

UNIVERSITÀ DEGLI STUDI DI PALERMO

Azienda Ospedaliera Universitaria
Policlinico Paolo Giaccone Palermo

Scuola di Medicina e Chirugia
Dipartimento Biomedico di Medicina Interna e Specialistica – Di. Bi. M. I. S.
Insegnamento di Endocrinologia
Scuola di Specializzazione in Endocrinologia e Malattie Metaboliche

Diabete di Tipo 1
Nuove modalità d'esordio

Carla Giordano

Disclosure information

La Prof. Carla Giordano dichiara di aver ricevuto dalle seguenti Aziende Farmaceutiche i seguenti compensi per le seguenti motivazioni:

Research support

- **Eli Lilly, Novo Nordisk, Novartis, Astra Zeneca, MSD, Takeda, MSK, Sanofi**

Advisory Board

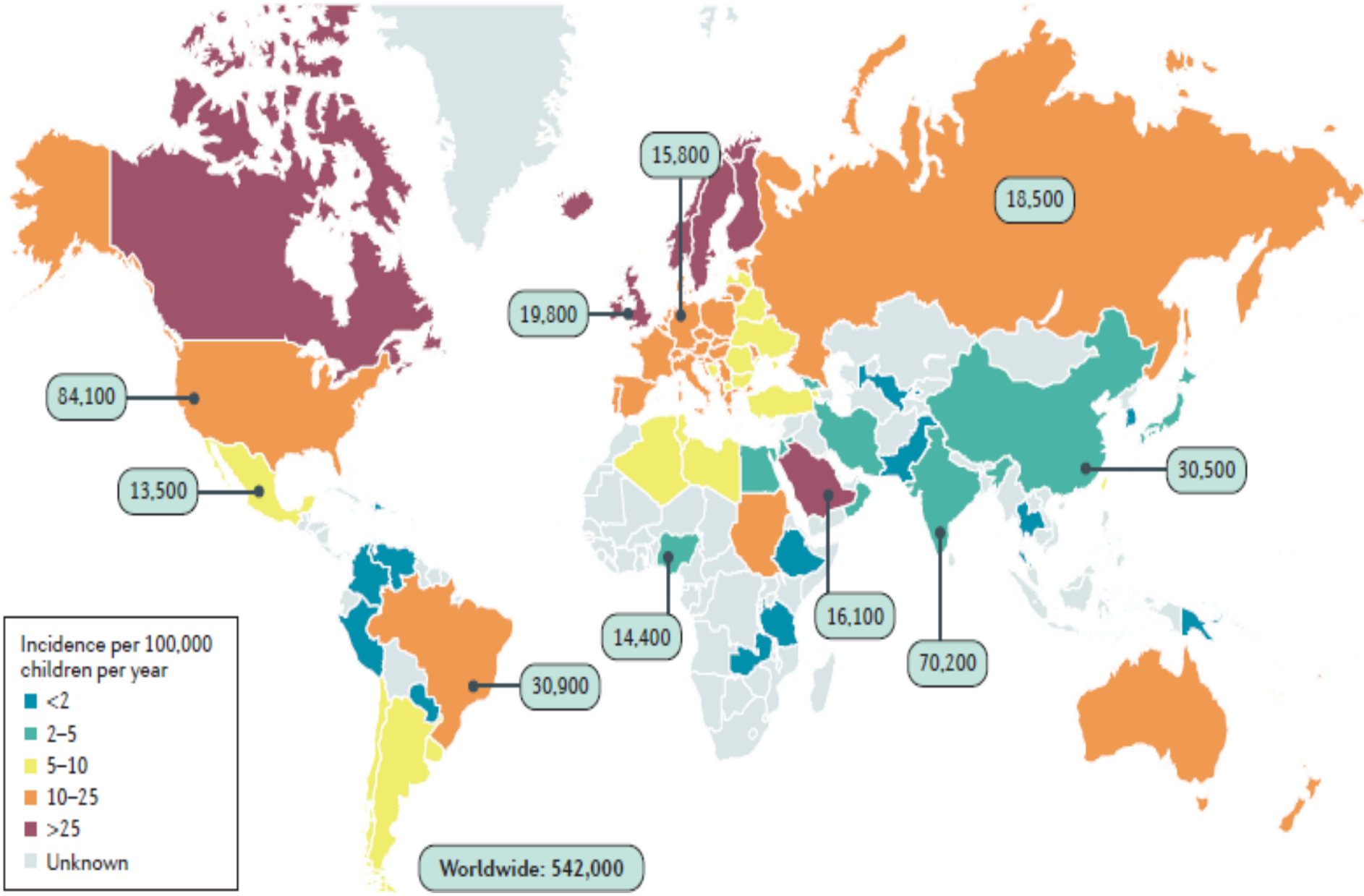
Boheringer Ingelheim, Eli Lilly, Novo Nordisk, Janssen, Shire, Astra



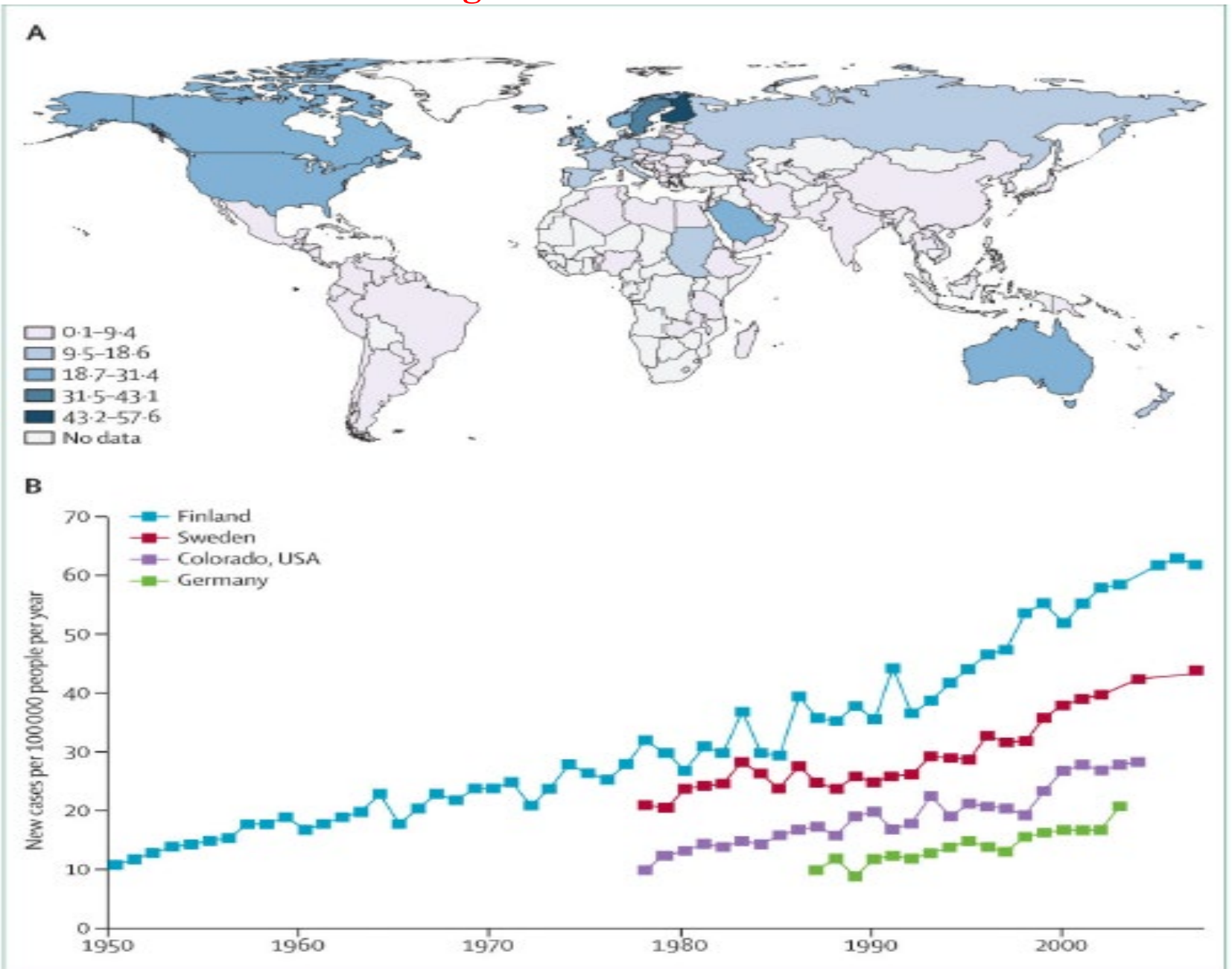
Esprimo massima gratitudine alla Società Italiana di Diabetologia per avermi formata, stimolata, sostenuta e gratificata in quasi 40 anni di professione.

SID è nel mio cuore e SID è la mia seconda casa

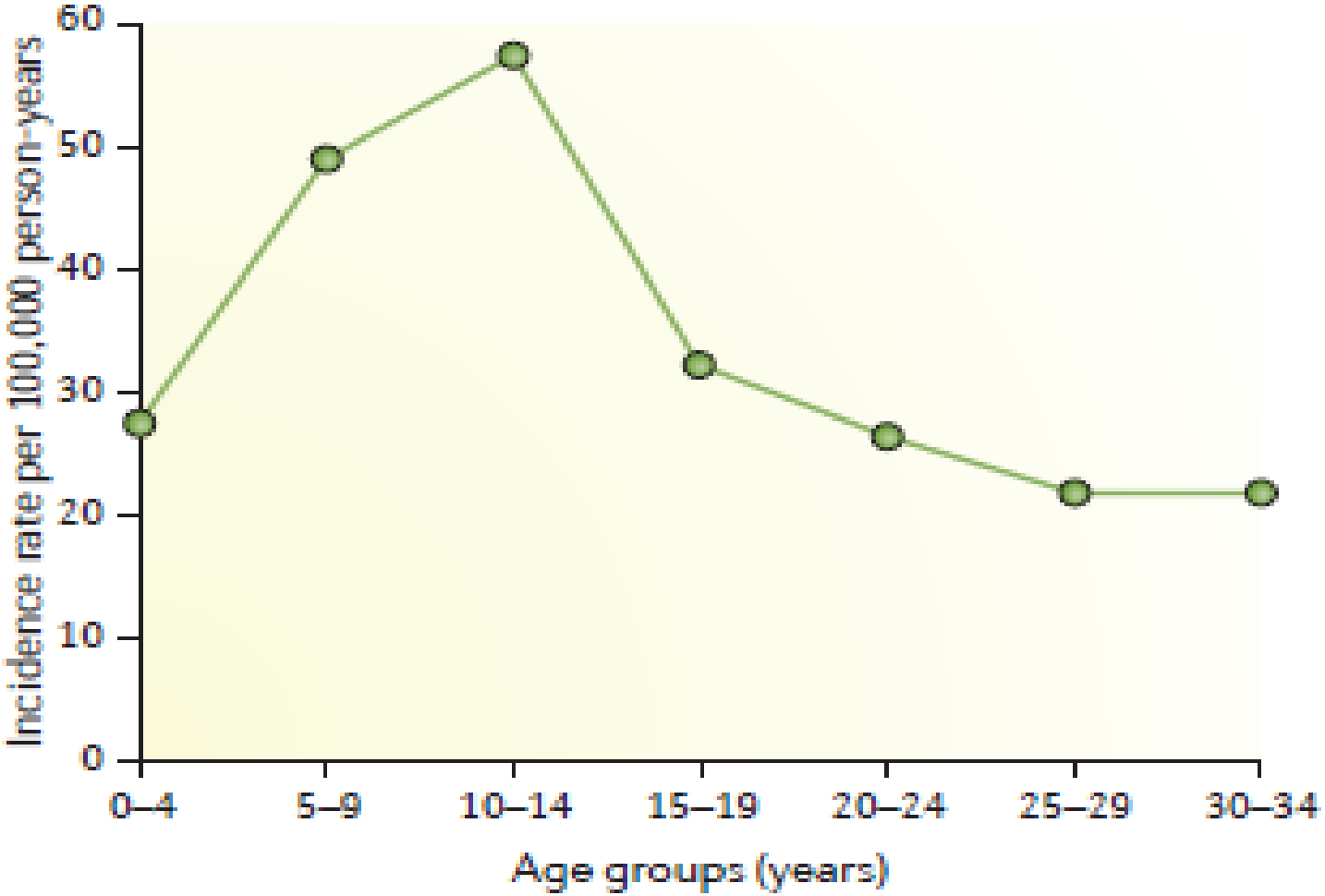
The incidence and prevalence of T1DM in children



Incidence of type 1 diabetes in children aged 0–14 years, by geographical region and over time

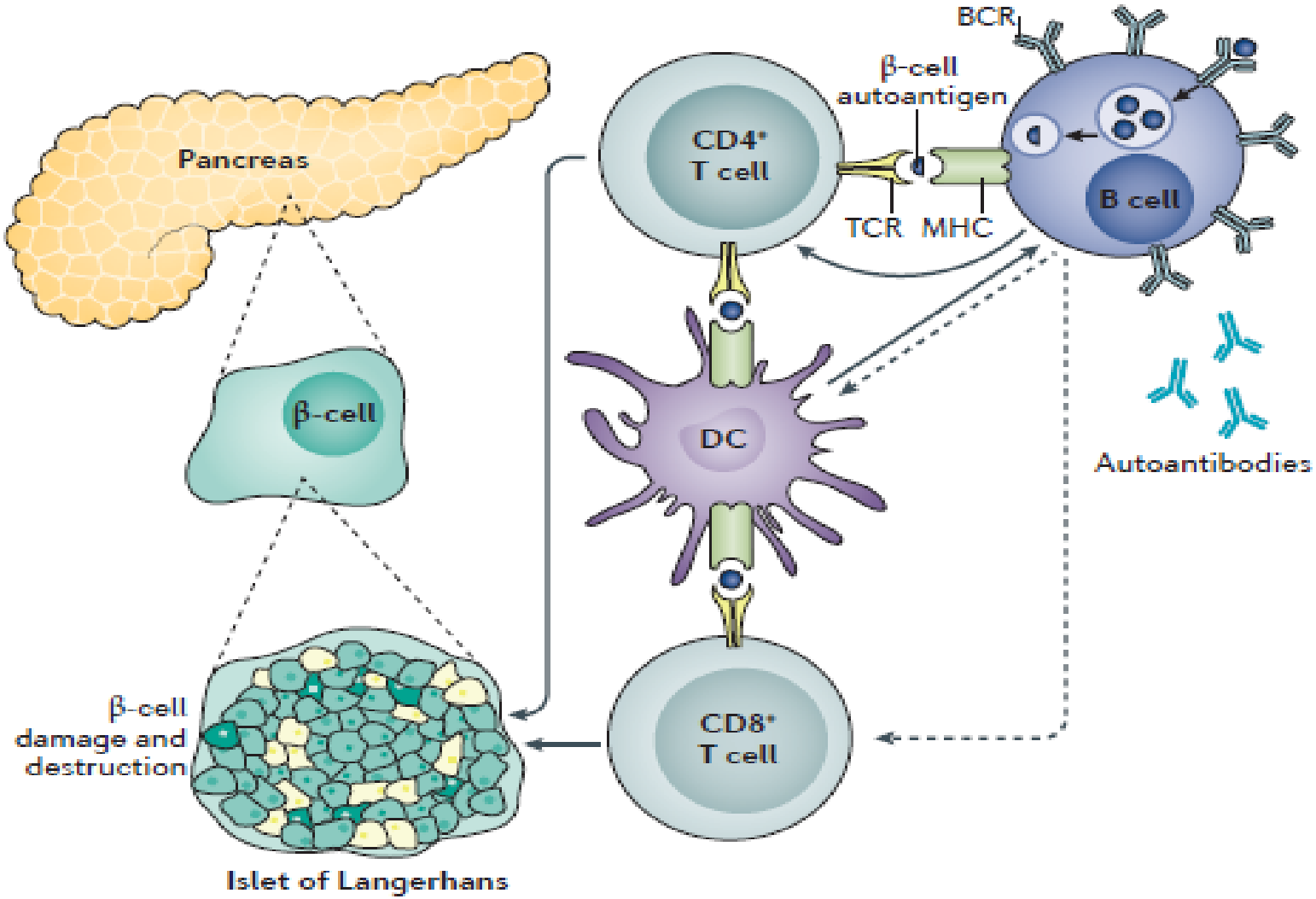


Age-specific incidence rates of T1DM

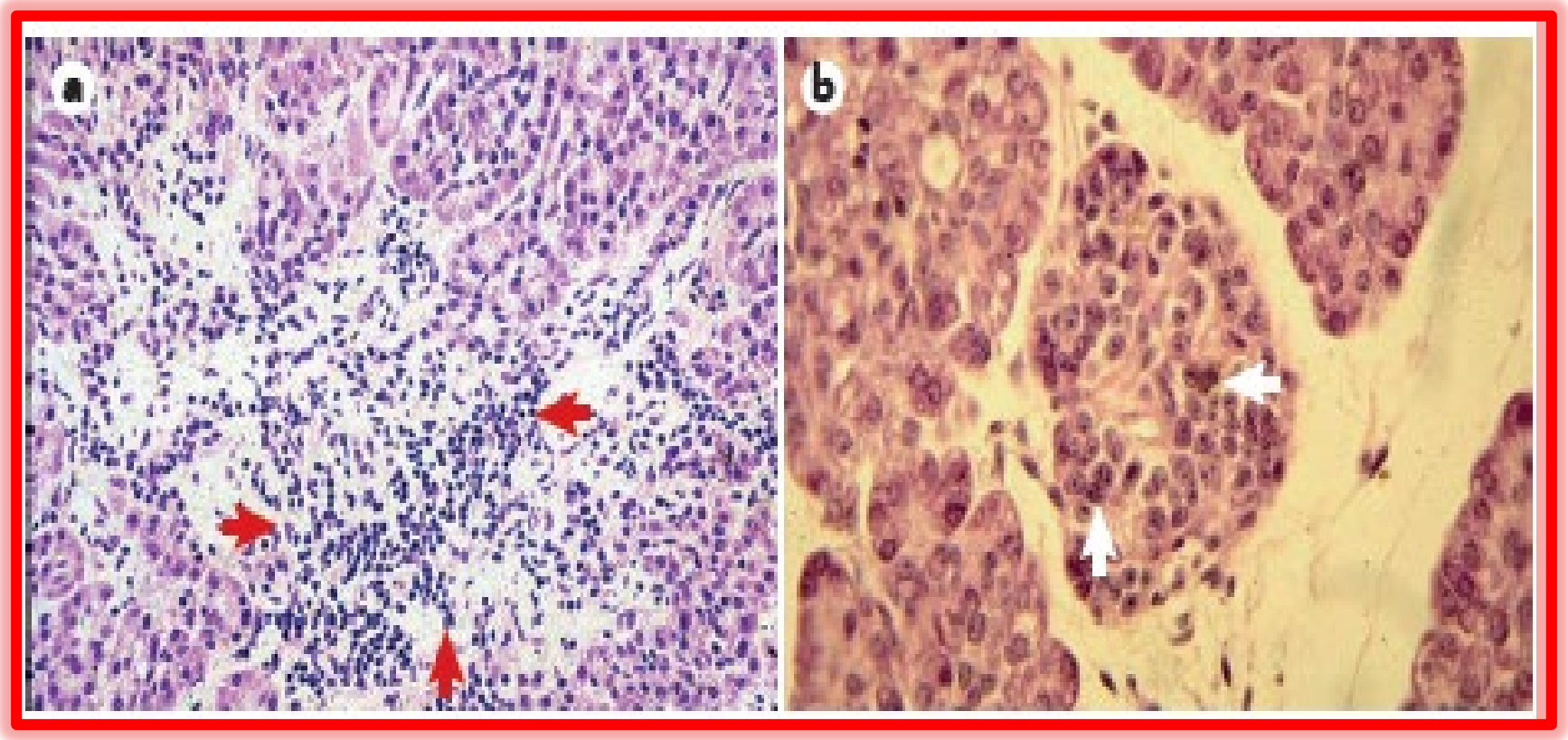


Anastasia Katsarou et al., NATURE REVIEWS | **DISEASE PRIMERS , 2017**

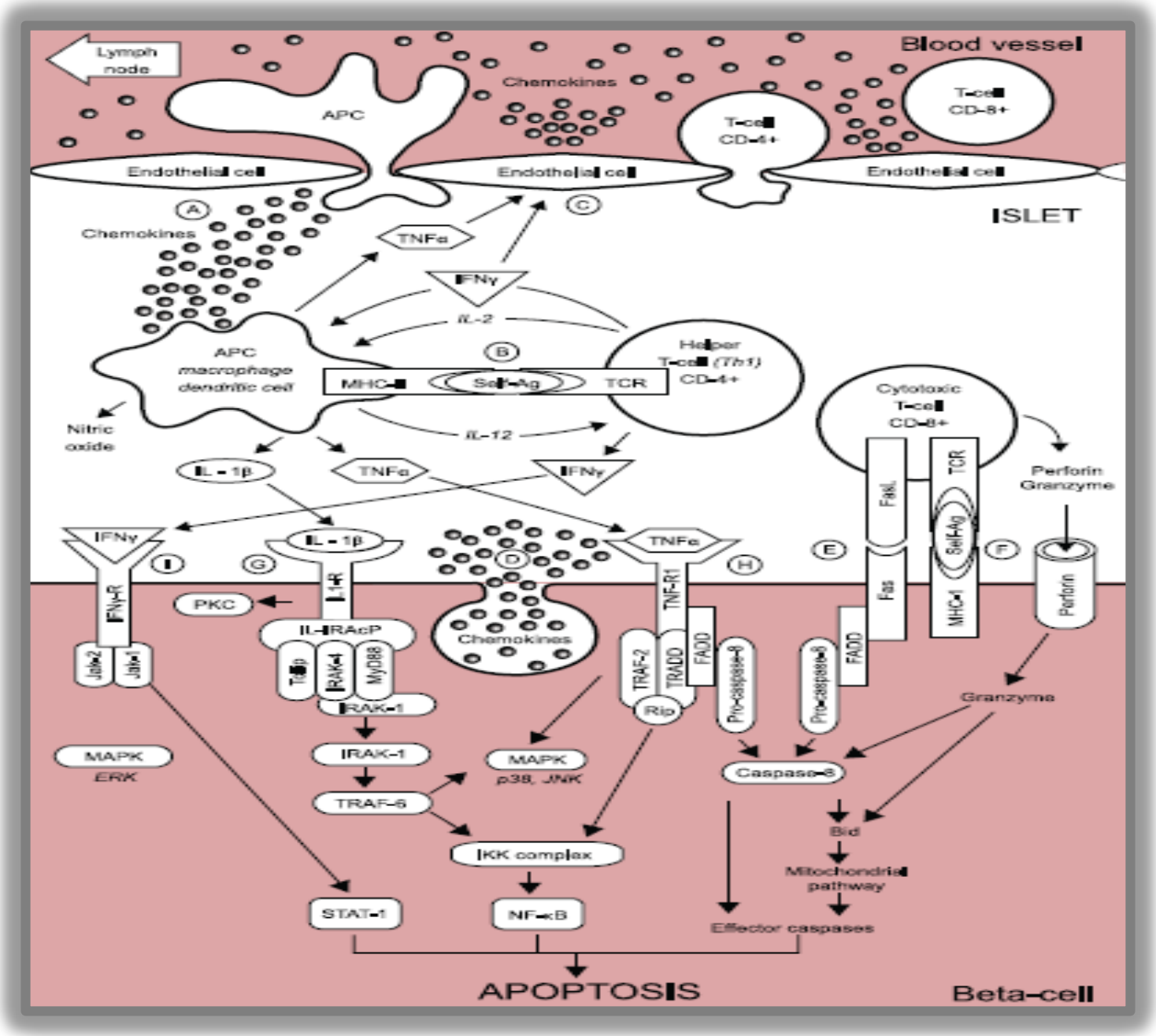
Pathogenesis of T1DM

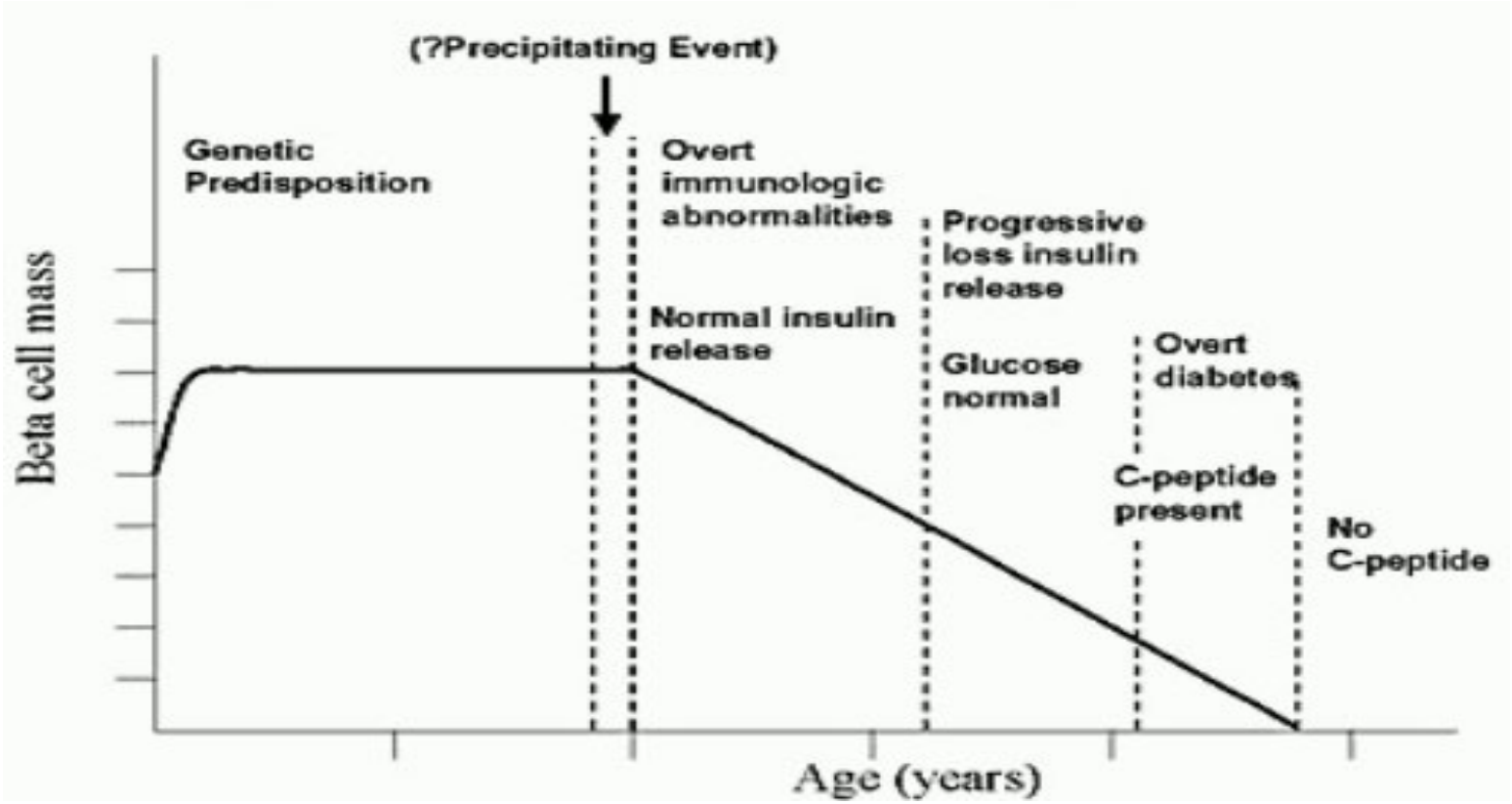


Pancreatic inflammation and insulitis in T1DM



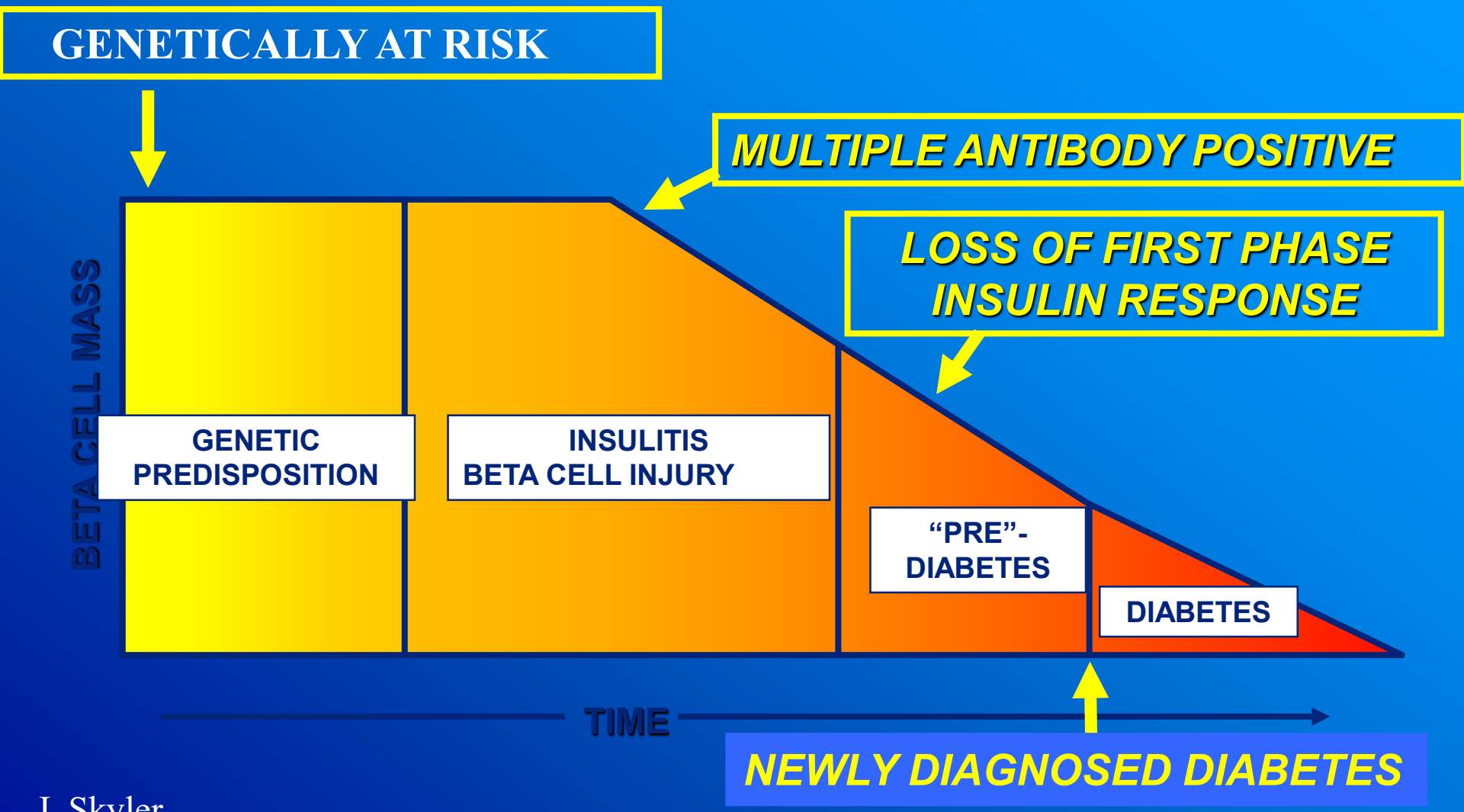
The auto-immune attack to the beta-cells in Type 1 DM





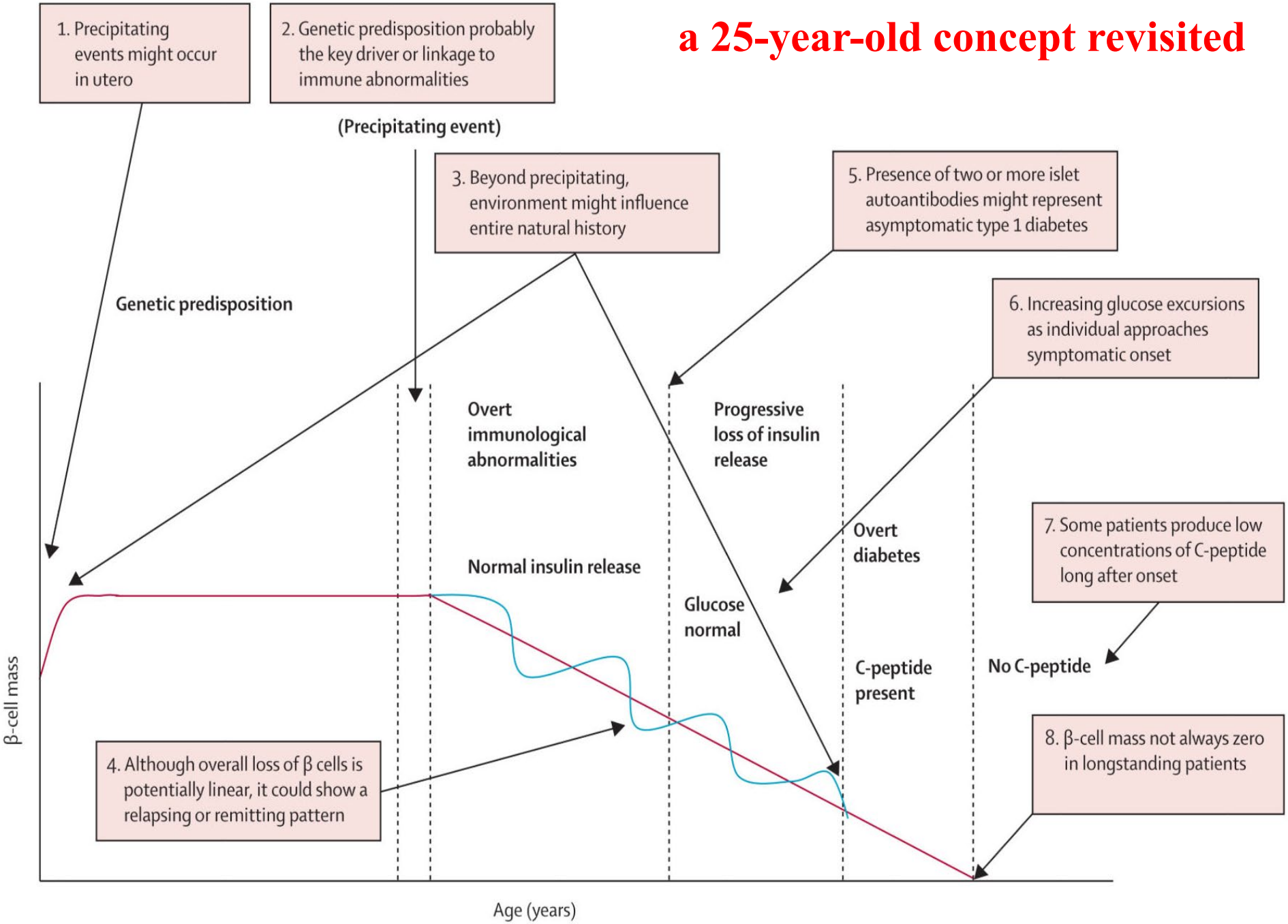
George Eisenbarth, 1986

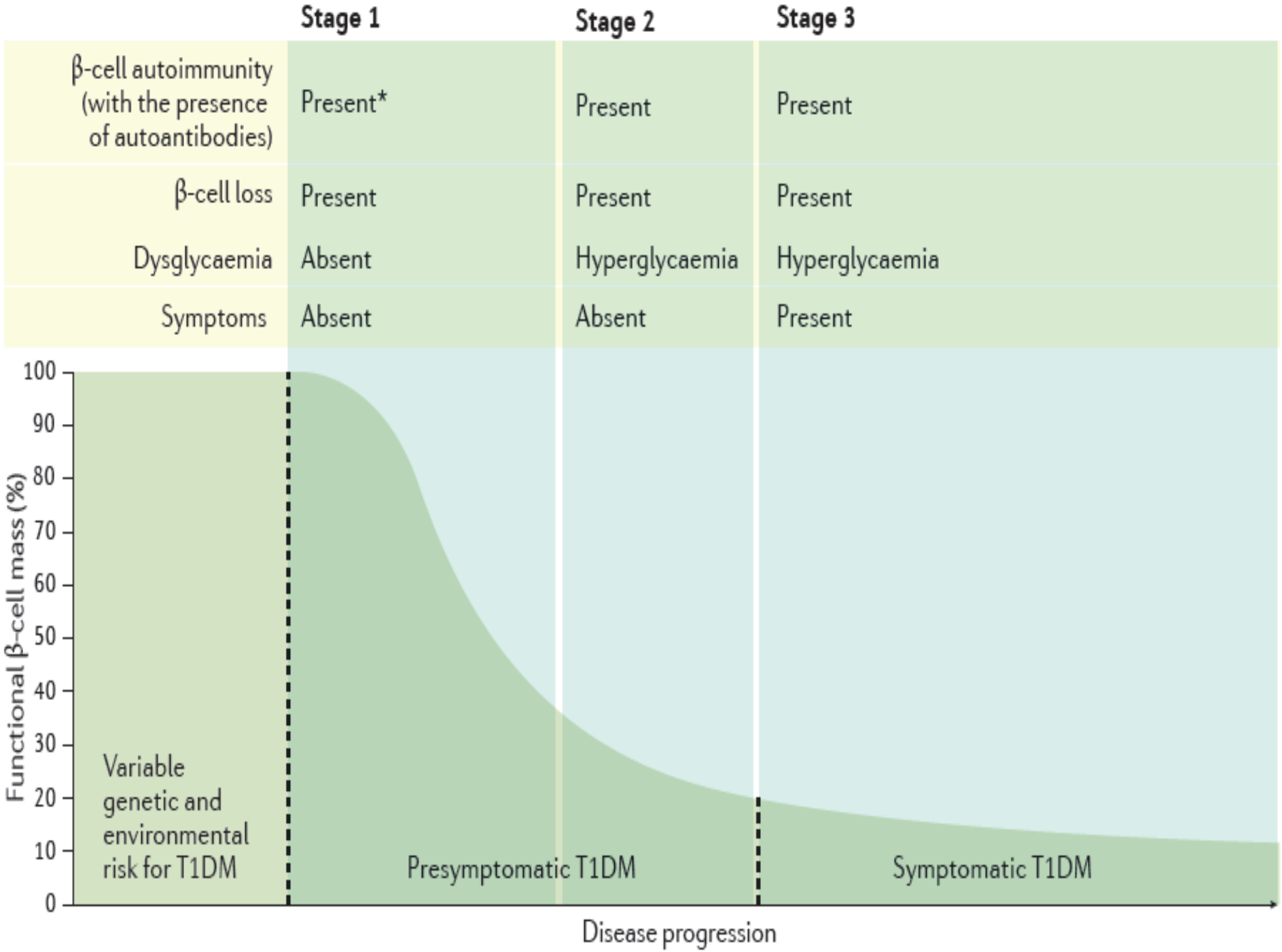
Stages in Development of Type 1 Diabetes



J. Skyler

a 25-year-old concept revisited




Stage 1
Stage 2
Stage 3
β-cell autoimmunity (with the presence of autoantibodies)
Present*
Present
Present
β-cell loss
Present
Present
Present
Dysglycaemia
Absent
Hyperglycaemia
Hyperglycaemia
Symptoms
Absent
Absent
Present
Functional β-cell mass (%)
100
90
80
70
60
50
40
30
20
10
0
Variable genetic and environmental risk for T1DM
Presymptomatic T1DM
Symptomatic T1DM
Disease progression

Incidence of Diabetic Ketoacidosis of New-Onset Type 1 Diabetes in Children and Adolescents in Different Countries Correlates with Human Development Index (HDI): An Updated Systematic Review, Meta-Analysis, and Meta-Regression

Johann Große[1], Henriette Hornstein[1], Ulf Manuwald[1], Joachim Kugler[1], Ingmar Glauche[2], Ulrike Rothe[1]

Worldwide, approximately 79 000 children aged less than 15 years are diagnosed with T1DM every year. In total, 497 100 children in 2013 and 542 000 children in 2015 were diagnosed with T1DM globally.

Globally, there is a large variation in DKA rates. The rates for children is in the range between 15 and 80 % for new-onset T1DM and between 5 and 7 % for already diagnosed T1DM

Horm Metab Res 2018; 50: 209–222

► Table 1 Included studies with extracted informations of each study.

Authors	Country	Region/City	Study size	Study period or year	Age range	Design
Willis et al., 2013 [56]	Australia	Brisbane	1091	2001–2011	0 to < 18	R
Fritsch et al., 2013 [59]	Austria	Nationwide	4038	1989–2011	0 to < 15	P
Pecheur et al., 2014 [60]	Belgium	Brussels	242	1994–2008	0 to < 17	R
Jackman et al., 2015 [32]	Canada	St. John's	163	2007–2011	0 to < 18	R
Stipancic et al., 2011 [61]	Croatia	Nationwide	607	1995–2003	0 to < 15	R
Andersen et al., 2013 [36]	Denmark	n. a.	129	2004–2006	0 to < 17	P
Fredheim et al., 2013 [62]	Denmark	n. a.	2964	1996–2009	0 to 18	R
Handberger et al., 2014 [63]	Denmark	Nationwide	283	2009	0 to 14.9	R
Hekkala et al., 2011 [64]	Finland	Nationwide	1455	2002–2005	0 to < 15	R
Choleau et al., 2014 [65]	France	n. a.	1299	2009	0 to < 15	P
Karges et al., 2011 [35]	Germany and Austria	n. a.	16562	1995–2009	0 to < 18	P
Handberger et al., 2014b [63]	Iceland	Nationwide	14	2009	0 to 14.9	R
de Vries et al., 2013 [66]	Israel	Tel Aviv	406	1986–2007[a]	0 to < 20	R
Gruber et al., 2015 [67]	Israel	Tel Hashomer	81	2007–2014	6 Months to 18	R
Marigliano et al., 2013 [68]	Italy	Verona, Pavia, and Genoa	510	2000–2011	0 to < 17	R
Salaradi et al., 2016 [44]	Italy	n. a.	230	1981–1992	0 to > 9	R
Formosa et al., 2011 [69]	Malta	Nationwide	81	2006–2010	0 to < 14	P
Jefferies et al., 2015 [70]	New Zealand	Auckland	730	1999–2013	0 to < 15	R
Onyiriuka and Ifebi, 2013 [71]	Nigeria	Benin	48	1996–2011	0 to > 15	R
Handberger et al., 2014c [63]	Norway	Nationwide	325	2009	0 to 14.9	R

► Table 1 Continued

Authors	Country	Region/City	Study size	Study period or year	Age range	Design
Szypowska and Skórka, 2011 [22]	Poland	Warsaw and Mazowieckie	187	2006–2008	0 to< 16	R
Małachowska et al., 2014 [72]	Poland	Lodz	652	2004–2012	n. a.	R
Al Rashed, 2011 [73]	Saudi Arabia	Jeddah	369	1993–2005	0 to< 15	R
Al Alwan et al., 2012 [74]	Saudi Arabia	Riyadh	98	2000–2007	0 to< 12	R
Alanani and Alsulaimani, 2013 [75]	Saudi Arabia	Taif	99	2011–2013	0 to 12	P
Ješić et al., 2013 [76]	Serbia	Belgrade	720	1992–2011[a]	0 to < 18	R
Oyarzabal Irigoyen et al., 2012 [77]	Spain	Nationwide	1151	2004–2008	0 to< 15	R
Handberger et al., 2014d [63]	Sweden	Nationwide	688	2009	0 to 14.9	R
Ardicil et al.,2014 [78]	Turkey	Ankara	354	1990–2010	0 to < 18	R
Uçar et al., 2013 [79]	Turkey	Istanbul	401	2003–2012	0 to < 15	R
Demirbilek et al., 2013 [80]	UK	Diyarbakir	41	2010–2011	0 to 14	R
Lokulo-Sodipe et al., 2014 [81]	UK	England, Wales, and Northern Ireland	261	2011–2012	0 to < 17	P
Usher-Smith et al., 2015 [82]	USA	East of England	87	2013–2014	0 to < 16	R
Dabelea et al., 2014b [83]	USA	Ohio, Washington, South Carolina, and Colorado	5615	2002–2010[a]	0 to 19	R

► Table 1 Continued

Authors	Country	Region/City	Study size	Study period or year	Age range	Design
Redondo et al., 2013 [84]	USA	Houston	607	2007–2010[b]	0 to < 19	R
Cengiz et al., 2013 [85]	USA	Nationwide	857	2009–2011	0 to < 19	P
Rewers et al., [2015] [55]	USA	Colorado	3439	1998–2012	0 to < 18	R

[a] Breaks in study period

[b] Information received from author

* Deviation of stated limit of bicarbonate < 15 mmol/l [31, 32]

Δ Deviation of stated limit of blood glucose > 11 mmol/l [31, 32], and glucose in mmol/l from original studies

► Table 2 DKA frequency and additional characteristics of the country of each study.

Authors	Country	Study size	Study duration in years	DKA rate in %	Incidence rates of T1DM (0–14 years) cases/100000	
Willis et al., 2013 [56]	Australia	1091	11	31.9	20.9	[37]
Fritsch et al., 2013 [59]	Austria	4038	23	37.5	9.1	[35]
Pecheur et al., 2014 [60]	Belgium	242	15	25.6	11.6	[35]
Jackman et al., 2015 [32]	Canada	163	5	22.1	21.7	[38]
Stipancic et al., 2011 [61]	Croatia	607	8	36.4	6.8	[35]
Andersen et al., 2013 [36]	Denmark	129	3	14.7[a]	19.4	[36]
Fredheim et al., 2013 [62]	Denmark	2964	14	17.9	19.4	[36]
Handberger et al., 2014 [63]	Denmark	283	1	20.0	22.2	[38]
Hekkala et al., 2011 [64]	Finland	1455	3	19.2	37.4	[38]
Choleau et al., 2014 [65]	France	1299	0.5	43.9	12.2	[38]
Karges et al., 2011 [35]	Germany and Austria	16562	14.75	20.8b	10.9b	[36]
Handberger et al., 2014b [63]	Iceland	14	1	36.0	14.7	[38]
de Vries et al., 2013 [66]	Israel	406	22c	33.7	5.9	[35]
Gruber et al., 2015 [67]	Israel	81	7.08	42.0	10.4	[39]
Marigliano et al., 2013 [68]	Italy	510	12	34.7	8.4	[37]
Salaradi et al., 2016 [44]	Italy	230	12	56.0	8.4	[43]
Formosa et al., 2011 [69]	Malta	81	5	41.0	15.6	[38]
Jefferies et al., 2015 [70]	New Zealand	730	15	27.0	18.0	[37]
Onyiriuka and Ifebi, 2013 [71]	Nigeria	48	16	77.1	2.9	[15]
Handberger et al., 2014c [63]	Norway	325	1	22.0	27.9	[38]
Szypowska and Skórka, 2011 [22]	Poland	187	2.25	26.0	13.0	[37]
Małachowska et al., 2014 [72]	Poland	652	9	30.1	12.9	[38]
Al Rashed, 2011 [73]	Saudi Arabia	369	13	49.9	5.0	[35]
Al Alwan et al., 2012 [74]	Saudi Arabia	98	8	49.0	12.3	[36]
Alanani and Alsulaimani, 2013 [75]	Saudi Arabia	99	2	79.8	31.4	[40]
Ješić et al., 2013 [76]	Serbia	720	20[c]	32.9	8.1[d]	[36]
Oyarzabal Irigoyen et al., 2012 [77]	Spain	1151	5	39.5	12.9	[37]

▶ Table 2 Continued

Authors	Country	Study size	Study duration in years	DKA rate in %	Incidence rates of T1DM (0–14 years) cases/100000	
Handberger et al., 2014d [63]	Sweden	688	1	18.0	41.0	[38]
Ardicil et al., 2014 [78]	Turkey	354	21	50.8	5.0	[35]
Uçar et al., 2013 [79]	Turkey	401	10	44.2	3.2	[38]
Demirbilek et al., 2013 [80]	Turkey	41	1	65.9	3.2	[41]
Lokulo-Sodipe et al., 2014 [81]	UK	261	0.25	25.0	28.2	[40]
Usher-Smith et al., 2015 [82]	UK	87	1	40.2	28.2	[15]
Dabelea et al., 2014 [83]	USA	5615	9[c]	30.1e	16.1	[37]
Redondo et al., 2013 [84]	USA	607	3	35.4	20.8	[38]
Cengiz et al., 2013 [85]	USA	857	1.75	33.0	23.7	[41]
Rewers et al., 2015 [55]	USA	3439	15	38.9	16.1	[37]

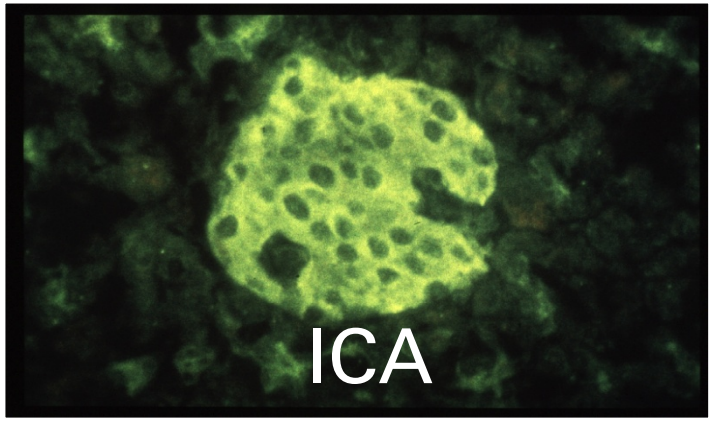
- **L'analisi indica che DKA è più comune nei paesi con un più basso indice di sviluppo**

- **Il fattore latitudine è associato a KDA ovvero i bambini vicino all'equatore (i tassi di DKA decrementano con l'aumentare della altitudine) hanno i più alti tassi di KDA rispetto ai bambini scandinavi**

- **I paesi con più alta incidenza e prevalenza di T1DM appaiono più efficienti nel riconoscimento dei sintomi della KDA e nell'insorgenza del T1DM**

- **Una più precoce diagnosi è avvantaggiata dal più alto livello di assistenza medica**

Major Islet Autoantigens



Insulin autoantibodies

- ?
- ZnT8
- IA-2 (ICA512BDC)
- GAA (GAD_{65})
- IAA

Table 1 Characteristics of the relevant autoantibodies in type 1 diabetes[125-134]

	Antigen	Sensitivity	Specificity	Percent at onset	Annotation
ICA	Islet cells	70%	99%	70%-90%	Single positivity similar predictive;

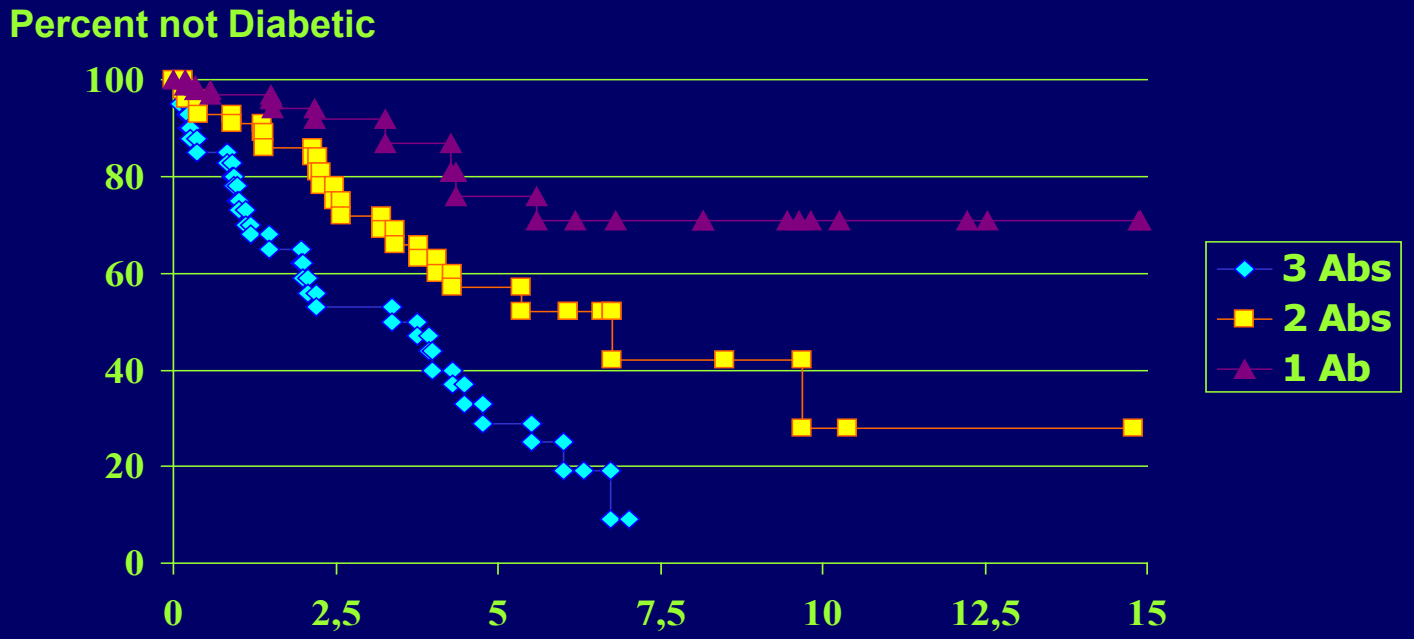
Table 3 Prevalence of associated autoimmunity in patients with type 1 diabetes[15,55,56,60,97,100,136-143]

Associated disease	Patients with type 1 diabetes		General population	
	Prevalence of organ-specific Abs	Overt disease	Prevalence of organ-specific Abs	Overt disease
Type 1 diabetes	ICA in 85%-90%	100%	ICA in 1%-3 %	0.1%-1.0%
Hashimoto's thyroiditis	TPO Abs in 15%-30%	10%-20%	TPO Abs in 2%-10%	0.5%-9.0%
Graves' disease	TSH-R Abs in 1%-18%	3%-6%	TSH-R Abs in 1%-2%	0.1%-2.0%
Addison's disease	21-OH Abs in 0.7%-2.0%	0.5%-0.8%	21-OH Abs in 0.6%	0.005%-0.140%
Autoimmune hypophysitis and/or hypopituitarism	Pituitary Abs in 3.6%	0.4%-0.9%	Pituitary Abs in 0.5%	0.24%-0.80%
Autoimmune type A gastritis and pernicious anemia	Gastric parietal cell Abs in 13%-25%	5%-10% (2%-6%)	Gastric parietal cell Abs in 2.5%-12.0%	2% (0.15%-1.00%)
Celiac disease	Transglutaminase Abs in 8%-12%	1%-9%	Transglutaminase Abs in 0.5%-1.0%	0.50%

Father	7%
Monozygotic twin	30%-50%
Dizygotic twin	6%-10%

T1D: Type 1 diabetes.

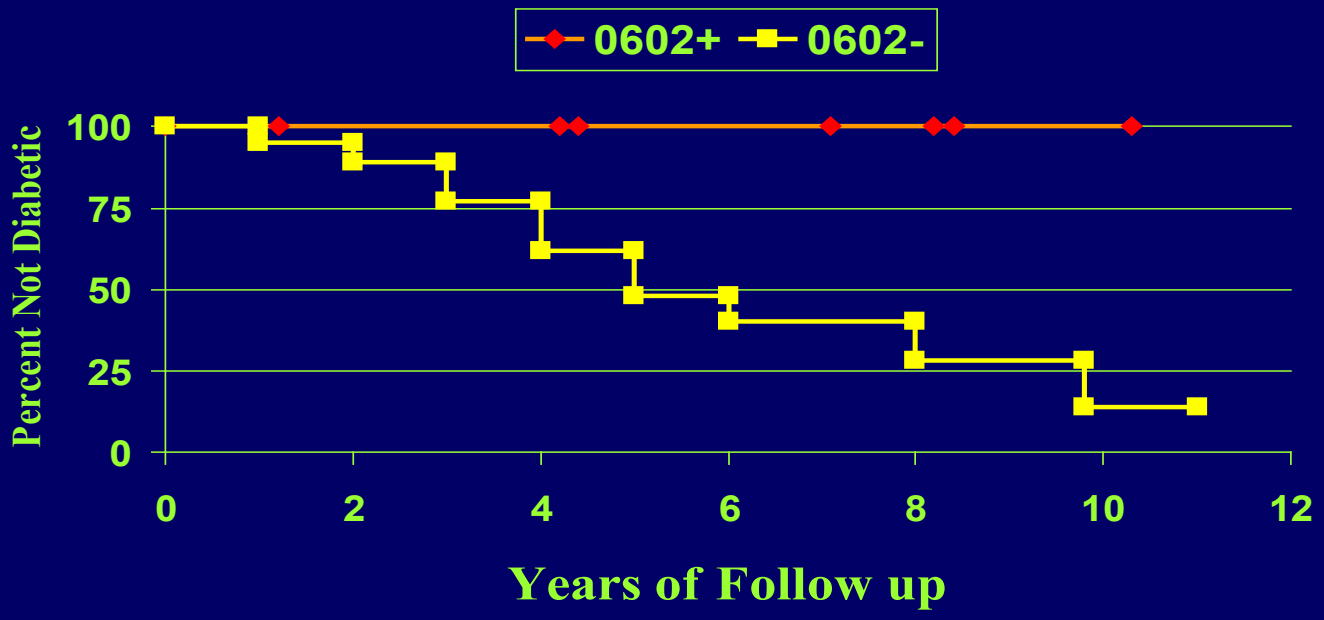
Progression to Diabetes vs Number of Autoantibodies (GAD, ICA512, Insulin)



3 Ab	n = 41	17	8	1		
2 Abs	n = 44	27	15	4	2	1
1 Abs	n = 93	23	14	10	6	4

Verge et al. Diabetes, 1996;45;926

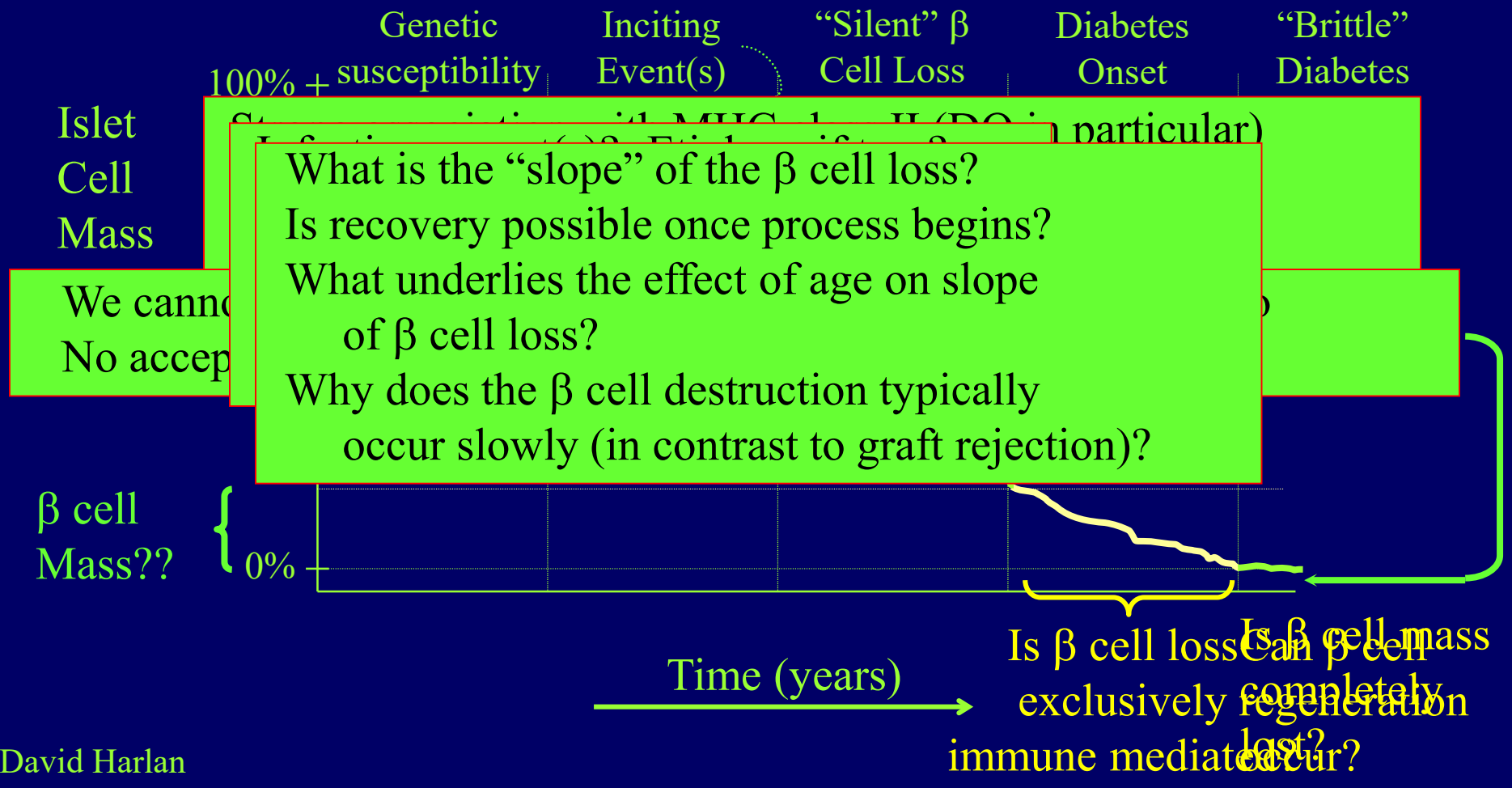
Lack of Progression to DM of ICA+ 0602+ Relatives



Pugliese et a.

BDC

T1DM- a slowly progressive T-cell mediated autoimmune illness



David Harlan

Current Diabetes Reviews, 2018, *14*, 266-272

REVIEW ARTICLE

Heterogeneity of Type 1 Diabetes: The Effect of Ethnicity



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ARTICLE HISTORY

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Abstract: ***Background*:** Most of the current understanding of type 1 diabetes (T1D) etiology and pathogenesis stemmed from studies conducted in majoritarily Non-Hispanic White (NHW) populations. However, evidence is emerging that unique mechanisms of disease may contribute to the development of T1D in individuals of Hispanic ethnicity.

***Objective*:** We reviewed the currently available literature on genetic, immunologic, metabolic and clinical characteristics of T1D in Hispanic as compared with NHW individuals.

***Methods*:** We searched PubMed, Google Scholar, and authors' bibliographies to collect information from relevant articles on the influence of ethnicity on T1D etiology and pathogenesis.

***Results*:** There are significant epidemiological variation based on ethnicity, with consistently higher T1D incidence and prevalence rate in NHWs than Hispanics. The frequencies of T1D high-risk HLA haplotypes and genotypes, as well as their susceptibility or protective effects show considerable ethnic differences. There are conflicting data on immunologic factors (*e.g.* islet autoantibody positivity) and markers of beta-cell function (*e.g.*, C-peptide levels), as well as in some clinical characteristics (*e.g.* frequencies of diabetic ketoacidosis and severe hypoglycemia), while age of onset is consistently similar between both groups. Higher prevalence of obesity, less intensive diabetes management, and poorer glycemic control were reported in Hispanics. Accordingly, ethnic disparities in clinical outcomes have been demonstrated as well.

***Conclusion*:** There are considerable differences in T1D characteristics between NHWs and Hispanics. Better insight into these ethnic differences would not only affect patient care of patients with T1D, but may also inform the design of future prediction and prevention trials.

- **Hispanics are under-represented in T1D research despite being the largest minority and fastest growing immigrant population in the US. About 1 in 6 people living in the US are Hispanic, which could be nearly 1 in 4 by 2035**

- **Studies in patients with T1D suggest that Hispanics have unique genetic, immunologic, metabolic and clinical characteristics, although there are discrepancies among the reports**

- **Better understanding of the effect of ethnicity in T1D may explain some of the differences in glycemic control and clinical outcomes among ethnic groups. It may also shed light on research gaps and set the stage for future advancement in the field**.

Table 1. T1D incidence rates by ethnicity in different registries/studies.

Registry/Study Name	Cohort Date	Ages	Incidence in Hispanics (per 10^5)	Incidence in NHW (per 10^5)
Lorenzi *et al.* 1985	1978-1981	0-19	3	7.2
Colorado	1978-1988	0-17	8.7	15.5
Chicago	1994-2003	0-17	9.1	15.3
Philadelphia	2000-2004	0-14	19.6	19.2
SEARCH	2002-2005	0-14	15-16.2	27-27.9

Beta-cell Autoantibodies

- **Newly diagnosed NHWs with T1D were found more likely to be positive for multiple autoantibodies as compared to Hispanics**

- **Conflicting results have been reported on the prevalence of positivity for glutamic acid decarboxylase autoantibody (GAD), compared with NHW, with lower prevalence (54%) in Hispanic children with T1D in some studies and higher (79.3% vs. 60.1%) prevalence for GAD as well as for IA-2 (74.7% vs. 67%) in others, while similar frequencies were observed for zinc transporter 8 autoantibody (ZnT8A) in both groups in a T1DGC study**

- **The differences on islet autoantibody levels by race/ethnicity were observed in a population based cohort of Colorado infants and toddlers with increased genetic T1D risk in the DAISY (The Diabetes and Autoimmunity Study in the Young) study: lower levels of GAD and to a lesser degree insulin autoantibodies (IAA) in NHWs than in minority children (86% Hispanic)**

Beta-cell Autoantibodies

Current Diabetes Reviews, 2018, *Vol. 14, No. 0* *Elin Pettersen Sørgjerd*

Table 1. A summarizing of the type 1 diabetes associated autoantibodies regarding appearance, prevalence and prediction in autoimmune diabetes (ab=autoantibody).

-	GADA	IA-2A	ZnT8A	Insulin
First appearance	Likely first ab present in adolescent and adults	-	-	Likely first ab present in children
Prevalence at diagnosis	About 60% in children -Most common in adults, LADA	-The most frequent, about 80% in children	-About 60% in children	The less frequent, about 60% in children
Prediction	Suggestive evidence of prediction in adults	Levels can predict progression to diabetes in children	-	Levels can predict progression to diabetes in children

Beta-cell Autoantibodies

- **Autoantibody markers appear months or years before the onset of type 1 diabetes and can occur as early as in the first year of life. Autoantibodies associated with type 1 diabetes have been detected in children as early as 3 months of age.**

- **The Environmental Determinants of Diabetes in the Young (TEDDY) study did show an overall autoantibody incidence of 16.1/1000 person-years until 6 years of age in children at genetic risk. However, the highest peak in incidence was found between 9 and 24 months of age which was similar in both children with family history of type 1 diabetes and from the general population.**

- **IAA is likely the most common and the first autoantibody present in young children before clinical onset. IAA is also reported to be associated with younger seroconversion (first time present)**

- **GADA is usually the first autoantibody present before onset in adolescent and adulthood and also in children if IAA is not present. The order of appearance was also shown to be related to HLA-genotypes in the TEDDY study.**

- **GADA, IA-2A and ZnT8A are shown to be more persistent than IAA in children. Almost all children, 90-100%, with initial GADA, IA-2A and ZnT8A positivity before clinical onset were also positive for the same autoantibodies at diagnosis compared to IAA (75%).**

Metabolic Characteristics

- Hispanic adults are consistently reported to be more obese [39] and insulin resistant than NHWs. They were shown to have higher insulin and C-peptide levels, higher insulin area-under-the-curve (AUC) in response to a standard 75-g oral glucose tolerance test (OGTT), and lower insulin sensitivity. In children, prevalence of obesity was significantly higher in Hispanic than NHW youth (21.9% vs. 14.7%) based on data from the National Health and Nutrition Examination Survey in 2011-2014

- Hispanic youth with T1D were reported to have higher overweight and obesity prevalence (up to 45.9% in Hispanics vs. 31.1% in NHWs), higher body mass index (BMI), and BMI z-score.

- Although higher residual beta cell function was shown in Hispanics previously, there was no association found between C-peptide and ethnicity in 1,662 participants in a SEARCH study and 524 children with newly diagnosed T1D at Texas Children's Hospital.

Clinical Characteristics

Approximately one third of the children presents with diabetic ketoacidosis (DKA) at the onset of T1D, which can be associated with significant morbidity and mortality. Hispanic children have been reported to present with higher rate of DKA at the onset of T1D than NHWs in multiple studies. Even though socio-demographic differences are considered as important confounders, NHWs still had lower rate of DKA at the onset after adjustment for those factors in a study including 5615 children with T1D. Nevertheless, similar rates of DKA at the onset were shown in a Pediatric Diabetes Consortium Study (n=805) and a SEARCH for Diabetes in Youth Study (n=2824).

Management and Clinical Outcomes

- **Hispanic youth are less likely to be treated with intensive insulin therapy than NHWs: less likely to be provided a sliding scale with carbohydrate counting and less likely to be treated with pump therapy after adjustment for sociodemographic factors**

- **Not surprisingly, higher rate of Continuous Glucose Monitoring (CGM) use in NHWs compared to Hispanics was reported in children less than 13 years of age in T1D Exchange clinic registry**

- **Hispanic youth were 1.6-2.3 times more likely to have poor glycemic control (defined by HbA1c above 9.5%) than NHWs on two different SEARCH studies**

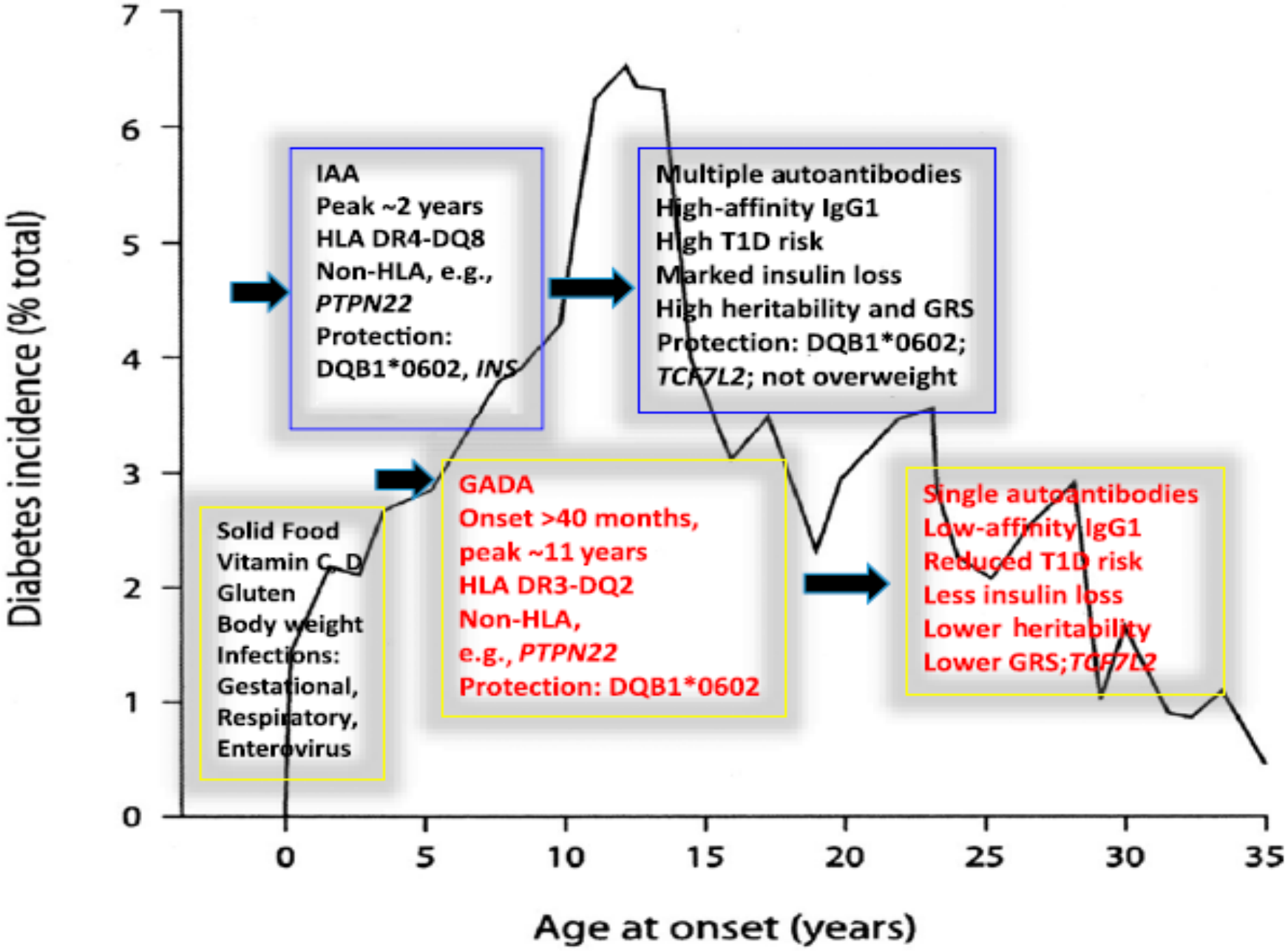
The Dynamic Origins of Type 1 Diabetes

R. David Leslie[1] and Struan F.A. Grant[2]

Diabetes Care 2018;41:2441–2443 | https://doi.org/10.2337/dci18-0034

To leverage the TrialNet study of subjects with a single diabetes associated autoantibody at screening in order to explore factors determining progression to multiple autoantibodies and, subsequently, the pathogenesis of T1D.

Many observations hint at distinct disease-associated networks leading to T1D, perhaps induced by distinct nongenetic events. Such disease-associated pathways could operate in unison, especially in children with T1D, who often have multiple autoantibodies.


Diabetes incidence (% total)
7
6
5
4
3
2
1
0
0
5
10
15
20
25
30
35
Age at onset (years)
IAA
Peak ~2 years
HLA DR4-DQ8
Non-HLA, e.g.,
PTPN22
Protection:
DQB1*0602, INS
Multiple autoantibodies
High-affinity IgG1
High T1D risk
Marked insulin loss
High heritability and GRS
Protection: DQB1*0602;
TCF7L2; not overweight
Solid Food
Vitamin C, D
Gluten
Body weight
Infections:
Gestational,
Respiratory,
Enterovirus
GADA
Onset >40 months,
peak ~11 years
HLA DR3-DQ2
Non-HLA,
e.g., PTPN22
Protection: DQB1*0602
Single autoantibodies
Low-affinity IgG1
Reduced T1D risk
Less insulin loss
Lower heritability
Lower GRS;TCF7L2

TCF7L2 Genetic Variants Contribute to Phenotypic Heterogeneity of Type 1 Diabetes

*Maria J. Redondo,[1] Susan Geyer,[2] Andrea K. Steck,[3] Jay Sosenko,[4] Mark Anderson,[5] Peter Antinozzi,[6] Aaron Michels,[3] John Wentworth,[7] Ping Xu,[2] and Alberto Pugliese,[4] and the Type 1 Diabetes TrialNet Study Group**

Table 1—Characteristics of study subjects (*n* = 810)

Age at T1D diagnosis	
Median (range), years	13.6 (3.3–58.6)
<18 years	584 (72)
≥18 years	226 (28)
Sex	
Female	363 (45)
Male	444 (55)
Not reported (*n*)	3
Race	
Nonwhite	56 (7)
White	744 (93)
Missing/unknown (*n*)	10
Ethnicity	
Hispanic or Latino	76 (9.5)
Not Hispanic or Latino	724 (90.5)
Missing/unknown (*n*)	10

810

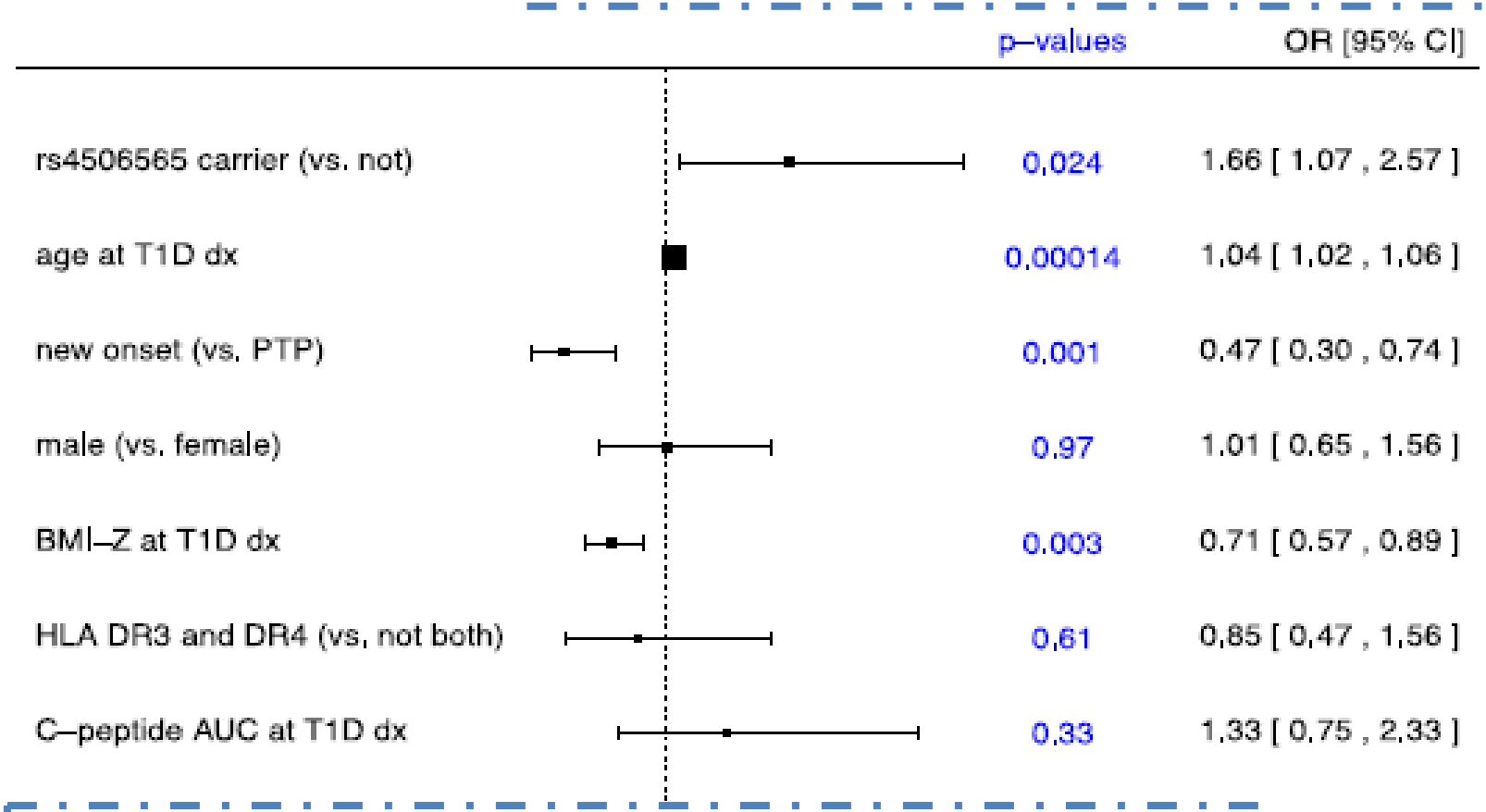
BMI z-score at diagnosis	
Median (range)	0.49 (−2.8 to 3.1)
Normal/underweight	644 (81.1)
Overweight/obese	150 (18.9)
Missing (*n*)	16
Positive islet autoantibodies at diagnosis (*n*)	
1	119 (14.7)
2	192 (23.7)
3	276 (34.1)
4	202 (24.9)
5	21 (2.6)
Single	119 (14.7)
Multiple (≥2)	691 (85.3)
HLA DR3/DR4-DQ8†	
No	648 (82.4)
Yes	138 (17.6)
Missing (*n*)	24
HLA DR3 and/or DR4-DQ8†	
No	200 (25.4)
Yes	586 (74.6)
Missing (*n*)	

Redondo and Associates **2017**

Fasting glucose	
Median (range), mmol/L	5.89 (3–16.06)
Missing (*n*)	25
Mean AUC glucose	
Median (range), mmol/L	9.29 (4.76–18.71)
Missing (*n*)	23
Fasting C-peptide	
Median (range), nmol/L	0.36 (0.02–3.53)
Missing (*n*)	27
Mean AUC C-peptide	
Median (range), nmol/L	0.69 (0.01–2.70)
Missing (*n*)	51

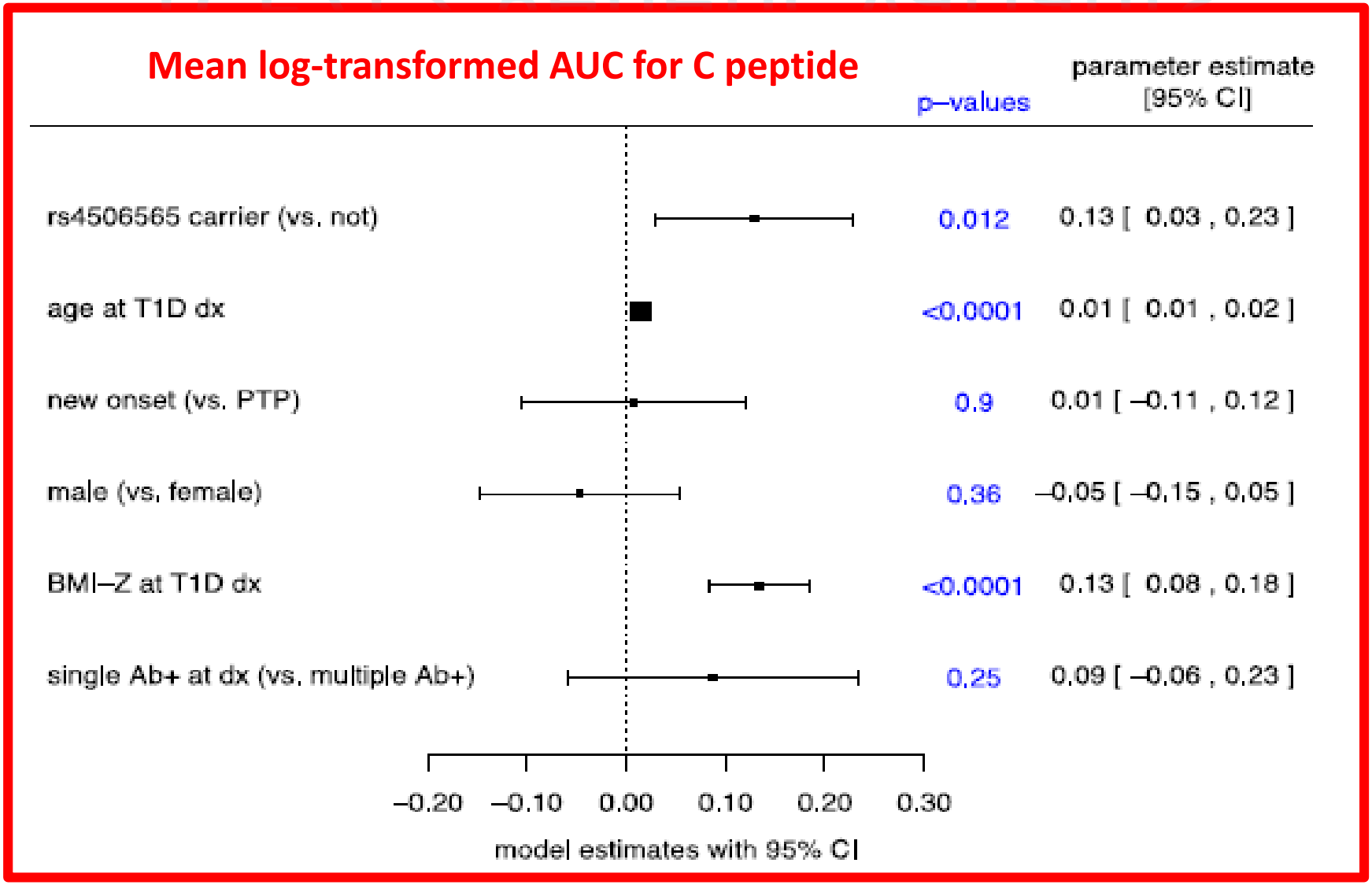
TCF7L2 genetic variants

ORs >1 reflect higher relative likelihood of being single-autoantibody positive at diagnosis



ORs <1 reflect a lower relative likelihood (lower odds) of having a single autoantibody (i.e., higher relative odds of having multiple-autoantibody positive at diagnosis).

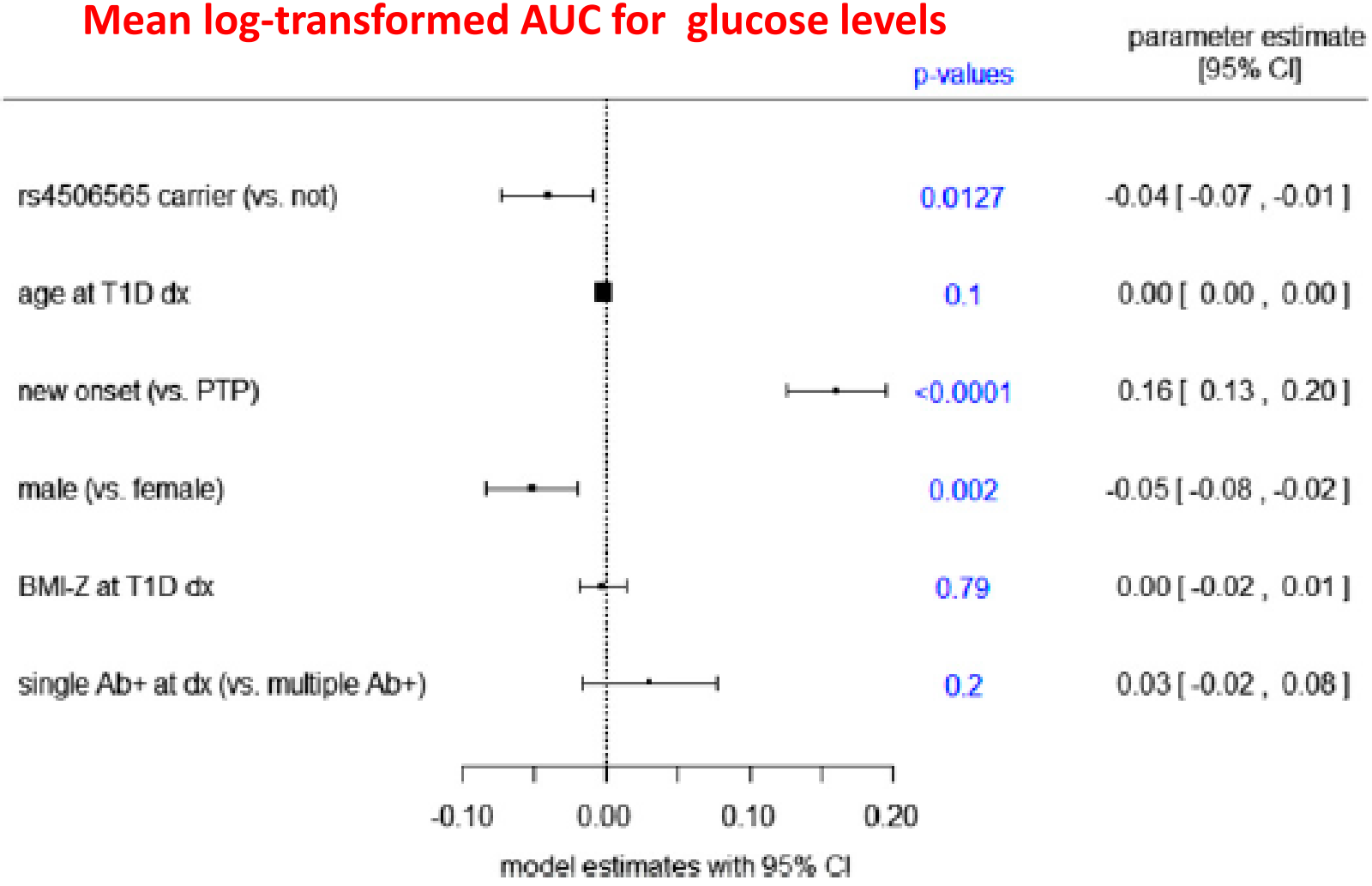
TCF7L2 genetic variants



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TCF7L2 genetic variants

Mean log-transformed AUC for glucose levels



Redondo and Associates

SUMMARY

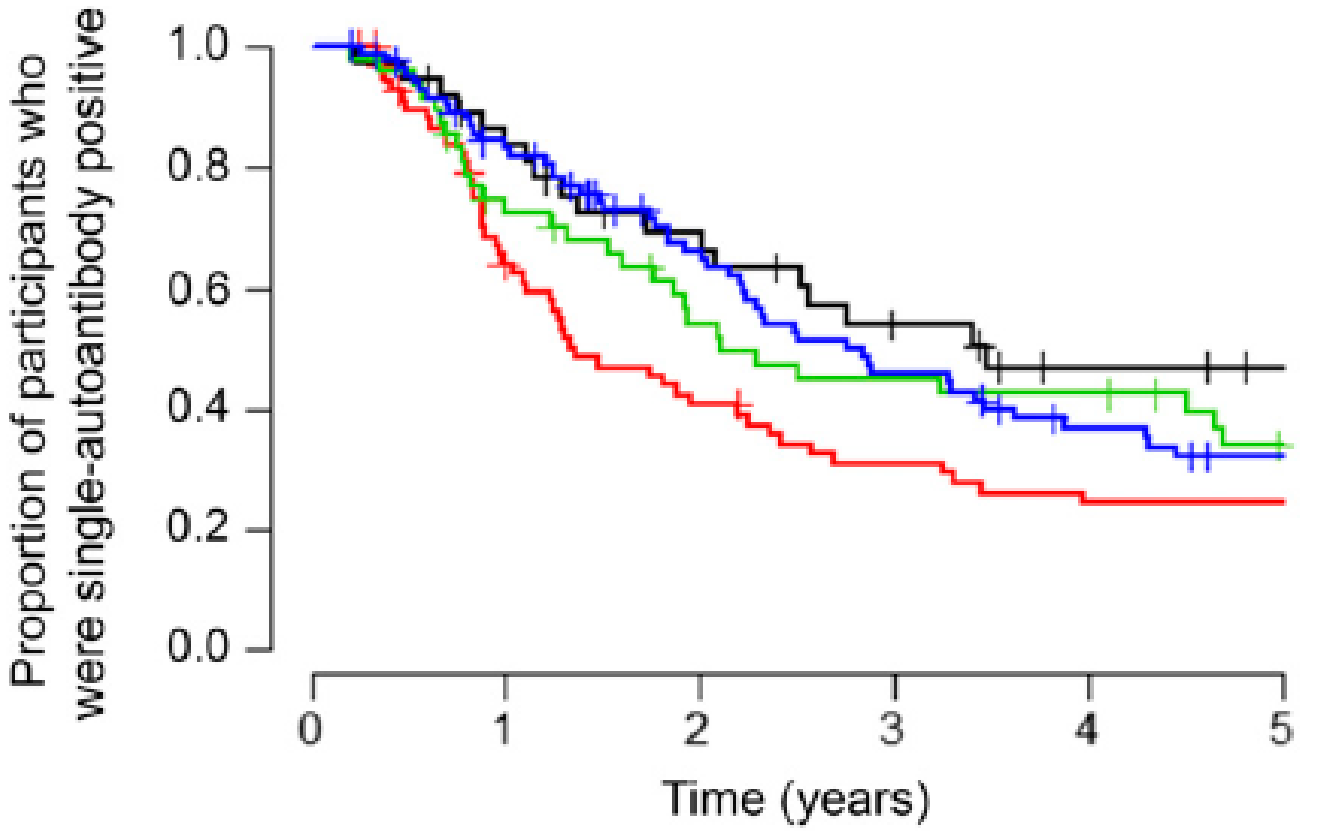
- **La variante genetica TCF7L2 associata al diabete di tipo 2 gioca un ruolo importante negli individui più anziani**

- **Gli individui più giovani manifestano forma più aggressiva di malattia, più rapido declino della funzione β-cellulare prima e dopo l'insorgenza della malattia, più alta frequenza di chetoacidosi correlata a più severa insulino-deficienza e più bassi livelli di C peptide alla diagnosi.**

- **Gli individui più anziani presentano meno alleli HLA correlati al diabete di Tipo 1 e meno autoanticorpi, ovvero presentano una forma meno aggressiva e progressiva di autoimmunità insulare**

244 pts

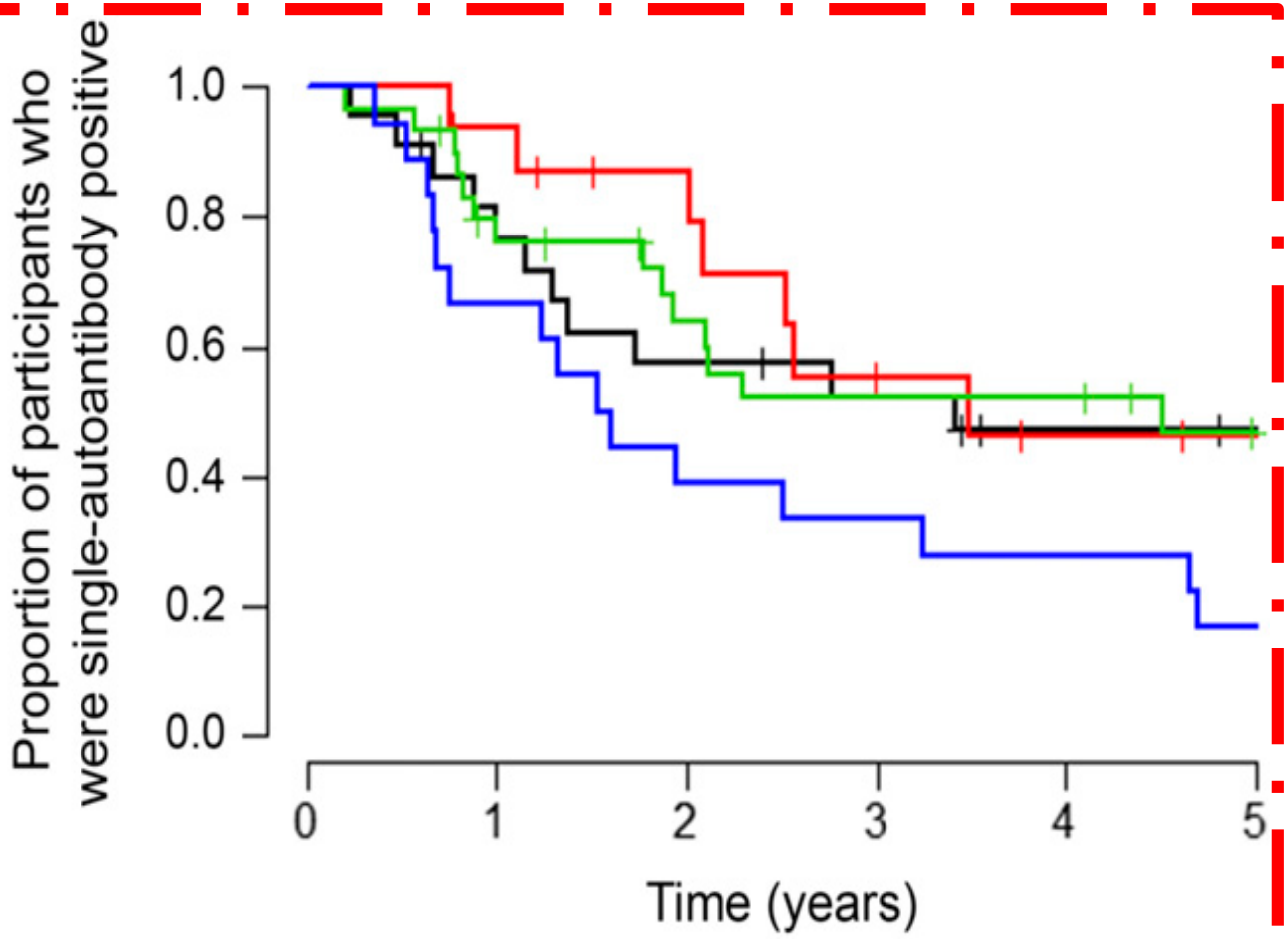
TCF7L2 carrier status



N at risk

noncarrier, non-GADA+	38	30	23	16	11	9
noncarrier, GADA+	71	41	26	19	15	15
carrier, non-GADA+	48	33	23	19	18	11
carrier, GADA+	87	68	48	33	23	18

TCF7L2 carrier and Overweight/ obese status



N at risk

noncarrier, not overweight/obese	22	16	12	10	7	6
noncarrier, overweight/obese	16	14	11	6	4	3
carrier, not overweight/obese	30	21	16	13	13	8
carrier, overweight/obese	18	12	7	6	5	3

The Impact of Pancreatic Beta Cell Heterogeneity on Type 1 Diabetes Pathogenesis

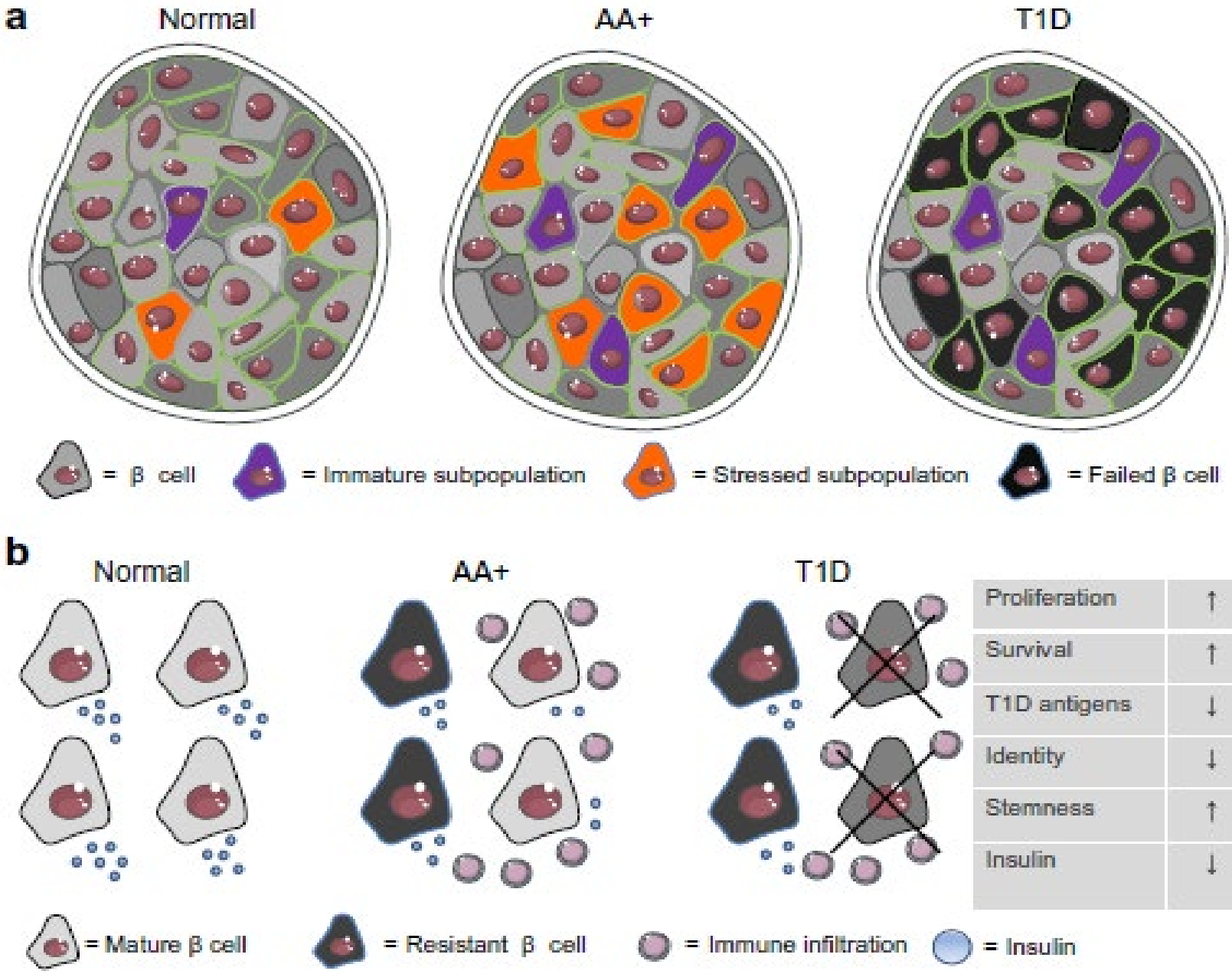
Richard K. P. Benninger[1,2] · Craig Dorrell[3] · David J. Hodson[4,5,6] · Guy A. Rutter[7]

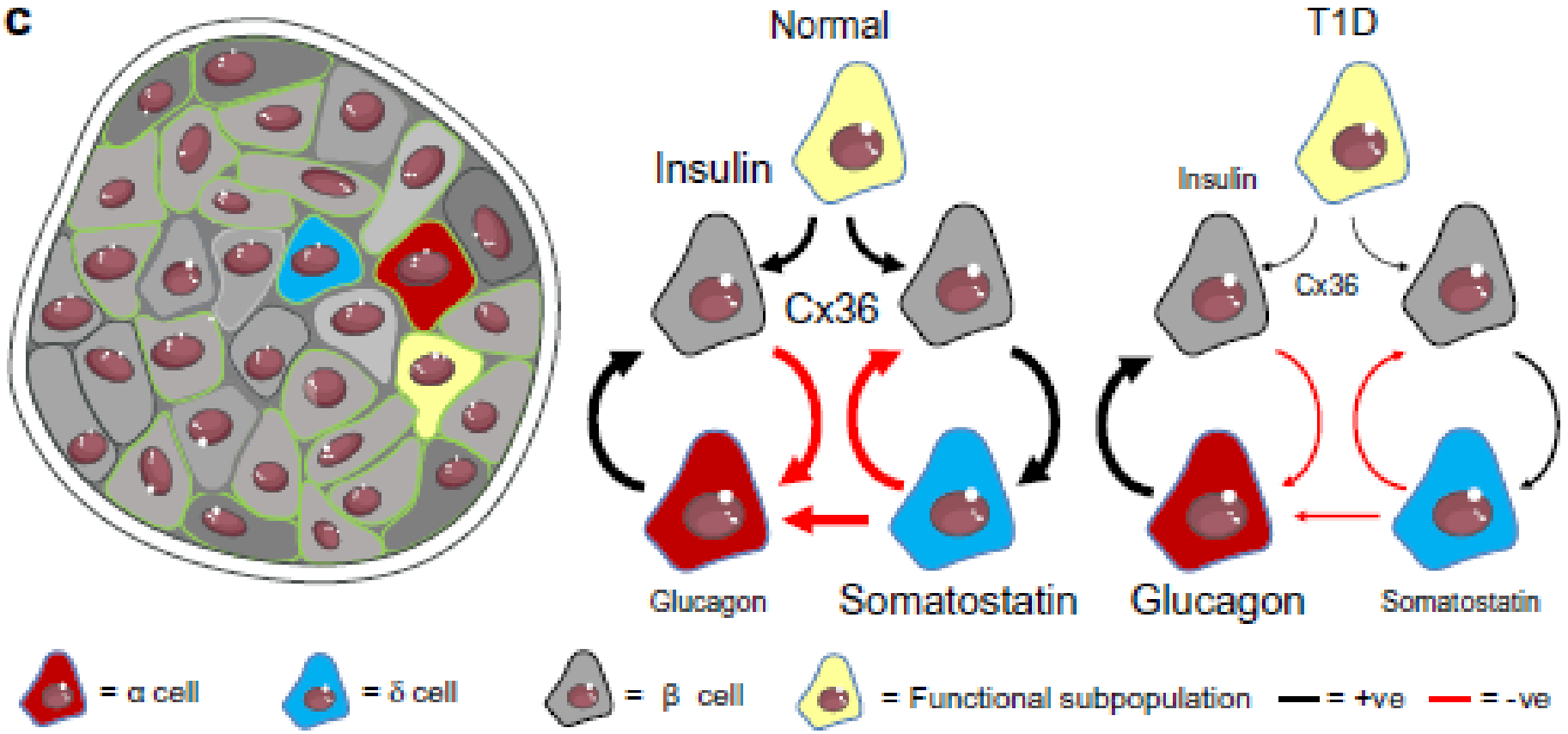
Published online: 24 September 2018

Current Diabetes Reports (2018) 18: 112

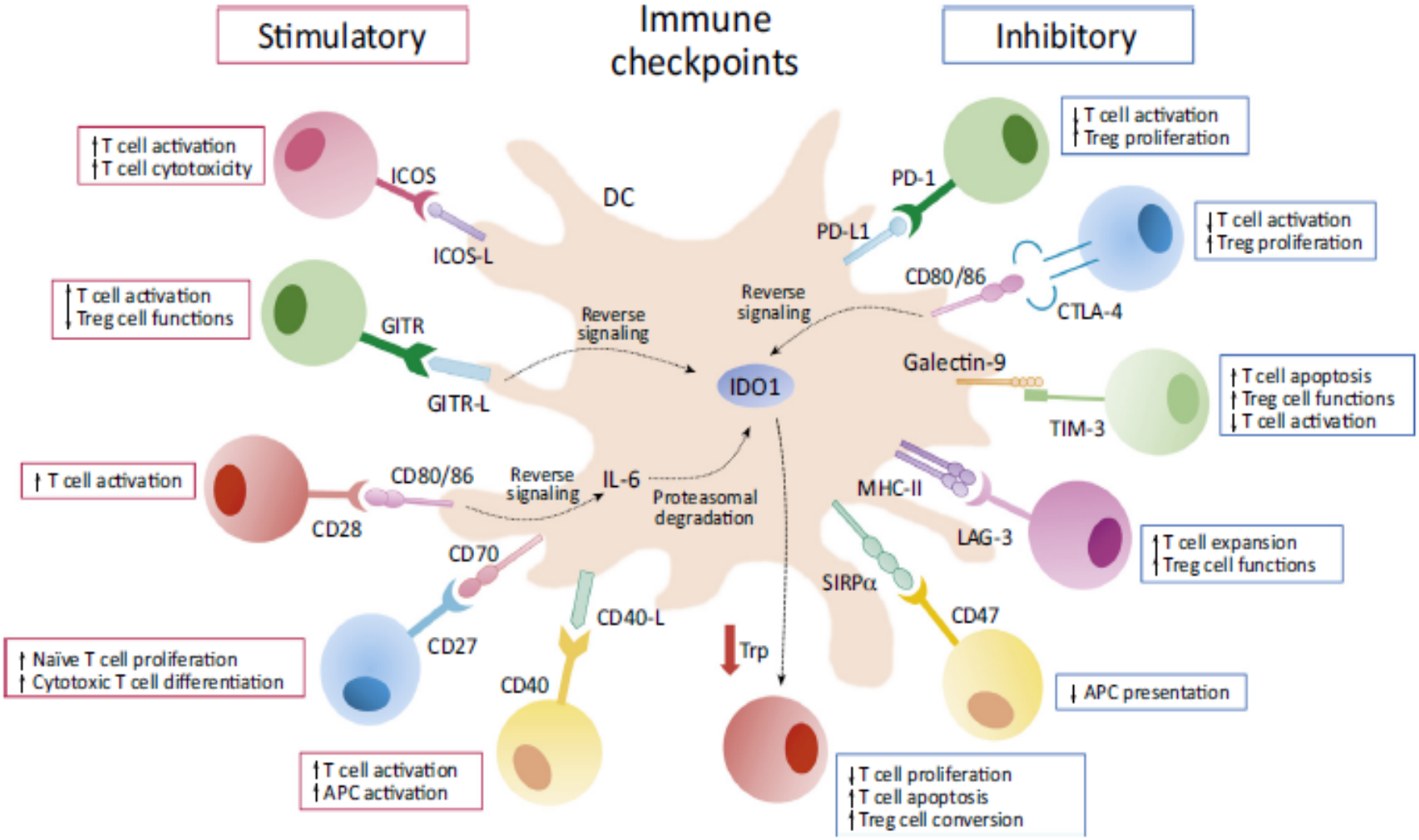
Islet function is impaired prior to the onset of diabetes in animal models of T1D. In human, in vivo measurements show signs of beta-cell dysfunction up to 5 years prior to diabetes onset. These findings suggest that beta cells become defective before they are killed outright.

Correspondingly, insults that pertain to T1D, e.g., the release from inflammatory cells of sub-lethal cytotoxic cytokines such as interferon γ (IFNγ), interleukin-1β (IL-1β), and tumor necrosis factor-α (TNF-α), impair beta cell metabolism and the usual increases in cytosolic ATP/ADP ratio following nutrient stimulation.

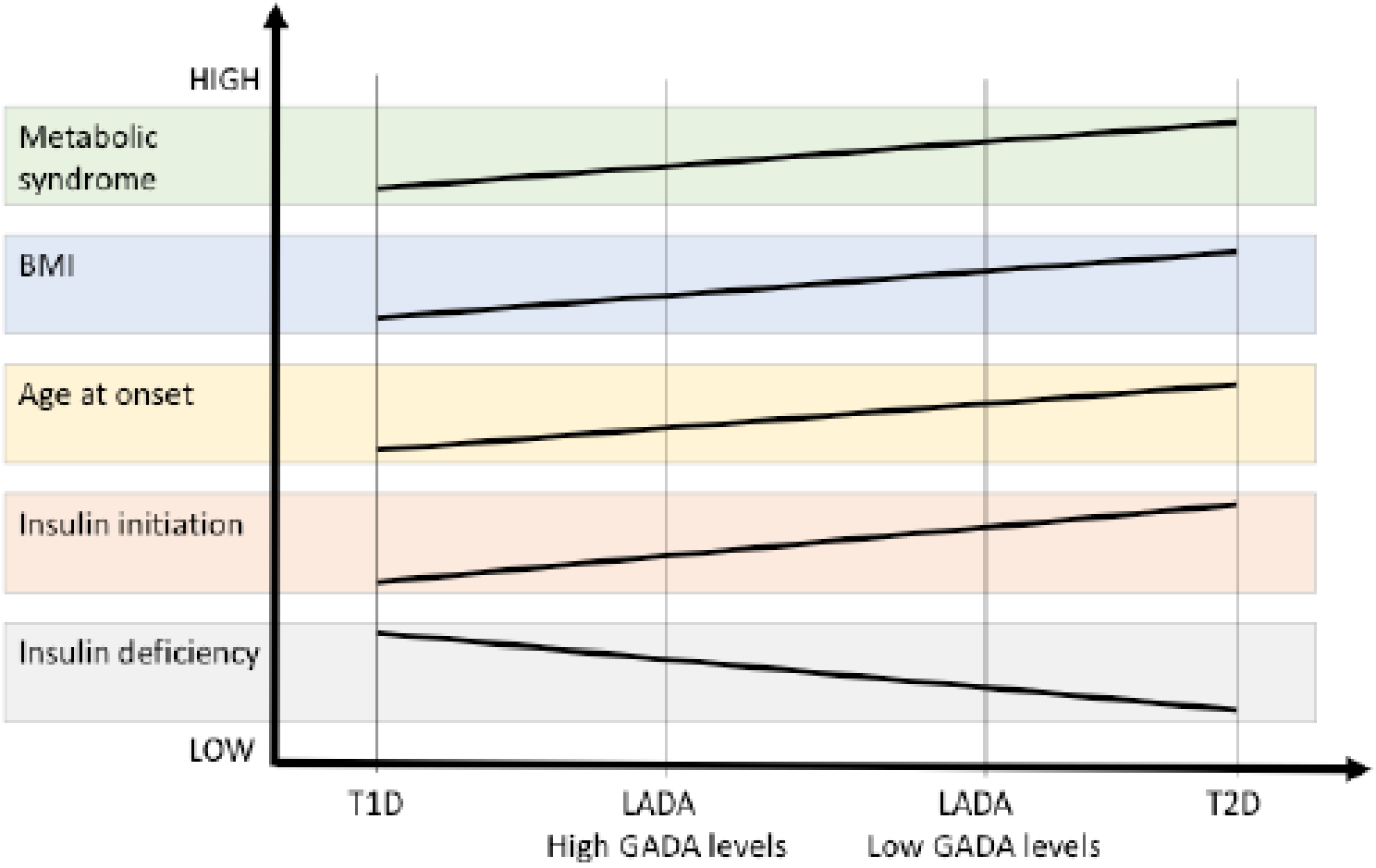

a
Normal
AA+
T1D
= β cell
= Immature subpopulation
= Stressed subpopulation
= Failed β cell
b
Normal
AA+
T1D
Proliferation ↑
Survival ↑
T1D antigens ↓
Identity ↓
Stemness ↑
Insulin ↓
= Mature β cell
= Resistant β cell
= Immune infiltration
= Insulin



Curr Diab Rep (2018) 18: 112


Stimulatory
Immune checkpoints
Inhibitory
↑T cell activation
↑T cell cytotoxicity
ICOS
ICOS-L
DC
↓T cell activation
↑Treg proliferation
PD-1
PD-L1
↓T cell activation
↑Treg proliferation
CD80/86
CTLA-4
↓T cell activation
↑Treg cell functions
GITR
GITR-L
Reverse signaling
Reverse signaling
IDO1
Galectin-9
TIM-3
↑T cell apoptosis
↑Treg cell functions
↓T cell activation
↑T cell activation
CD80/86
CD28
Reverse signaling
IL-6
Proteasomal degradation
MHC-II
LAG-3
↑T cell expansion
↑Treg cell functions
CD70
CD27
SIRPα
CD47
CD40-L
CD40
Trp
↑Naïve T cell proliferation
↑Cytotoxic T cell differentiation
↓APC presentation
↑T cell activation
↑APC activation
↓T cell proliferation
↑T cell apoptosis
↑Treg cell conversion

Diverse Modalità d'esordio



Novembre 2018, GDM




AGIRE OGGI PER UN FUTURO SERENO
Attività fisica regolare



Grazie dell’attenzione