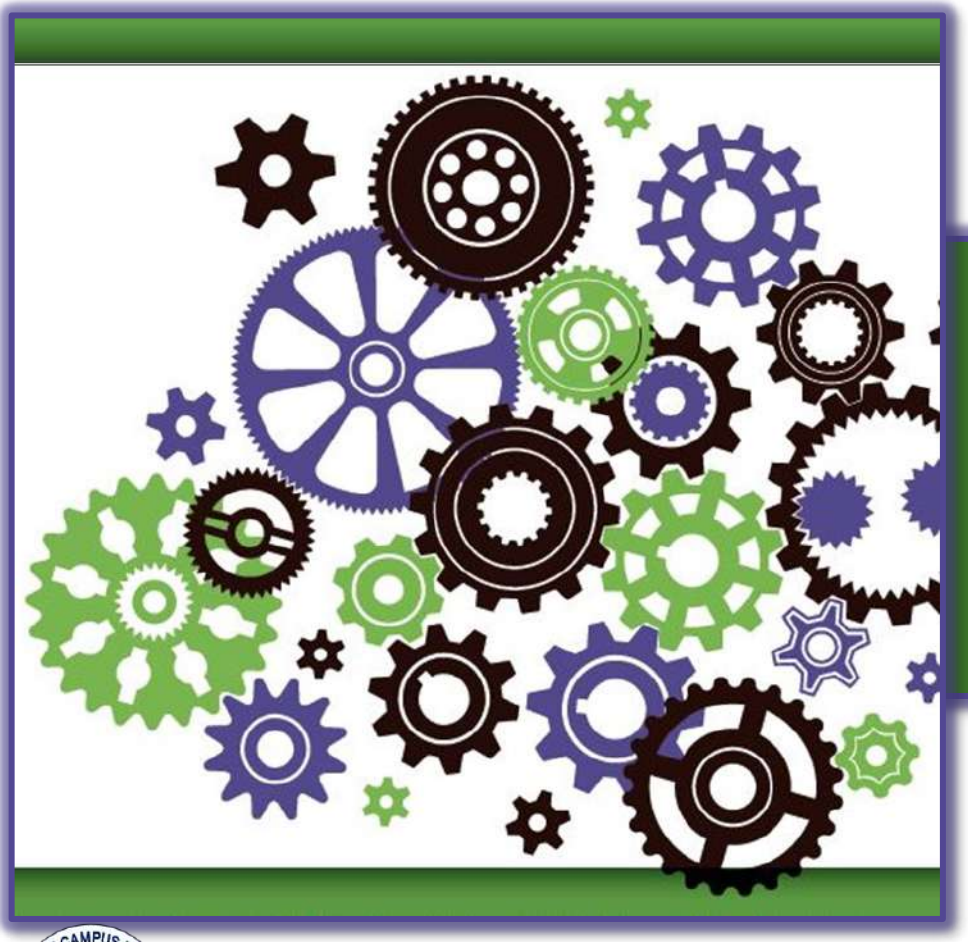
ROMA - 7/8 OTTOBRE 2022

CONGRESSO REGIONALE
AMD-SID LAZIO

Il DIABETE OGGI:

UNA MALATTIA SEMPRE PIÙ COMPLESSA



Quando l'obesità coesiste con il diabete di tipo 1

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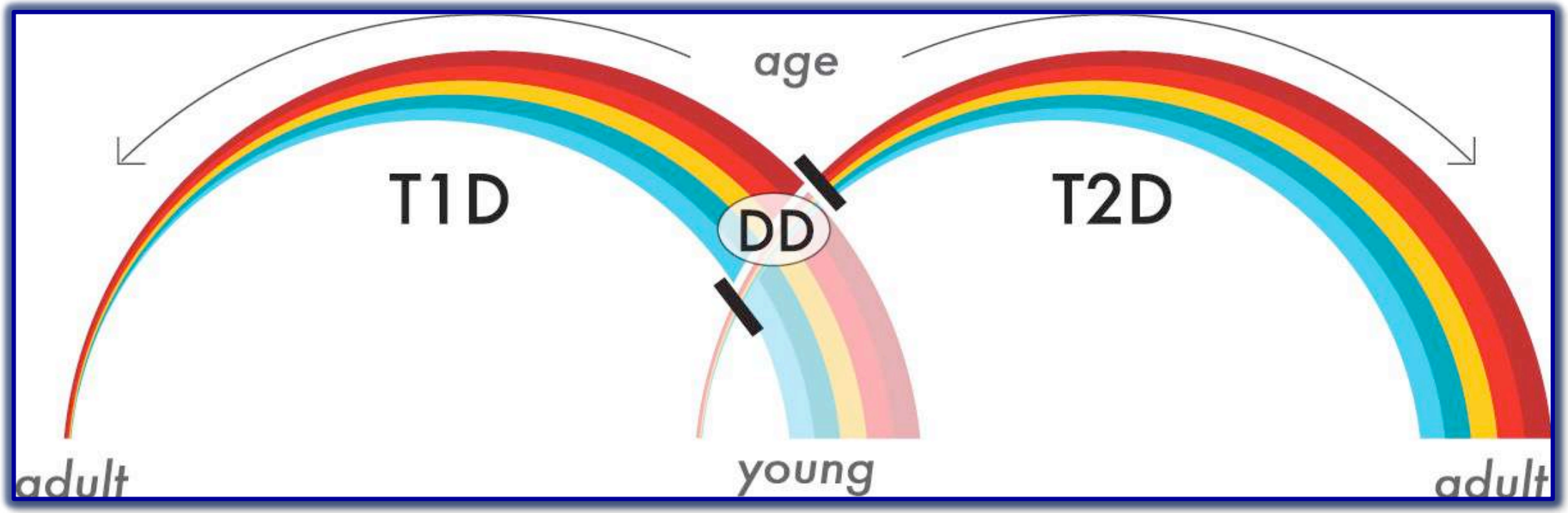
DISCLOSURE STATEMENT

Speakers Name: Prof. Paolo Pozzilli

☒ I have the following potential conflicts of interest to report:

- ***Advisory Board Member*: Dompè, Altheia**
- ***Consulting Fee*: Sanofi, Eli Lilly & Company.**
- ***Grant Recipient*: Amgen Inc, Sanofi, Dompè, Abbott, Novo Nordisk**
- ***Speaker*: Eli Lilly & Company, Dompè**

A new expression of diabetes: double diabetes



The incidence of both type 1 and type 2 diabetes has shown a rise, in parallel with a notable increase in the incidence of a new expression of the disease in children and adolescents, with the characteristics of a mixture of the two types of diabetes, and referred to as 'double diabetes'.

Insulin resistance and obesity, together with the presence of markers of pancreatic autoimmunity - namely, autoantibodies to islet cell antigens - typically define this condition.

Pozzilli P., Buzzetti R., Trends Endocrinol Metab. 2007

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COMMENTARY

WILEY

Impact of obesity on the increasing incidence of type 1 diabetes

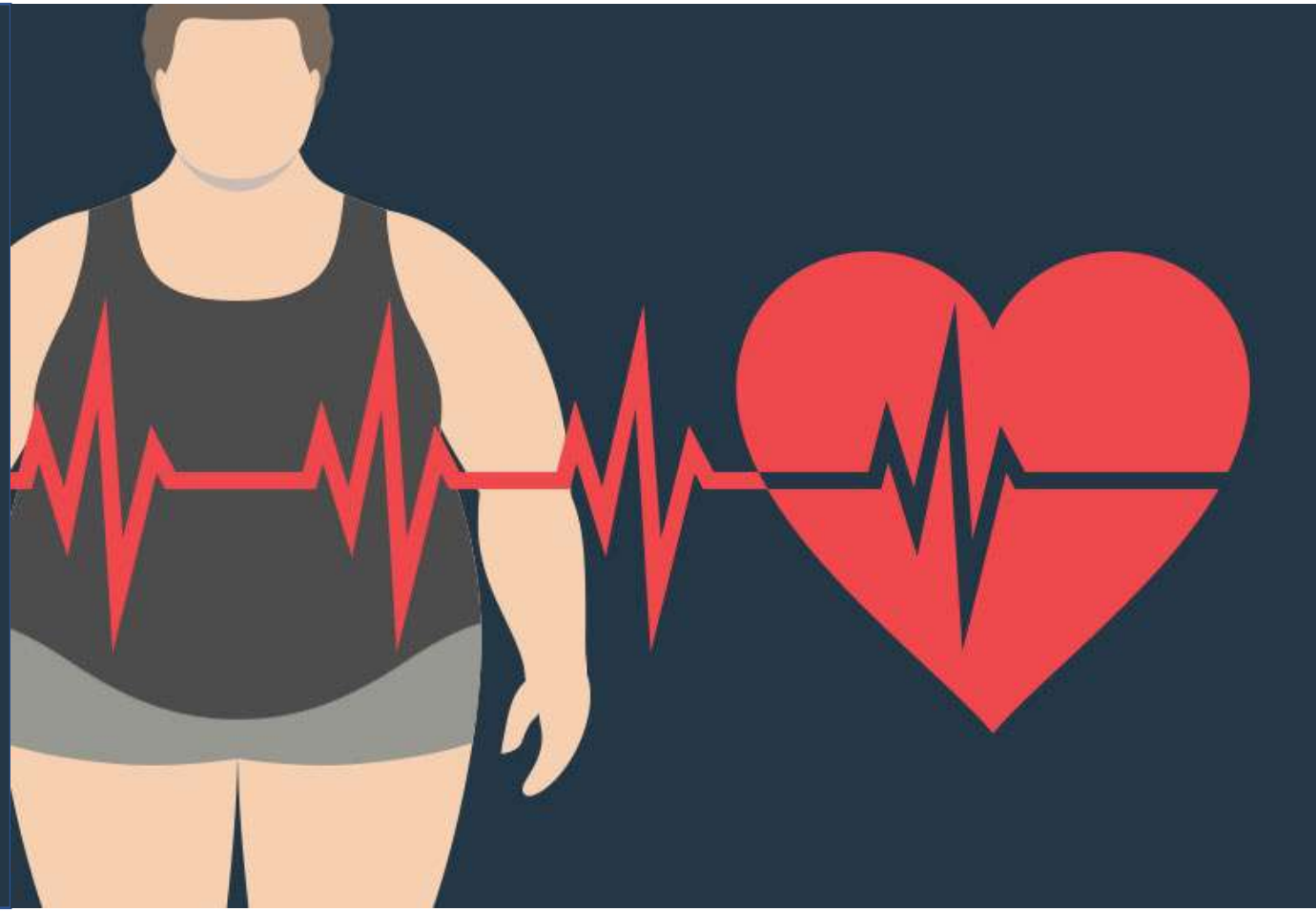
Raffaella Buzzetti MD[1] | Simona Zampetti PhD[1] | Paolo Pozzilli MD[2,3]

Buzzetti R.,…,Pozzilli P. Diabetes Obes Metab 2020

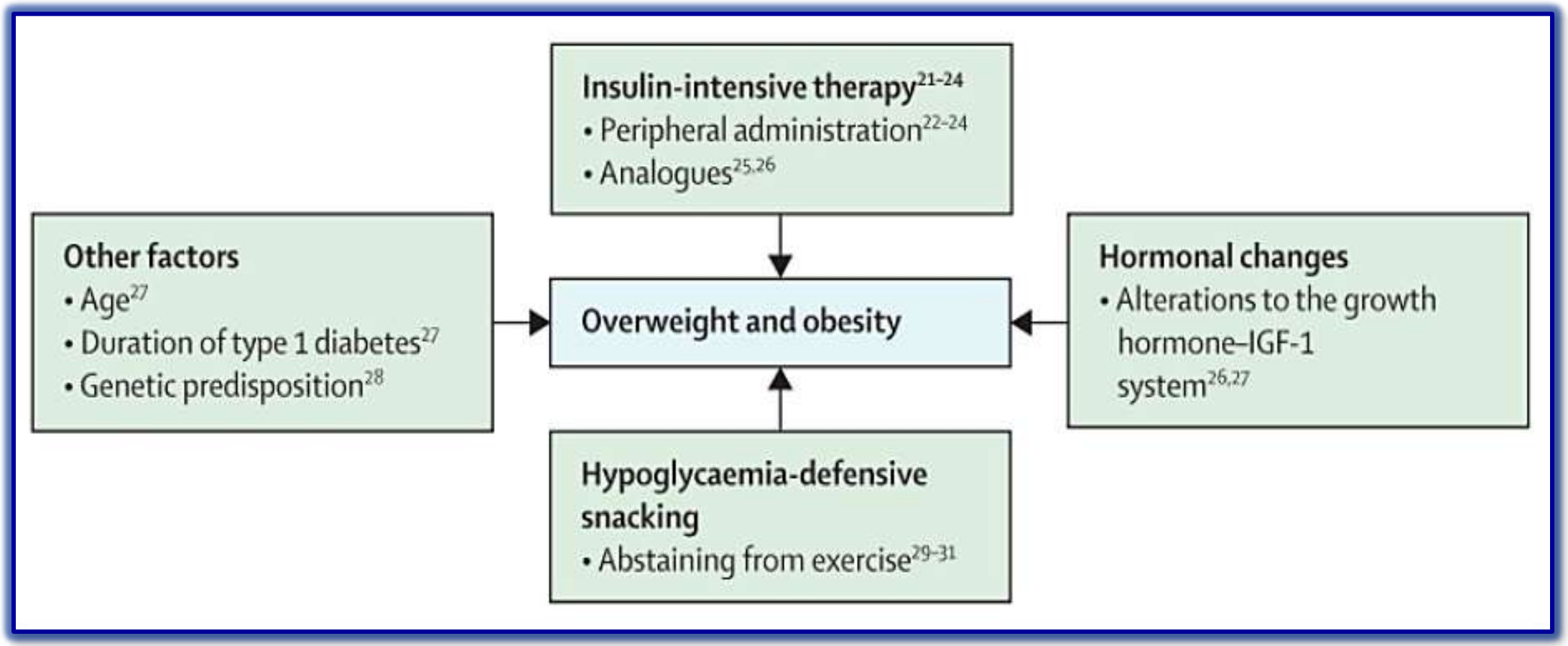
Obesity and type 1 diabetes

Obesity affects large numbers of patients with type 1 diabetes (T1D) across their lifetime, with rates ranging between 2.8% and 37.1%

Patients with T1D and obesity are characterized by presence of insulin resistance, high insulin requirements, a greater cardio-metabolic risk and an enhanced risk of developing chronic complications when compared to normal-weight people with T1D.



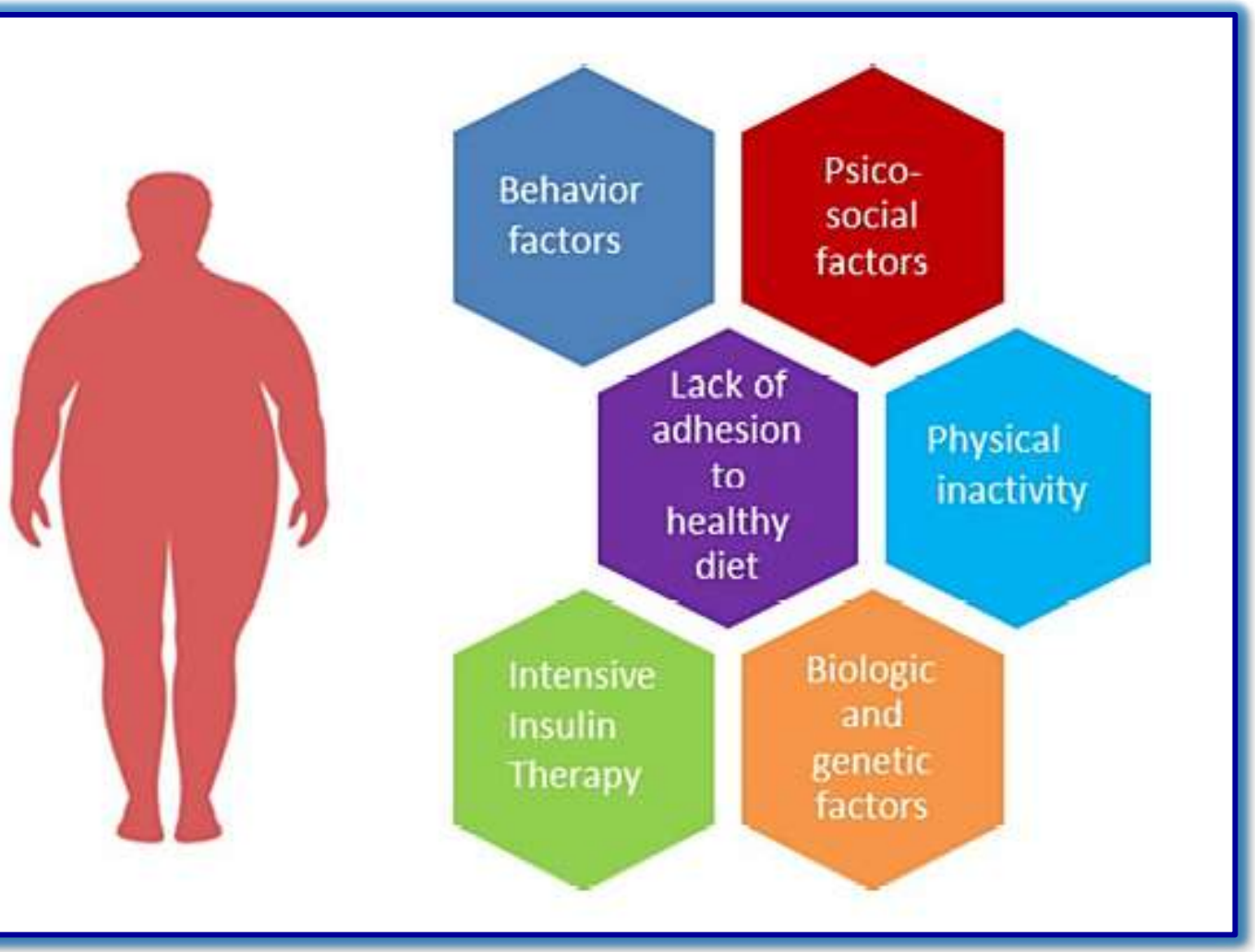
Drivers of overweight and obesity in people living with T1D



The drivers of weight gain in people with T1D are several and complex.

Mathieu C. et al., Lancet Diabetes Endocrinology 2021

Causes of Increasing Prevalence of Obesity in T1D

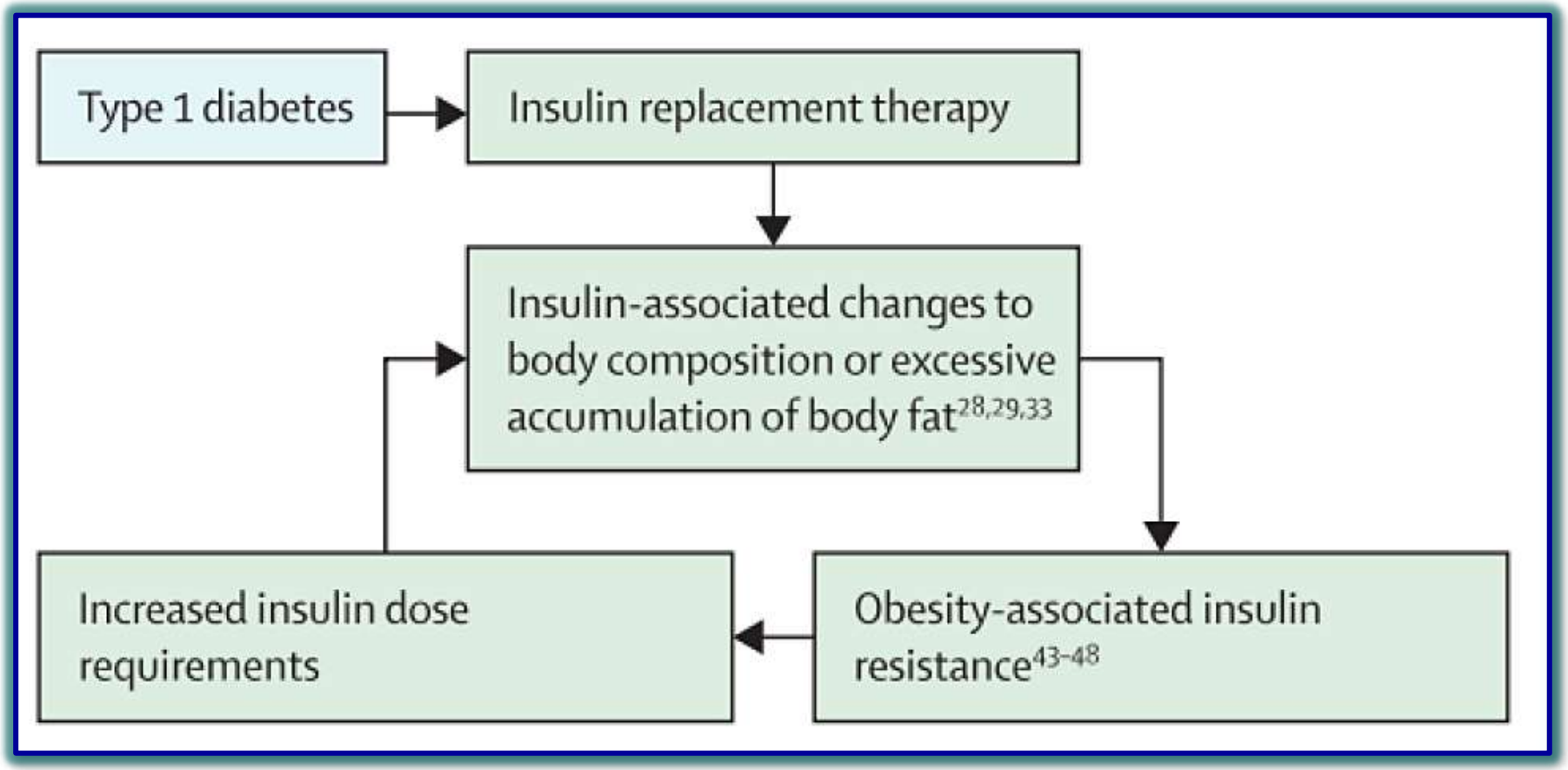


The trigger of the increasing prevalence of obesity in T1D is the obesogenic environment.

Obesity is a complex multifactorial chronic disease; besides unhealthy habits, other exogenous factors such as the presence of altered eating behaviour, eating disorders, short sleep duration, chronic stress and other psychosocial factors are implicated in its aetiology.

Vilarrasa N et al., Diabetes, Metabolic Syndrome and Obesity: Targets and Therapy 2021

The vicious cycle of insulin-associated weight gain

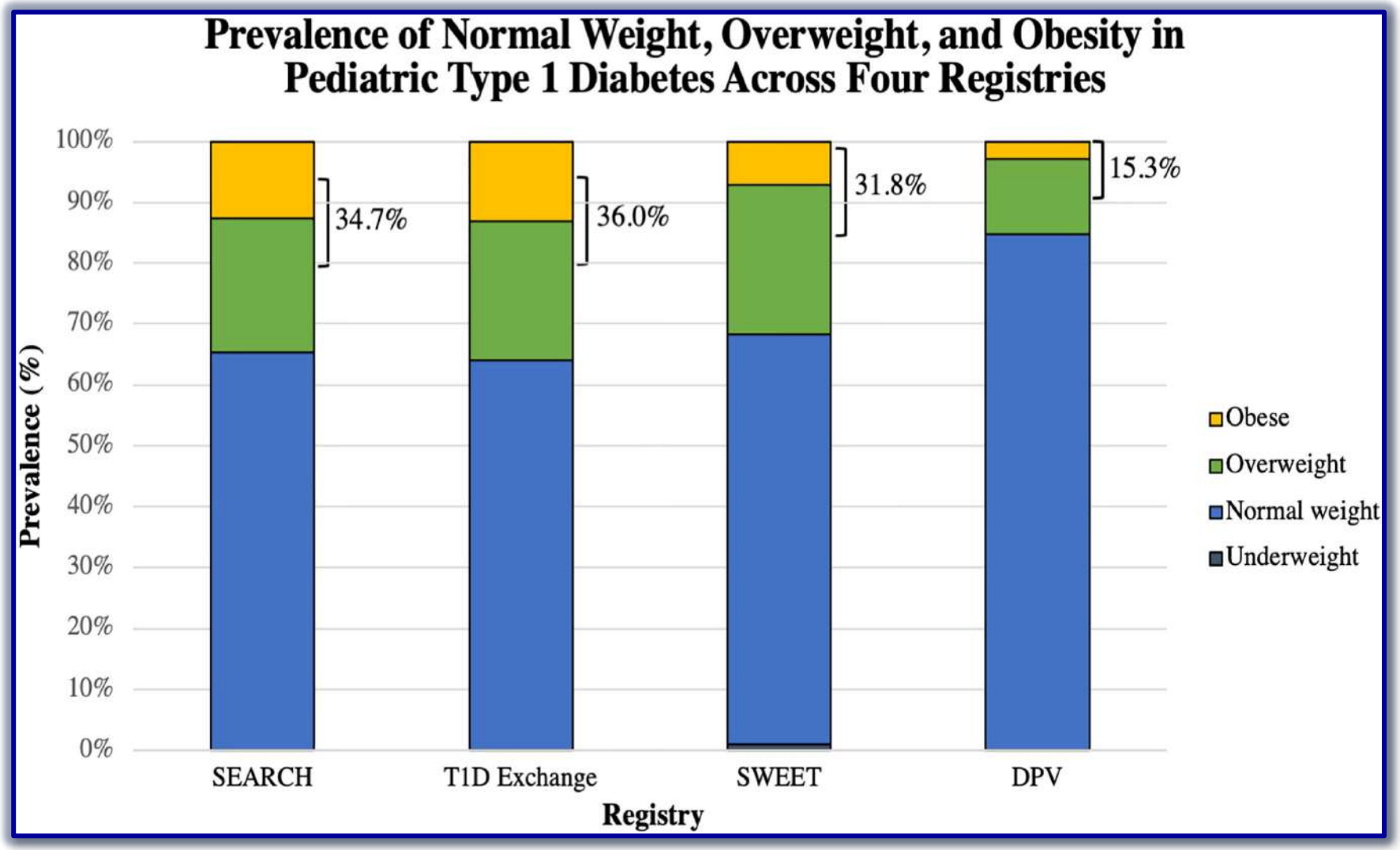


Insulin replacement therapy is believed to be one of the biggest contributors to weight gain in T1D patients.

Weight gain associated with intensive insulin therapy increases insulin resistance, leading to increased insulin dose requirement, which promotes further insulin-associated weight gain.

Mathieu C. et al., Lancet Diabetes Endocrinology 2021

Obesity in Children and Adolescents With Type 1 Diabetes

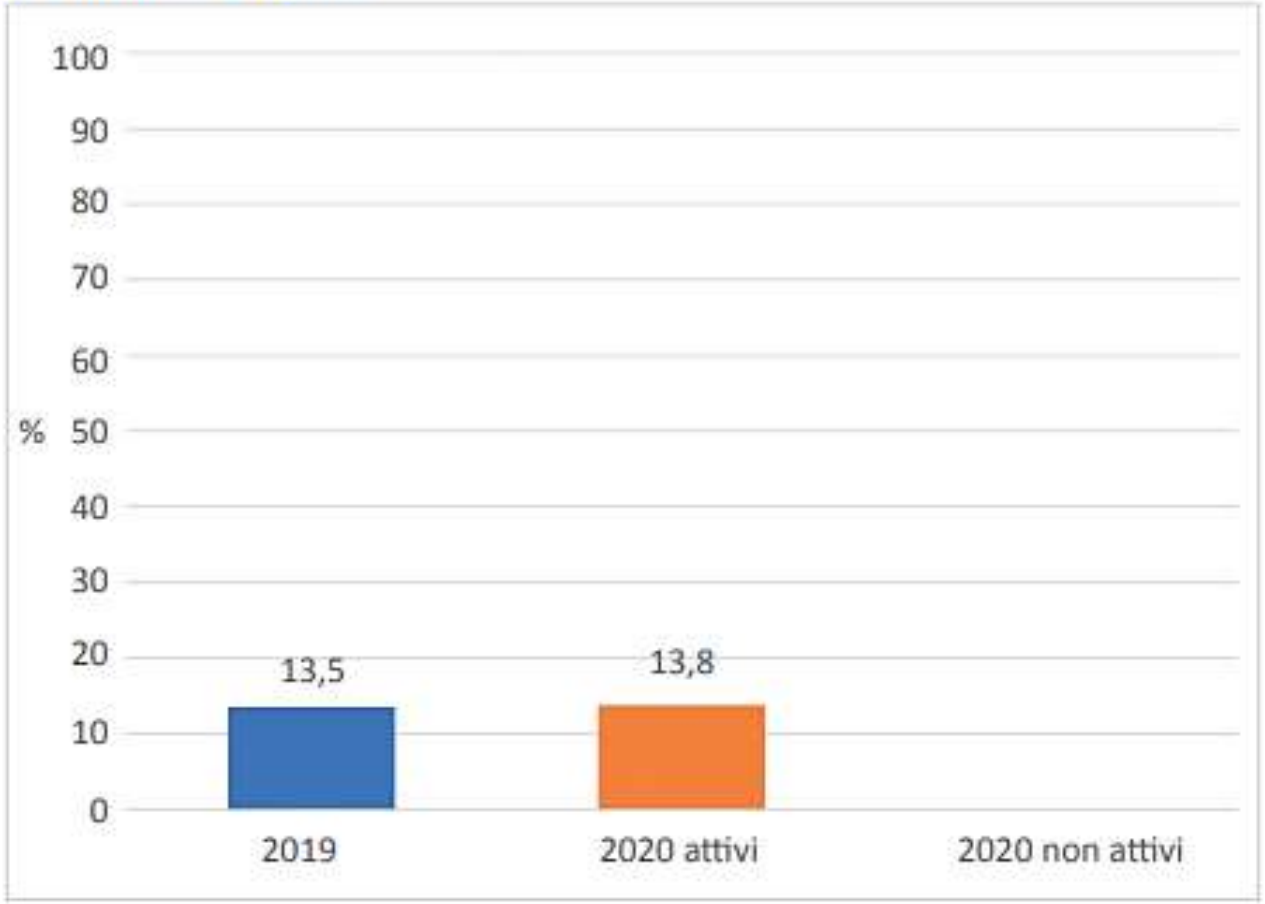


With the increasing incidence of both T1D and obesity, the prevalence of overweight and obesity in youths with T1D at diagnosis has also increased.

Unlike T2D, where obesity is a known risk factor, children with new-onset T1D in the past were not overweight at diagnosis and traditionally thought to be thin.

Libman IM et al., Frontiers in Endocrinology, 2021

Soggetti con BMI ≥30 Kg/m²



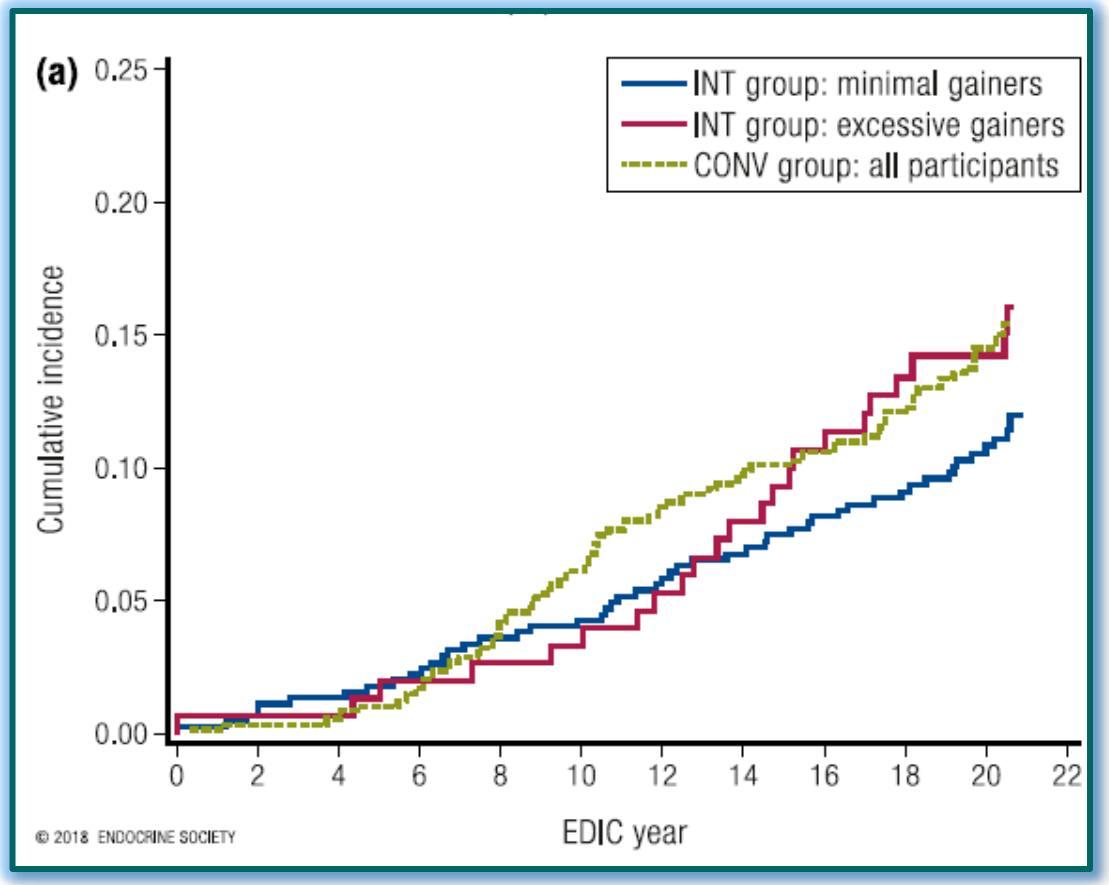
Complessivamente, il 13,5% della popolazione con DM1 è risulta obesa nel 2019. Nel 2020, la percentuale è risultata analoga.

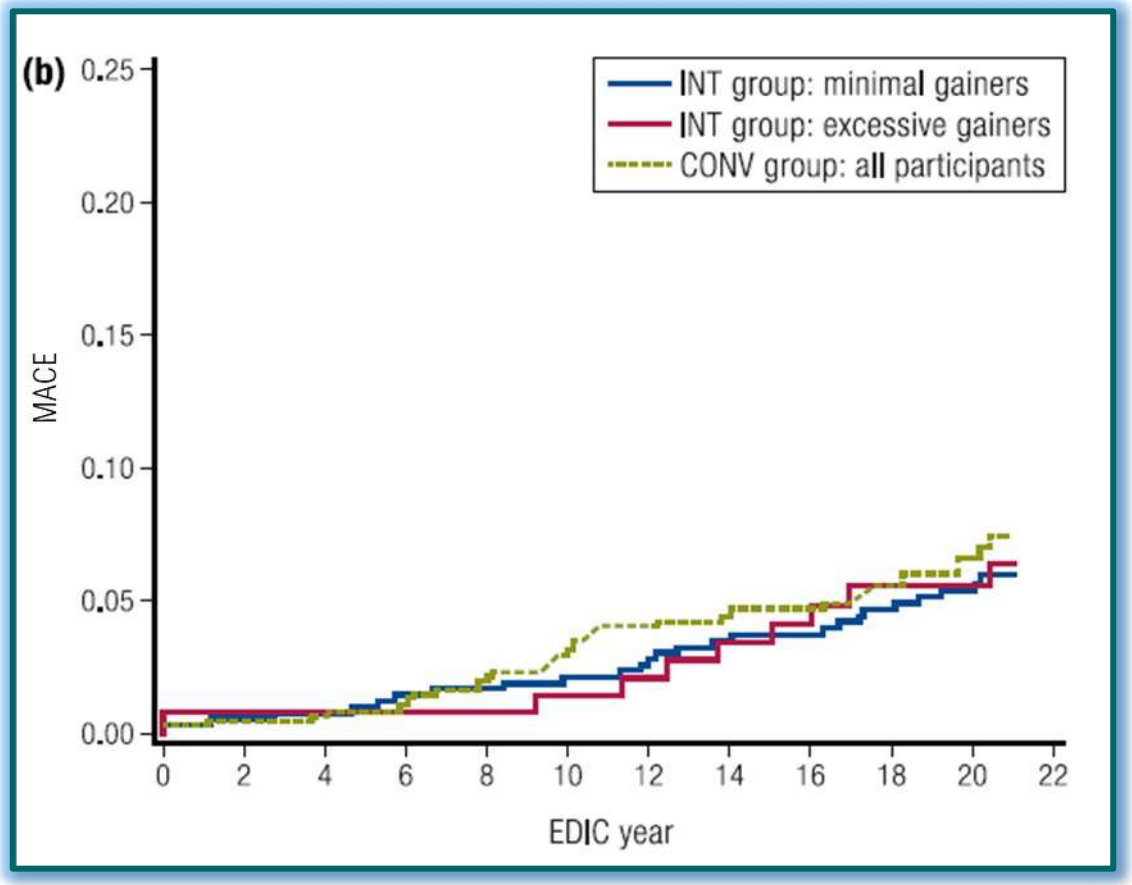
Consequences of overlapping T1D and obesity complications

T1D complications	Obesity complications	Consequences of overlapping
Macrovascular: atherosclerosis, thrombosis atherogenic lipid profile	Dyslipidemia Increased coronary artery calcium index Increased thickness of intima-media	Hypertension Increased risk of premature cardiovascular diseases Strokes
Hyperglycaemia	Insulin resistance Abdominal obesity Hyperlipidemia Hypertension	Metabolic syndrome
Hyperglycaemia	Adipose tissue dysfunction Elevated alanine aminotransferase	NAFLD-> CVD events, polyneuropathy, incidence of chronic kidney diseases
Impaired glucose tolerance Hyperinsulinemia	Dyslipidemia Insulin resistance Psychological comorbidities	PCOS: problems with fertility or higher risk for the development of endometrial cancer
Increased risk of nephropathy and albuminuria	High blood cholesterol Albuminuria	Kidney diseases, including end-stage renal disease

Ciężki S et al., Frontiers in Endocrinology 2022

Weight gain impacts cardiovascular event rates after 14 years of follow-up in the EDIC trial





At year 14 of EDIC, the cardiovascular event curves began to diverge in the intensive insulin therapy group only through the 20-year follow-up.

A Cox proportional hazard model showed that after year 14, the cardiovascular events in the intensive insulin therapy group (INT) with the most weight gain were significantly higher than the minimal weight gain group.

Corbin KD et al., Endocrine Reviews 2018

Preventing and treating excessive weight gain in people living with T1D

Diet and exercise

- Risk of hypoglycaemia might influence defensive snacking and exercise absenteeism
- Weight regain is likely with wavering commitment to treatment

Bariatric surgery

- Increased risk of hypoglycaemia and diabetic ketoacidosis
- Under-researched

Pharmaceuticals

- Restricted by market authorisations
- Require chronic use
- High cost and inadequate reimbursement
- Issues with tolerability
- SGLT inhibitors associated with diabetic ketoacidosis risk
- GLP-1 receptor agonists require additional injections

Many weight management strategies for people living with diabetes have been implemented for T2D.

Whether or not these same strategies are effective for people living with T1D is unknown.

All approaches to weight loss present specific difficulties for people living with T1D: Hypoglycaemia when fasting, cutting carbohydrates, or during exercise.

Mathieu C. et al., Lancet Diabetes Endocrinology 2021

A review of potential adjuvant pharmacological therapies to insulin in obese patients with T1D

Name of the drug	Mechanism of action	The benefits for obese patients with T1DM	Side effects
Metformin	• Reducing gluconeogenesis in the liver, promoting glucose uptake in peripheral tissues	• Reducing cardiovascular risk, improving insulin sensitivity, reducing weight, BMI and adiposity	• Increased prevalence of minor gastrointestinal side effects
GLP-1 receptor agonists	• Increasing the secretion of insulin and decreasing the release of glucagon in a glucose-dependent manner	• Reducing HbA1c, BMI, fasting and postprandial blood glucose levels and insulin dose	• Increased prevalence of gastrointestinal side effects
DPP-4 inhibitors	• Inhibition of GLP-1 degradation	• No significant effect on the reduction of HbA1c, body weight, BMI or insulin dose	• Unknown
Pramlintide	• Decreasing postprandial glucagon output, delaying gastric emptying, promoting satiety	• Improving glycaemic control, reducing insulin dose and body weight	• Transient hypoglycemia, gastrointestinal side effects
SGLT-2 inhibitors	• Inhibiting glucose reabsorption in proximal tubule of nephron	• Reduction in HbA1c level, body weight and total daily insulin dose	• Euglycemic diabetic ketoacidosis, urinary tract and genital infections

Ciężki S et al., Frontiers in Endocrinology 2022

GLP-1 RA liraglutide as adjunct therapy in people living with T1D

	ADJUNCT-ONE[73] (n=1398; 52 week follow-up; randomisation 3:1)			ADJUNCT-TWO[74] (n=835; 26 week follow-up; randomisation 3:1)			
	Liraglutide 1·8 mg	Liraglutide 1·2 mg	Liraglutide 0·6 mg	Liraglutide 1·8 mg	Liraglutide 1·2 mg	Liraglutide 0·6 mg	Placebo
Mean effect on body weight, kg	−4·90 (−5·70 to −4·20)	−3·60 (−4·30 to −2·80)	−2·20 (−2·90 to −1·50)	−5·10 *vs* baseline*	−4·00 *vs* baseline*	−2·50 *vs* baseline*	−0·20 *vs* baseline*
Mean effect on HbA_{1c}	−0·20% (−0·32 to −0·07)	−0·15% (−0·27 to −0·03)	−0·09% (−0·21 to 0·03)	−0·35% (−0·50 to −0·20)	−0·23% (−0·38 to −0·08)	−0·24% (−0·39 to −0·10)	NA
Estimated treatment ratio for effect on insulin dosage	0·92 (0·88 to 0·96)	0·95 (0·91 to 0·99)	1·00 (0·96 to 1·04)	0·90% (0·86 to 0·93)	0·93% (0·90 to 0·96)	0·95% (0·92 to 0·99)	NA
Estimated treatment ratio for symptomatic hypoglycaemic events	1·31 (1·07 to 1·59)	1·27 (1·03 to 1·55)	1·17 (0·97 to 1·43)	NS	1·33 (1·07 to 1·67)	NS	NA

Data are mean (95% CI) or estimated treatment ratio (95% CI) for comparison against placebo, unless otherwise stated. NA=not applicable. NS=not significant versus placebo (actual p value not reported). Symptomatic hypoglycaemic events are typical symptoms of hypoglycaemia plus a measured plasma glucose concentration ≤70 mg/dL. *p<0·0001.

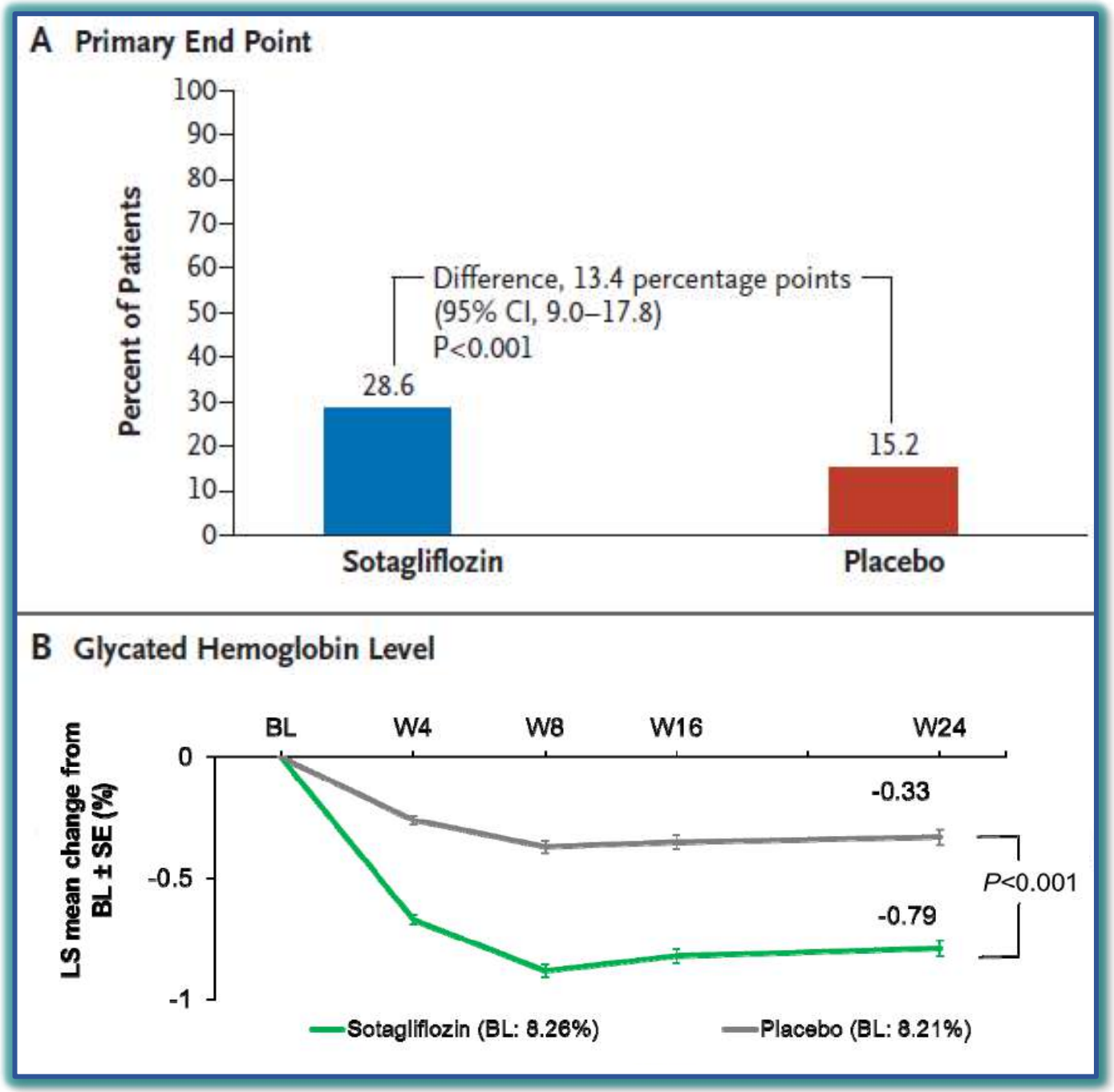
Mathieu C. et al., Lancet Diabetes Endocrinology 2021

SGLT-2 inhibitors as adjunct therapy in people living with T1D

	Pooled analysis of DEPICT-1 and DEPICT-2 studies[78]			Phase 3 trial[79] (n=175)	Pooled analysis of Tandem1[80] and Tandem2[81] (n=1575)		
	Dapagliflozin 5 mg/day (n=548)*	Dapagliflozin 10 mg/day (n=566)	Placebo	Ipragliflozin 50 mg/day	Sotagliflozin 200 mg/day	Sotagliflozin 400 mg/day	Placebo
Effect on bodyweight	−3·11% (−3·61 to −2·62)	−3·71% (−4·20 to −3·22)	NA	−2·87 kg (−3·58 to −2·16)	−2·17% (−2·54 to −1·80)	−3·02% (−3·39 to −2·65)	NA
Effect on HbA_{1c}	−0·41% (−0·48 to −0·31)	−0·43% (−0·52 to 0·34)	NA	−0·36% (−0·57 to −0·14)	−0·36% (−0·44 to −0·29)	−0·38% (−0·45 to −0·31)	NA
Effect on insulin dosage	−9·57% (−12·01 to −7·07)	−11·75% (−14·13 to −9·30)	NA	−7·35 IU (−9·09 to −5·61)	7·10 % (SE 1·30); p<0·001 *vs* placebo at 52 weeks	−10·33 % (SE 1·30); p<0·001 *vs* placebo at 52 weeks	NA
Adverse events: diabetic ketoacidosis†	2·00%	1·90%	0·60%	No diabetic ketoacidosis reported in either group	2·90 %	3·80 %	0·20 %

Data are mean (95% CI) for comparison with placebo at 24 weeks, unless otherwise stated. Dapagliflozin is an SGLT2 inhibitor approved for use in Europe and Japan. Ipragliflozin is an SGLT2 inhibitor approved for use in Japan. Sotagliflozin is a dual SGLT1/2 inhibitor approved by the European Medicines Agency. NA=not applicable. IU=international units. *p<0·0001. †Other adverse events were not reported consistently between studies.

Mathieu C. et al., Lancet Diabetes Endocrinology 2021

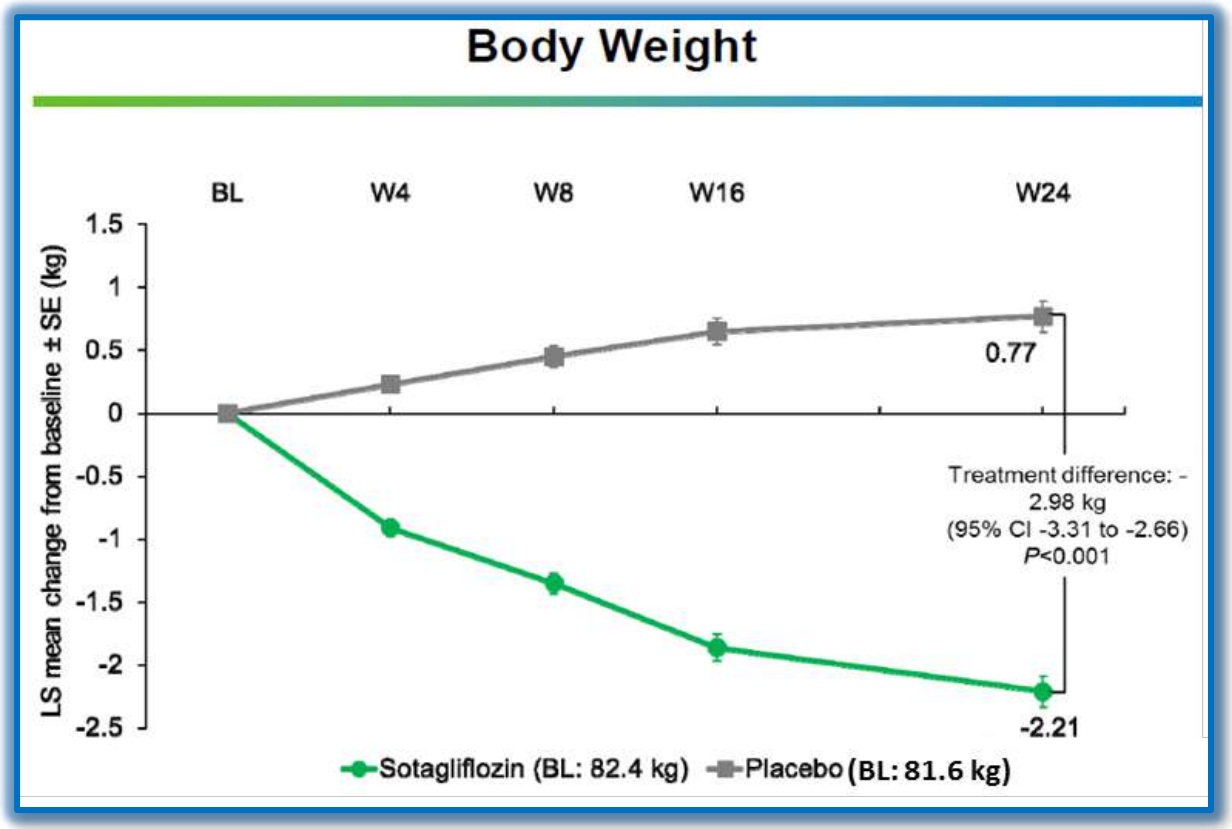


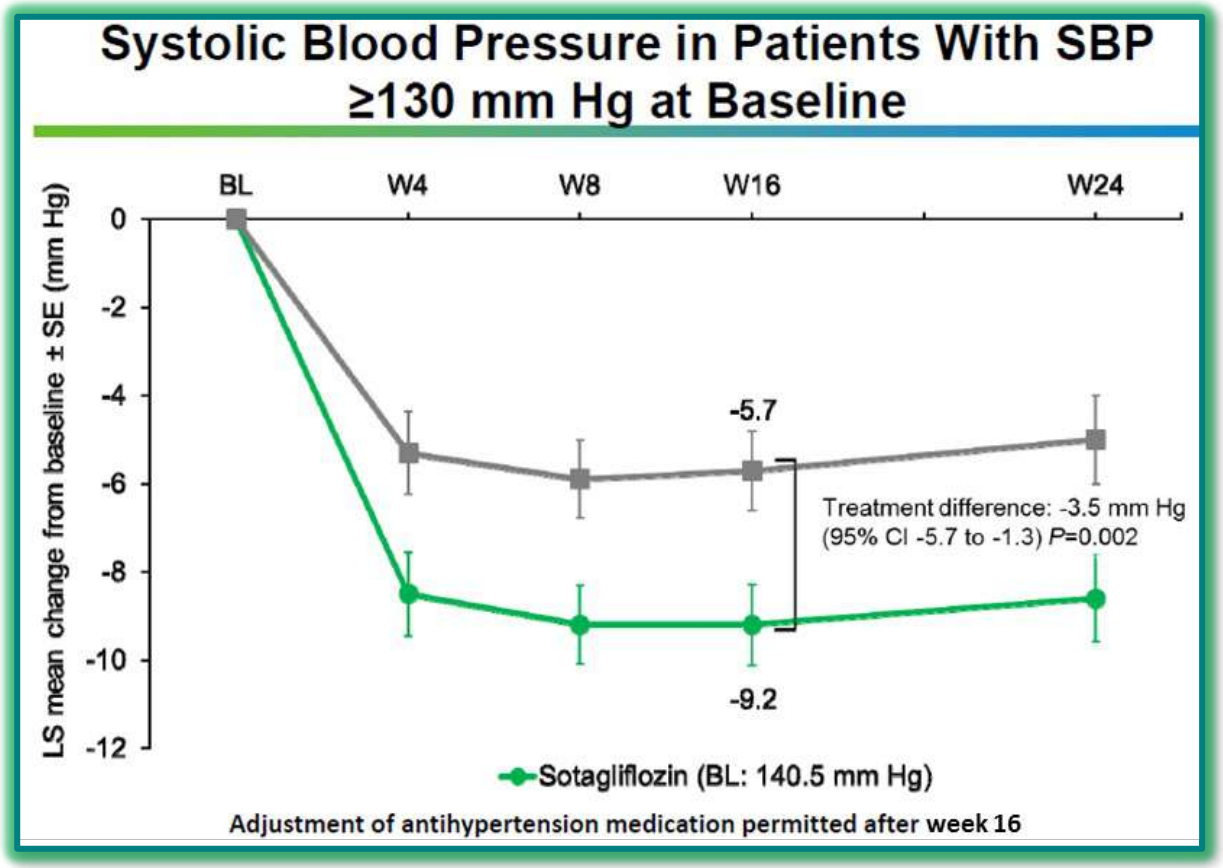
In TANDEM-3 Trial Sotaglifozin in T1D with mean BMI 28.6

Among patients with type 1 diabetes who were receiving insulin, the proportion of patients who achieved a glycated hemoglobin level lower than 7.0% with no severe hypoglycemia or diabetic ketoacidosis was larger in the group that received sotagliflozin than in the placebo group.

Garg SK,…,Pozzilli P. et al., NEJM, 2017

In TANDEM-3 Trial Sotaglifozin in T1D with mean BMI 28.6





Garg SK,…,Pozzilli P. et al., New Engl J Med, 2017

Conclusions

Genetic risk and environmental factors may lead to coexisting features of type 1 and 2 diabetes, with added implications for both pathogenesis and long-term health: Double Diabetes.

Overweight and obesity are increasingly common in youth and adults with T1D, perhaps a consequence of changing cultural practices surrounding diet, nutrition and exercise over the past several decades.

In the setting of widespread use of intensive insulin therapy, poor dietary choices and over-treatment of hyperglycemia may both contribute to weight gain.

There is limited evidence for a beneficial effect of currently available adjuvant therapies apart from lifestyle adjustments and SGLT2 inhibitors (off label). These all need further investigation for both the delay of T1D and the prevention of complications in those patients with double diabetes.