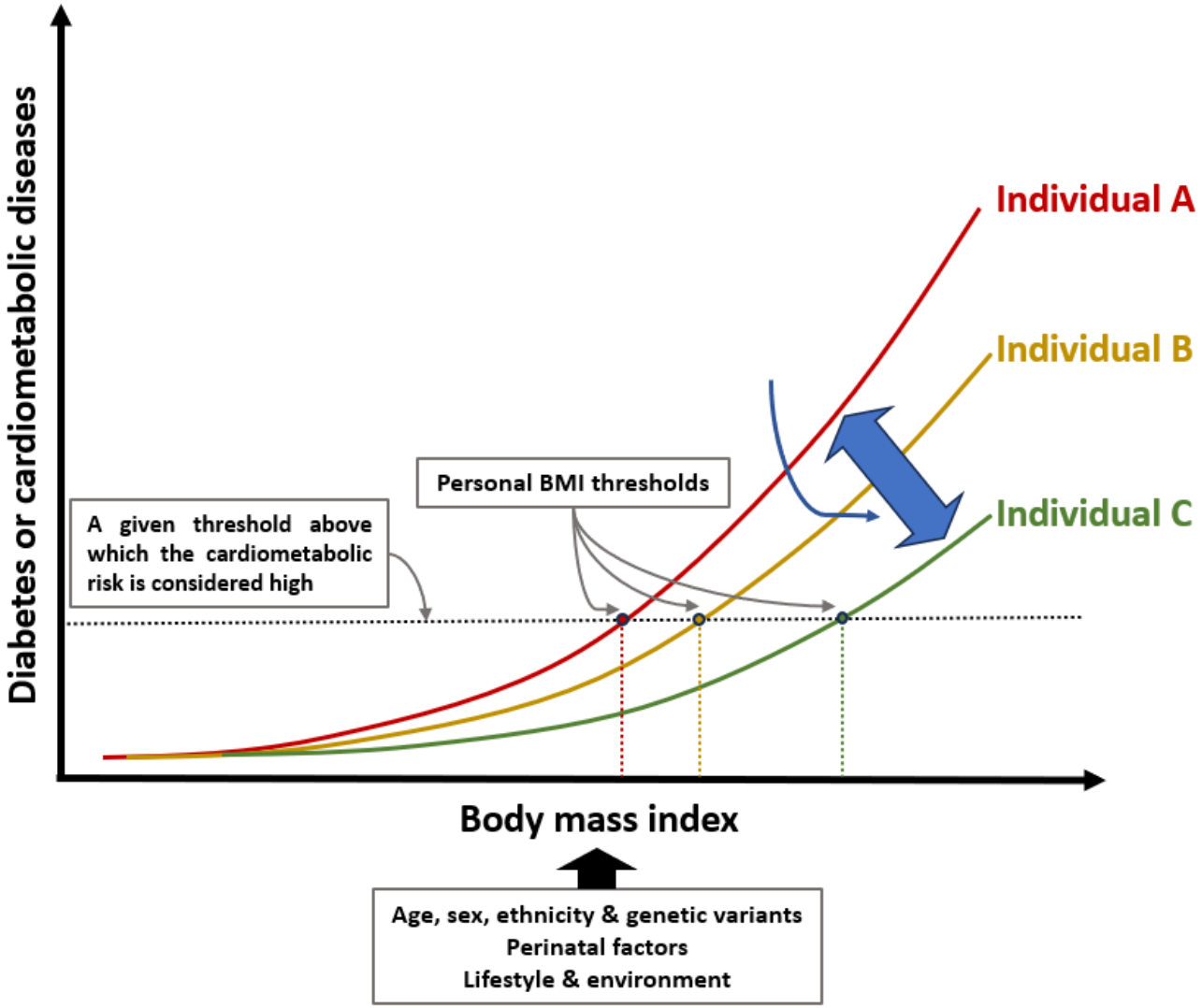
Sakuraba H, et al. Diabetologia 2002; Zhao HL, et al. Diabetes 2003

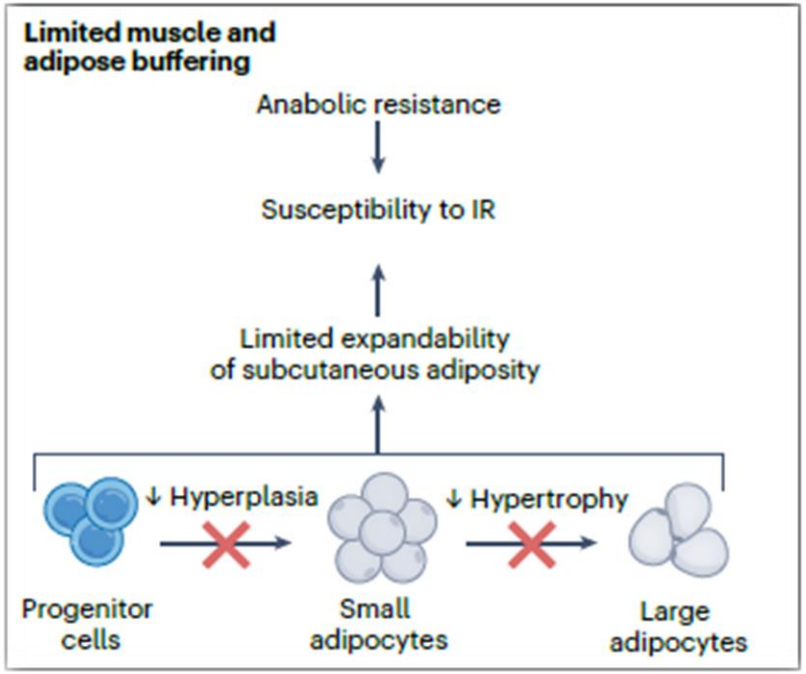
Multidimensional nature of type 2 diabetes

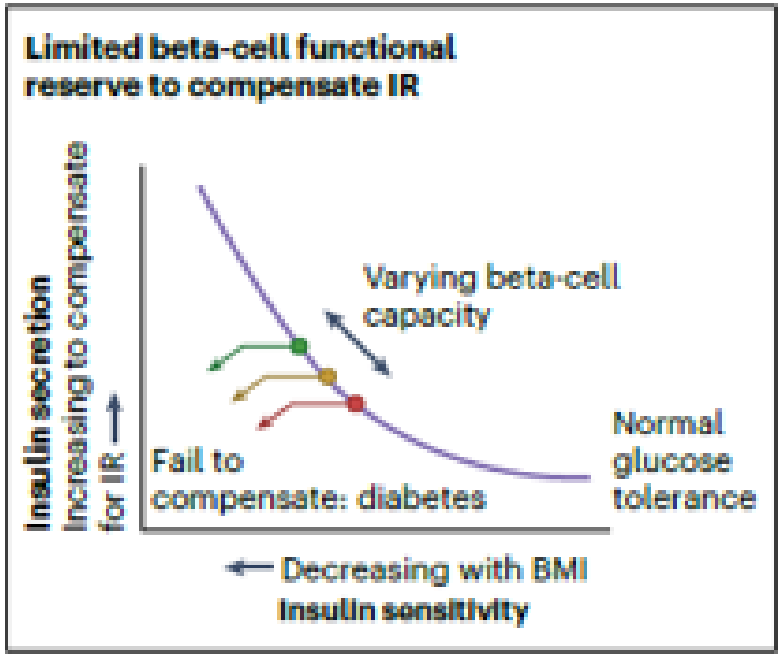


Ma R and Chan JC Ann. NY Acad Sci 2023

Personal threshold for obesity for diabetes risk

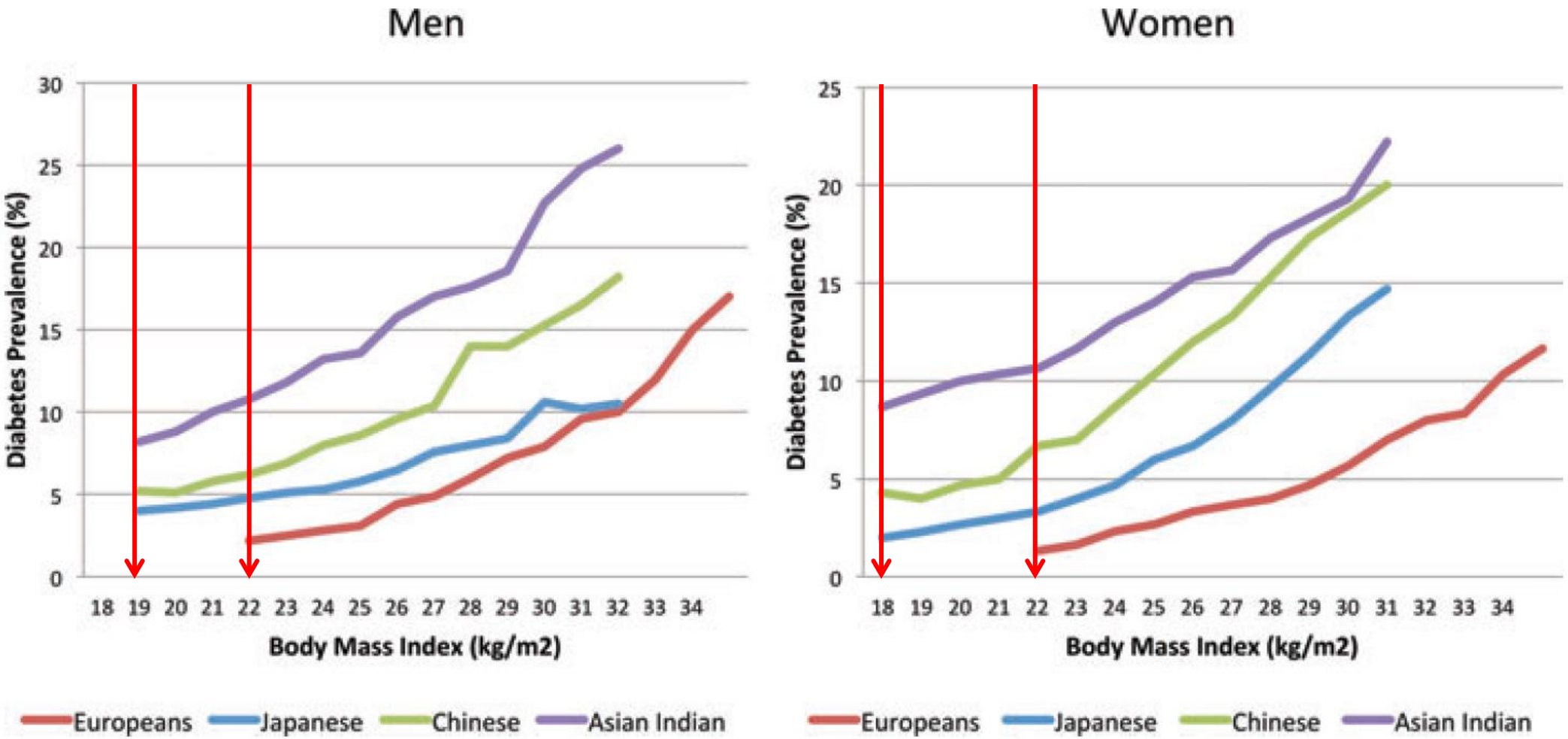






O C-K et al. Nature Metabolism 2024

Higher risk of diabetes for same BMI in non-European populations



Ma R and Chan JC Ann. NY Acad Sci 2023

Asian phenotype
A phenotype in transition

Low body mass index
Increased body fat, especially visceral fat
High rate of central obesity and metabolic syndrome
Increased inflammatory markers
Insufficient beta cell response to counter insulin resistance
Low rate of autoimmune type 1 diabetes
High rate of young-onset type 2 diabetes
High rate of childhood obesity
High rate of gestational diabetes
Social disparity and psychosocial stress
High rate of renal disease
High rate of cancer especially those with viral causes, e.g. liver cancer

Chan JC et al DRCP2015, Chan JC et al JAMA 2019

NHANES: Obesity only explains 40% of population attributable fraction (PAF) of diabetes risk in multi-ethnic groups

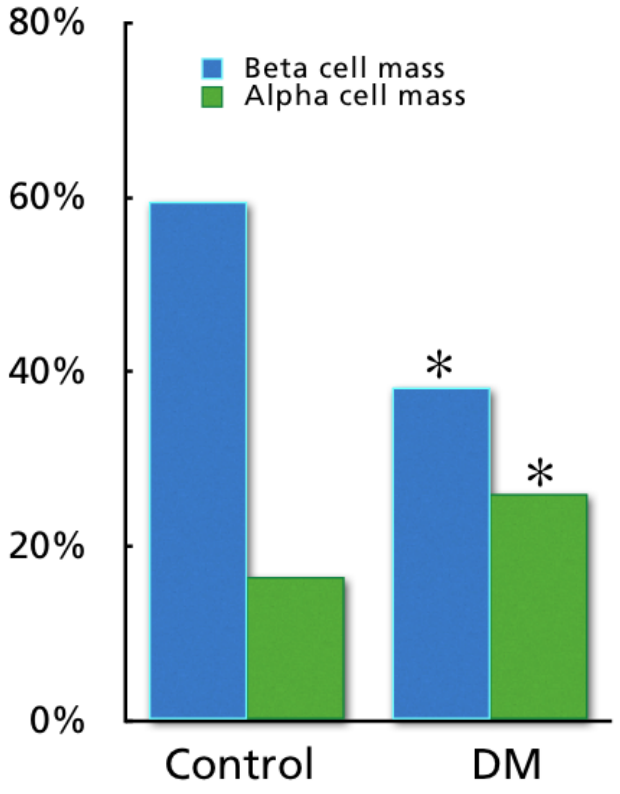
	Unadjusted population attributable fraction (PAF) (95% CI)	Adjusted population attributable fraction (PAF) (95% CI)
Overall	0.44 (0.41–0.47)	0.41 (0.36–0.46)
Men		
NHW	0.34 (0.32–0.37)	0.36 (0.24–0.47)
NHB	0.34 (0.30–0.38)	0.30 (0.19–0.40)
MA	0.51 (0.46–0.55)	0.38 (0.25–0.50)
Women		
NHW	0.56 (0.53–0.60)	0.53 (0.43–0.63)
NHB	0.42 (0.38–0.46)	0.39 (0.24–0.55)
MA	0.41 (0.36–0.47)	0.42 (0.21–0.63)

NHANES, National Health and Nutrition Examination Survey
MA, Mexican American
NHB, non-Hispanic Black
NHW non-Hispanic White
PAF adjusted for age, study site, physical activity, diet, annual family income, and education level.

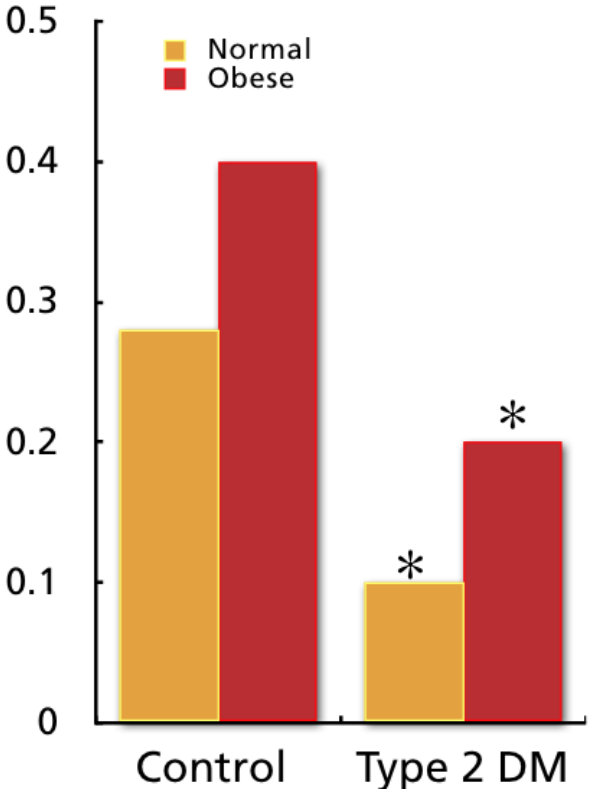
Cameron NA et al JAHA 2021

Loss of beta cell mass is a hallmark of T2D

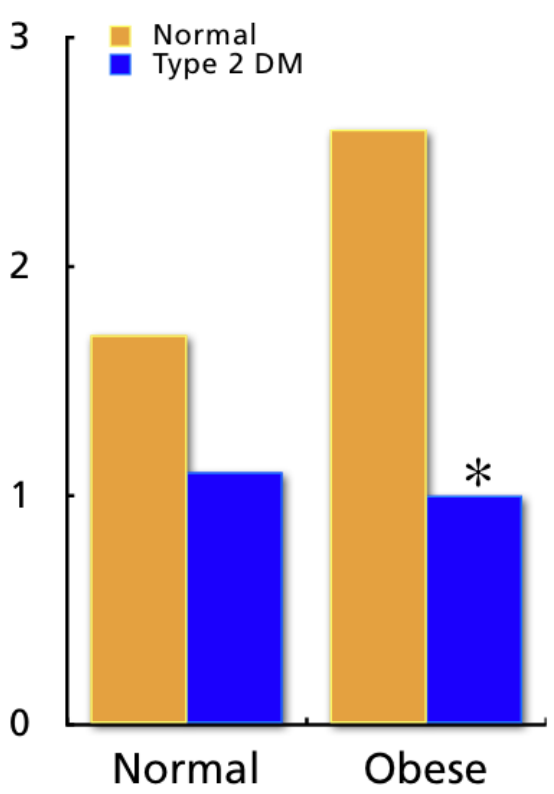
2003
Beta-cell, alpha-cell mass[1]



1985
Beta-cell volume[2]

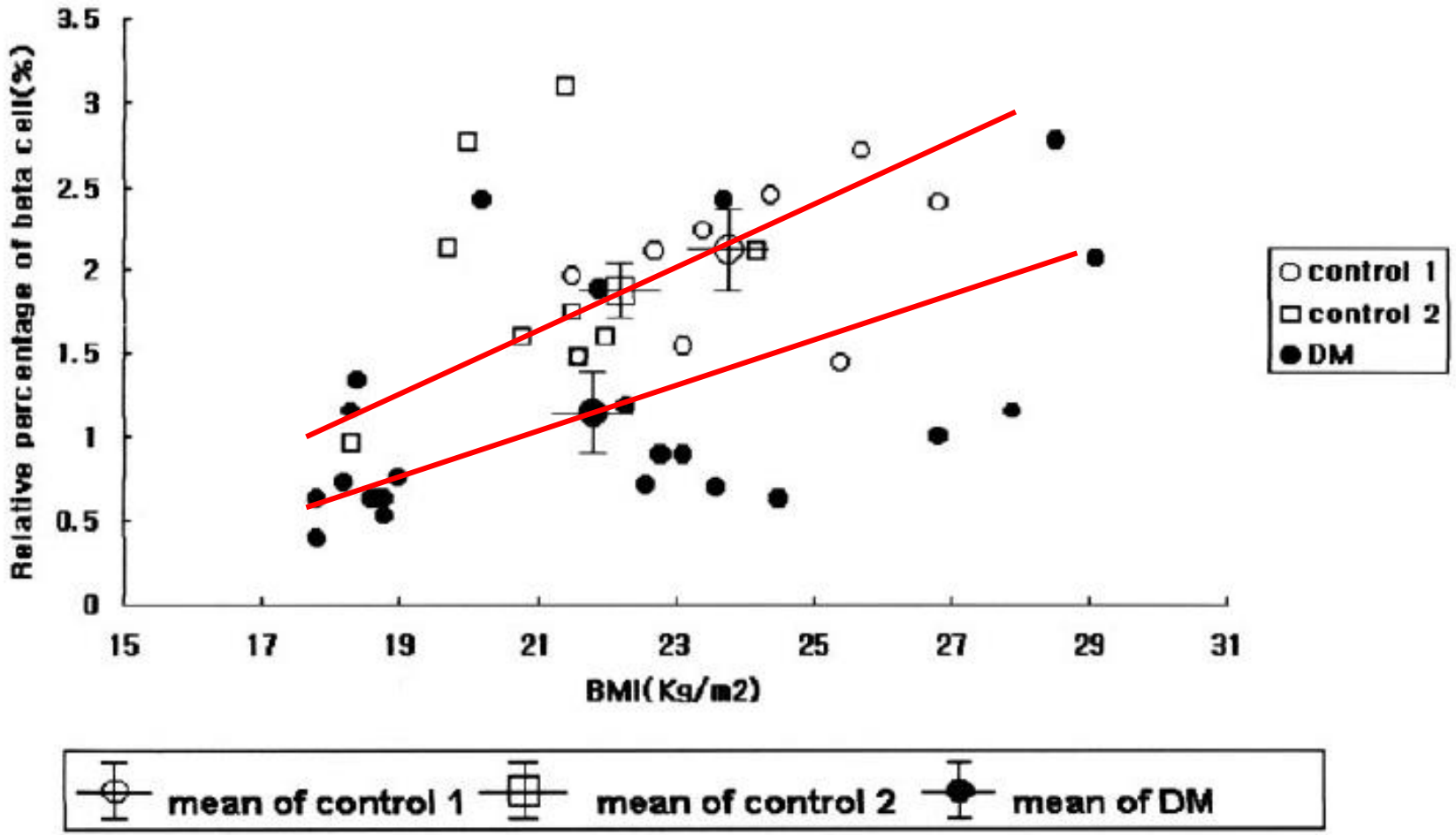


2003
Beta-cell volume[3]



[1]Yoon KH et al. J Clin Endocrinol Metab 2003; [2]Kloppel G et al. Surv Synth Path Res 1985; [3]Butler AE et al. Diabetes 2003

Correlation between BMI and beta cell mass in Korean autopsy cases with and without diabetes

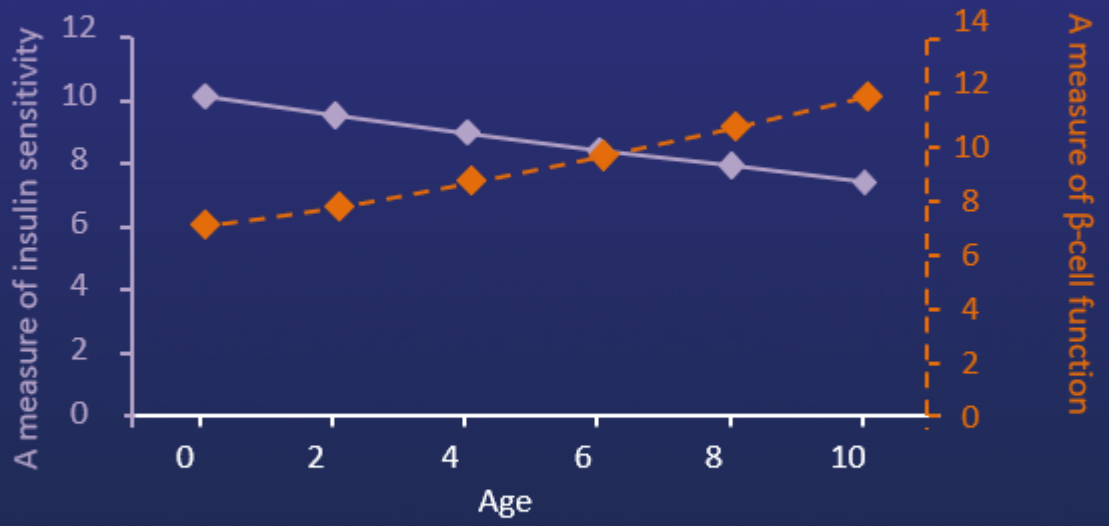


Yoon KH et al JCEM 2003

Insufficient insulin response to overcome reduced insulin insensitivity leads to diabetes in Koreans

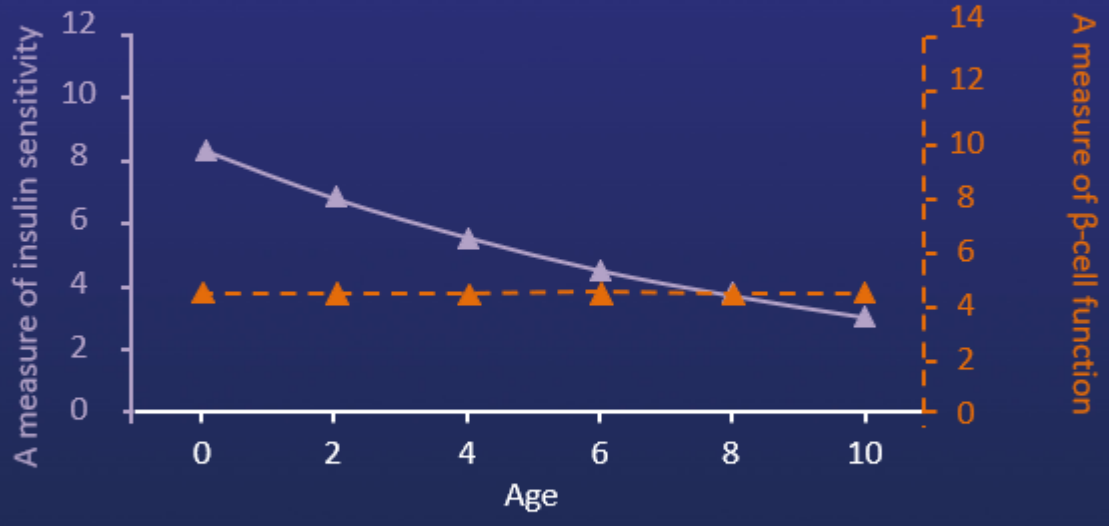
- A large-scale, 10-year follow-up, prospective analysis of 4106 participants from Korea examined β-cell function and insulin sensitivity in T2DM pathogenesis

Non-progressors (healthy)



Throughout the study period, insulin sensitivity dropped with age. In non-progressors, this is compensated with improved β-cell function

Progressors (T2DM)

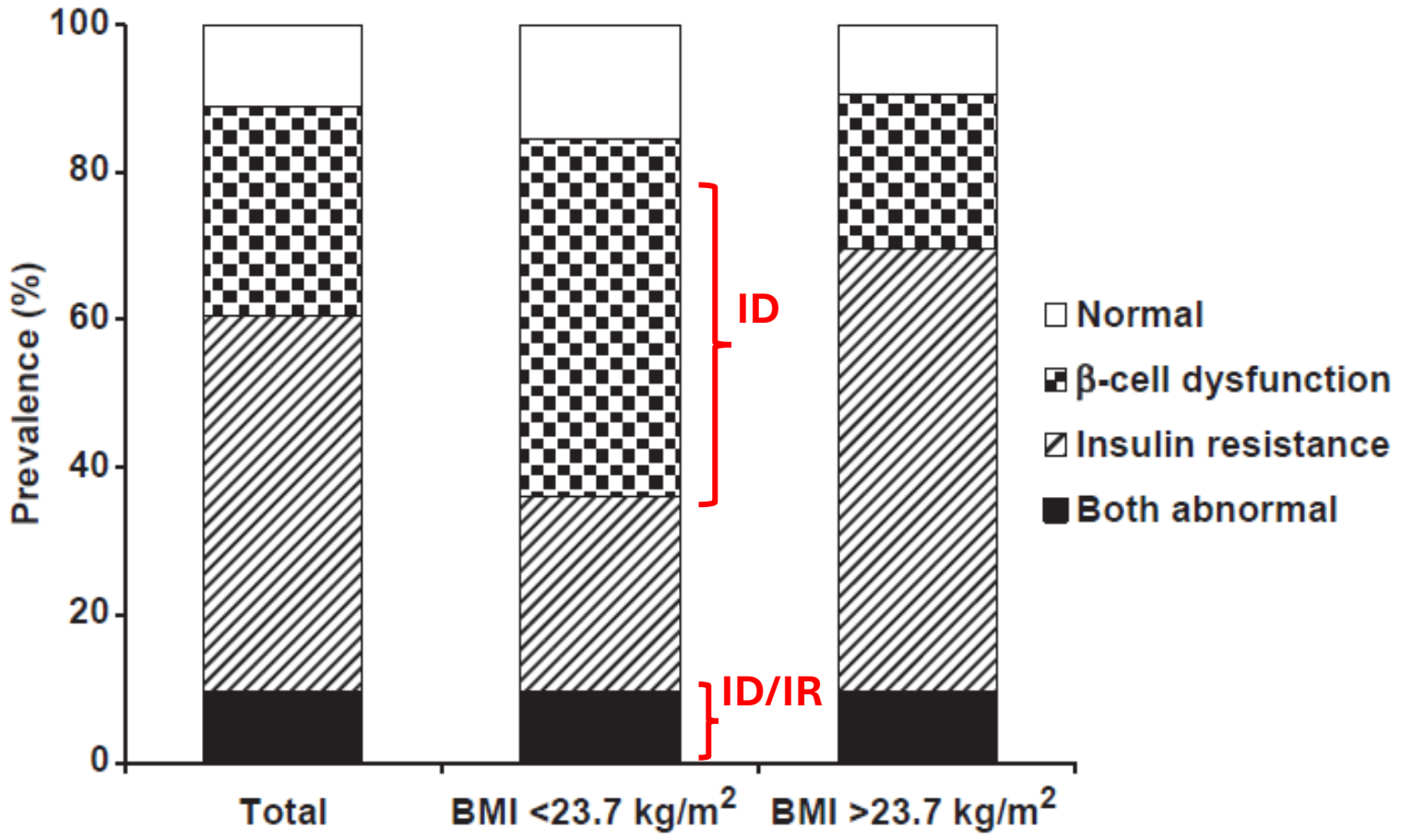


In patients that progressed to diabetes, β-cell function did not increase

Ohn JH et al TLDE 2016

BMI, β cell dysfunction & diabetes in Koreans

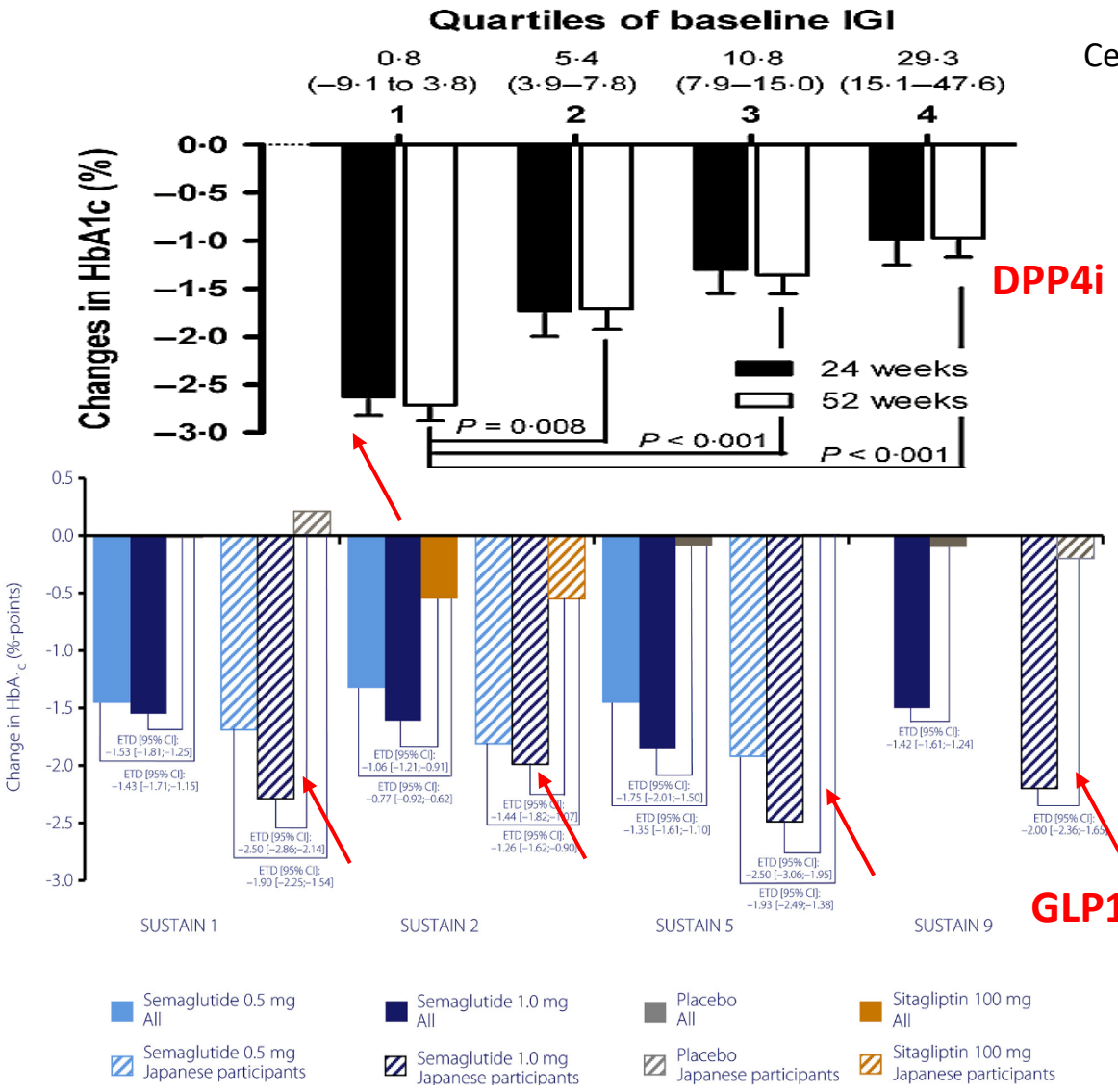
17,878 Korean adults (age 20-79 years)
FU 3.5 years, 4.1% (n=732) developed diabetes



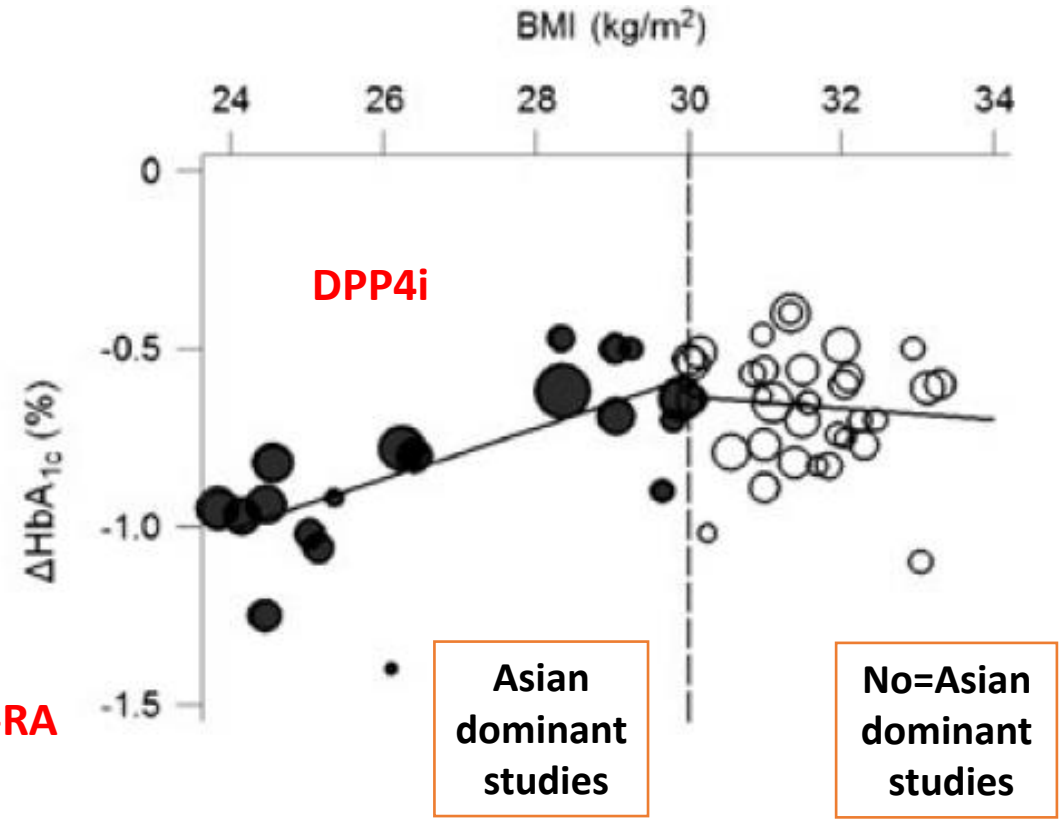
Kim CH et al et al Diabetic Med 2013

People with low BMI and beta-cell function, notably Asians, respond well to DPP4i and incretin-based therapy

Cersosimo, E et al. Diabetes Obes Metab. 2018
Lim S et al. Clin Endocrinol 2012

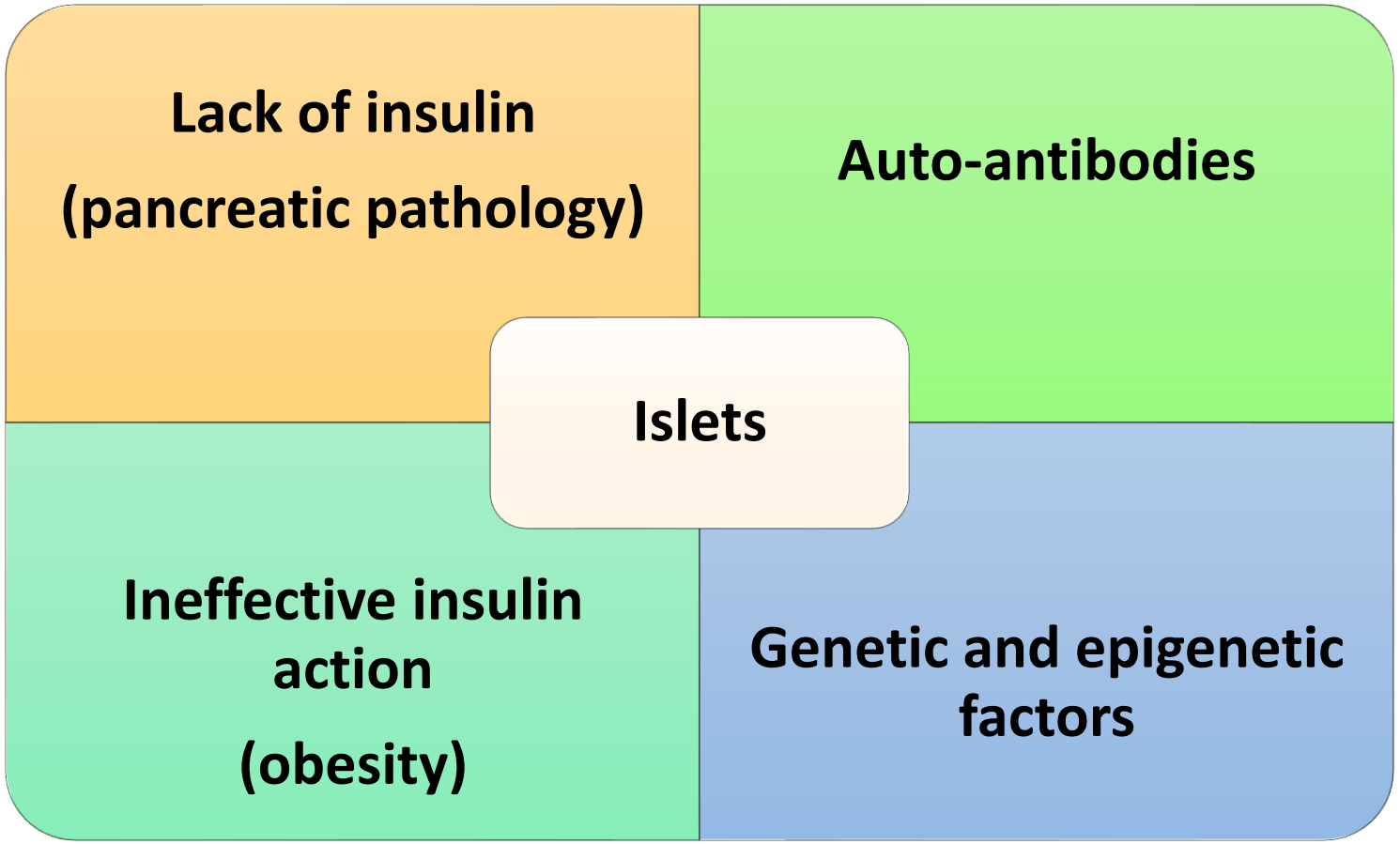


Kim YG et al Diabetologia 2014



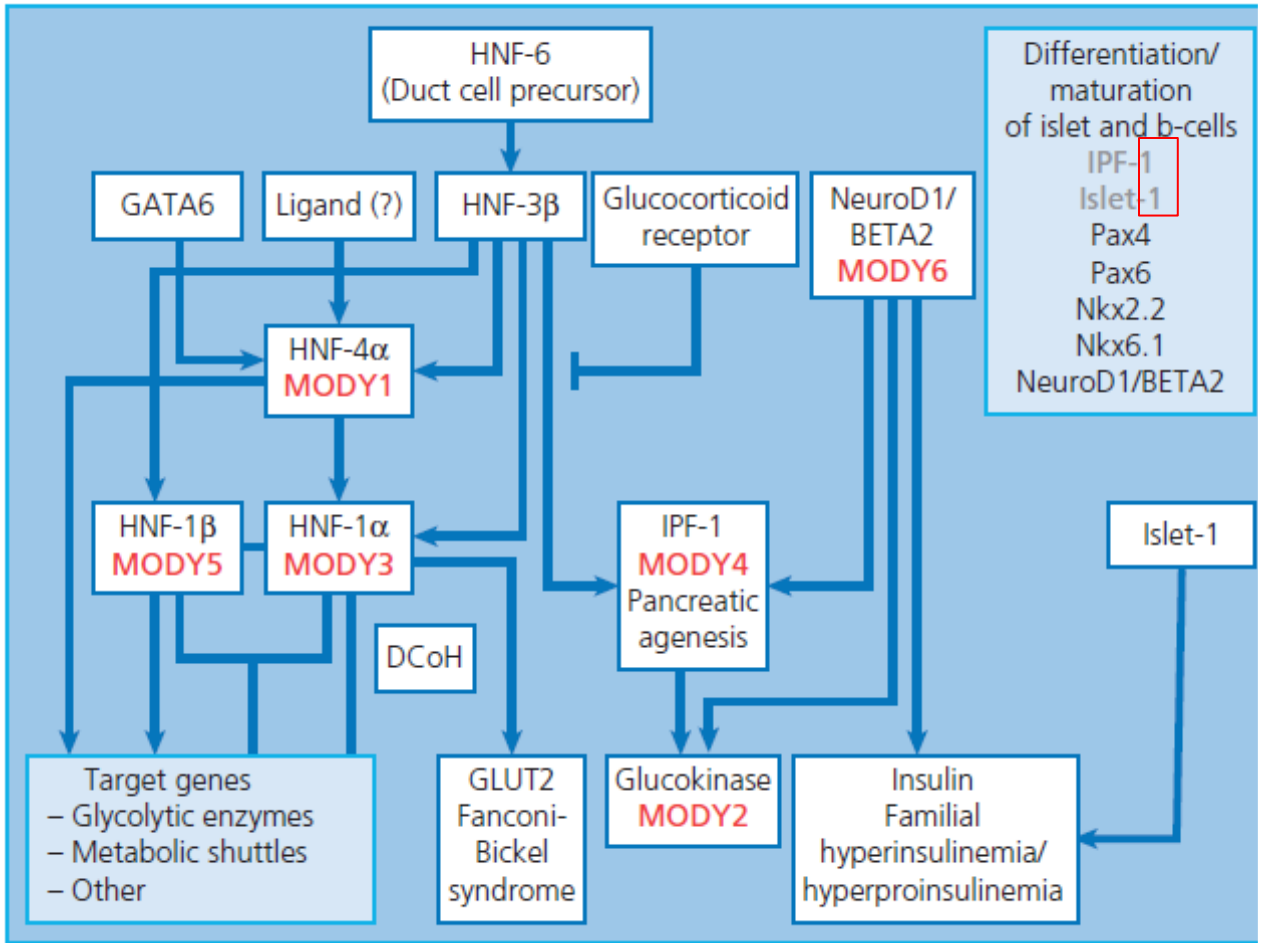
Araki E et al JDI 2022

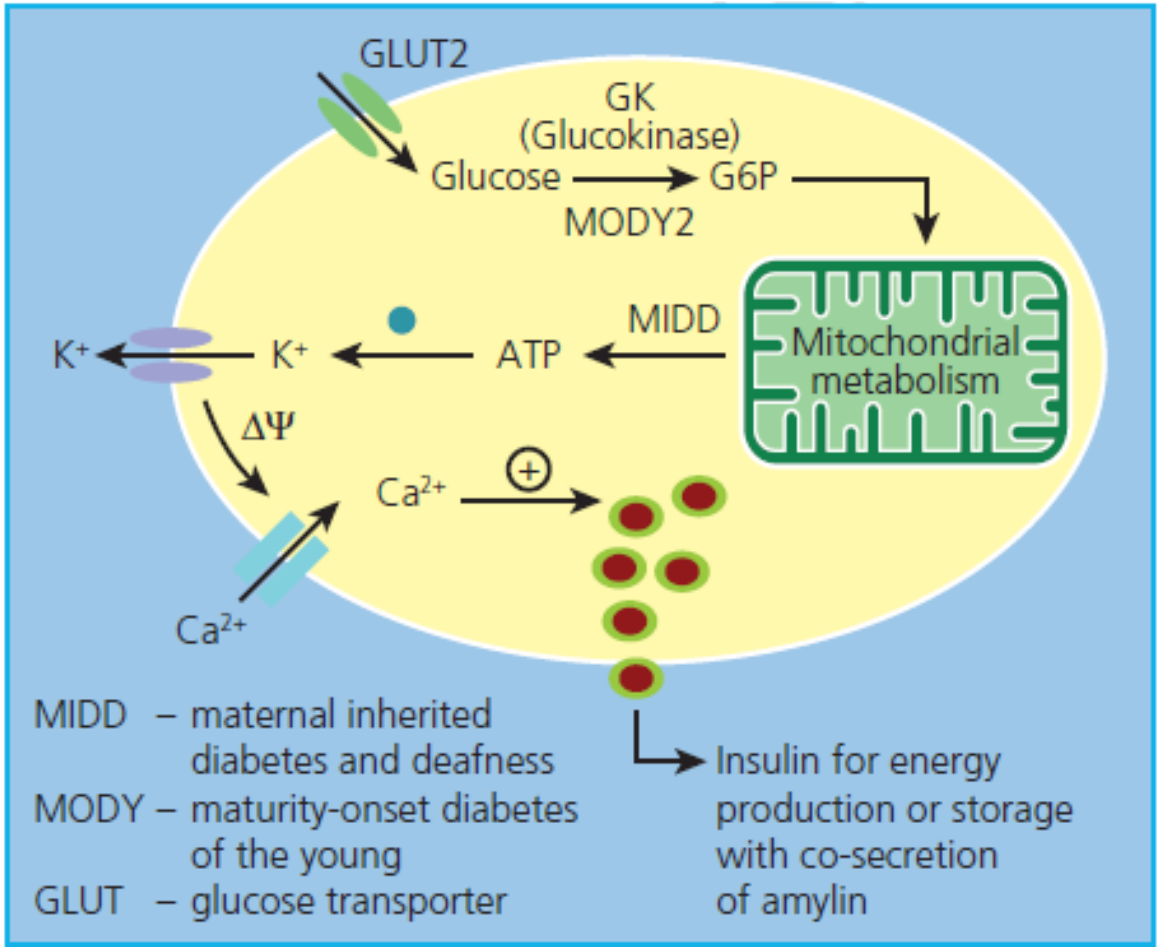
Why do beta-cell fail?



Luk A et al Diabetes Care 2019
Fan B et al DMRR 2021

Genetic factors implicated in beta cell biology from differentiation to glucose sensing to insulin secretion

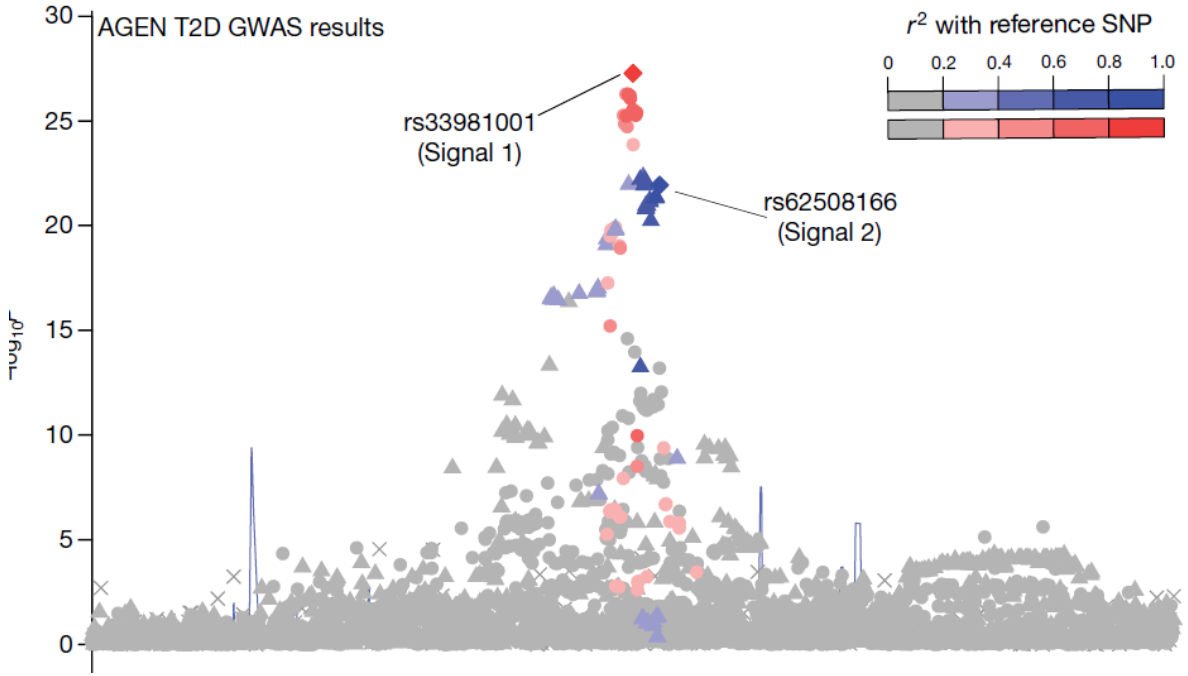


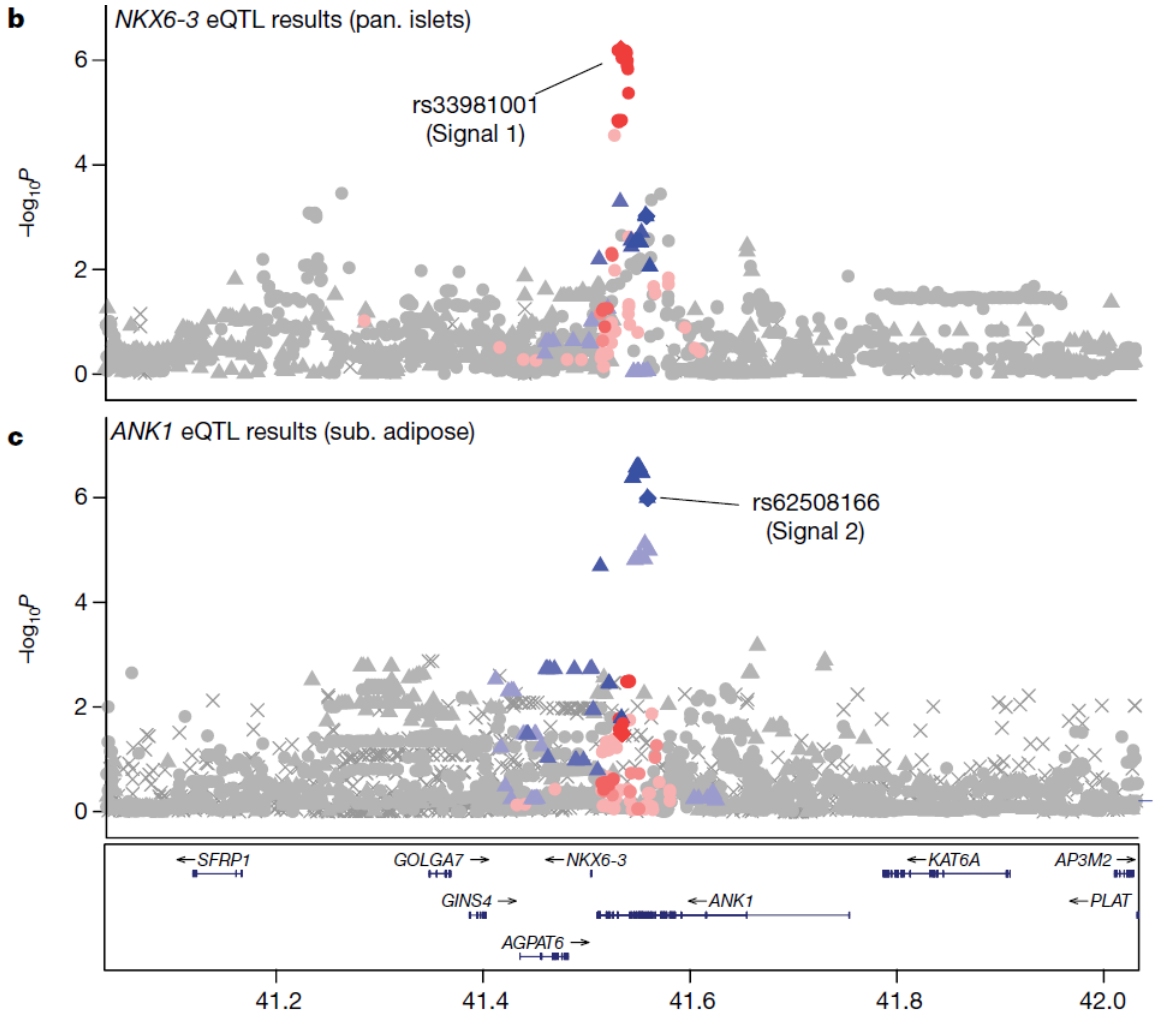


Kong AP et al Textbook of Diabetes 2017

Genome wide association studies (GWAS) discover hundreds of loci associated with pancreatic, adipose and muscle tissue biology

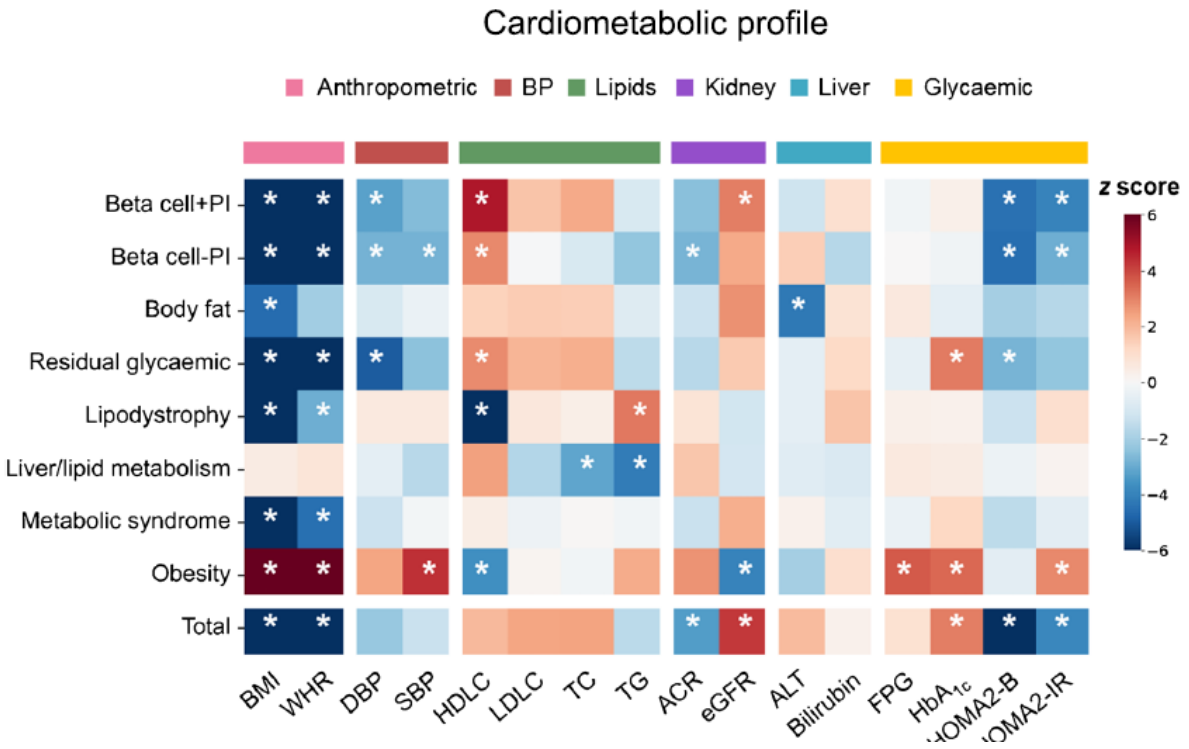
Identification of type 2 diabetes loci in 433,540 East Asian individuals



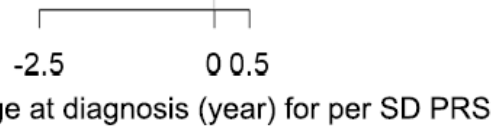


Spracklen CN et al Nature 2020

T2D pathway-specific polygenic risk scores associated with earlier age of diagnosis and clustering of cardiometabolic risk factors

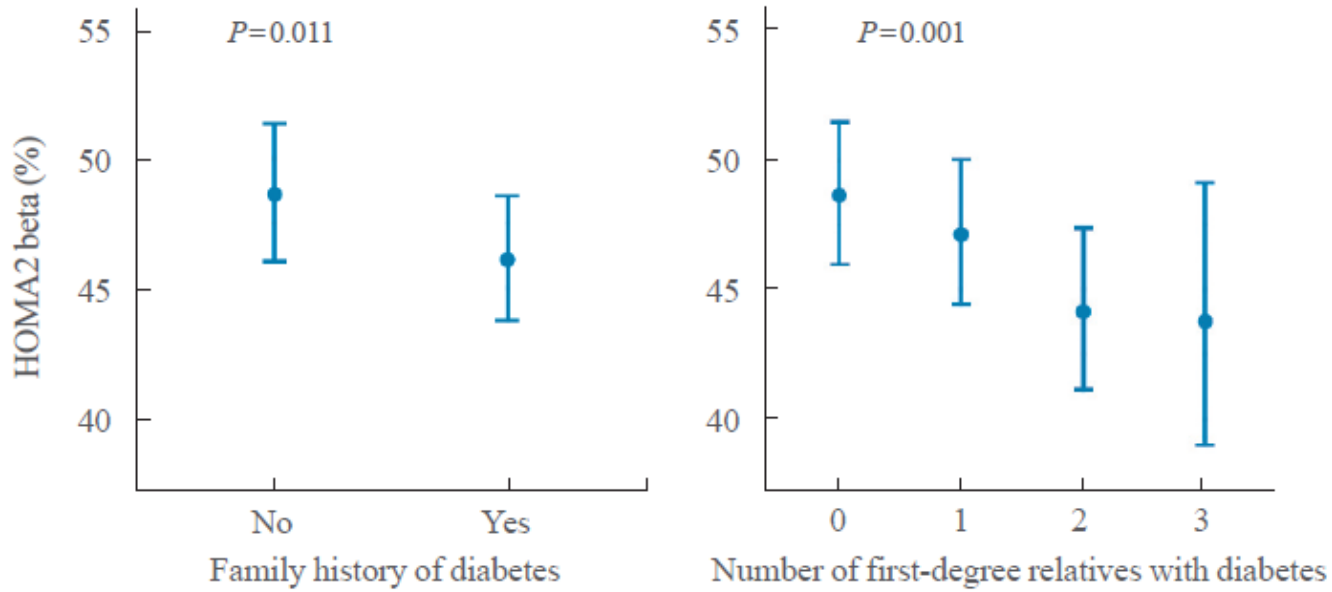


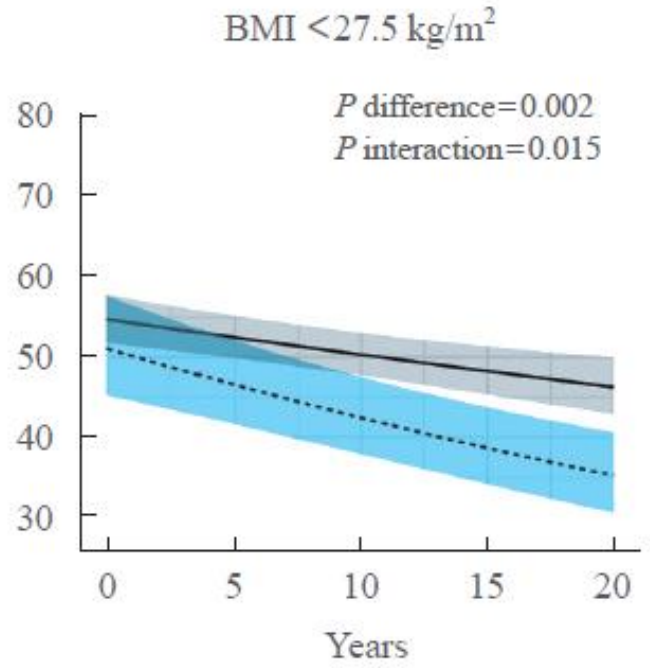
PRS (per SD)	No. of SNPs	β	95% CI	*p*
Beta cell+PI	91	-0.89	(-1.06, -0.72)	<0.0001*
Beta cell-PI	89	-0.74	(-0.91, -0.57)	<0.0001*
Body fat	273	-0.65	(-0.99, -0.31)	0.0002*
Residual glycaemic	389	-1.14	(-1.31, -0.97)	<0.0001*
Lipodystrophy	45	-0.48	(-0.66, -0.31)	<0.0001*
Liver/lipid metabolism	3	-0.17	(-0.43, 0.08)	0.1863
Metabolic syndrome	166	-0.50	(-0.79, -0.21)	0.0006*
Obesity	233	-0.77	(-0.95, -0.58)	<0.0001*
Total	1289	-1.97	(-2.14, -1.8)	<0.0001*



Yu G et al Diabetologia 2024

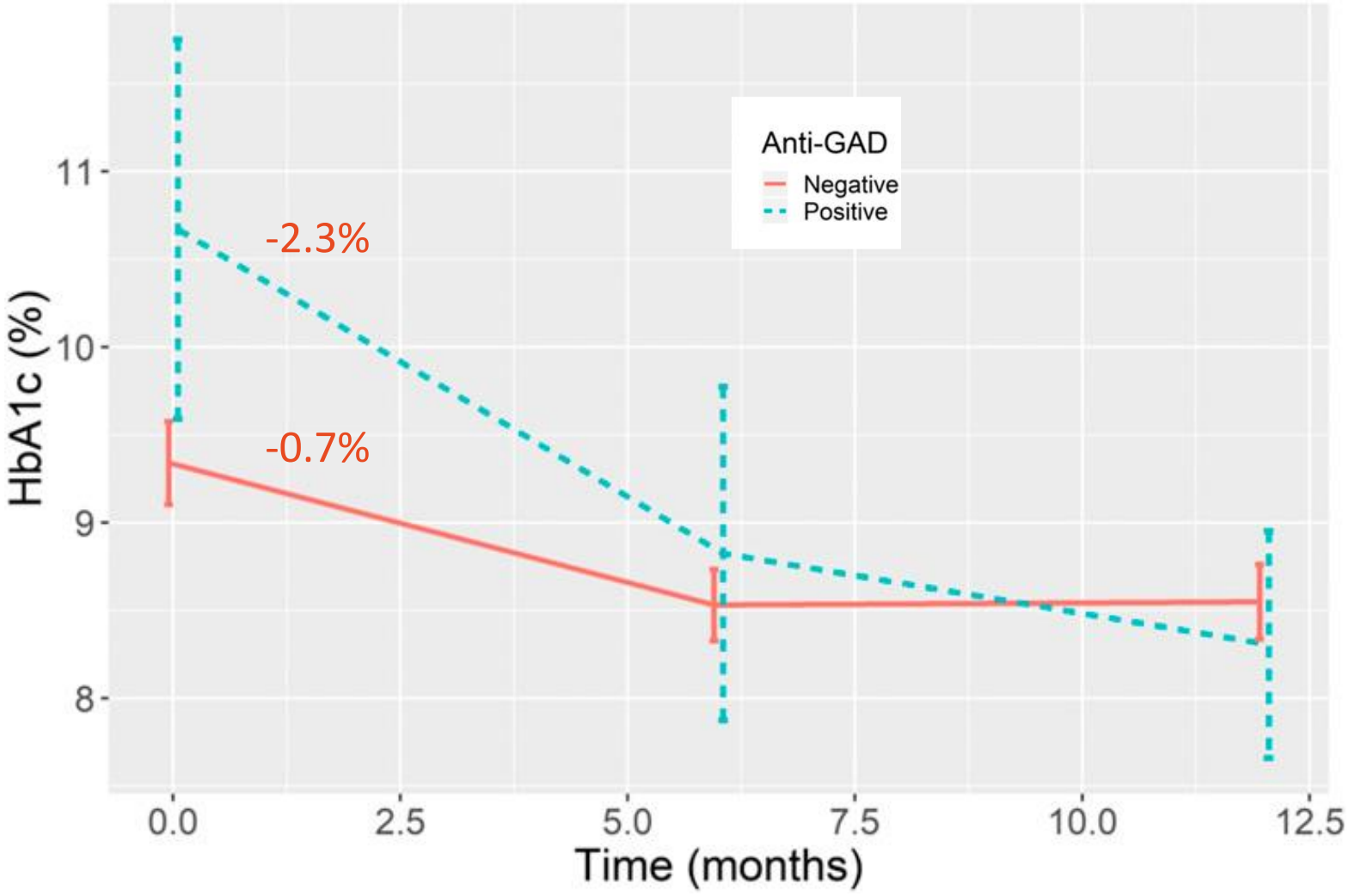
More rapid rate of decline in beta-cell function in familial-YOD versus late onset diabetes especially in lean people





Fan Y et al DRCP 2024

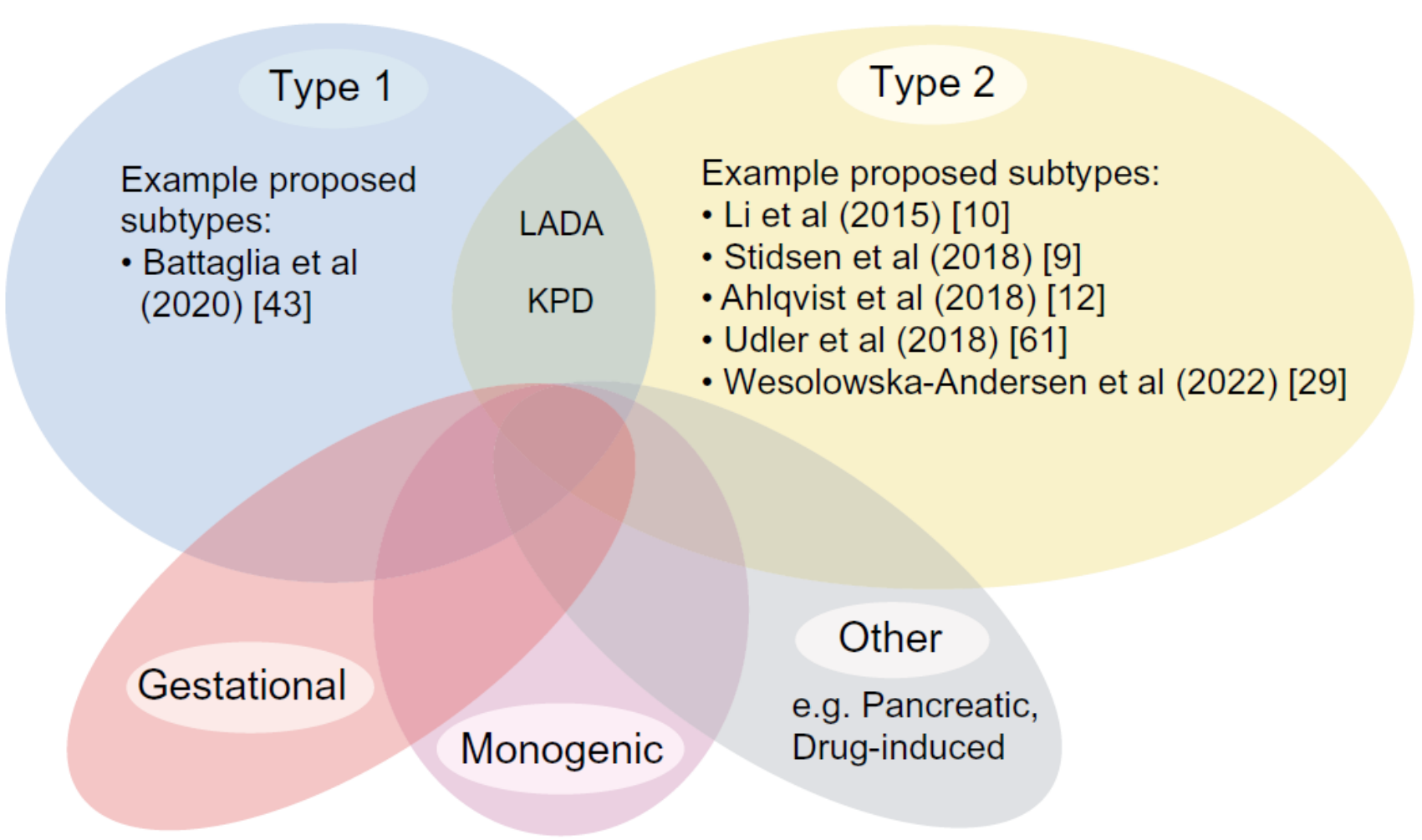
Slow progressive autoimmune type 1 diabetes in patients with young-onset T2D phenotypes



- **8% of YOD: glutamic acid auto-antibodies (GADA) positive**
- YOD-GADA+ vs YOD-GADA-ve
  - 57% ↓ risk for CVD
  - 1.6 fold ↑risk for severe hypo
- **GADA-YOD vs classical T1D**
  - **3-fold ↑risk of ESKD**

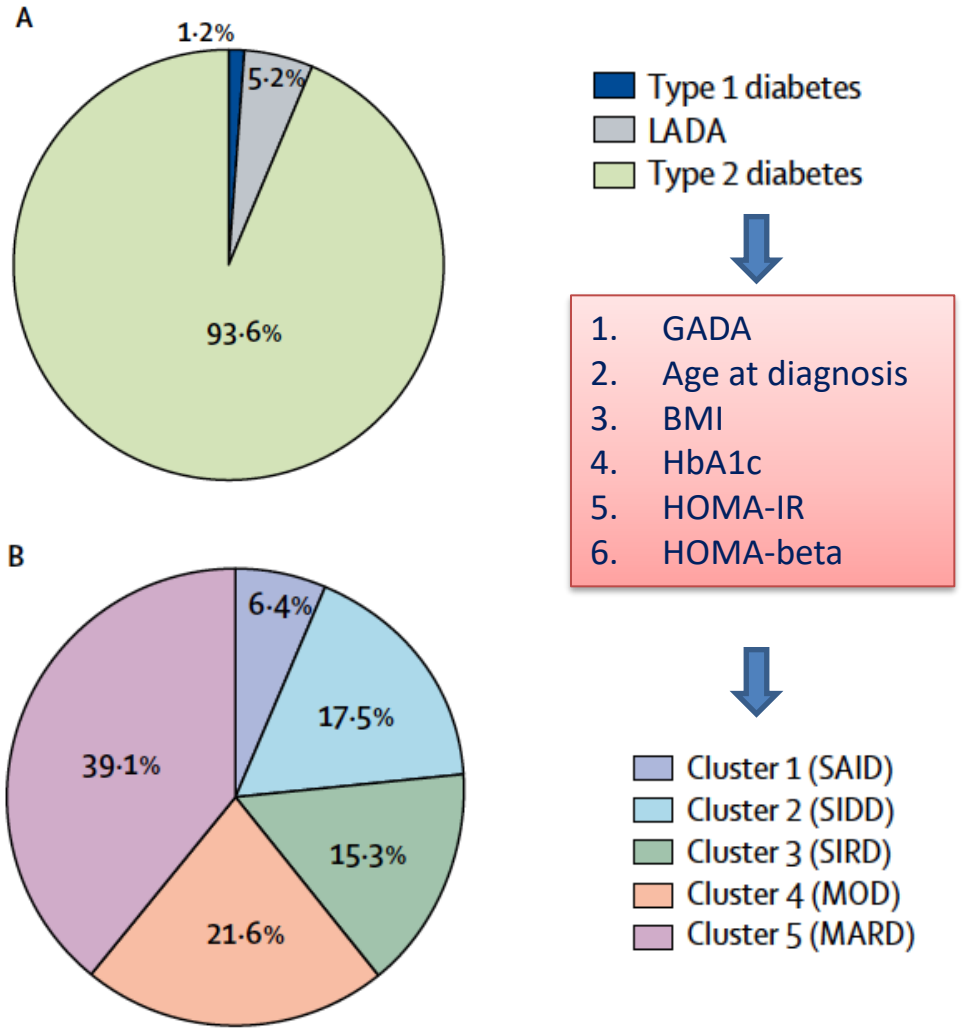
Luk A et al Diabetes Care 2019

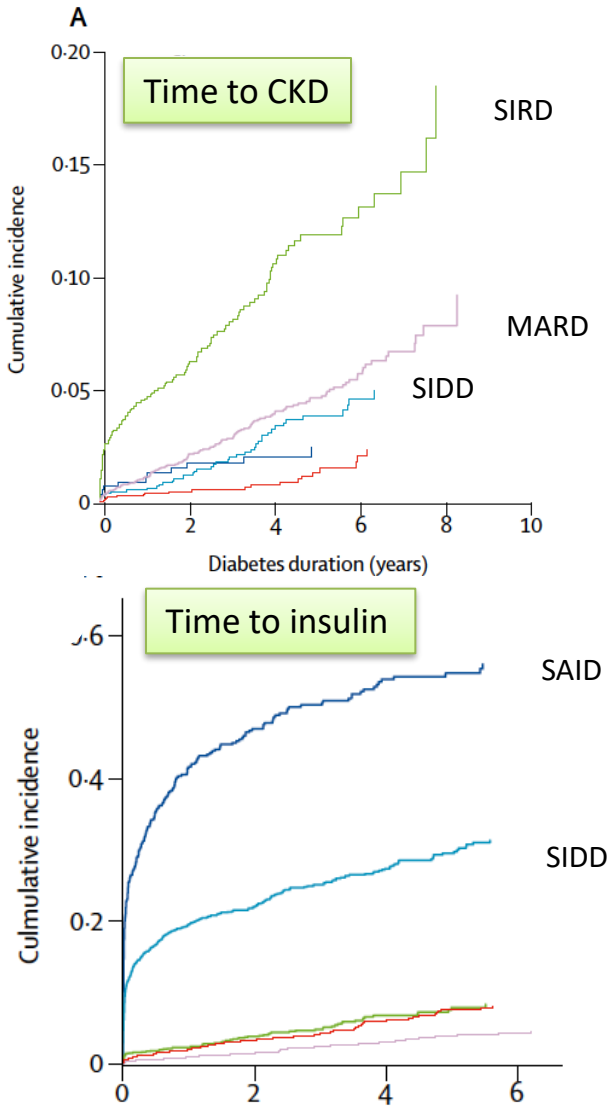
Diabetes subtypes with overlapping phenotypes



Ahlqvist E et al TLDE 2018
Deutsch AJ et al Diabetologia 2022

Using simple biomarkers to redefine diabetes subtypes with implications on prognosis and treatment





SAID Severe autoimmune diabetes; SIDD Severe insulin deficient diabetes; SIRD Severe insulin resistance diabetes; MOD mild obesity related diabetes; MARD mild age related diabetes; LADA: latent autoimmune diabetes in adult

Ahlqvist Storm et al Lancet DE 2018

In Europeans and Asians, every 16 patients diagnosed with T2D, one had T1D with autoimmune antibodies and islet dysfunction

Parameter	Sweden	India		China[a]		
	ANDIS	INSPIRED[110]	INDIAB[110]	Li et al.[111]	CNDMDS[114]	Xiong et al.[112] [b]
Sample size (*n*)	8,980	19,084	2,204	15,772	2,316	5,414
Newly diagnosed	Yes	No	No	Yes	Yes	No
Disease duration (years; mean (s.d.))	0 (0.0)	<5	Unknown	0 (0.0)	0 (0.0)	8.6 (6.3)
Setting	Clinic	Clinic	Survey	Clinic	Survey	Clinic
Location	Scania	Nine states	Fifteen states	National	National	Hunan
Severe autoimmune diabetes mellitus						
Frequency (%)	6.4	NA	NA	6.2	NA	3.7
Age at diagnosis (years; mean (s.d.))	50.5 (17.9)	NA	NA	42.7 (14.0)	NA	49.3 (12.1)
HbA_{1c} (%; mean (s.d.))	9.5 (2.8)	NA	NA	10.7 (5.3)	NA	8.9 (2.4)
BMI (kg/m^2; mean (s.d.))	27.5 (6.4)	NA	NA	22.0 (3.8)	NA	24.3 (3.9)
HOMA-β (mean (s.d.))	56.7 (44.7)	NA	NA	21.9	NA	84.0 (112.8)
HOMA-IR (mean (s.d.))	2.2 (1.6)	NA	NA	0.7	NA	3.7 (7.9)

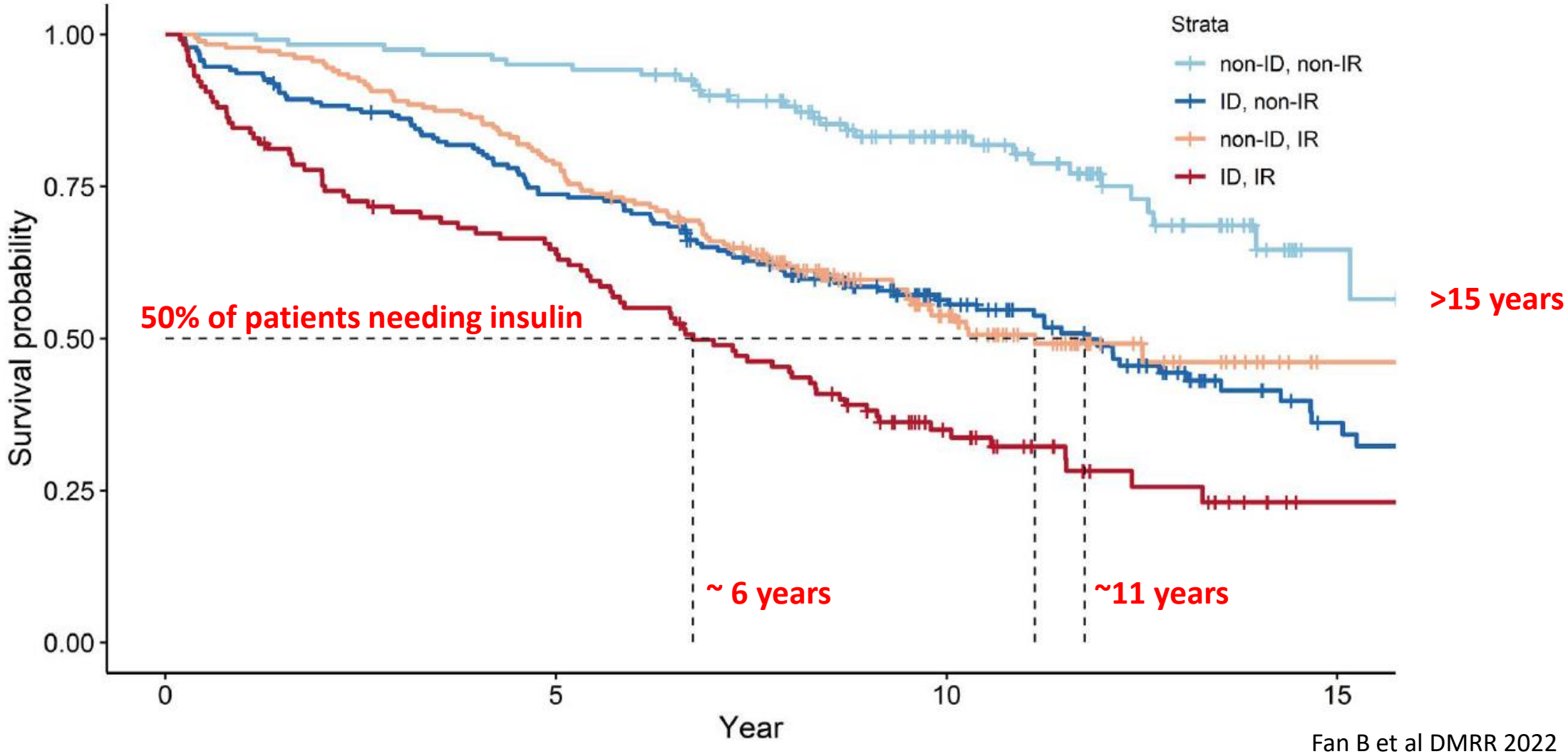
Ke C et al Nature Review Endocrinology 2022

Insulin insufficiency, low BMI and poor A1c control are important phenotypes in Asian patients with type 2 diabetes

Parameter	Sweden	India		China[a]		
	ANDIS	INSPIRED[110]	INDIAB[110]	Li et al.[111]	CNDMDS[114]	Xiong et al.[112] [b]
Severe insulin-deficient diabetes mellitus						
Frequency (%)	17.5	26.2	27.4	24.8	13.5	41.2
Age at diagnosis (years; mean (s.d.))	56.7 (11.1)	42.5 (10.8)	40.1 (9.8)	50.5 (11.6)	52.4 (11.9)	46.6 (10.7)
HbA_{1c} (%; mean (s.d.))	11.5 (1.8)	10.7 (2.1)	10.0 (2.1)	12.5 (4.0)	NA	10.2 (1.9)
BMI (kg/m^2; mean (s.d.))	28.9 (4.8)	24.9 (3.5)	22.7 (3.1)	22.5 (2.6)	25.4 (3.2)	25.0 (3.7)
HOMA-β (mean (s.d.))	47.6 (28.9)	38.8 (26.9)	NA	20.2	NA	32.2 (19.5)
HOMA-IR (mean (s.d.))	3.2 (1.7)	2.8 (1.6)	NA	1.1	NA	1.3 (0.8)
Severe insulin-resistant diabetes mellitus[c]						
Frequency (%)	15.3	12.1	7.6	16.6	8.6	NA
Age at diagnosis (years; mean (s.d.))	65.3 (9.3)	42.1 (9.8)	45.4 (10.2)	51.8 (11.0)	47.4 (13.4)	NA
HbA_{1c} (%; mean (s.d.))	7.1 (3.6)	9.1 (1.9)	9.0 (2.0)	7.2 (3.6)	NA	NA
BMI (kg/m^2; mean (s.d.))	33.9 (5.2)	26.5 (3.1)	25.0 (2.9)	27.0 (3.2)	27.8 (4.3)	NA
HOMA-β (mean (s.d.))	150.5 (47.2)	64.5 (37.7)	NA	98.6	NA	NA
HOMA-IR (mean (s.d.))	5.5 (2.7)	3.8 (1.9)	NA	2.2	NA	NA

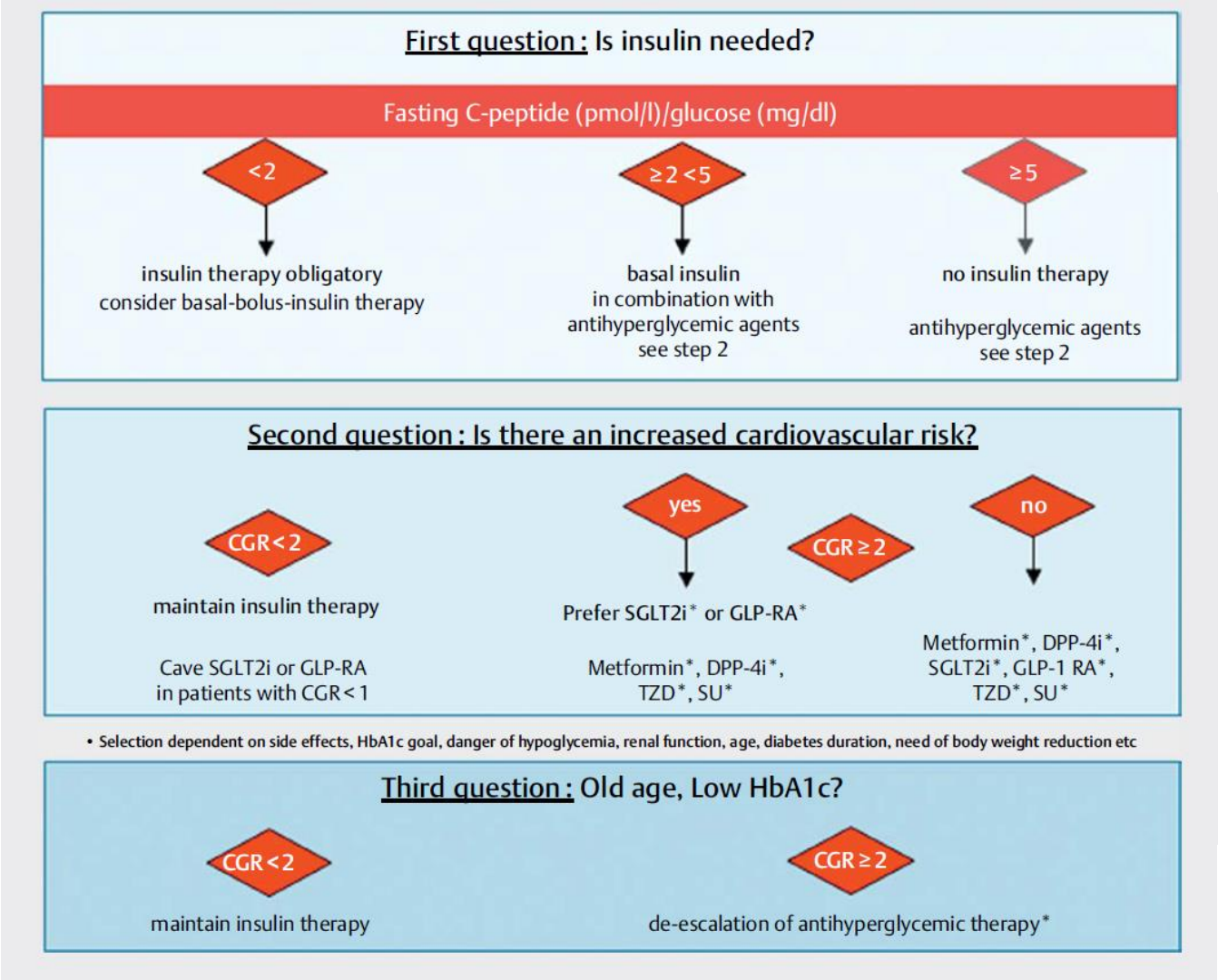
Ke C et al Nature Review Endocrinology 2022

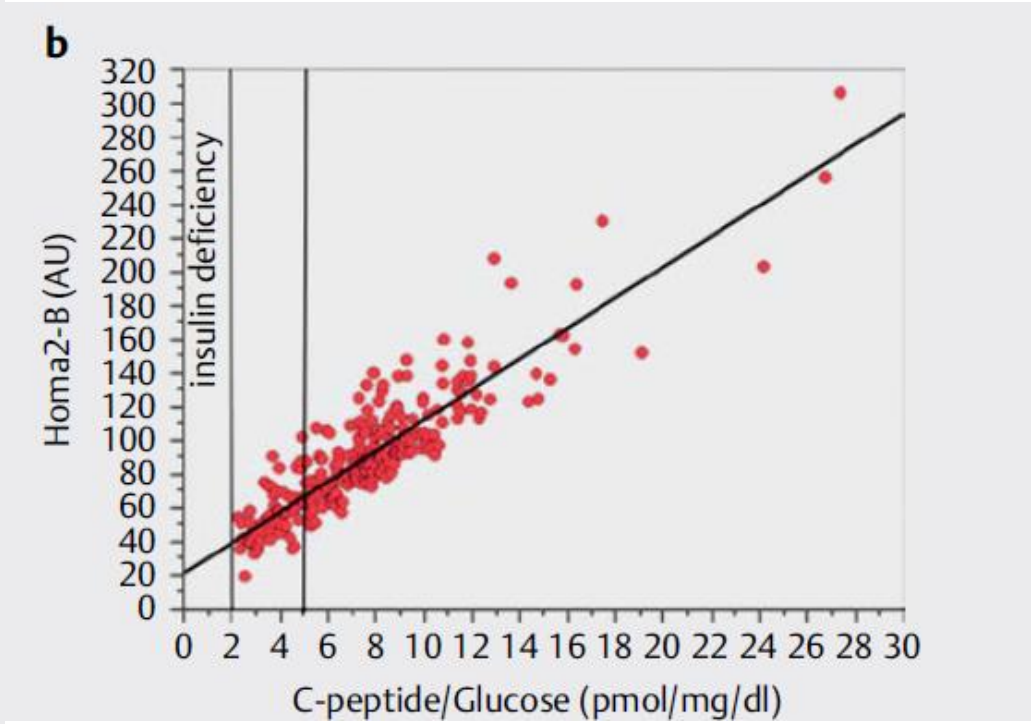
Both HOMA-beta and HOMA-IR predict early insulin requirement in young onset diabetes



Fan B et al DMRR 2022

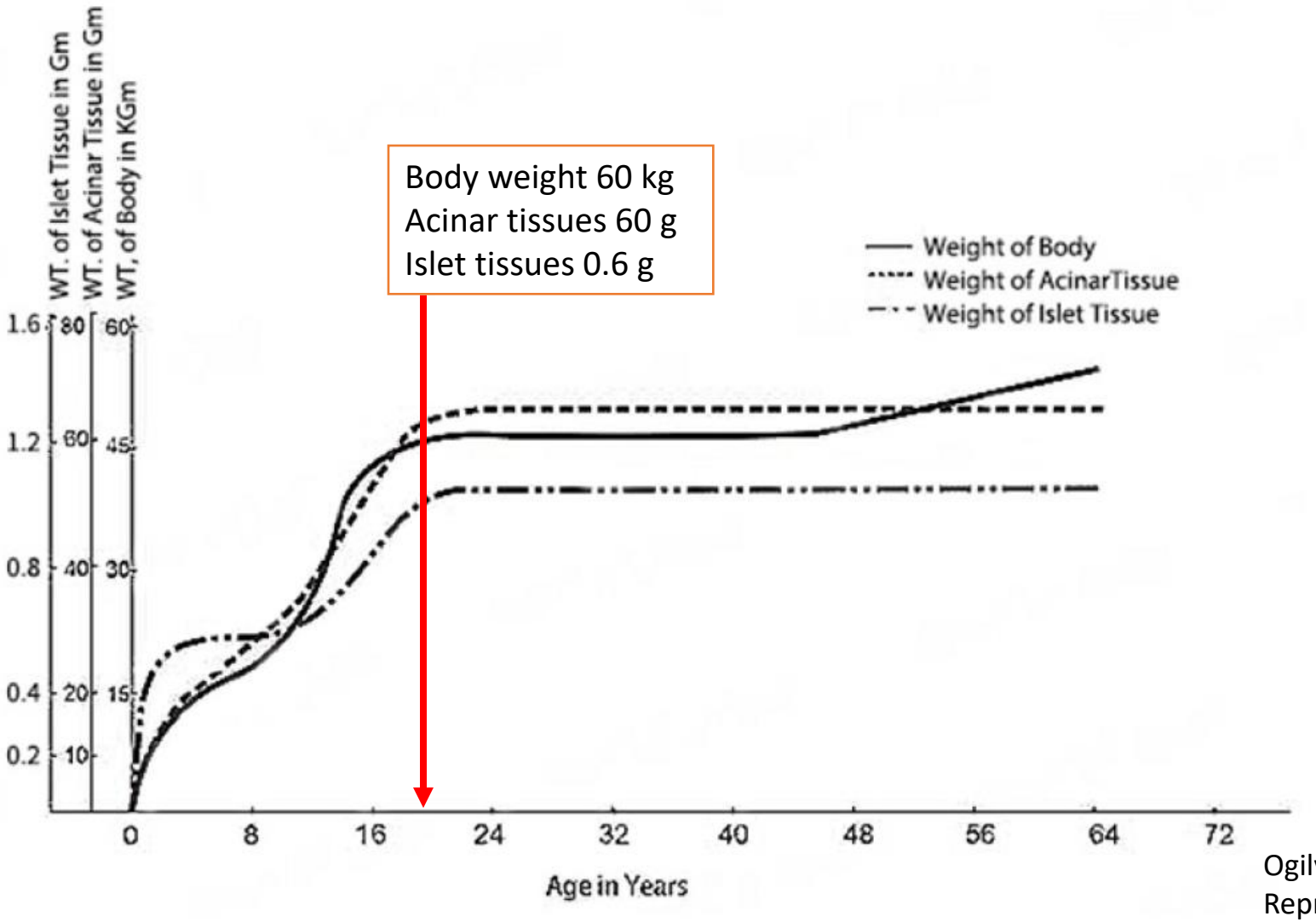
Using C Peptide/Glucose index to identify insulin insufficiency





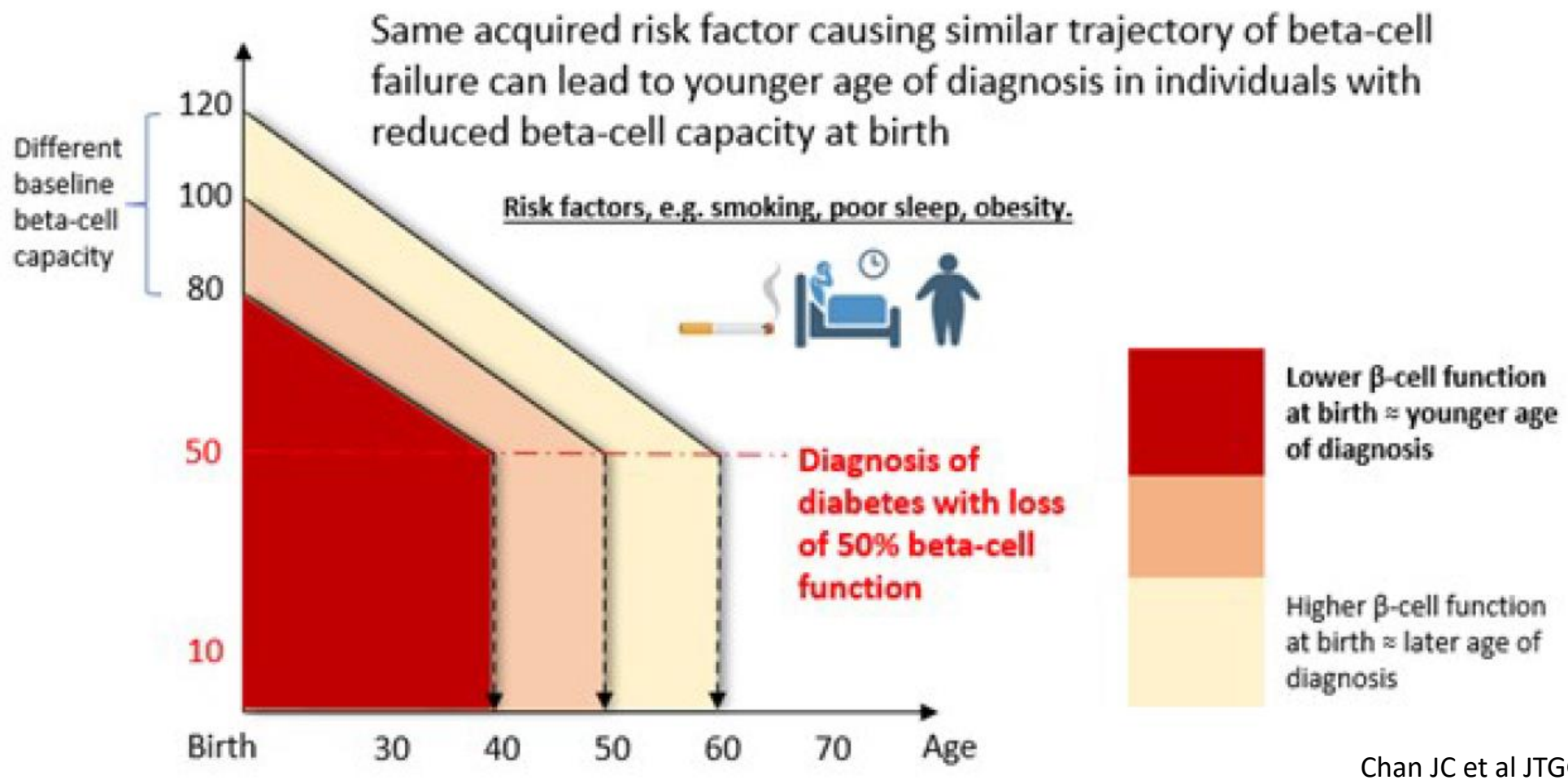
Fritsche A et al Exp Clin Endocrinol Diabetes 2022

Endowment of number of islets at birth and during early development



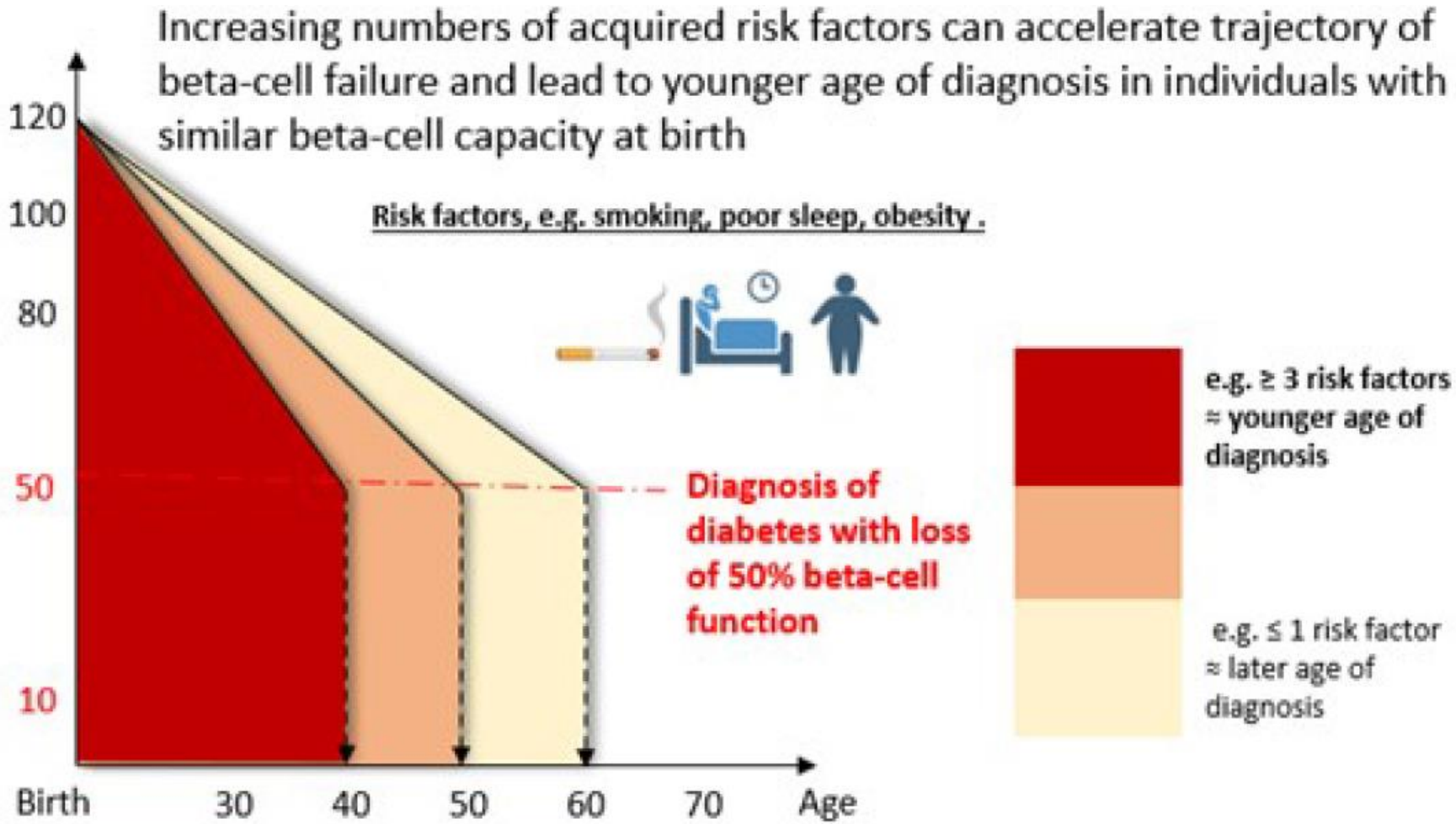
Ogilvie RF QMJ 1937
Reproduced in Chan JC et al JTGG 2024

Same beta-cell function trajectory, different beta-cell capacity, different age of diagnosis



Chan JC et al JTGG 2024
Chan JC et al EnM 2024

Same beta-cell capacity, different beta-cell trajectory, different age of diagnosis

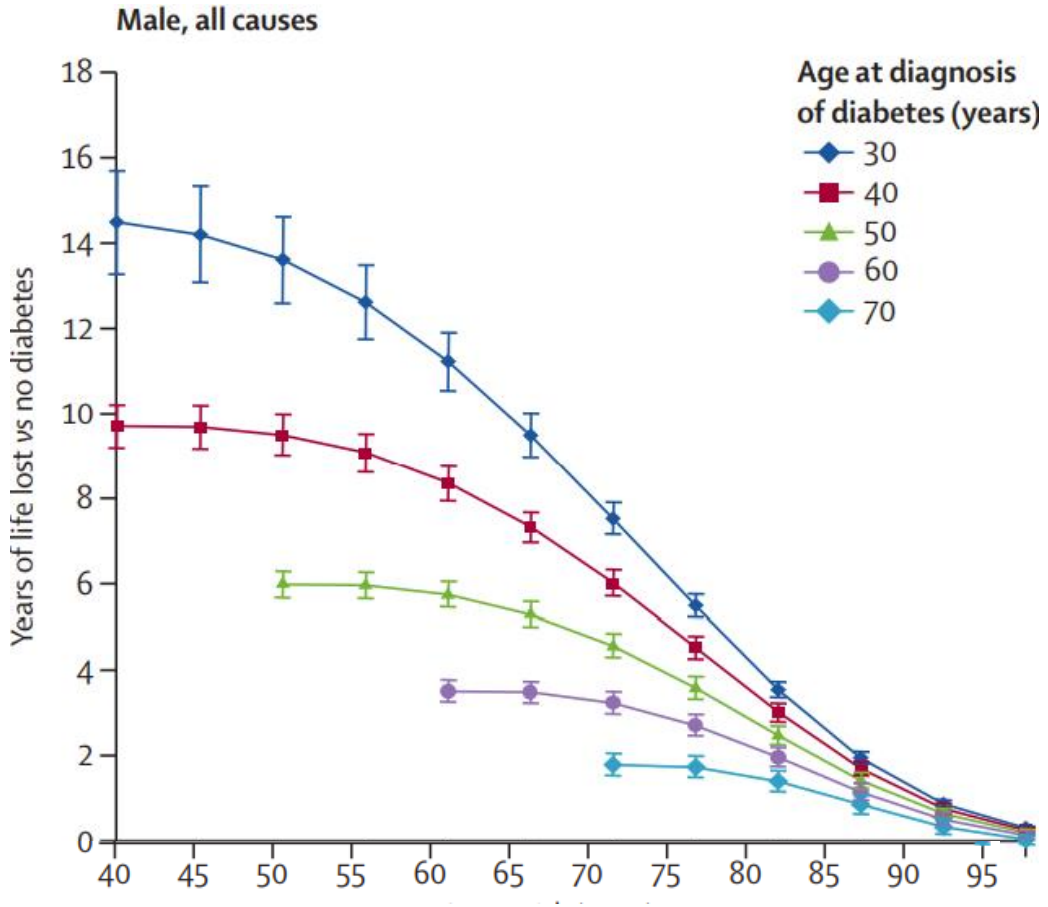


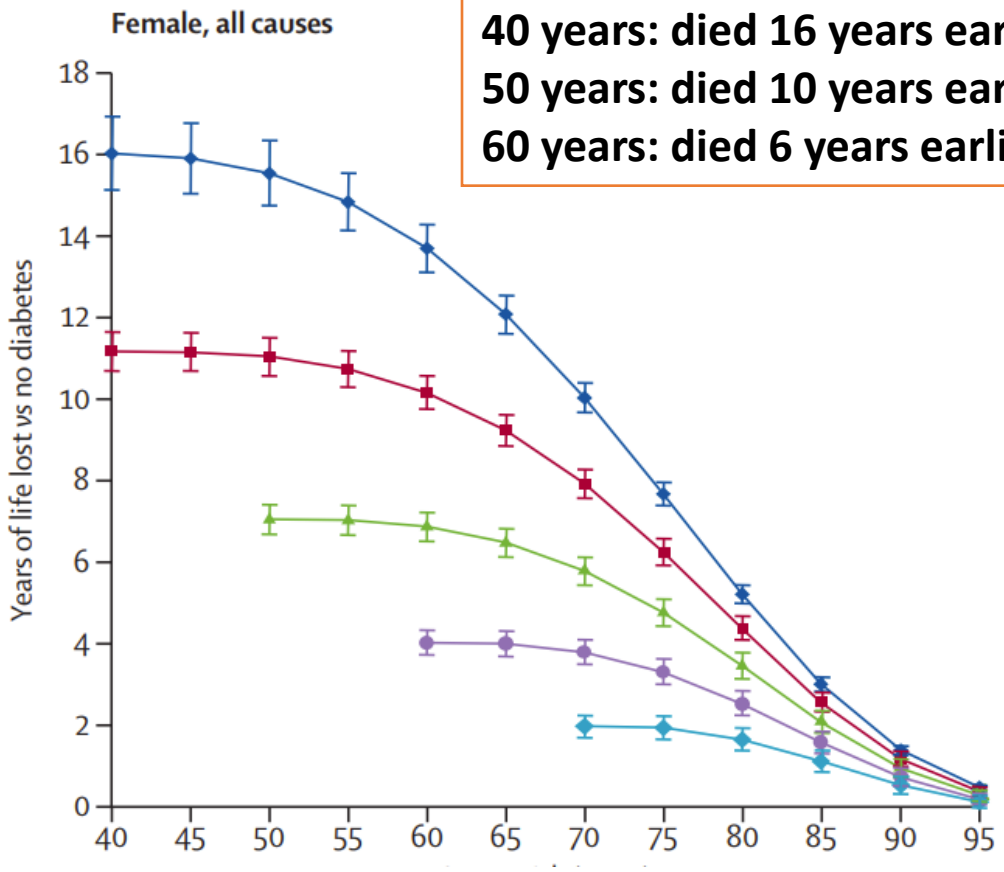
Chan JC et al JTGG 2024
Chan JC et al EnM 2024

Emerging Risk Factor Collaboration and UK Biobank

age of diagnosis of diabetes and years of life lost versus no diabetes

1,515,718 participants with 23·1 million person-years of follow-up





Age of diagnosis
40 years: died 16 years earlier
50 years: died 10 years earlier
60 years: died 6 years earlier

Emerging Risk Factor Collaboration, TLDE 2023

Conclusions

- People with T2D have abnormal structure and function of pancreatic islets
- There are close correlations between body weight and beta cell mass
- Abnormal islet structure and function are due to many causes
  - Rare and common genetic variants
  - Perinatal and early childhood development
  - Autoimmunity
  - Gluco-lipotoxicity
  - Inflammation……
- Heterogeneity of phenotypes calls for reclassification and assessing beta-cell function to prognosticate and personalize treatment
- Early detection and intervention may preserve beta cell function to delay disease progression

Case Study

Juan Pablo Frías, MD
Chief Medical Officer and Head of Diabetes
Biomea Fusion

biomea FUSION™ We Aim to Cure™

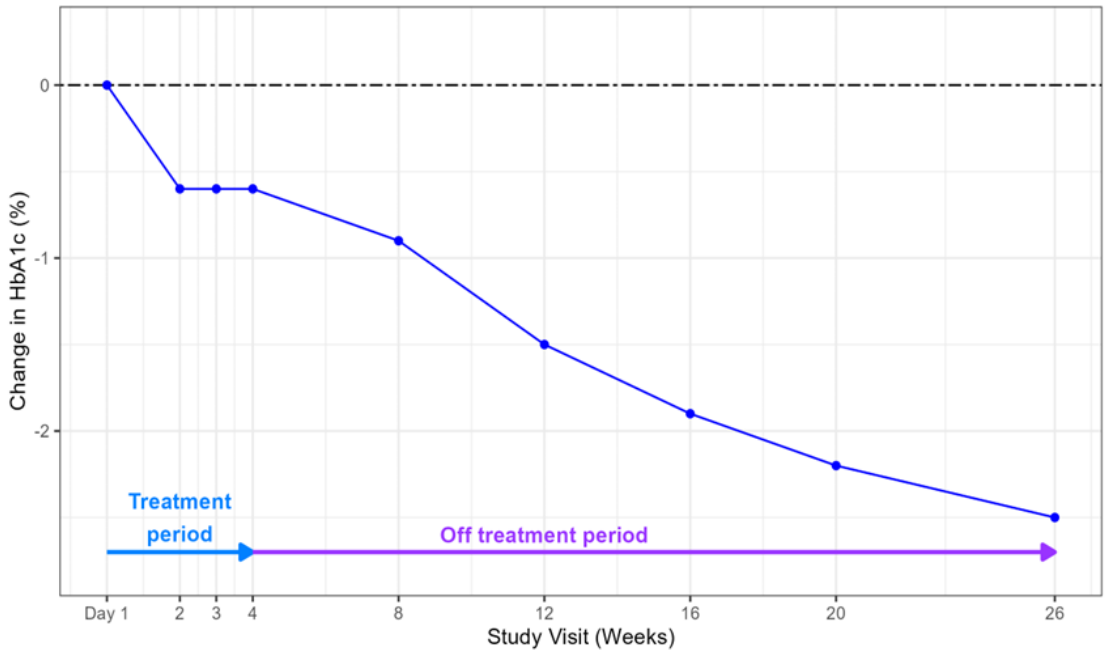
COVALENT-111 MAD Cohort

Case Study: 29-year-old man with 4-year history of T2D (insulin deficient subtype)

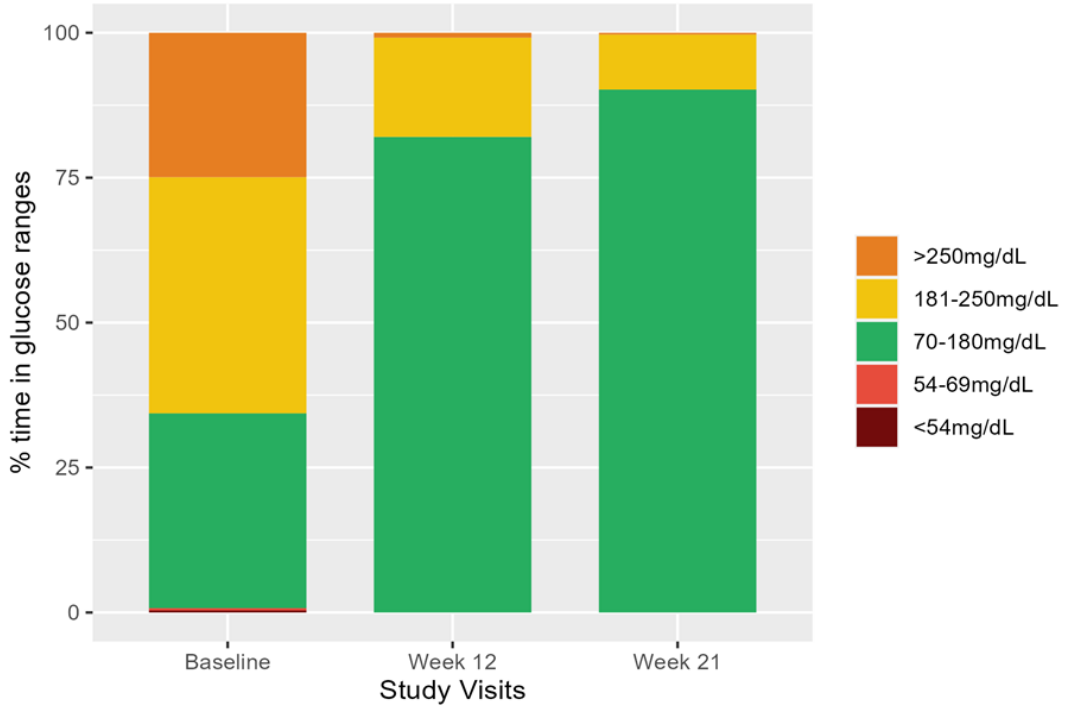
- 29-year-old man with 4-year history of T2D
- Metformin and empagliflozin
- HbA_{1c} 9.5%; FPG 146 mg/dL; BMI 25.6 kg/m^2

- Icovamenib 200 mg once daily without food for 4 weeks
- CGM at Week 26 with ~90% $TIR_{70\text{-}180\ mg/dL}$
- No tolerability issues or related adverse events

Change in HbA_{1c} (%)



Continuous Glucose Monitoring



Case Study: 29-year-old man with 4-year history of T2D (insulin deficient subtype)

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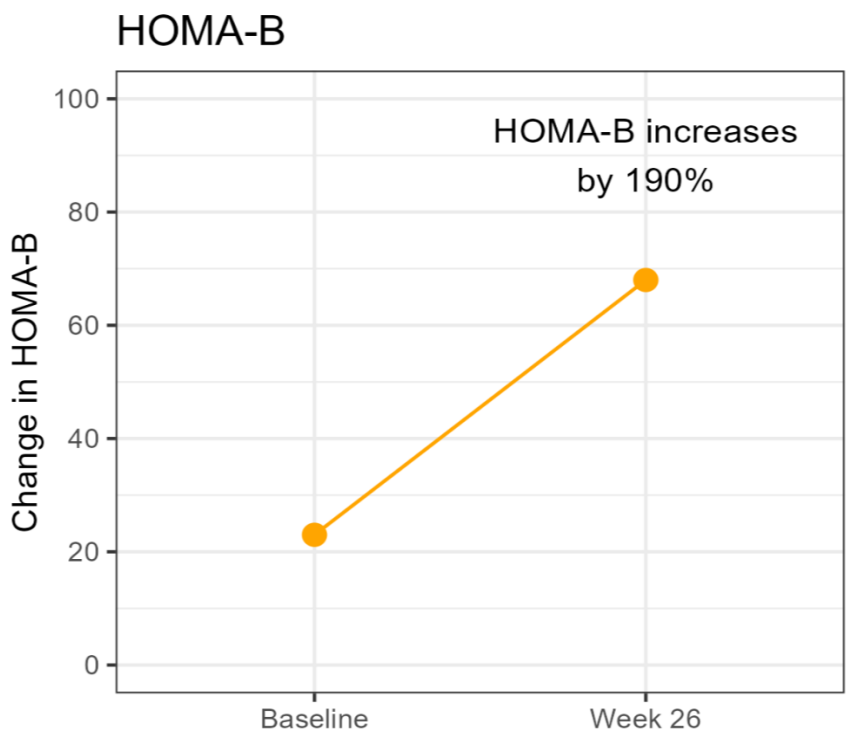
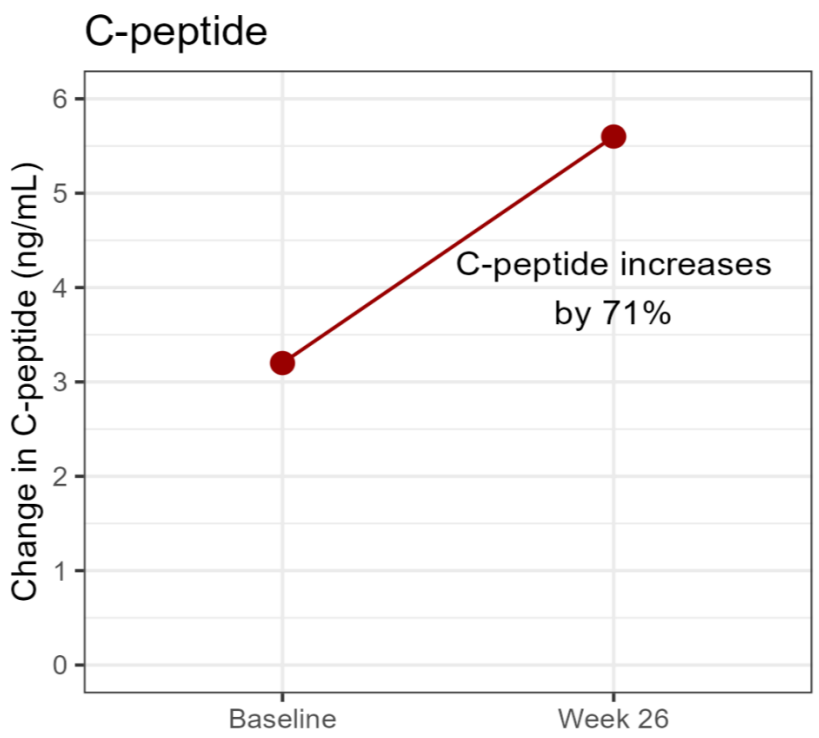
Change at Week 26





Menin suppresses GLP-1 receptor transcript levels

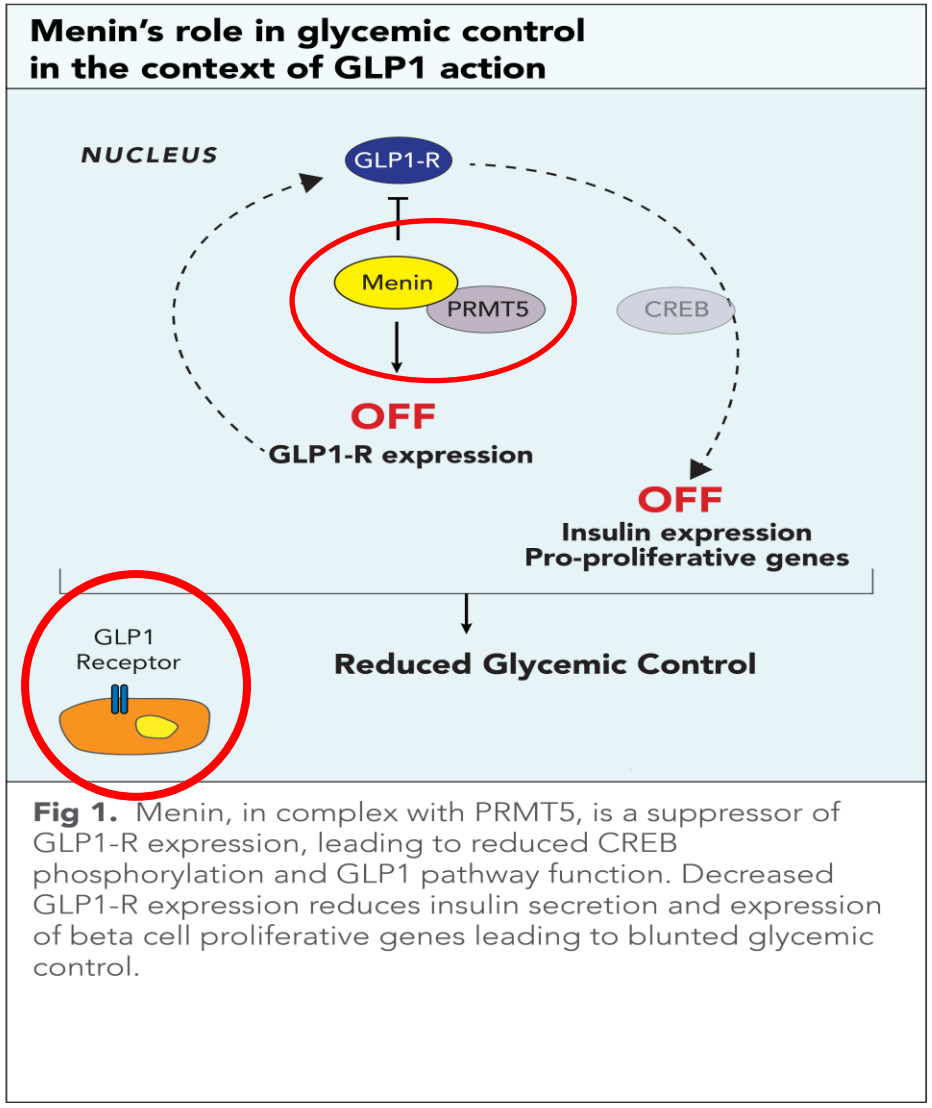


Fig 1. Menin, in complex with PRMT5, is a suppressor of GLP1-R expression, leading to reduced CREB phosphorylation and GLP1 pathway function. Decreased GLP1-R expression reduces insulin secretion and expression of beta cell proliferative genes leading to blunted glycemic control.

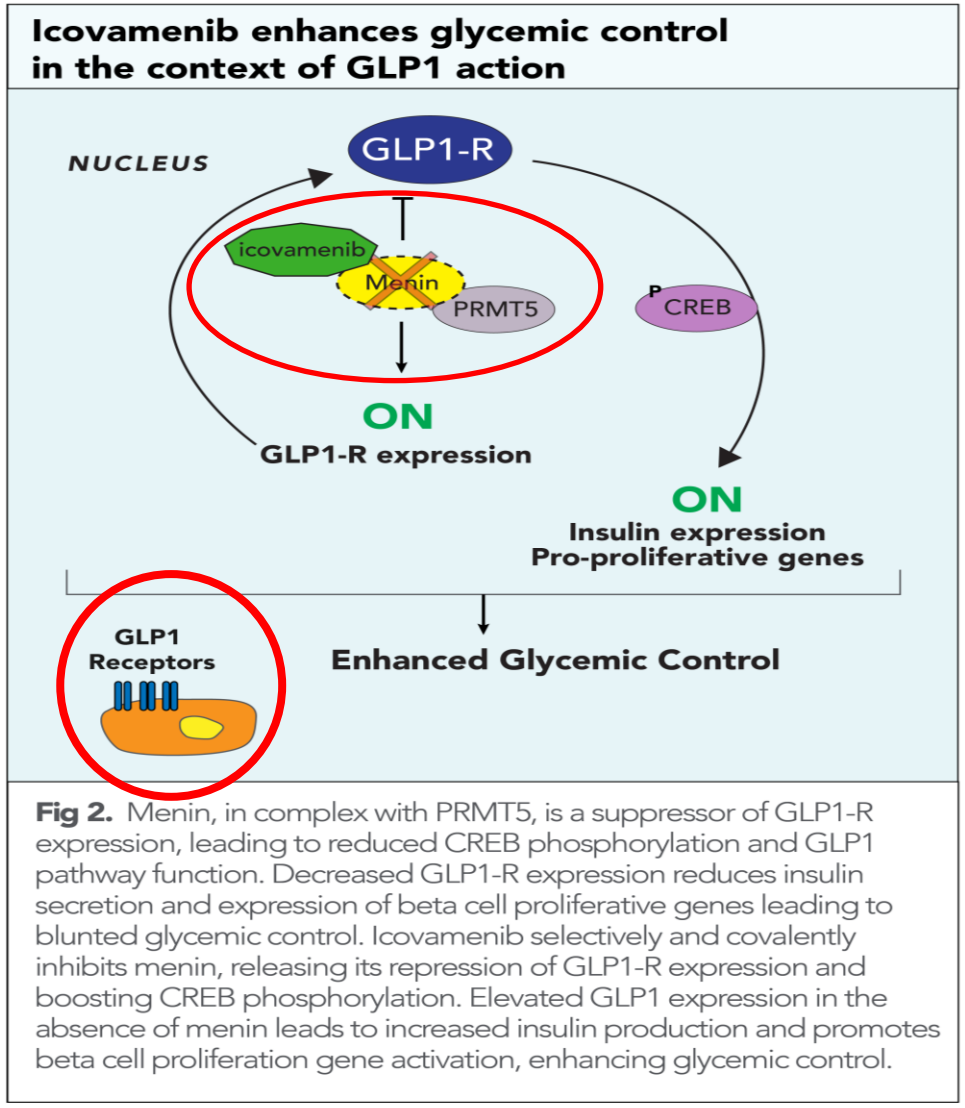
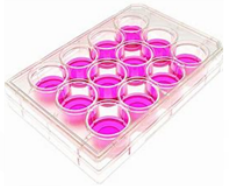


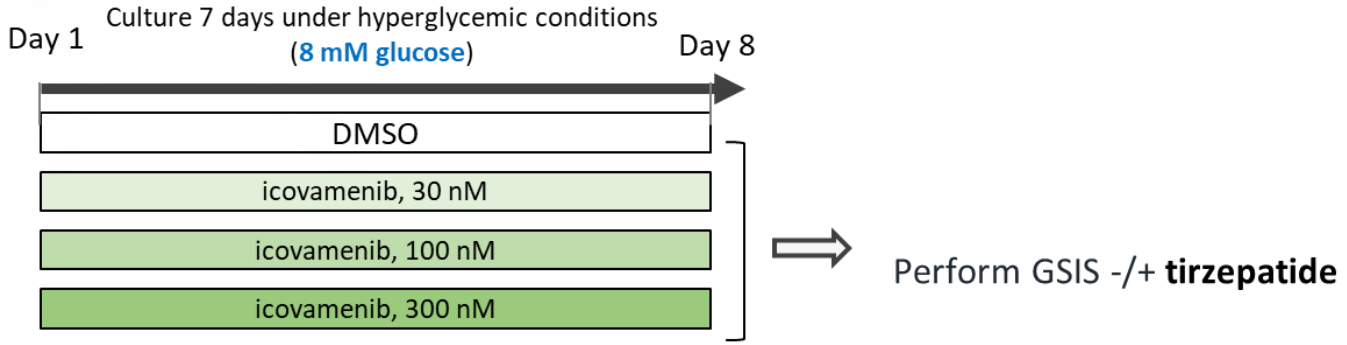
Fig 2. Menin, in complex with PRMT5, is a suppressor of GLP1-R expression, leading to reduced CREB phosphorylation and GLP1 pathway function. Decreased GLP1-R expression reduces insulin secretion and expression of beta cell proliferative genes leading to blunted glycemic control. Icovamenib selectively and covalently inhibits menin, releasing its repression of GLP1-R expression and boosting CREB phosphorylation. Elevated GLP1 expression in the absence of menin leads to increased insulin production and promotes beta cell proliferation gene activation, enhancing glycemic control.

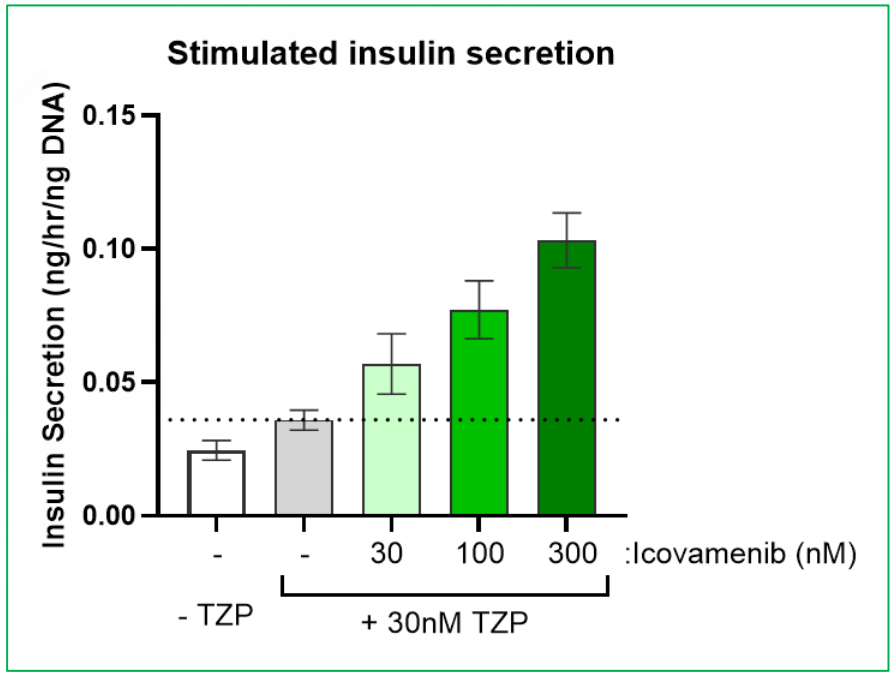
Combination treatment: Icovamenib enhanced responsiveness of islets to the dual GIP/GLP-1 receptor agonist tirzepatide

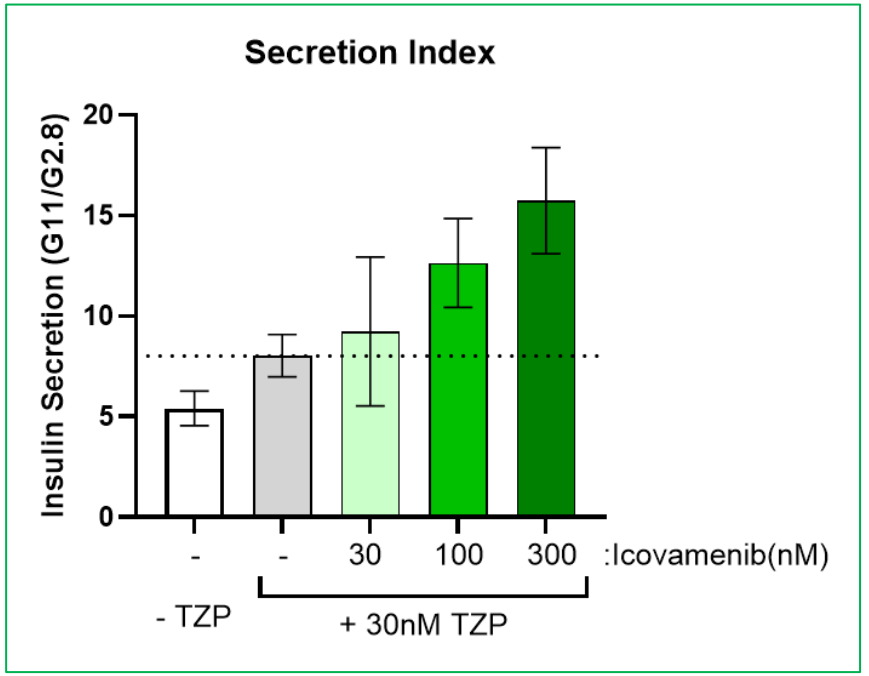
Cadaver derived human islets



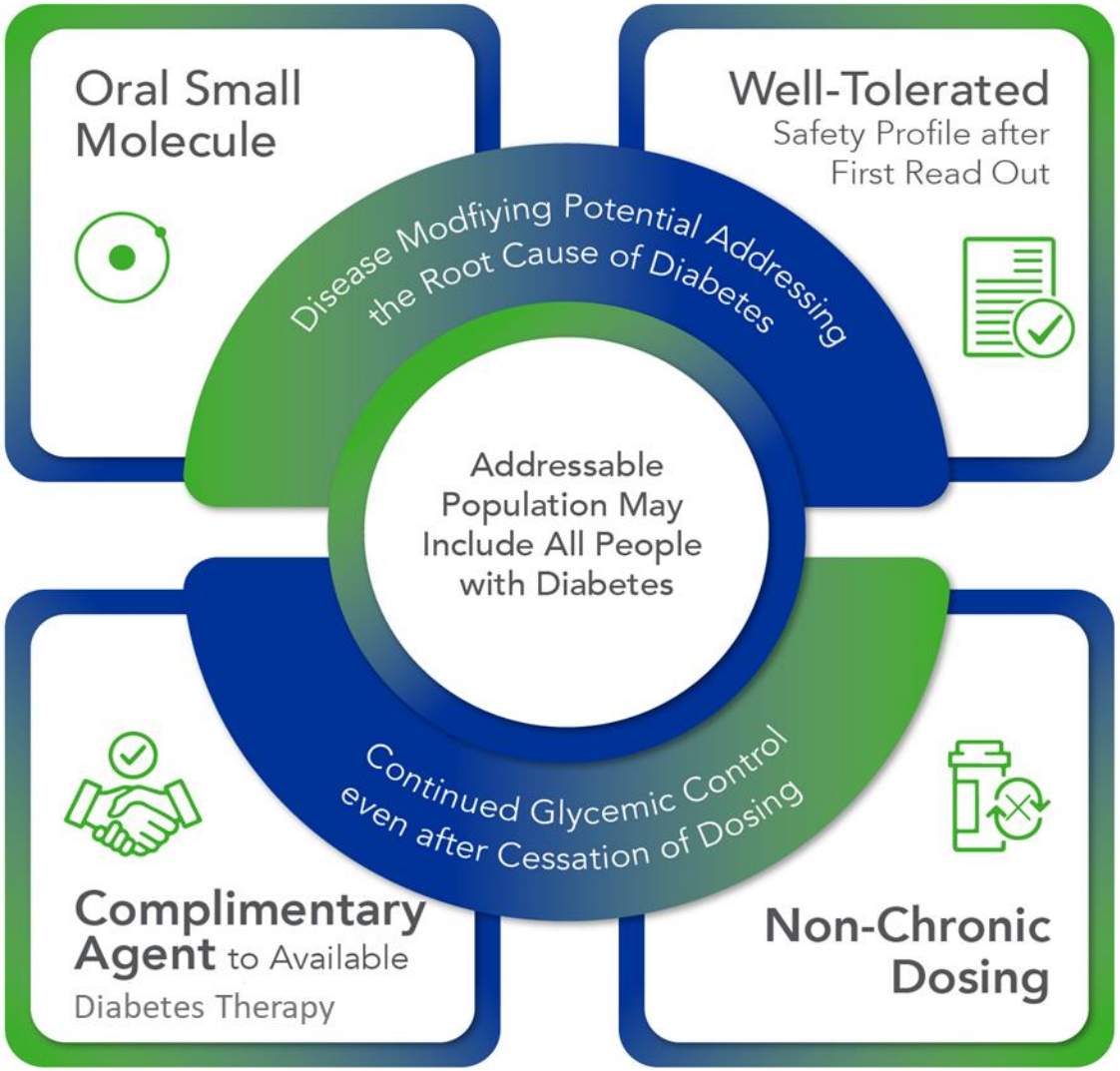
Donor (without diabetes):
38-year white male, BMI: 29.2 kg/m^2, HbA_{1C} 5.2%







Icovamenib – An investigational agent focusing on beta cell health



Q & A Session

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Biomea Fusion
900 Middlefield Road, 4th floor
Redwood City, CA, 94063
biomeafusion.com/diabetes-obesity

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