New Insights into the Pathophysiology of Type 1 and Type 2 Diabetes

April 30, 2025

New Insights into Metabolic and Cardiorenal Wellness in People with Diabetes: A Virtual CME Program for Africa

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Beth Israel Lahey Health
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DISCLOSURES

- I have no financial relationships with any commercial entity producing healthcare-related products and/or services
- I have not received grants, compensation, or other support from pharmaceutical companies or drug-manufacturing entities.

OBJECTIVES

- Review the interaction of genetic and environmental factors in the pathogenesis of type 1 and type 2 diabetes.
- Discuss key pathogenetic mechanisms for the development and progression of type 1 and type 2 diabetes.
- Outline the heterogeneity of diabetes presentations and associated risk of complications.

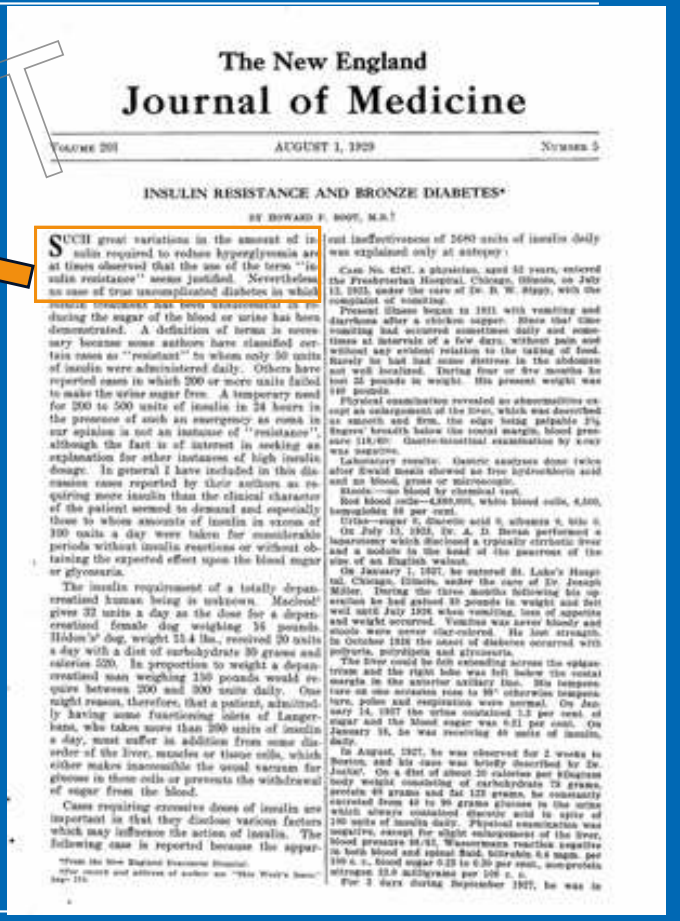
"*Chance favors only the prepared mind*" Louis Pasteur

Milestones in diabetes research and translation to treatment

Nobel Prizes for Diabetes-related Research

Year	Category	Recipient	Contribution
1923	Medicine	F.G. Banting and J.J.R. Macleod	Discovery of insulin
1947	Medicine	C.F. Cori and G.T. Cori	Discovery of the course of the catalytic conversion of glycogen
1947	Medicine	B.A. Houssay	Discovery of the role of hormones released by the anterior pituitary lobe in the metabolism of sugar
1958	Chemistry	F. Sanger	Work on the structure of proteins, especially insulin
1971	Medicine	E.W. Sutherland	Discoveries concerning the mechanisms of action of hormones
1977	Medicine	R. Yalow	Development of radioimmunoassays for peptide hormones
1992	Medicine	E.H. Fischer and E.G. Krebs	Discoveries concerning reversible protein phosphorylation as a biologic regulatory mechanism

Polonski KS NEJM 2012; 367:1132-1340



The New England
Journal of Medicine

AUGUST 1, 1929

INSULIN RESISTANCE AND BRONZE DIABETES*

BY HOWARD F. ROOT, M.D.†

SUCH great variations in the amount of insulin required to reduce hyperglycemia are at times observed that the use of the term "insulin resistance" seems justified. Nevertheless no case of true uncomplicated diabetes in which

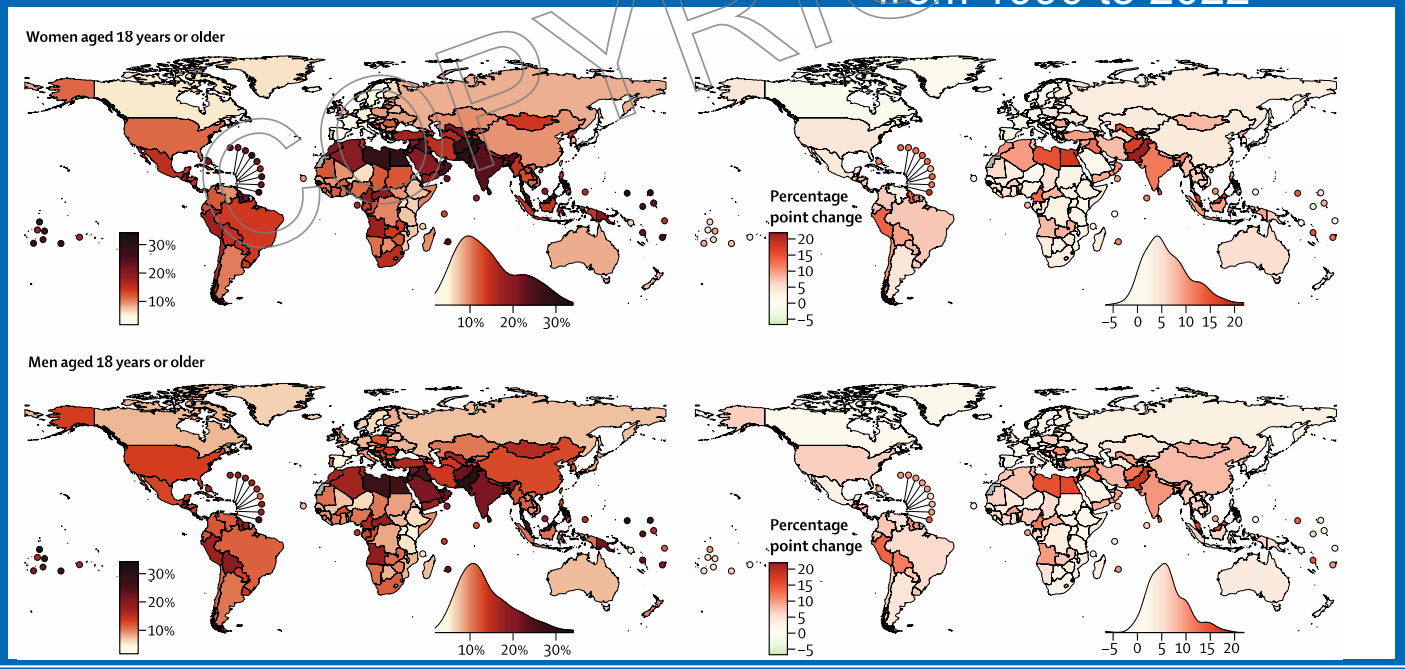
Such great variations in the amount of insulin required to reduce hyperglycemia are at times observed that the use of the term "insulin resistance" seems justified. H.F. Root

Worldwide trends in diabetes prevalence from 1990 to 2022

- In 2022, an estimated 828 million adults had diabetes
- The largest increase was noted in low-income and middle-income countries

Prevalence in 2022

Changes in prevalence from 1990 to 2022



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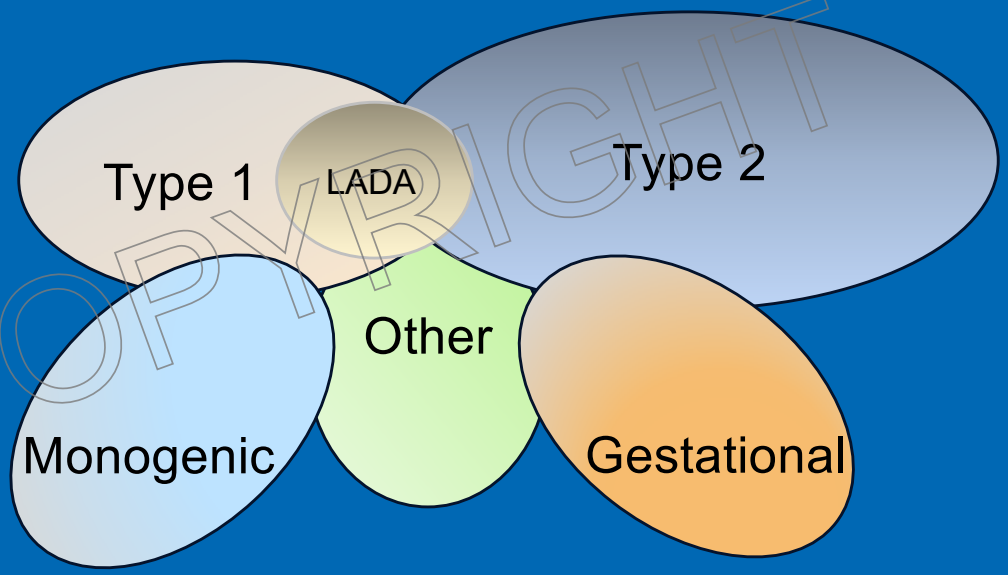
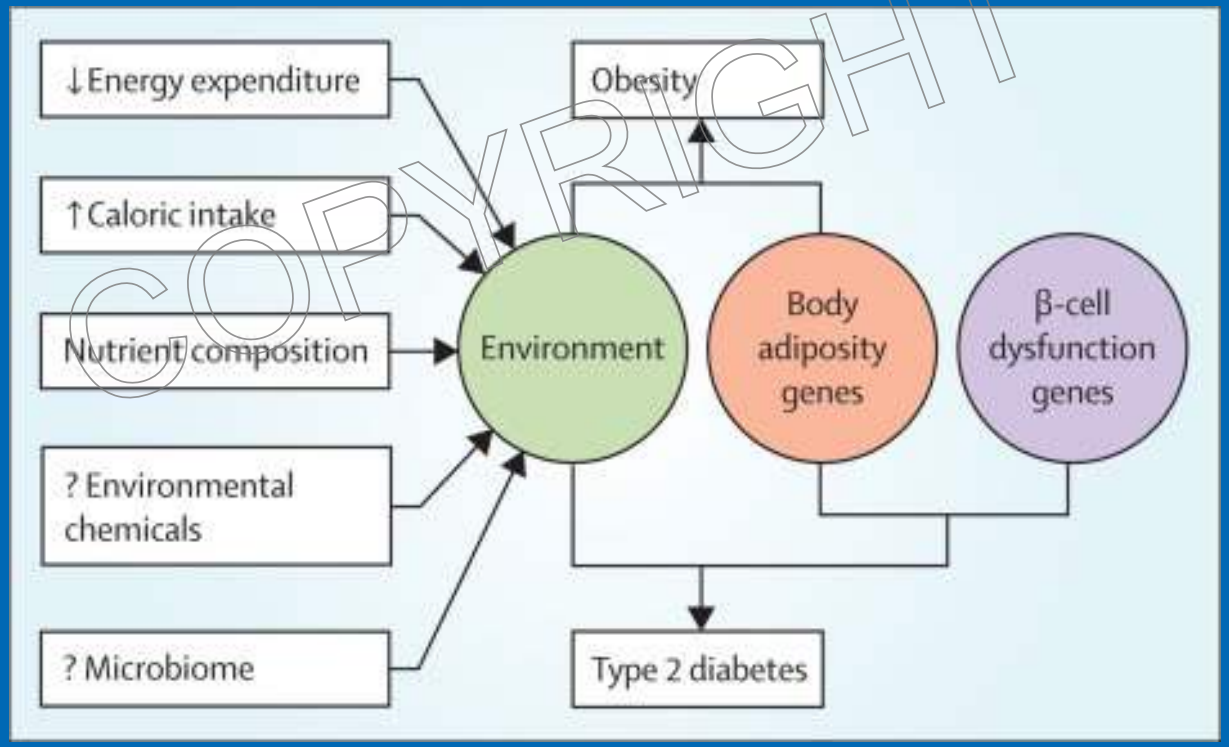
NCD Risk Factor Collaboration (NCD-RisC) Lancet 2024; 404:2077-2093

Classification of diabetes



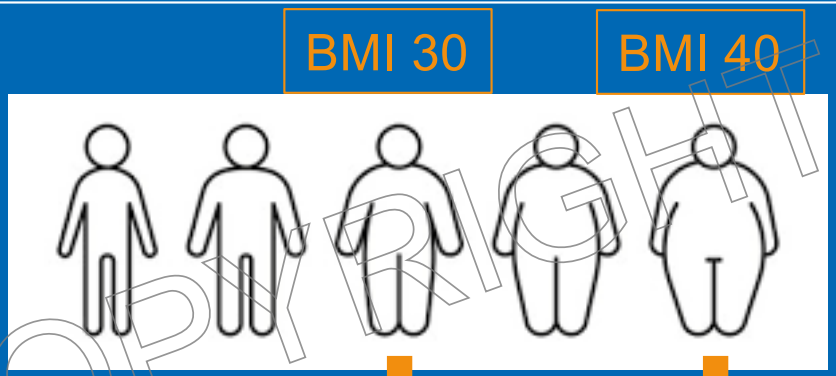
ADA Standards of Care Diabetes Care 2025; 48:S27-S49

Genes and environment interaction in the development of type 2 diabetes



Kahn SE et al Lancet 2014;383:1068-83

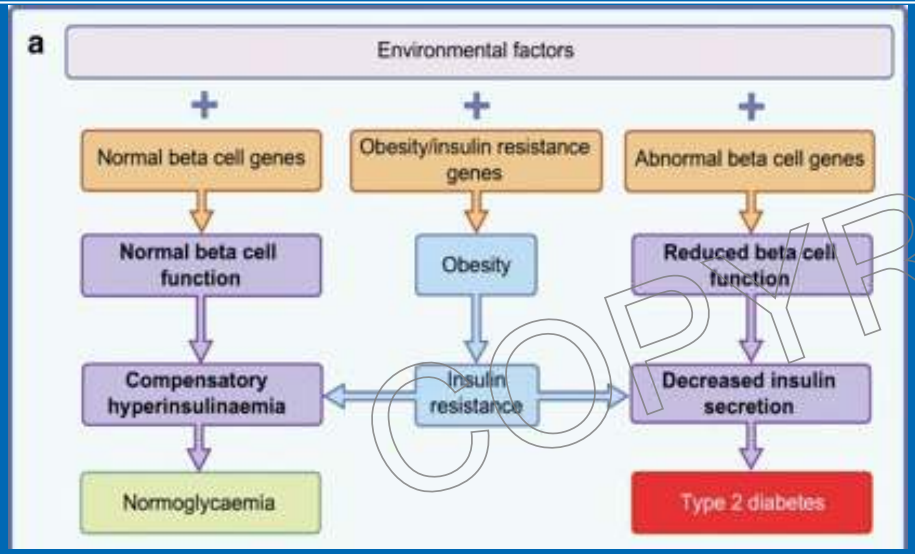
BMI alone is not a robust predictor of T2D risk

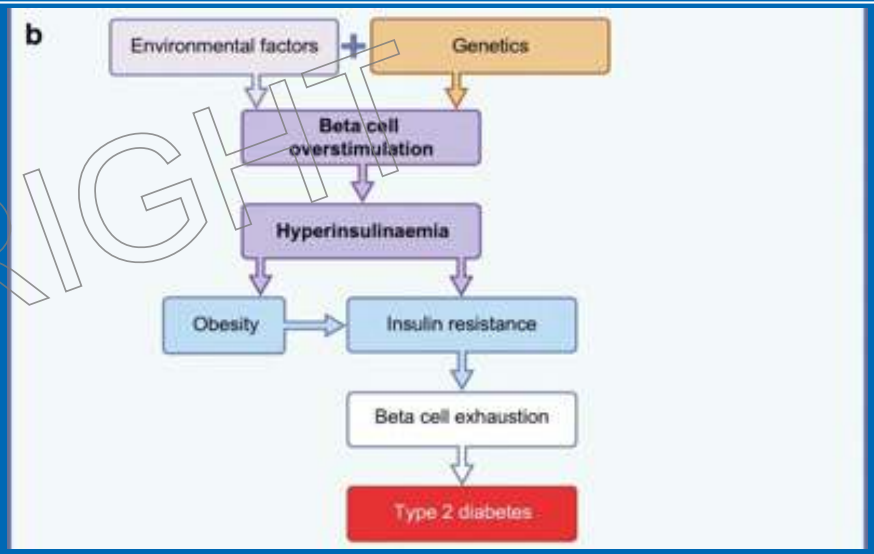


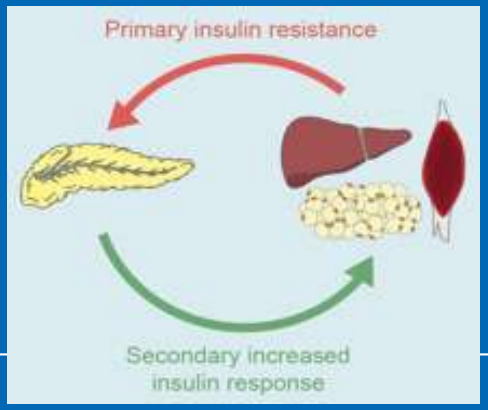
This person may develop T2D

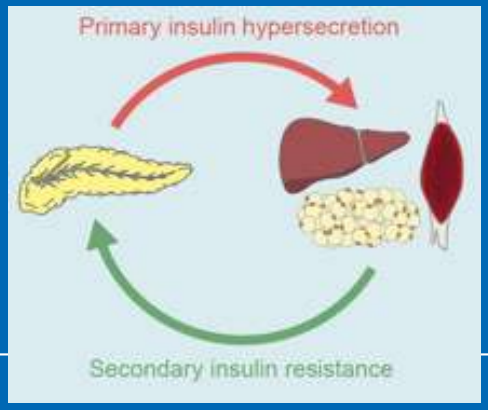
Whereas this person with a higher BMI may *not* develop T2D

Primary beta cell dysfunction vs insulin resistance: who's to blame (first)?









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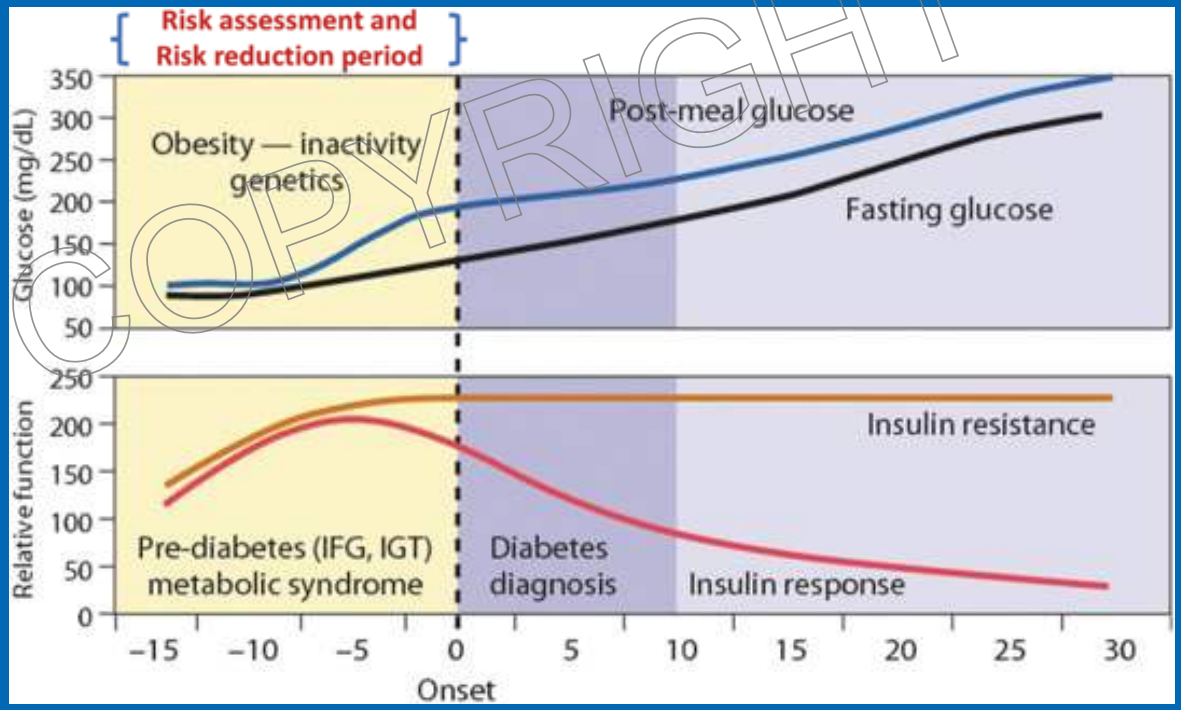
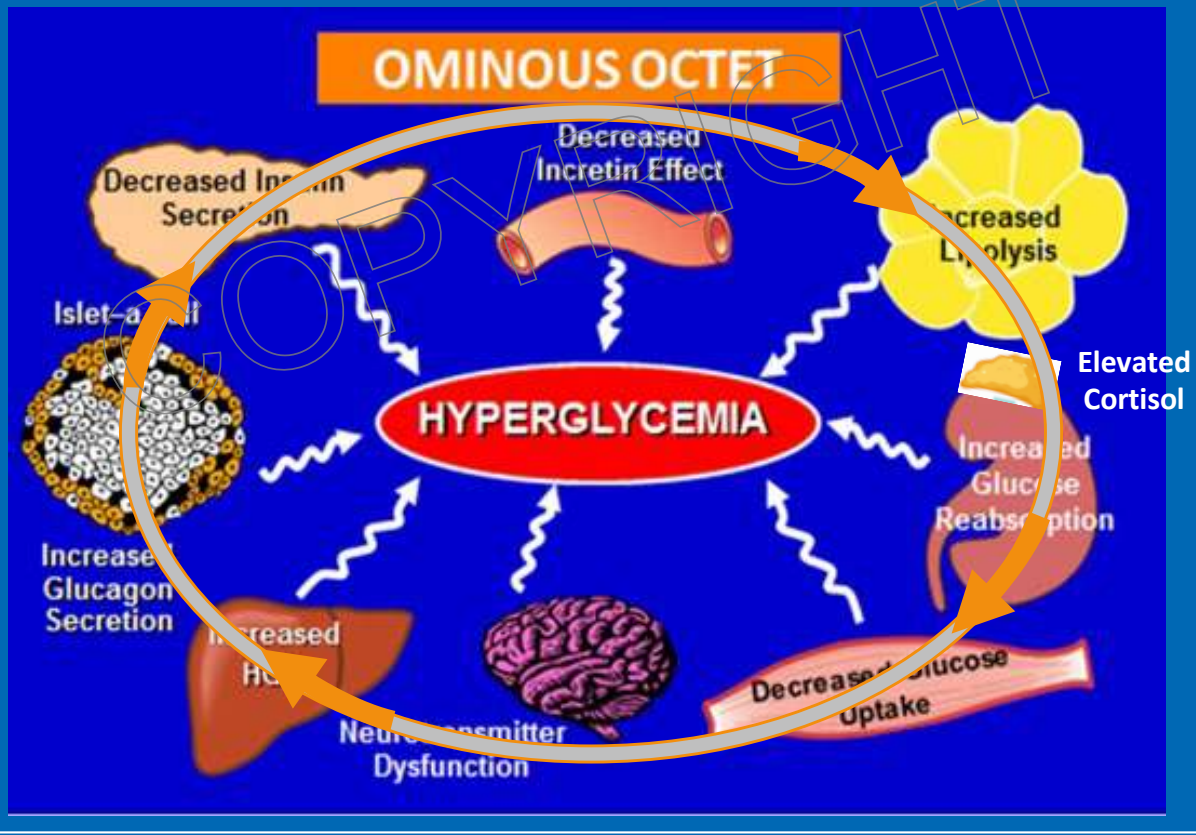
Esser N et al. Diabetologia 2020; 63:2007-2021

From ”prediabetes” to overt T2D: a continuum of glucose abnormalities and insulin secretory compensation



Adapted from Miller E et al. Diabetes Technol & Ther 2023: 25: S14-S20

From “ominous octet” to “noxious nine”: the evolving picture of the pathogenesis of T2D



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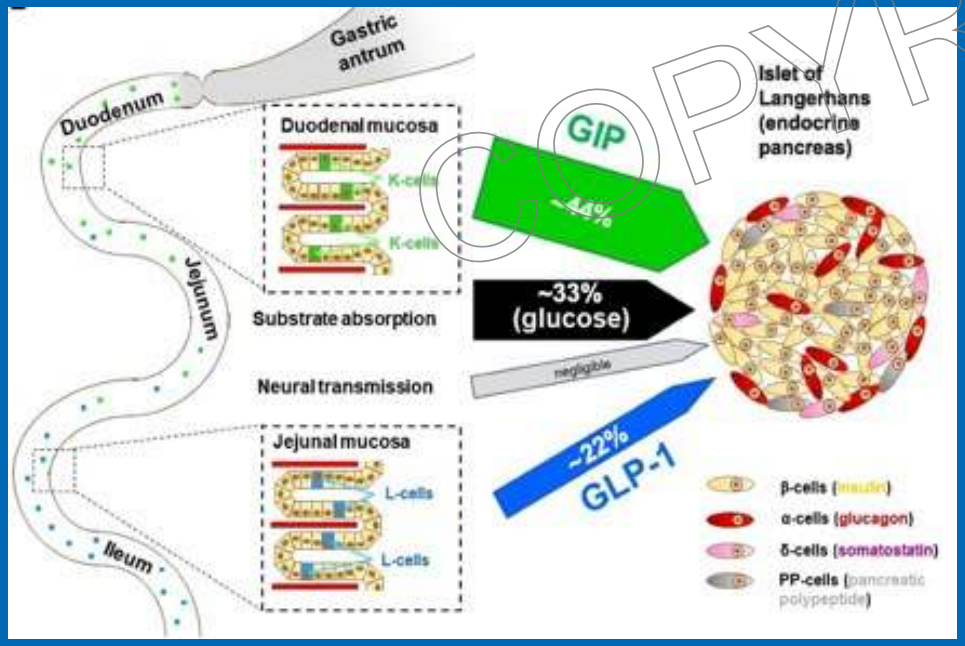
Adapted from DeFronzo RA et al. Diabetes 2009: 58: 773-795

The “incretin effect” is reduced in people with T2D

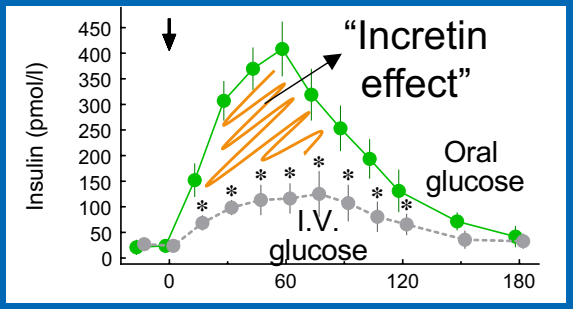
In people without diabetes, approximately 70% of the insulin secretion following a meal is related to the stimulatory effect of GIP & GLP-1

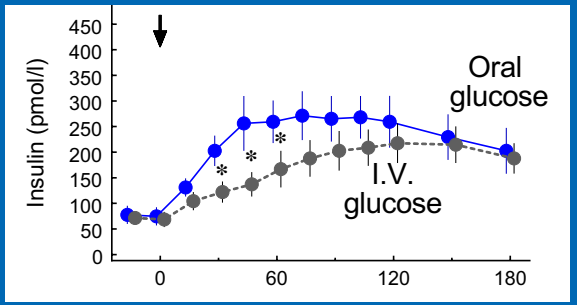


People without diabetes

People with T2D

Insulin secretion



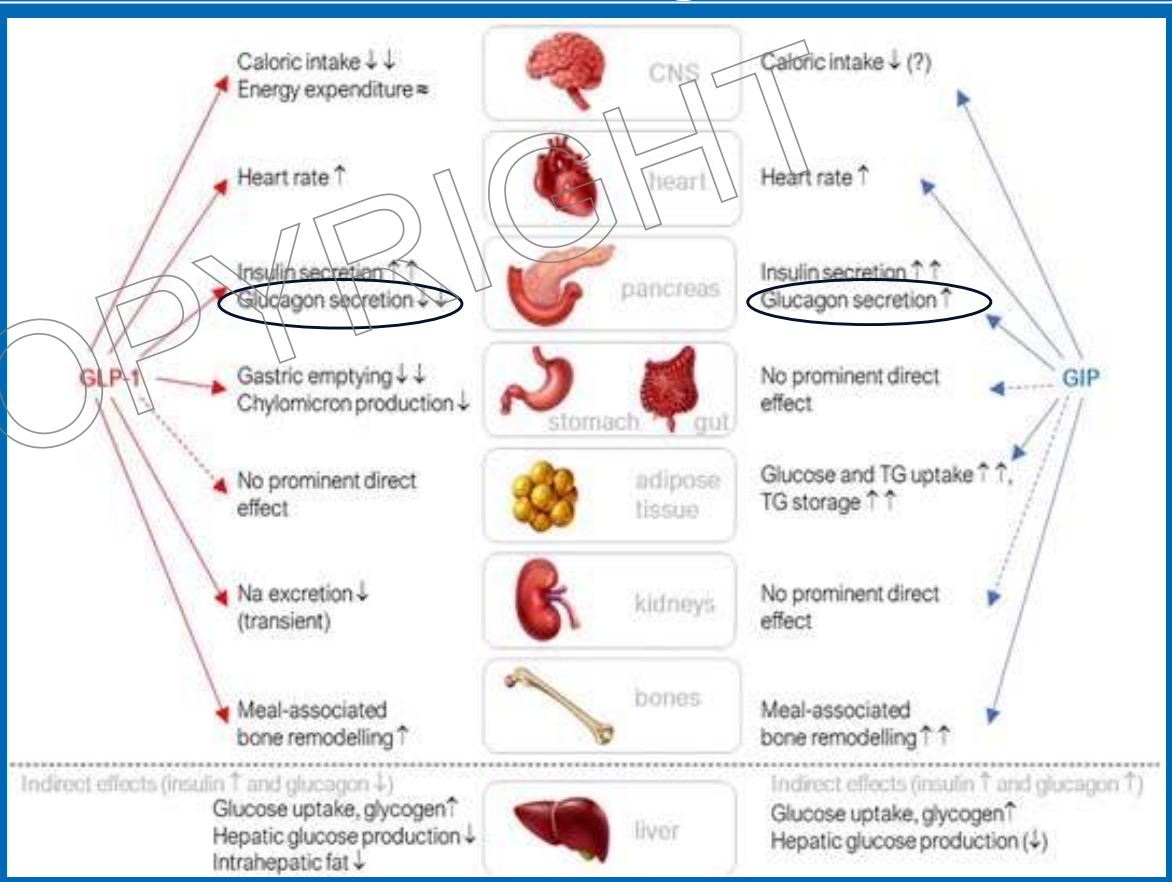


Adapted from Nauck MA et al. Diabetes 2019;68:897-900
Modified from Nauck MA et al. Diabetologia 2023: 66: 1780-1795

Overview of direct and indirect effects of GIP and GLP-1 in various tissues/organs

Direct effects:
GIP and GLP-1 receptors are expressed in the beta cells, brain, heart and in blood vessels

but NOT in the liver or muscle *(indirect effects)*



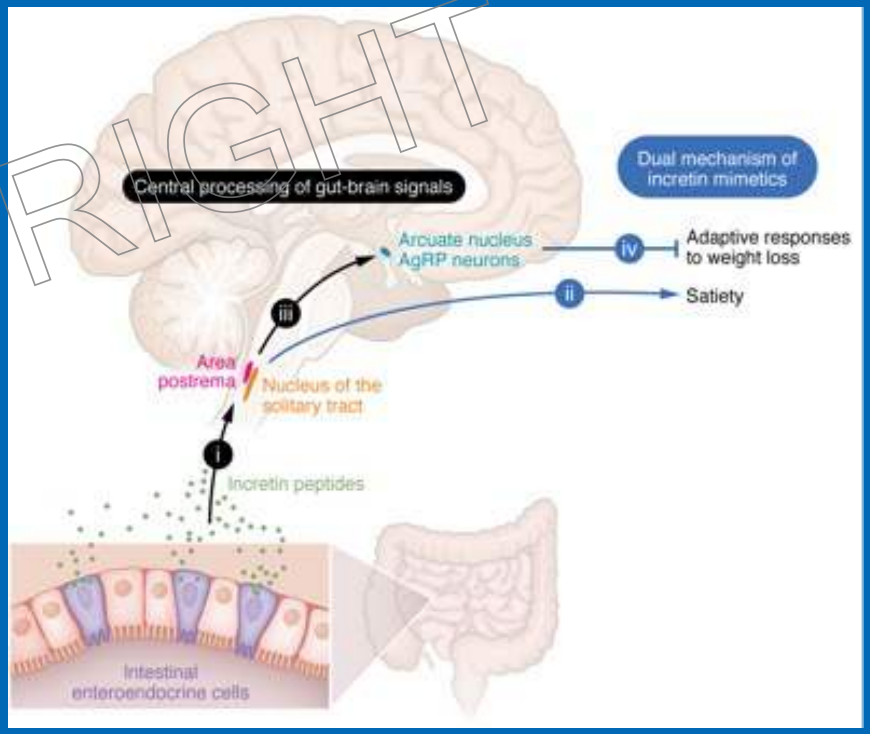
Nauck MA et al. Diabetes Obesity Metabolism 2021; 23 (S3): 5-29

Incretins and incretin mimetics induce satiety and reduce the adaptive response to weight loss

- Incretins and incretin mimetics engage the gut-brain axis.
- Due to their long-half life, weekly GLP-1RAs and dual agonists:

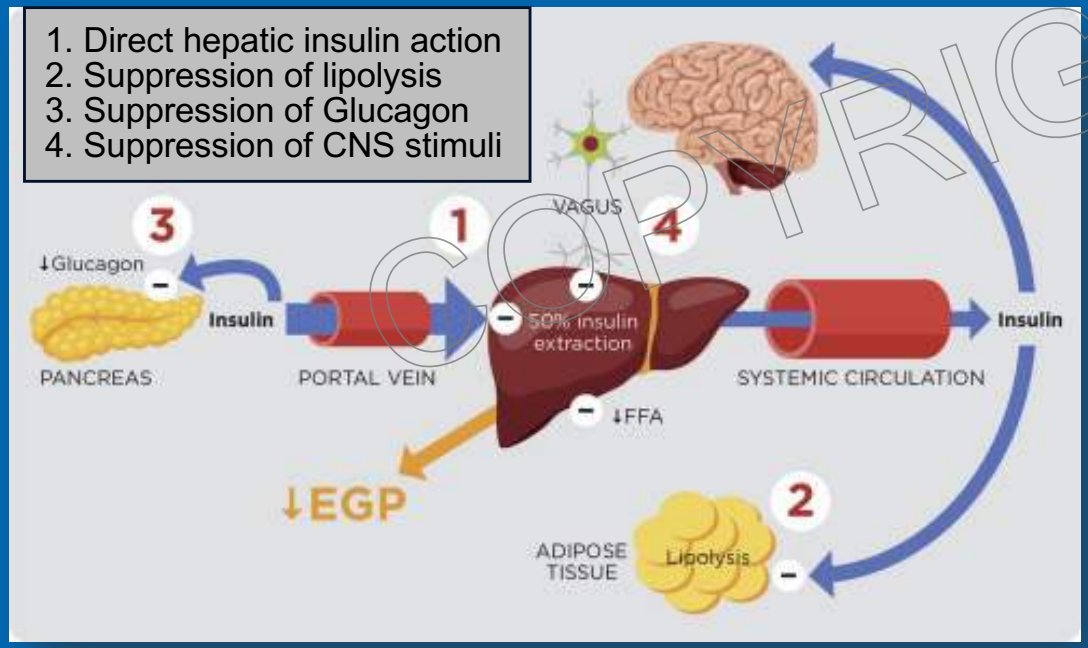
- persistently stimulate the sense of satiety

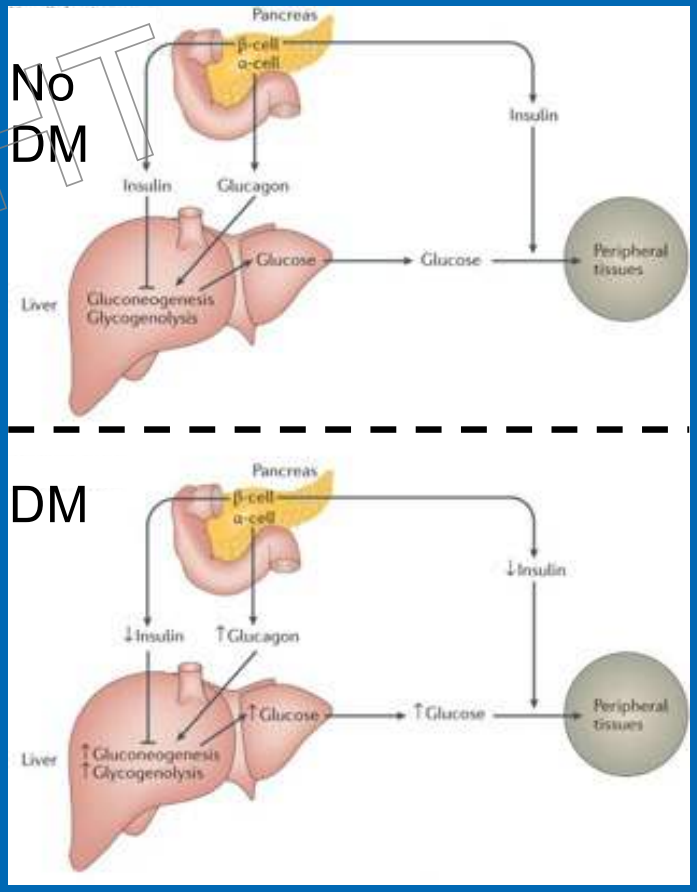
- blunt the adaptive response to weight loss



Gou Y and Schwartz MW. JCI 2023; 133 (19): e174597

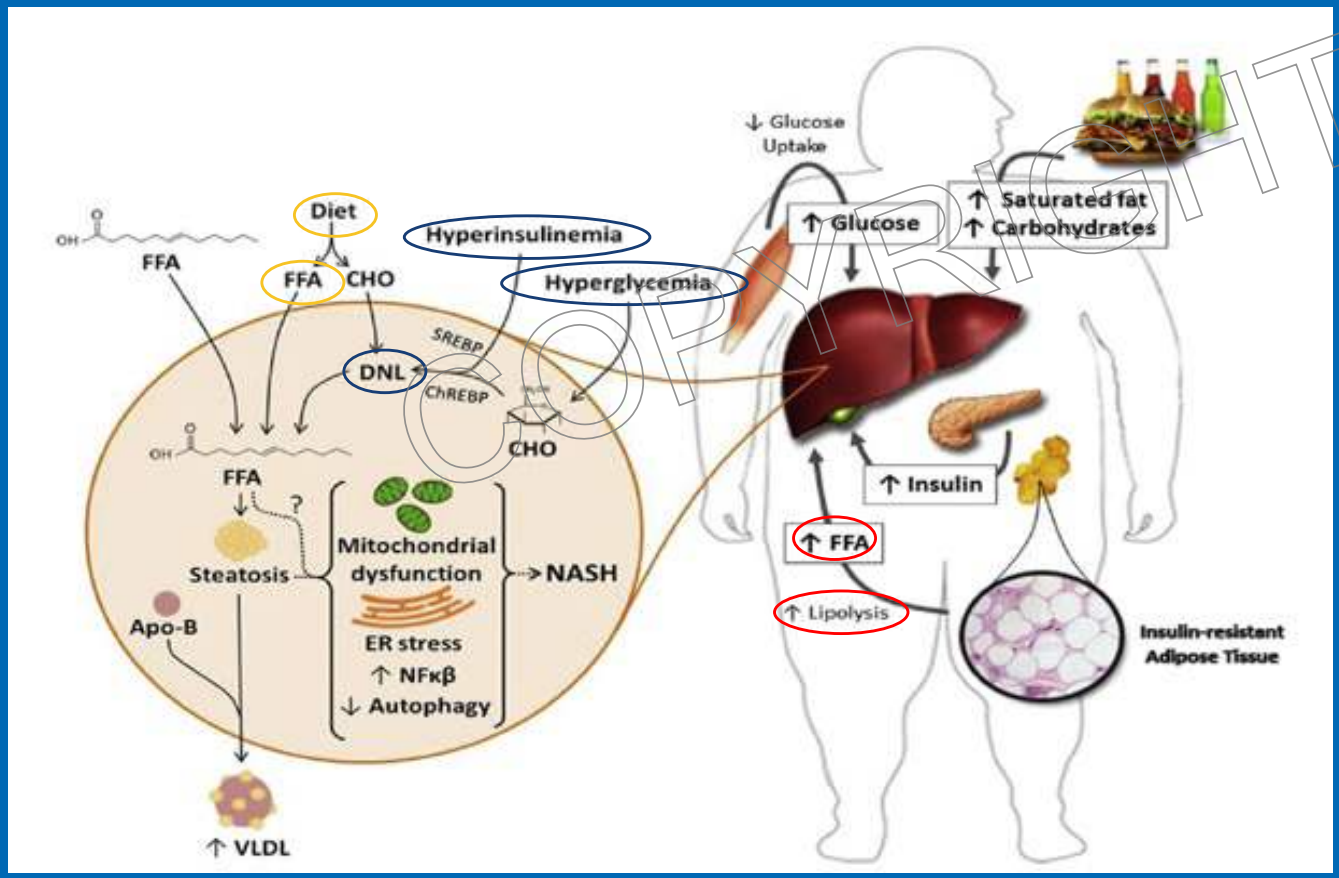
The abnormal balance between insulin and glucagon is a key factor for the excess hepatic glucose production in DM





Modified from Rines AK et al. Nature Reviews Drug Discovery 2016; 15:786–804
Modified from Lewis GF et al 2021;33:709-720

Increased *de novo* lipogenesis is a core defect of T2D and contributes to the accumulation of lipids in the liver

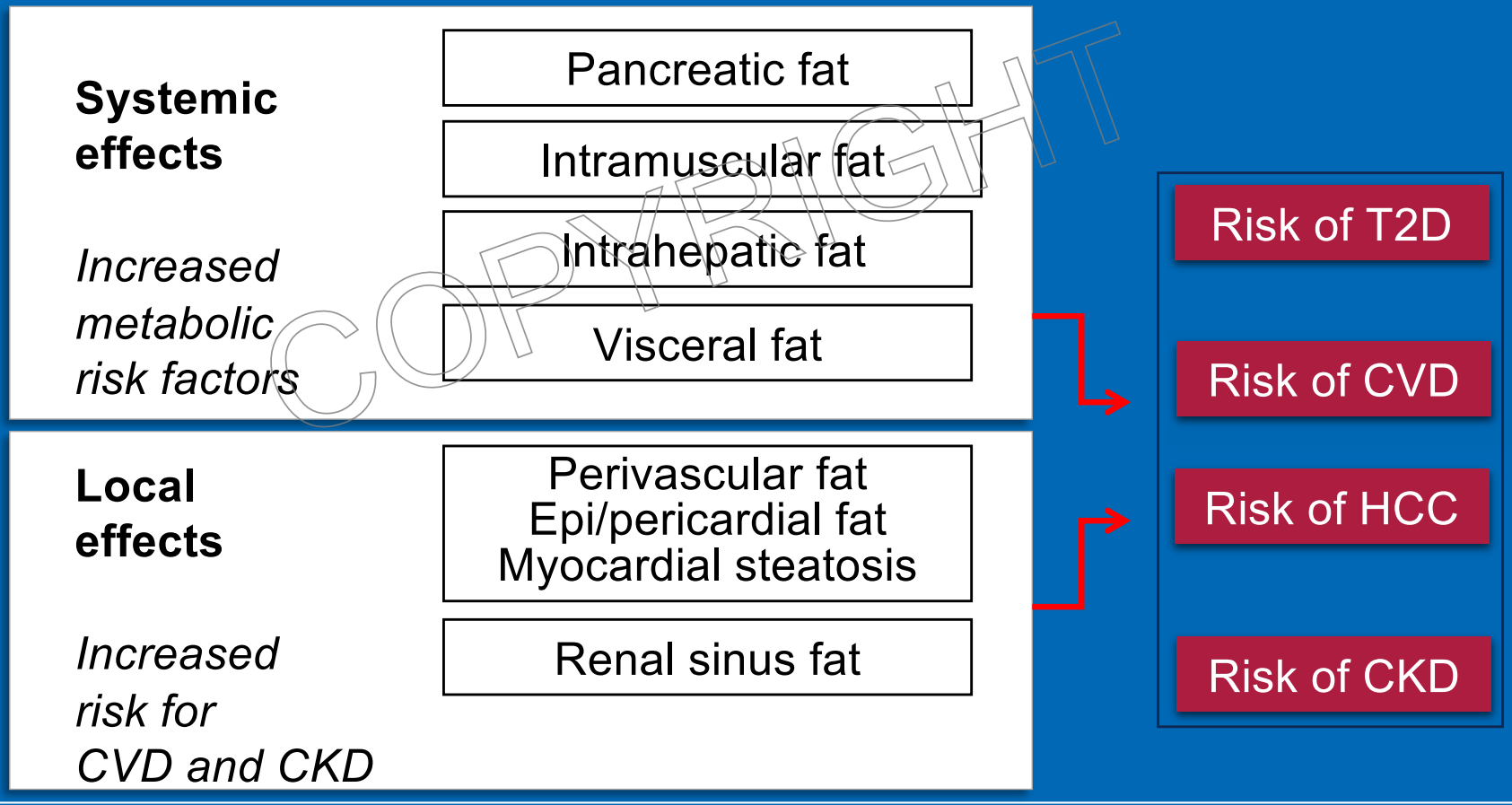


Potential mechanisms for excess FFA 'flux' to the liver:

- De Novo Lipogenesis
- Excess lipolysis
- Dietary intake

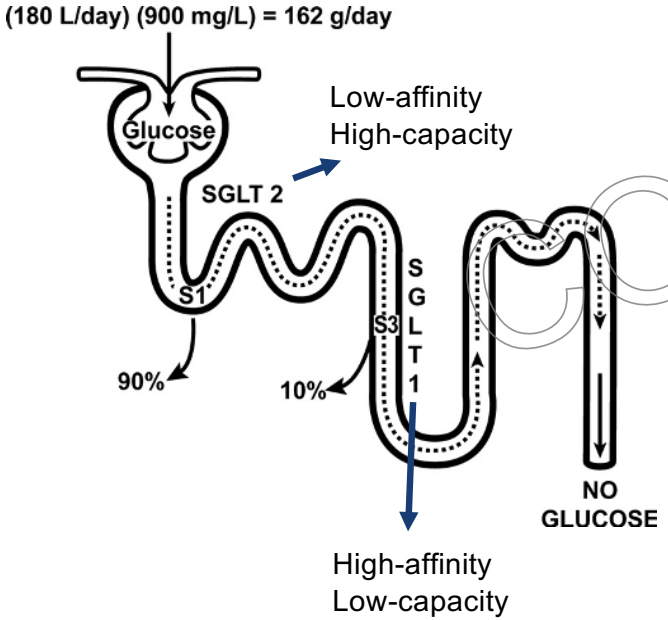
Bril, F et al. Endocrinol Metab Clin N Am 2016:765-781

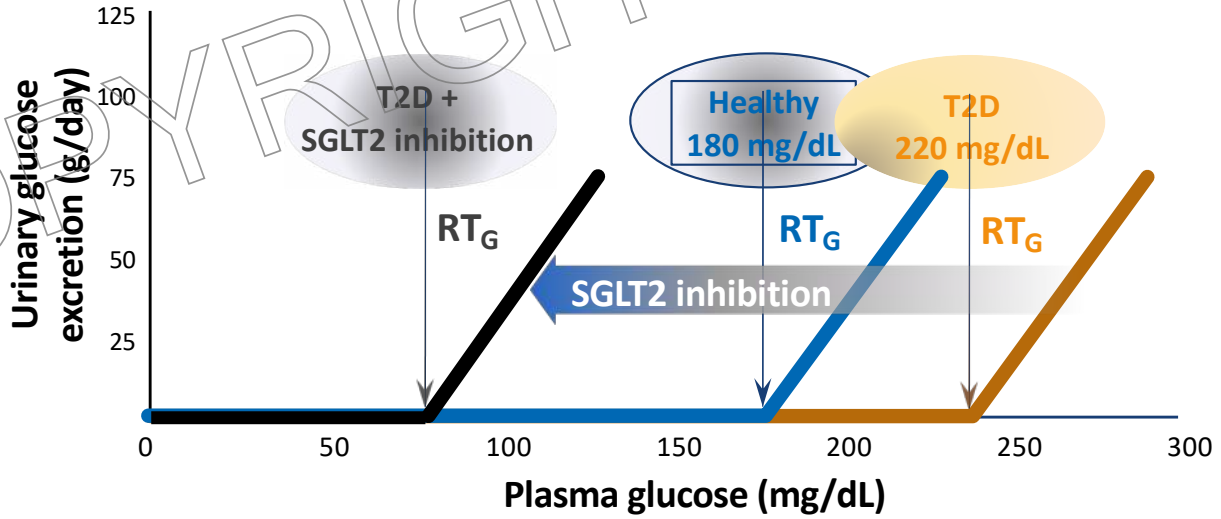
In people with insulin resistance, accumulation of fat in organs (beyond liver) increases risk of T2D, CVD, and CKD



B. Smith U. Atherosclerosis. 2015; 241:27-35

The increase threshold for glucose renal excretion contributes to hyperglycemia in people with T2D and is restored by SGLT2-inhibitors





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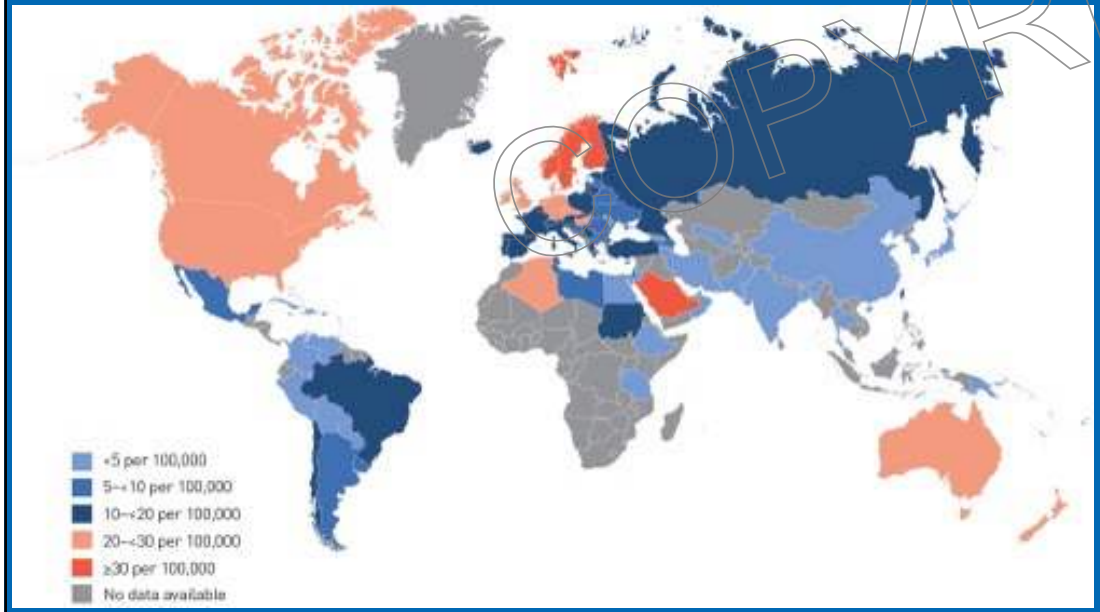
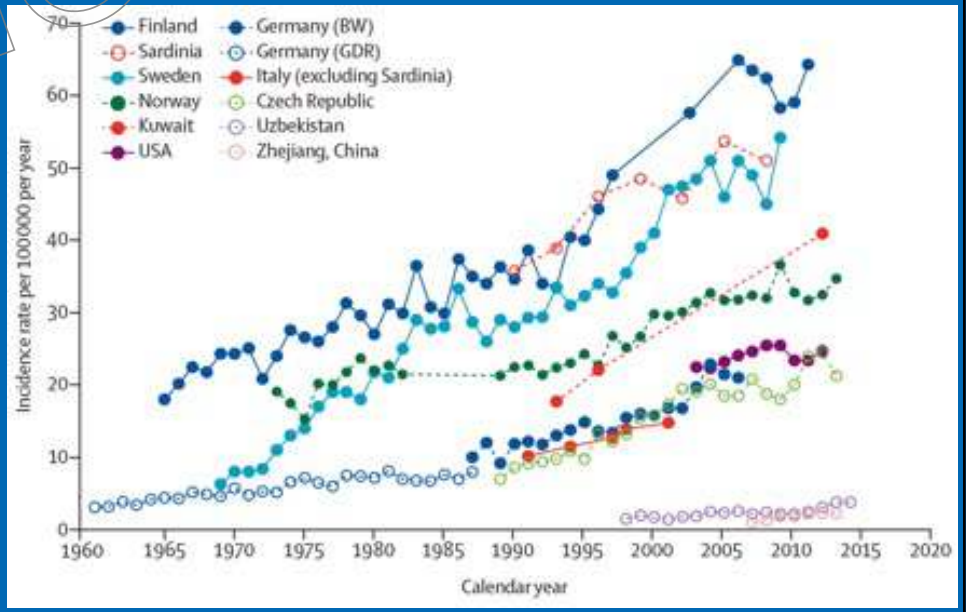
Abdul-Ghani MA, DeFronzo RA. *Endocr Pract*. 2008;14(6):782-790.
Nair S, Wilding JP. *J Clin Endocrinol Metab*. 2010;95(1):34-42.

Incidence of T1D Varies Between Countries and Over time

Map of age-sex standardized incidence rates (per 100,000) from publications of T1D in children aged under 15 years



Time trends in the incidence of T1D



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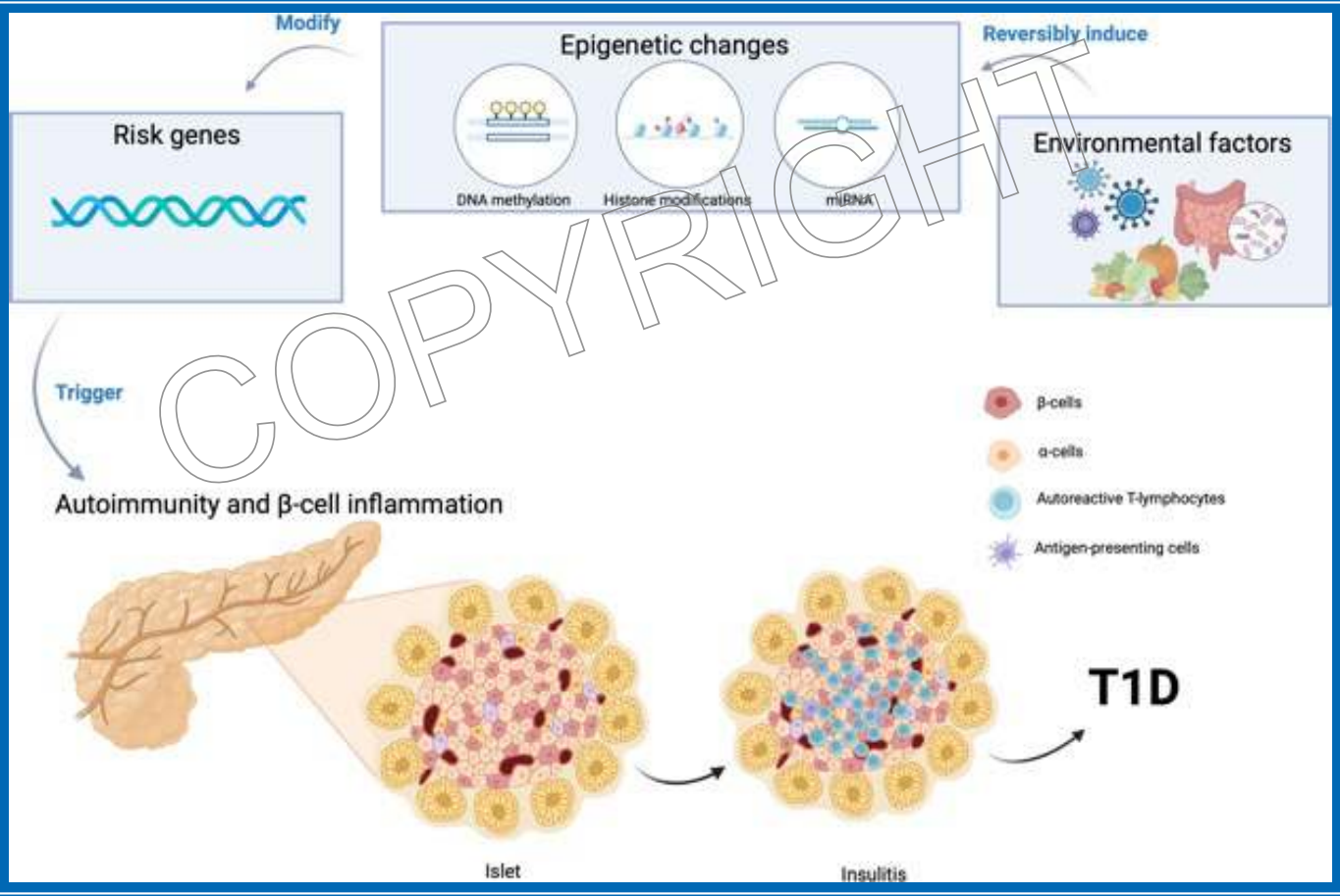
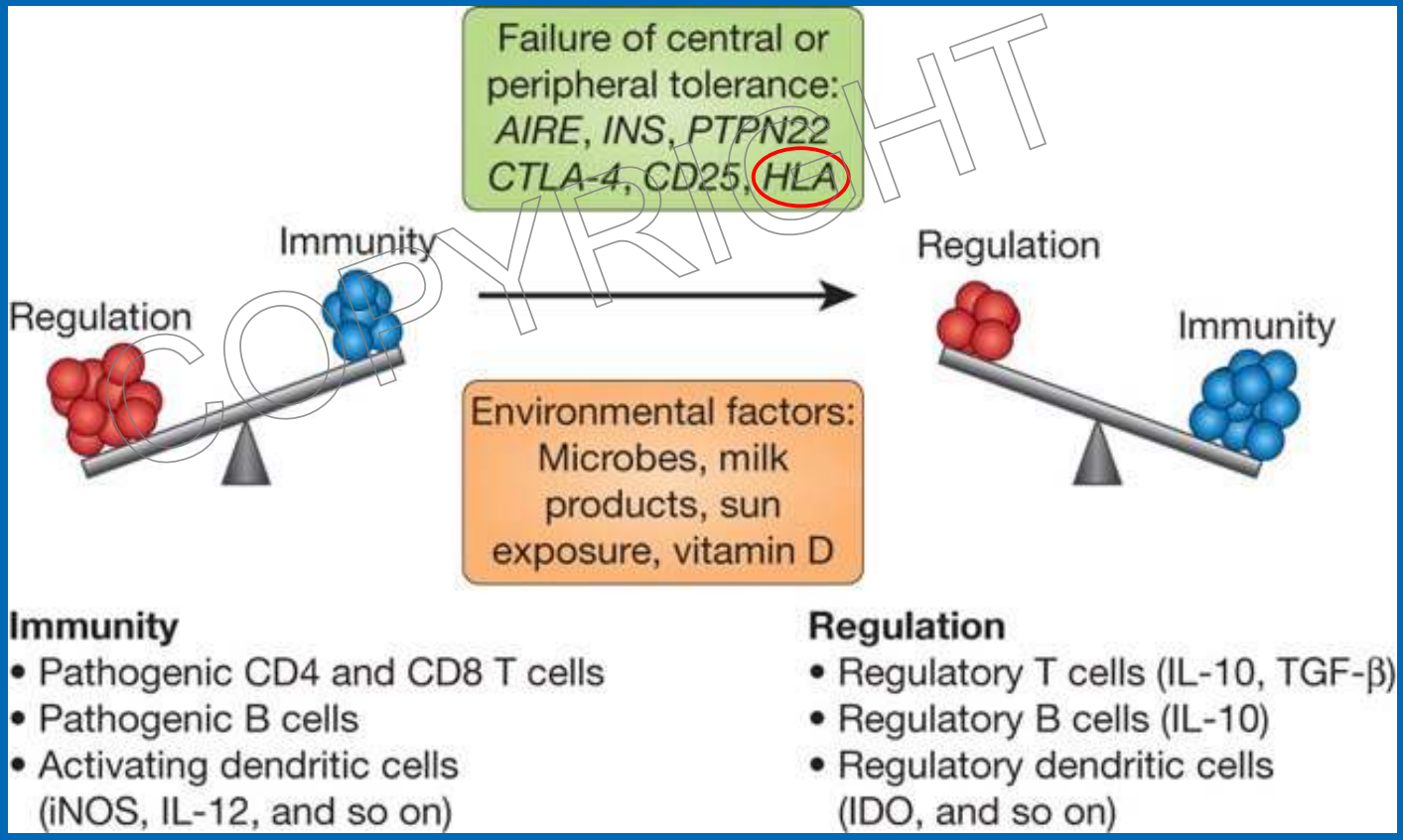
Patterson C et al. Diabetes Research and Clinical Practice 2019: 157:107842
Norris JM et al. Lancet Diabetes Endocrinol 2020:8(:226-238.

Risk genes and environmental factors underlying the insulitis associated with T1D



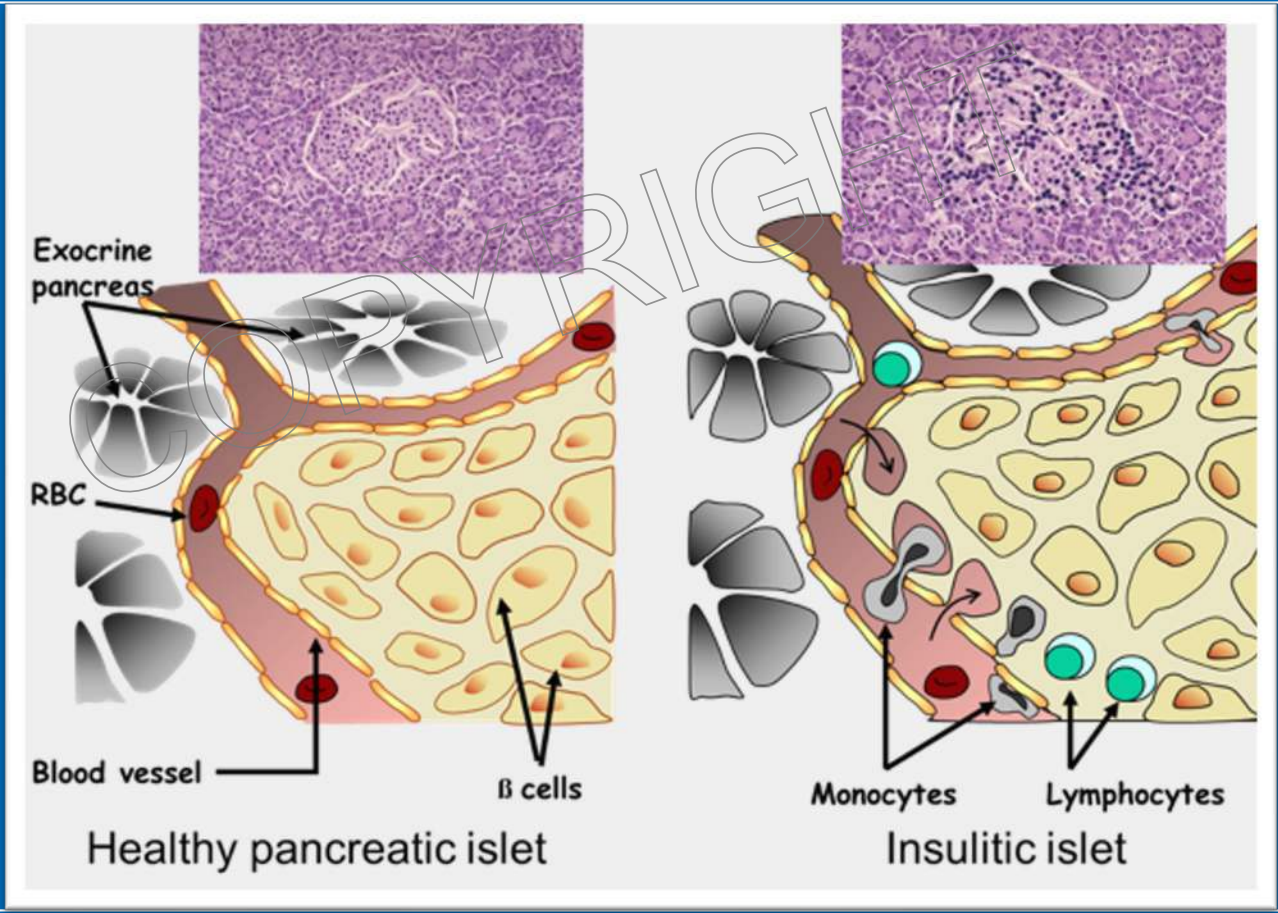
Mittal R et al. Front Endocrinol (Lausanne). 2024;15:1335435

Environmental factors play role in the balance between immune regulation and pathogenesis



Bluestone et al. Nature 2010; 464(29)1293-1300

Infiltration of auto-reactive CD8+ lymphocytes is a hallmark of insulitis in T1D



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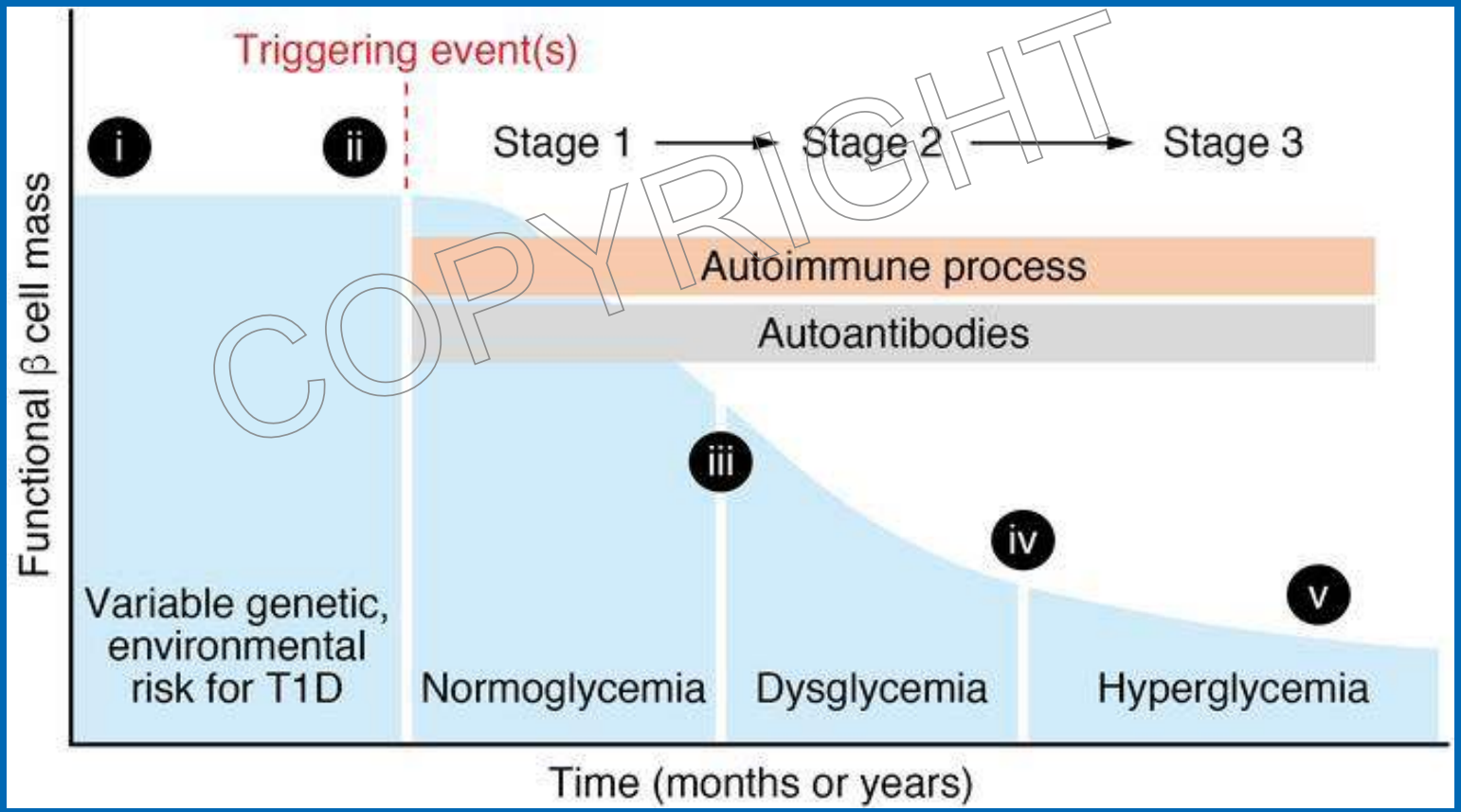
Patterson C et al. Diabetes Research and Clinical Practice 2019: 157:107842
Norris JM et al. Lancet Diabetes Endocrinol 2020:8(:226-238.

Autoimmune process and auto-antibody production precede clinical evidence of T1D

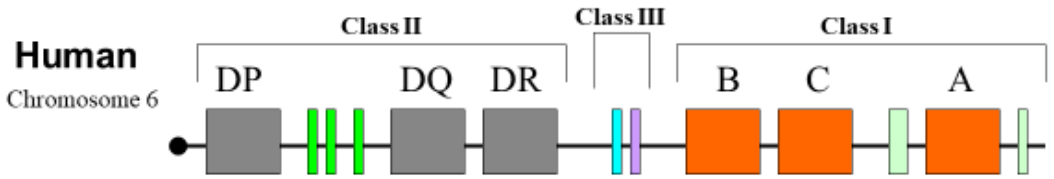


Powers AC J Clin Invest 2021: 131(8):e142242

HLA risk alleles T1D

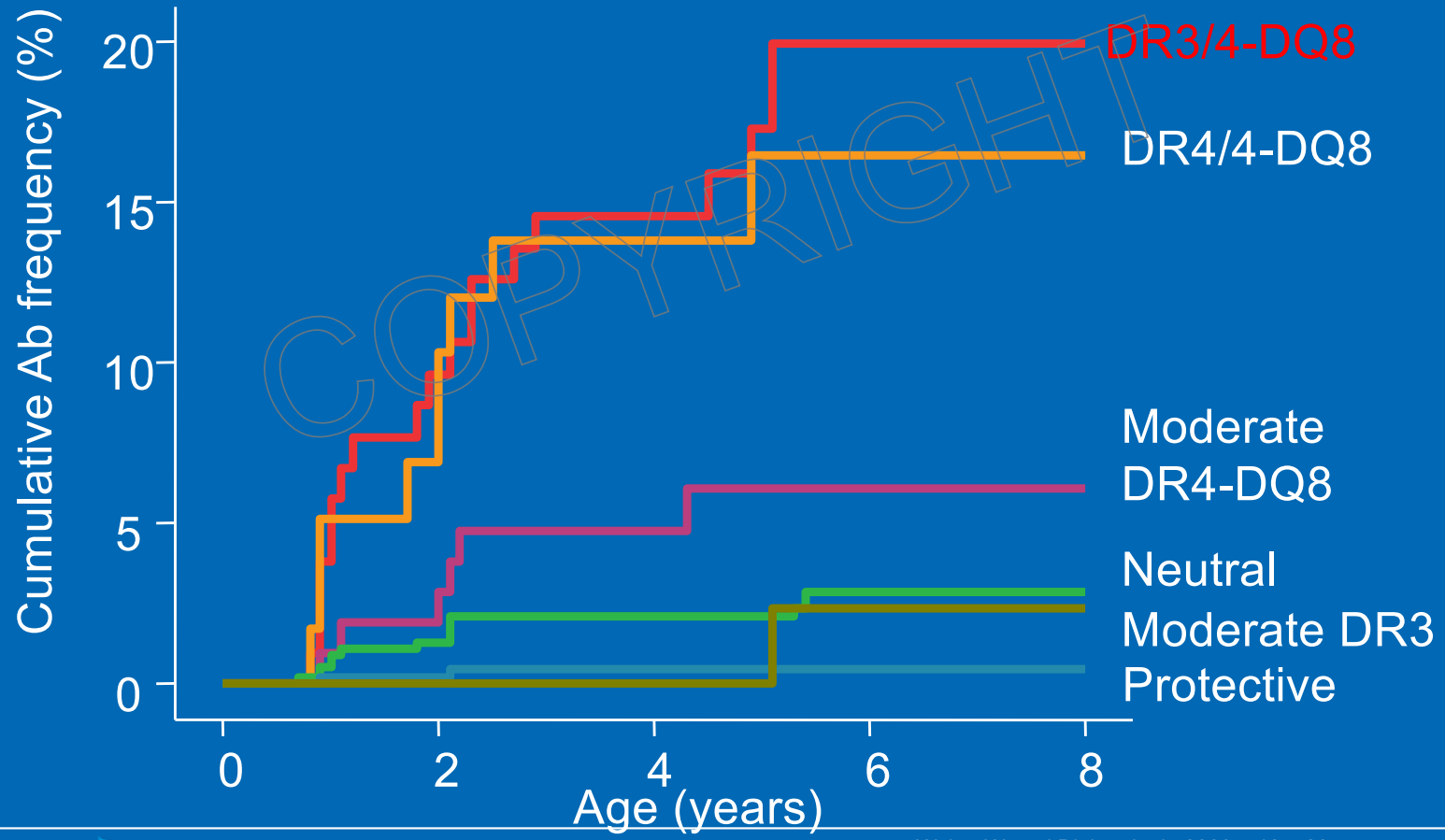
Diabetes Risk by HLA DQ and DR Haplotypes

RISK	DRB1		DQA1	DQB1
HIGH	0401,0405,0402	(DR4)	0301	0302
	0301	(DR3)	0501	0201
	0801		0401	0402
MODERATE	0401		0301	0301
	0401		0301	0303
	0403		0301	0302
	0101		0101	0501
	1601		0102	0502
LOW	1101		0501	0301
PROTECTIVE	1501	(DR2)	0102	0602
	0701		0201	0303
	1401		0101	0503



Battaglia M et al Diabetes Care 2020 Jan; 43(1): 5-12

Development of islet autoantibodies in the offspring of parents with T1D



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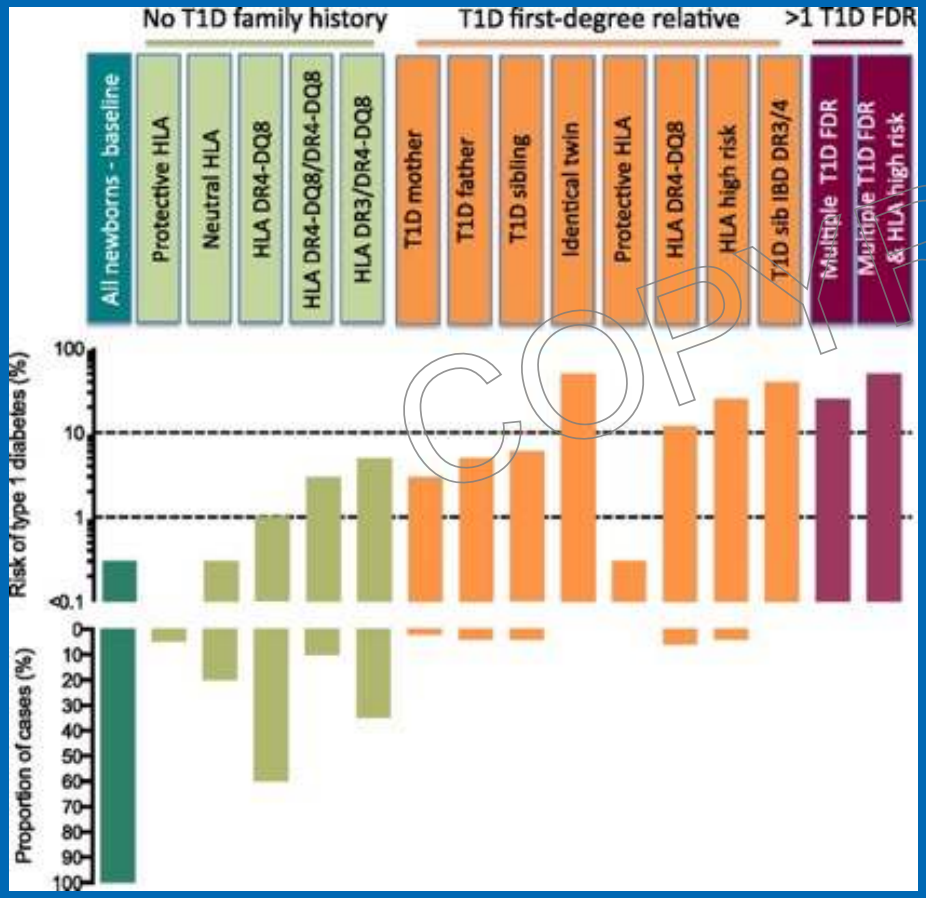
Walter W et al Diabetologia 2003: 712–720

Autoimmune process and auto-antibody production precede clinical evidence of T1D



- Offspring of an affected mother is 1% to 4%,
- Offspring of an affected father is 3% to 8%,
- Offspring of both affected parents is as high as 30%;
- Monozygotic twins, the risk of developing T1D the first ten years of diagnosis of the first twin 30%, with a lifetime risk of around 65%
- Vast majority of people diagnosed with T1D have no known family history of T1D

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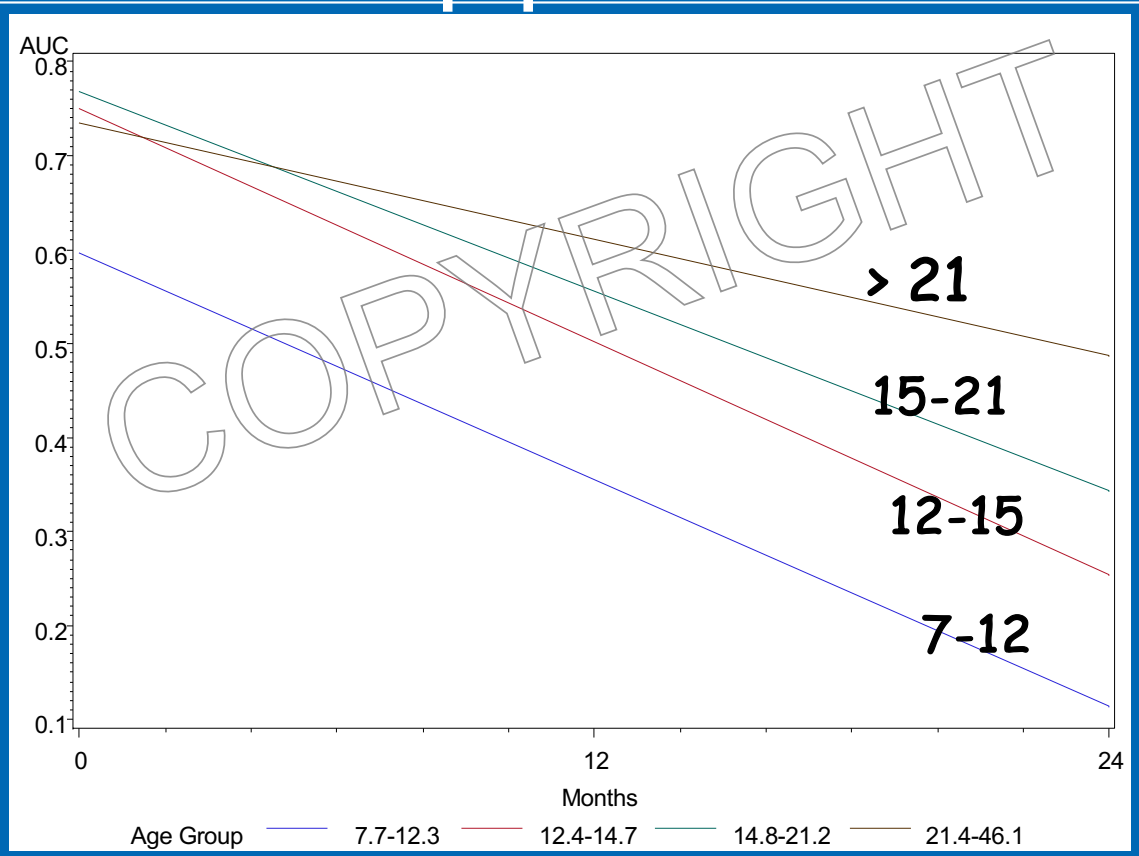
Bonifacio E Diab Care 2015:38:989-996

Impact of age of Diagnosis on progression of C-peptide decline

C-peptide area under curve



Months from diagnosis

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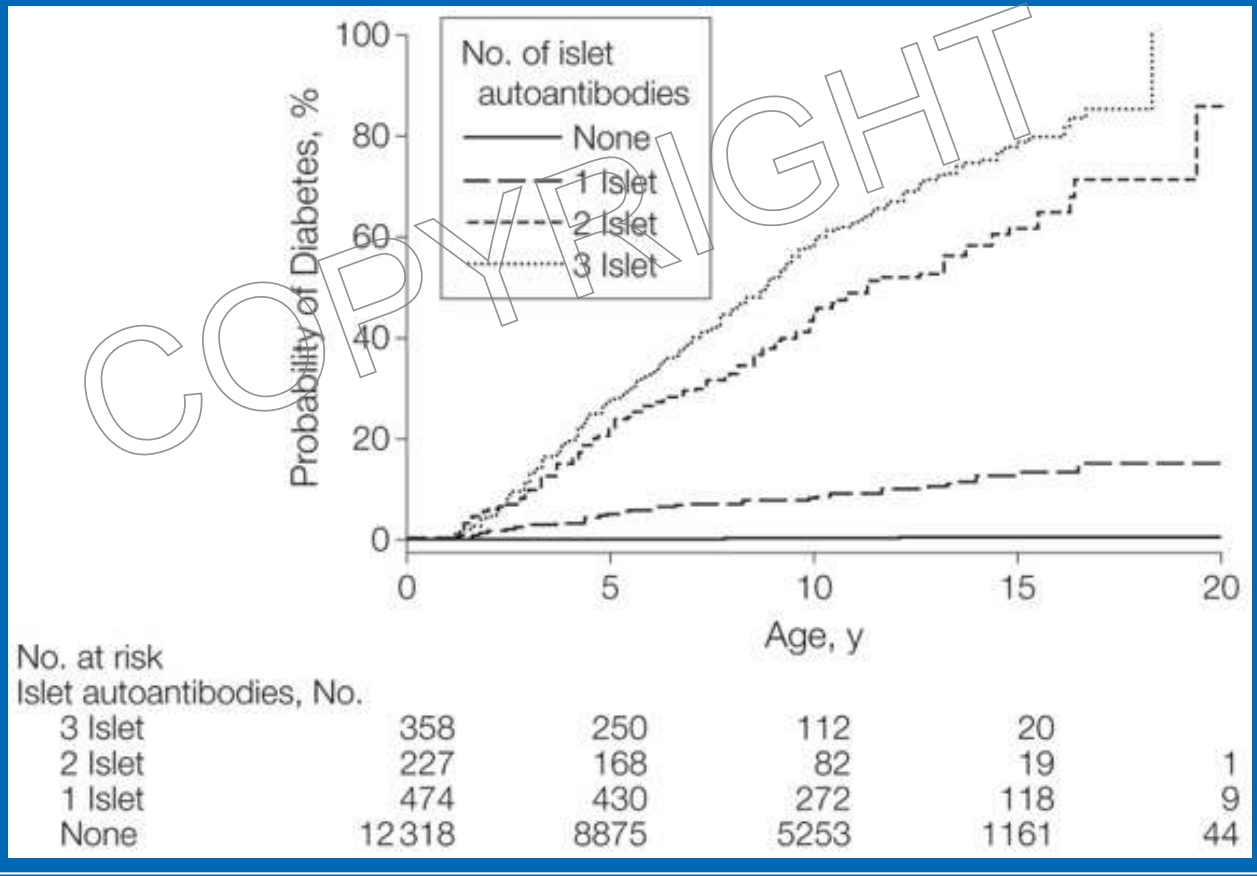
Greenbaum C.J Diabetes. 2012; 61:2066-2073.

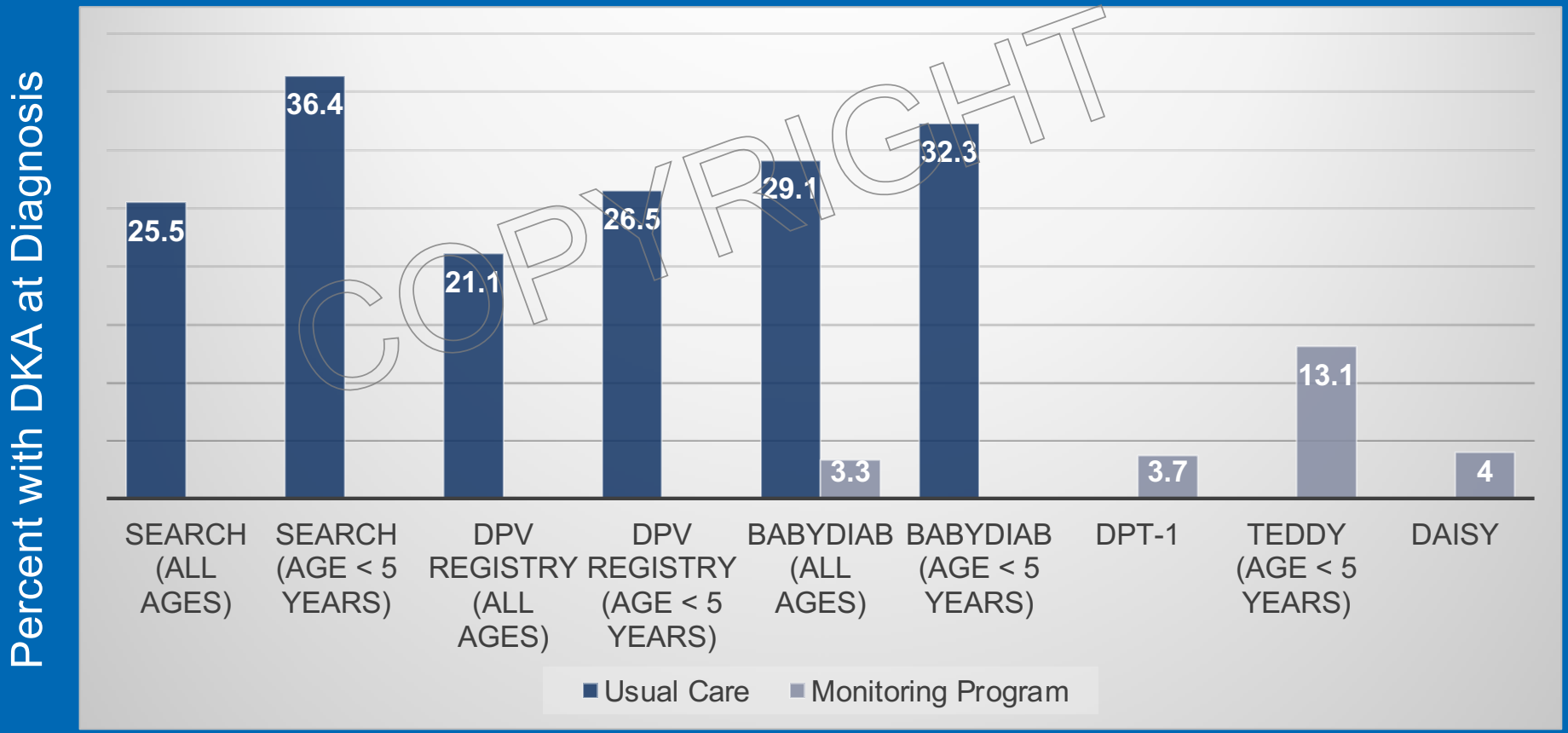
In at-risk-children, the number of autoantibodies predicts the risk of progression to T1D



No. at risk Islet autoantibodies, No.					
3 Islet	358	250	112	20	
2 Islet	227	168	82	19	1
1 Islet	474	430	272	118	9
None	12318	8875	5253	1161	44

Ziegler AC et al. JAMA. 2013;309(23):2473-2479.

Screening at-risk people decreases the risk of DKA at diagnosis

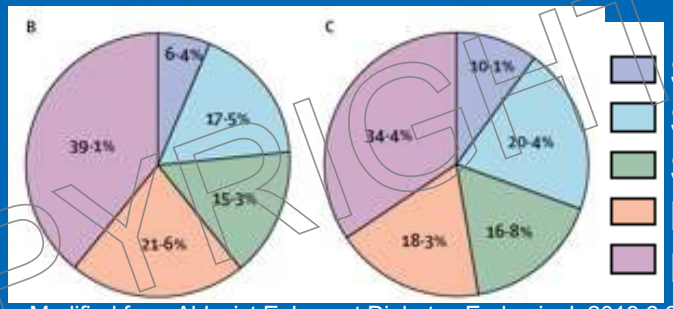


Adapted from Greenbaum CJ et al Drugs 2019;79:43-6

Subgroups of adult-onset diabetes and associations with outcomes

~9,000 people with DM from two independent cohorts were study clustered *at diagnosis* based on:

- GAD antibodies
- BMI
- Age
- HbA1c
- HOMA2-IR and HOMA2-B

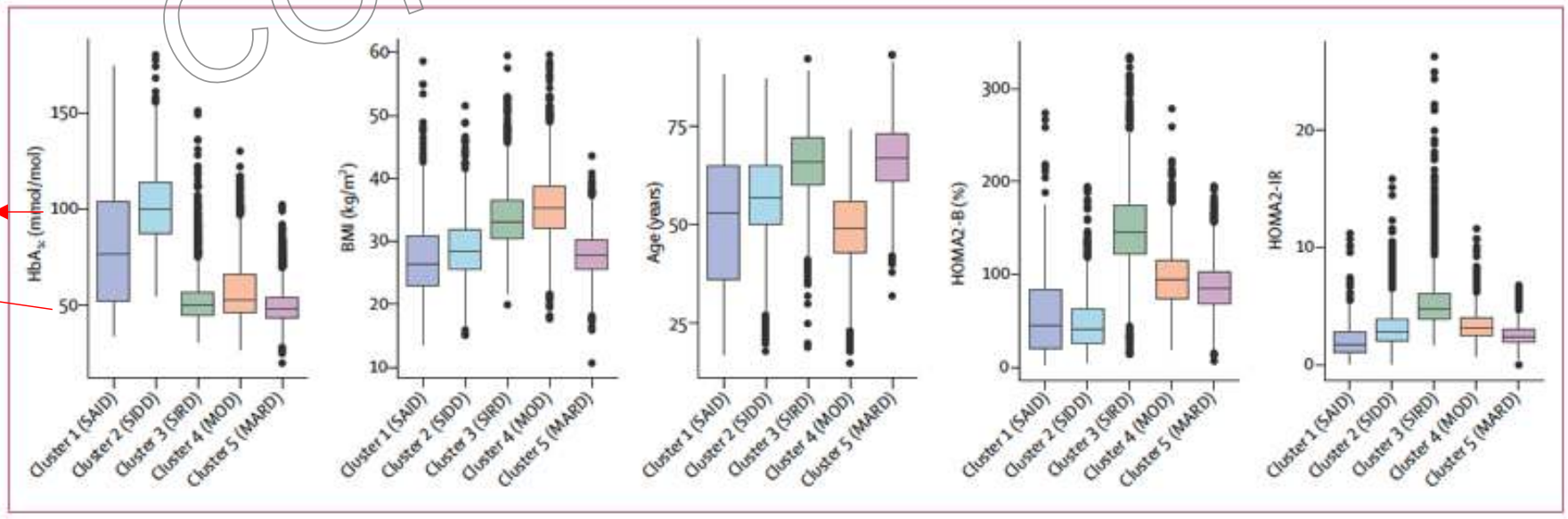


SAID= severe a.immune DM
SIDD= severe insulin-deficient DM
SIRD= severe insulin-resistant DM
MOD= mild obesity-related DM
MARD= mild age-related DM

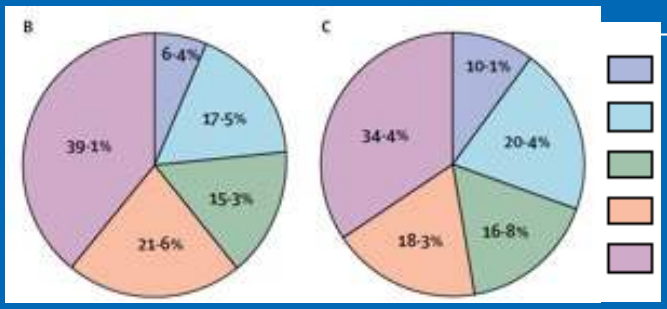
Modified from Ahlqvist E. Lancet Diabetes Endocrinol. 2018;6:361-369

11.3%

6.7%

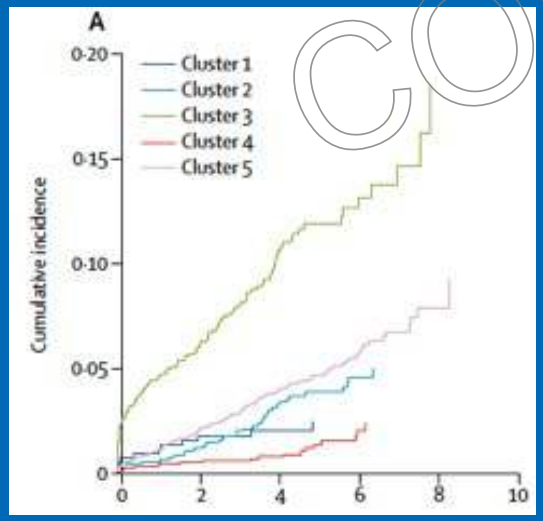


Incidence of complications over time by cluster



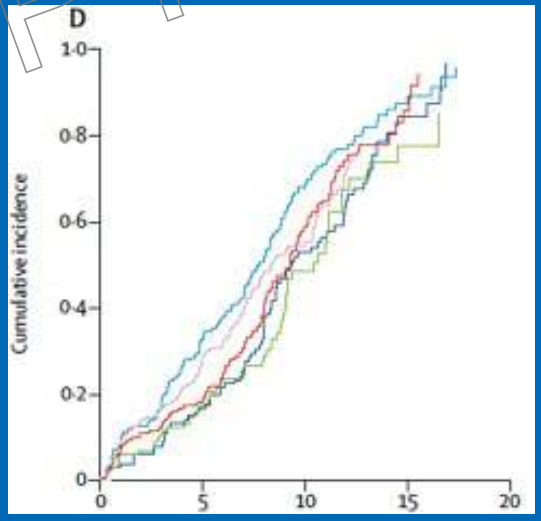
- SAID= severe a.immune DM
- SIDD= severe insulin-deficient DM
- SIRD= severe insulin-resistant DM
- MOD= mild obesity-related DM
- MARD= mild age-related DM

Time to CKD 3b-V



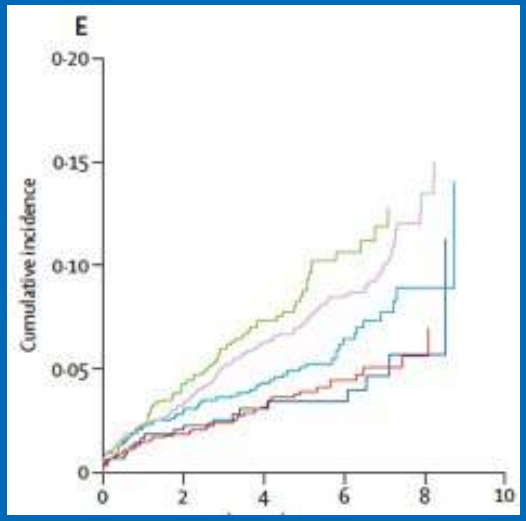
Diabetes Duration (years)

Time to NPDR



Diabetes Duration (years)

Time to coronary events



Diabetes Duration (years)

Modified from Ahlqvist E. Lancet Diabetes Endocrinol. 2018;6:361-369

Conclusions

- Both Type 1 and Type 2 diabetes results from the interaction of genetic and environmental factors, some of which are modifiable.
- Through rigorous research, multiple pathogenetic factors have been uncovered or are active areas of investigation.
- A better understanding of the communication between tissue and systemic modulators will be essential to guide more precise preventative, diagnostic, and treatment strategies.

Thank you

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