16° Congresso Nazionale AME

Joint Meeting with AACE Italian Chapter

Update in Endocrinologia Clinica

9-12 novembre 2017

Roma

Diabete ed obesità infantile

Fattori di rischio e familiarità

F. Mori

AZIENDA OSPEDALIERA SANT' ANDREA

FACOLTÀ DI MEDICINA E PSICOLOGIA

Il diabete tipo 2 negli adolescenti sta rappresentando uno dei disordini paradigmatici del 21° secolo.

Si tratta di una patologia ampiamente descritta ormai in tutto il mondo e legata ai rapidi cambiamenti socio-economici verificatisi negli ultimi 30 anni, maggiormente rappresentata nei paesi più ricchi, sebbene si stia diffondendo anche in paesi più deprivati.

La sua eziologia è eterogenea e comprende fattori di rischio ambientali, sociali e comportamentali, che amplificano e "svelano" la predisposizione genetica

Il rapido incremento della prevalenza che viene osservato non può essere spiegato soltanto con un incremento della "frequenza" di alcuni geni, ma deve per forza implicare altri fattori.

Type 2 diabetes mellitus in children and adolescents

World J Diabetes 2013 December 15; 4(6): 270-281

Lancet 2017; 389: 2252–60

Type 2 diabetes in adolescents: a severe phenotype posing major clinical challenges and public health burden

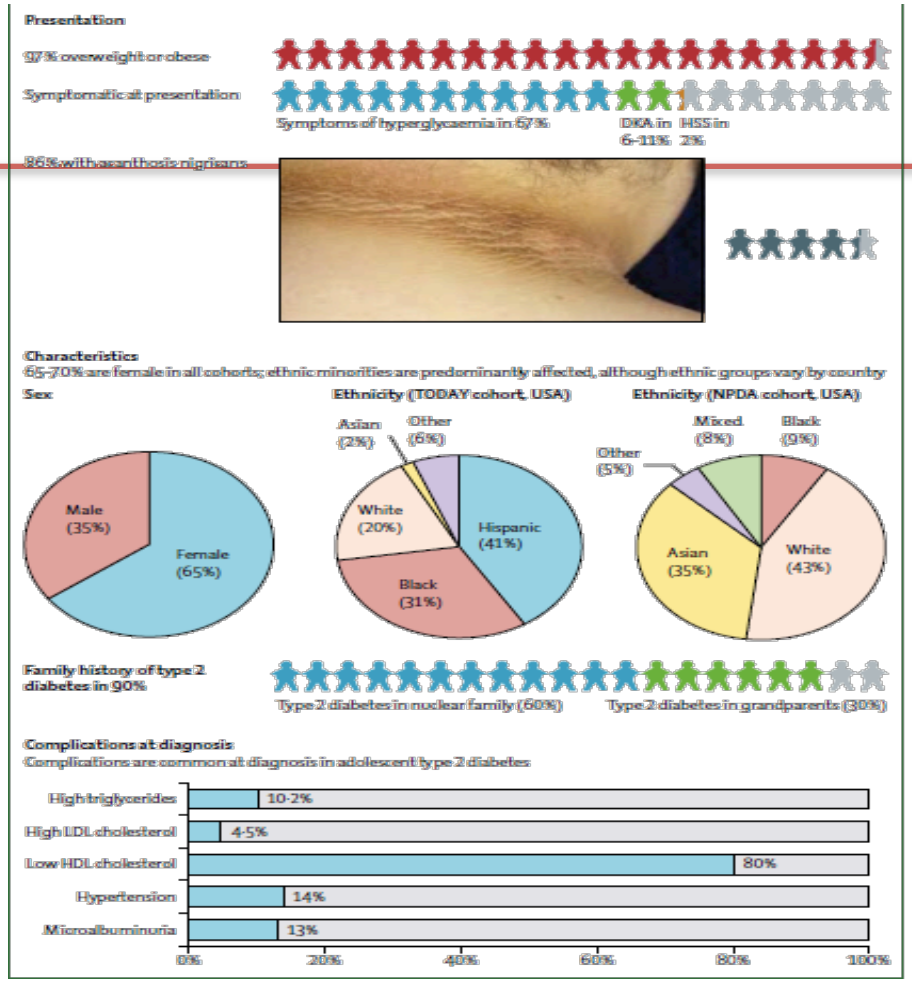
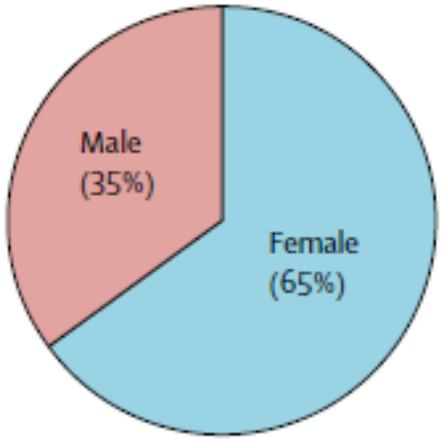
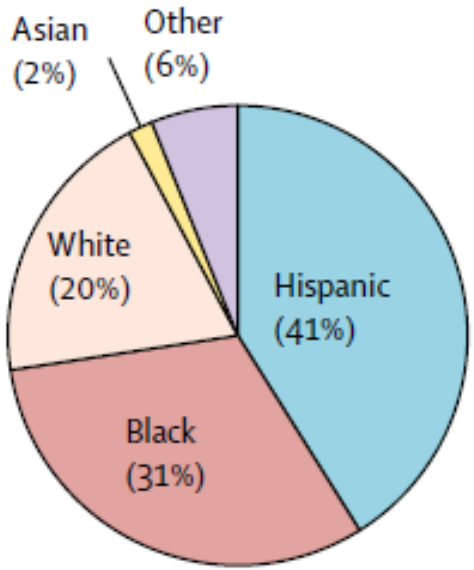


Figure: **Features of adolescent type 2 diabetes at diagnosis**
DKA=diabetic ketoacidosis. HHS=hyperglycaemic hyperosmolar syndrome.

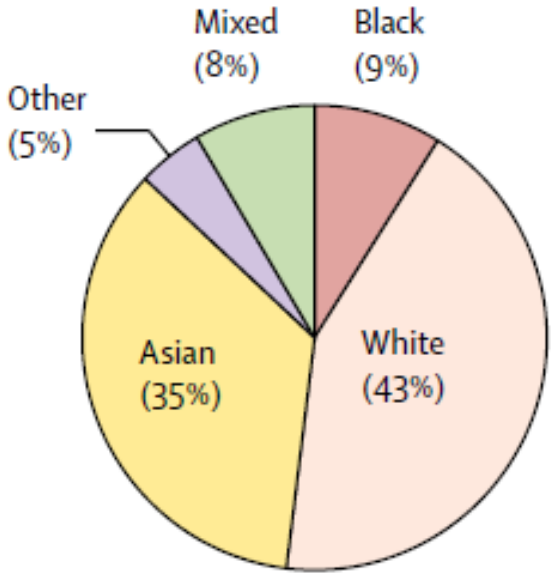
Sex

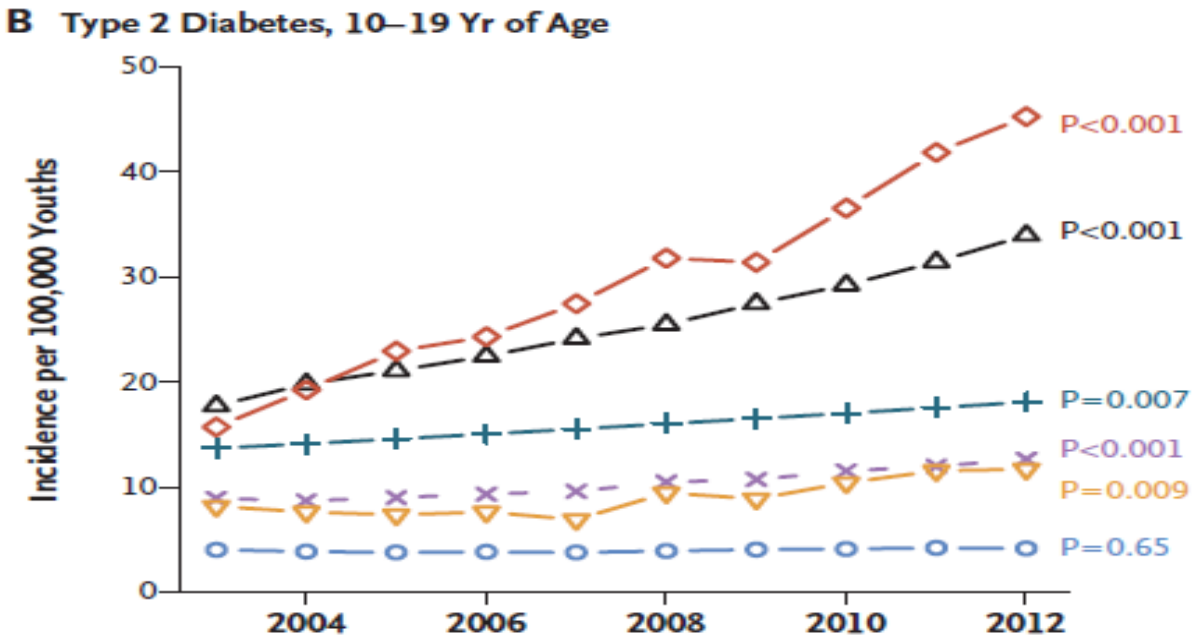


Ethnicity (TODAY cohort, USA)



Ethnicity (NPDA cohort, USA)





Sex														
Girls	19.2	19.1	19.3	19.7	20.7	21.6	21.6	19.7	19.5	19.9	0.7 (−0.9 to 2.3)	0.40	1.4 (0.3 to 2.5)	0.01
Boys	19.8	19.0	20.4	21.7	22.0	22.4	22.4	21.0	21.4	23.4	2.1 (0.7 to 3.5)	0.003	2.2 (1.3 to 3.1)	<0.001

Ethnic Minorities Are at Greater Risk for Childhood-Onset Type 2 Diabetes and Poorer Glycemic Control in England and Wales

Journal of Adolescent Health 59 (2016) 354–361

Table 2

Prevalence of type 2 diabetes by ethnic group and gender in children and young people aged <16 years in 2012–2013 in England and Wales

Ethnic group	Number of cases			Base population			Prevalence		
	Total	Males	Females	Total	Males	Females	Total (95% CI)	Males (95% CI)	Females (95% CI)
All	307	83	224	10,579,132	5,417,362	5,161,770	2.9 (2.6–3.2)	1.5 (1.2–1.8)	4.3 (3.8–4.9)
White	122	28	94	8,347,929	4,280,186	4,067,743	1.4 (1.2–1.7)	.6 (.4–.9)	2.3 (1.8–2.8)
Asian	81	19	62	1,037,325	530,449	506,876	8.0 (6.2–9.6)	3.5 (2.2–5.5)	12.2 (9.5–15.6)
Black	14	4	10	508,793	257,260	251,533	2.7 (1.6–4.5)	1.5 (.5–3.9)	3.9 (2.0–7.2)
Mixed	21	9	12	550,734	280,219	270,515	3.8 (2.4–5.7)	3.2 (1.6–6.0)	4.4 (2.4–7.6)
Other	8	6	2	134,351	69,248	65,103	6.0 (2.9–11.6)	8.6 (3.7–18.6)	3.0 (.7–11.2)
Not stated[a]	61	17	44	—	—	—	—	—	—

interval = 2.6–3.2) per 100,000. Prevalence of T2D differed significantly between ethnic groups (Table 2). The highest prevalence of T2D was observed in Asians (8.0 [6.2–9.6]/100,000) followed by the "other" (6.0 [2.9–11.6]/100,000) and mixed (3.8 [2.4–5.7]/100,000) ethnic groups (Table 2). The white group had the lowest prevalence of T2D (1.4 [1.2–1.7]/100,000). Overall, females had a higher prevalence compared with males

Ethnic Minorities Are at Greater Risk for Childhood-Onset Type 2 Diabetes and Poorer Glycemic Control in England and Wales

Journal of Adolescent Health 59 (2016) 354–361

Table 1
Characteristics of the 391 children and young people with type 2 diabetes included in the study by ethnicity

Characteristics	Ethnic group						
	White	Asian	Black	Mixed	Other	Not stated	All
	n = 153	n = 99	n = 25	n = 24	n = 13	n = 77	n = 391
Age at diagnosis (years)	12.98 (2.32)	12.77 (2.88)	12.85 (2.66)	13.13 (1.40)	13.19 (2.36)	13.32 (2.52)	13 (2.48)
Age at visit[b] (years)	14.77 (1.86)	14.71 (2.26)	15.24 (2.9)	14.7 (1.74)	15.21 (1.76)	15.1 (2.12)	14.85 (2.08)
Female (%)	73	76	72	54	46	70	71
Diabetes duration (years)	1.78 (1.87)	1.93 (2.06)	2.38 (1.68)	1.56 (1.82)	2.02 (1.6)	1.75 (1.61)	1.85 (1.85)
Mean HbA_{1c} (%)	7.8 (4.2)	8.1 (4.4)	7.9 (4.3)	9.8 (4.8)	8.2 (4.9)	7.7 (4.3)	8 (4.4)
mmol/mol	61.6 (22.24)	64.7 (24.71)	62.82 (23.9)	83.13 (28.74)	66.36 (29.77)	60.58 (23.13)	63.74 (24.27)
Proportions achieving HbA_{1c} target (%)							
<58 mmol/mol	49	50	60	33	54	54	50
≥58 mmol/mol	51	50	40	67	46	46	50
Mean BMI (kg/m^2)[c]	31 (4.92)	29 (5.4)	30.67 (4.18)	29.12 (4.36)	32.38 (4.07)	29.91 (6.1)	30.15 (5.22)
Mean BMI *z* scores[c]	2.61	2.24	2.62	2.40	2.85	2.34	2.45
BMI *z* score ≥85th percentile (%)[c]	93	87	100	100	100	89	92
Overweight or obese[c]— (BMI ≥ 25 kg/m^2 [%])	91	83	96	95	100	86	89
Socioeconomic status (mean IMD score)[d]	29.28 (17.25)	36.1 (16.15)	29.87 (11.84)	32.4 (14.98)	38 (16.47)	29.84 (17.38)	31.63 (16.73)

Index of multiple deprivation

Table 1—Baseline demographics of youth-onset diabetes cohorts

	Type 1 diabetes (n = 1,710)	Type 2 diabetes (n = 342)	P value
Age (years)	8.9 ± 4.3	13.5 ± 2.2	<0.0001
Male sex	53.2	37.8	<0.0001
BMIz	0.4 ± 1.0	1.9 ± 0.7	<0.0001
Urban	51.9	26.9	<0.0001
Low SES	11.4	59.1	<0.0001
HNF-1α polymorphism			
GS†	N/A	32.2	—
SS††	N/A	18.5	—
Elevated blood pressure	11.1	9.9	0.59
Albuminuria at diagnosis	13.5	27.1	0.0008
Mother with pregestational diabetes	2.7	15.9	<0.0001

Data are mean ± SD or %. N/A, not applicable. †Heterozygous for HNF-1α polymorphism. ††Homozygous for HNF-1α polymorphism.

Earlier Onset of Complications in Youth With Type 2 Diabetes

Diabetes Care 2014;37:436–443

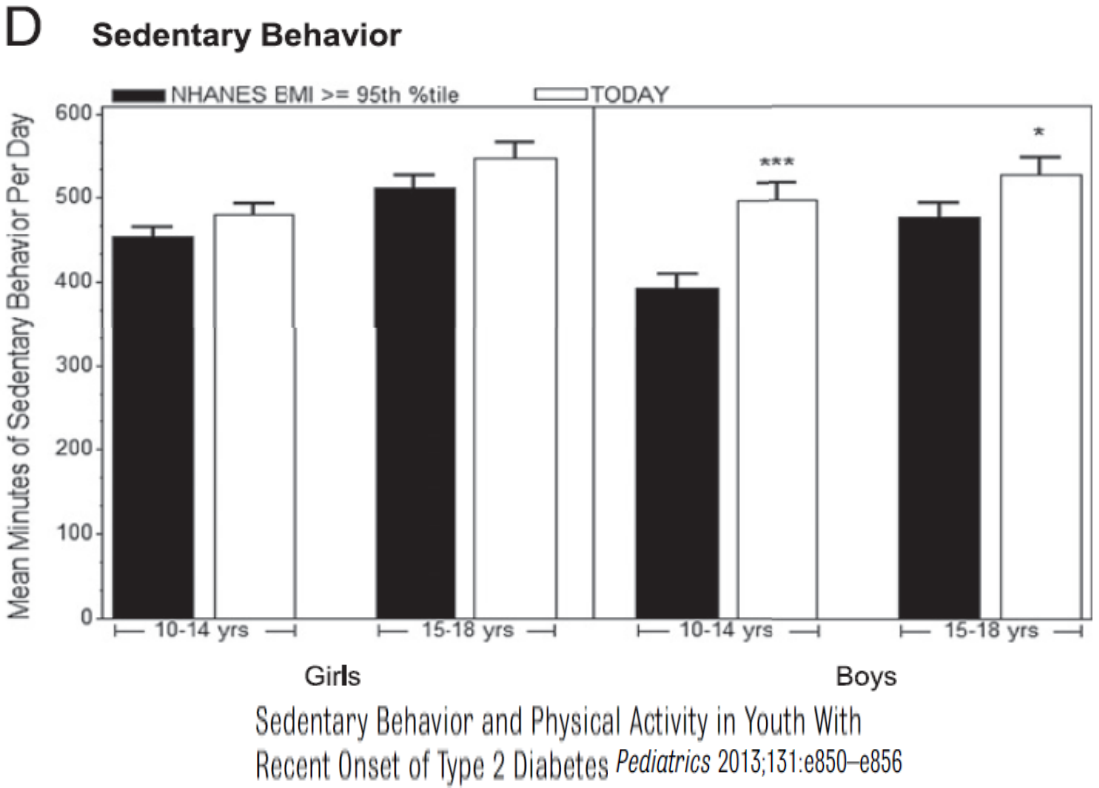
Characteristics of Adolescents and Youth with Recent-Onset Type 2 Diabetes: The TODAY Cohort at Baseline

Demographic characteristics and clinical/medical history	Overall (n = 704)
Age at randomization (yr)	14.0 (2.0)
BMI Z-score	2.15 (0.44)
Duration of diabetes (months)	7.8 (5.8)
Acanthosis present at neck	85.6%
Female sex	64.9%
Race/ethnicity	
NHW	19.6%
NHB	31.5%
Hispanic	41.1%
AI	6.1%
Asian	1.7%
Household income	
<$25,000	41.5%
$25,000–49,999	33.5%
>$49,999	25.0%
Parent/guardian highest level education	
12th grade or less	26.3%
High school graduate/GED/business/technical	25.2%
Some college/associates degree	31.7%
Bachelors degree or higher	16.8%
Presence of biological parent(s)	
Youth lives with both mother and father	38.7%
Youth lives with mother only	47.0%
Youth lives with father only	5.1%
Youth lives with neither mother or father	9.2%
Tanner stage 4 or 5	83.9%
Size at on-time birth (within 2 wk of due date)	
Small (<2500 g)	9.0%
Normal (2500–4000 g)	73.8%
Large (>4000 g)	17.2%
Mother had gestational diabetes with participant	33.3%
Nuclear family history of diabetes	59.6%
Nuclear family + grandparents history of diabetes	89.4%

TABLE 1. Baseline characteristics of 704 participants,

J Clin Endocrinol Metab, January 2011, 96(1):159–167

The TODAY study population is one of the largest cohorts of ethnically and geographically diverse youth with type 2 diabetes ever gathered. This current effort suggests that the cohort tended to be less active, less physically fit, and more sedentary when compared with similarly aged youth without diabetes from other large-scale investigations.



Sedentary Behavior and Physical Activity in Youth With Recent Onset of Type 2 Diabetes *Pediatrics* 2013;131:e850–e856

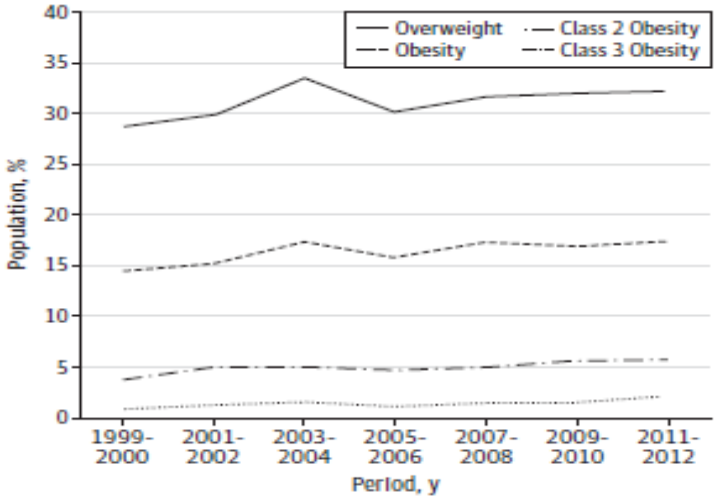
L' appartenenza ad una determinata etnia ed essere di sesso femminile sembrano effettivamente aumentare il rischio di diabete tipo 2.

Tuttavia gli studi osservazionali sembrano suggerire la presenza di altri possibili fattori di rischio:

- ✓ basso reddito
- ✓ vivere in contesti sociali periferici e degradati
- ✓ nuclei familiari disgregati
- ✓ scarsa attività fisica
- ✓ obesità

97% overweight or obese

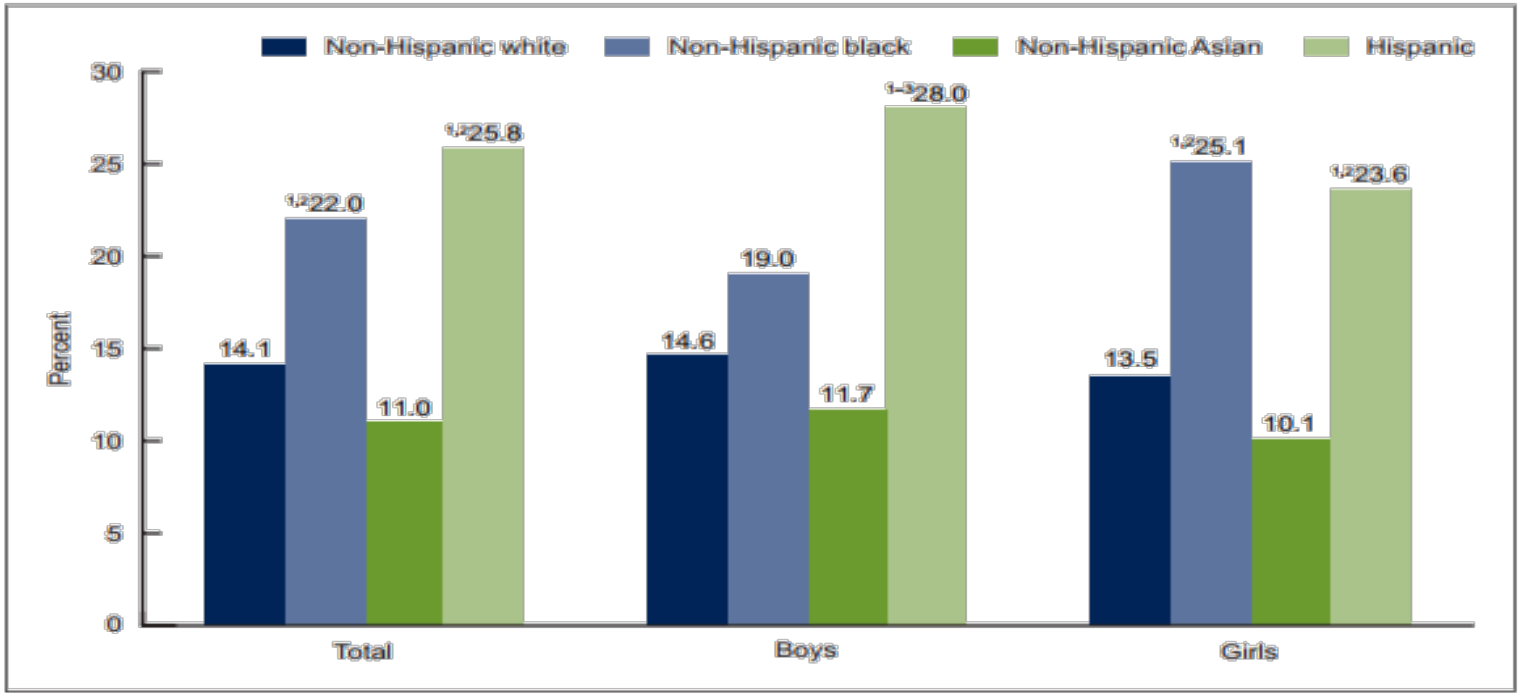
Figure. Prevalence of Overweight, Obesity, Class 2 Obesity, and Class 3 Obesity Among Children in the United States by Year



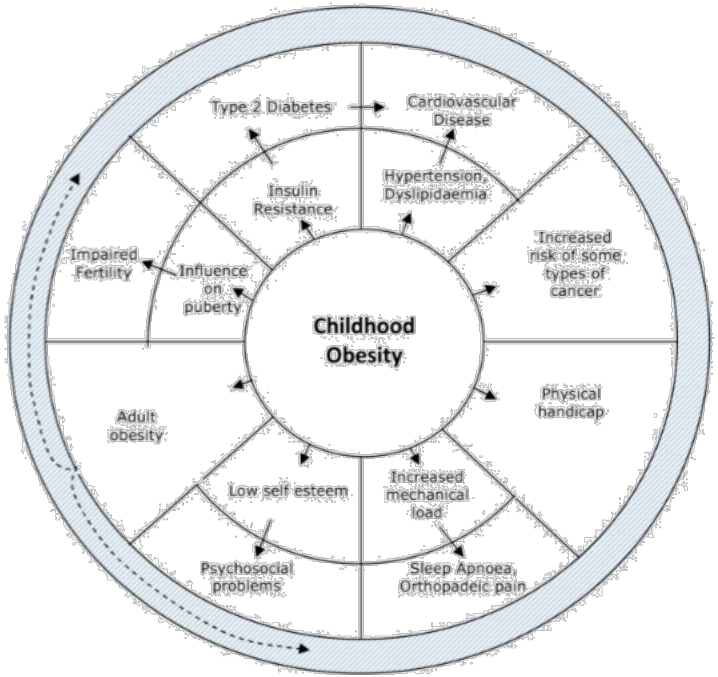
Our findings reflect those of earlier work using the NHANES where younger children and nonwhite participants were at greater risk for obesity and severe obesity.[6,17] The greater prevalence rates of class 2 and class 3 obesity are particularly notable in adolescents and non-Hispanic black individuals. Additionally, overweight and obesity at all levels of severity are increasing significantly among Hispanic girls and non-Hispanic black boys. Future research should determine whether there are specific factors that can be addressed in these high-risk groups.

JAMA Pediatrics Published online April 7, 2014

Figure 4. Prevalence of obesity among youth aged 2–19 years, by sex and race and Hispanic origin: United States, 2015–2016



[1]Significantly different from non-Hispanic Asian persons.
[2]Significantly different from non-Hispanic white persons.
[3]Significantly different from non-Hispanic black persons.
NOTE: Access data table for Figure 4 at: https://www.cdc.gov/nchs/data/databriefs/db288_table.pdf#4.
SOURCE: NCHS, National Health and Nutrition Examination Survey, 2015–2016.



Un elevato BMI è associato a
- ✓aumento del rischio cardiovascolare in età adulta
- ✓alterazione della omeostasi glicidica ed insulinica

I ragazzini obesi sono iperinsulinemici ed hanno circa il 40% in meno di secrezione insulinica in confronto ai coetanei non obesi

International Journal of Obesity (2014) **38,** 40–45;

World J Diabetes 2013 December 15; 4(6): 270-281

Table 1
Comparison of Demographic, Comorbidity, and Medication Characteristics Between Obese and Morbidly Obese Pediatric Patients

	Obese (n = 274)	Morbidly obese (n = 837)	*P* value[a]
Demographics			
Age in years, n (%)			
<9	16 (5.8)	144 (17.2)	**<.0001**
9-13	88 (32.1)	307 (36.7)	
>13	170 (62.0)	386 (46.1)	
Male, n (%)	81 (29.6)	315 (37.6)	**.0155**
Race, n (%)			
NHW	100 (36.5)	25 (30.3)	**.0003**
African American	145 (52.9)	490 (58.5)	
Hispanic	17 (6.2)	19 (2.3)	
Other	12 (4.4)	17 (8.8)	
Comorbidities			
Hypertension, n (%)	91 (33.2)	307 (36.7)	.2989
Low HDL, n (%)	48 (17.9)	171 (20.7)	.3169
Diabetes, n (%)			
Nondiabetic	100 (40.7)	150 (20.3)	**<.0001**
Prediabetic	48 (19.5)	202 (27.3)	
Diabetic	98 (39.8)	388 (52.4)	
Medications			
Antihypertensives, n (%)	19 (6.9)	58 (6.9)	.9978
Anti-asthma, n (%)	39 (14.2)	175 (20.9)	**.0147**
GERD, n (%)	13 (4.7)	62 (7.4)	.1273
Antipsychotic, n (%)	15 (5.5)	44 (5.3)	.8924
ADHD, n (%)	19 (6.9)	54 (6.5)	.7796

Abbreviations: ADHD = attention deficit hyperactivity disorder; GERD = gastroesophageal reflux disease; HDL = high-density lipoprotein; NHW = non-hispanic white.
[a] Estimated from chi-square test. Significant differences shown in bold.

Comorbidities in Obese and Morbidly Obese Children, *Endocr Pract.* 2015;21(No. 9)

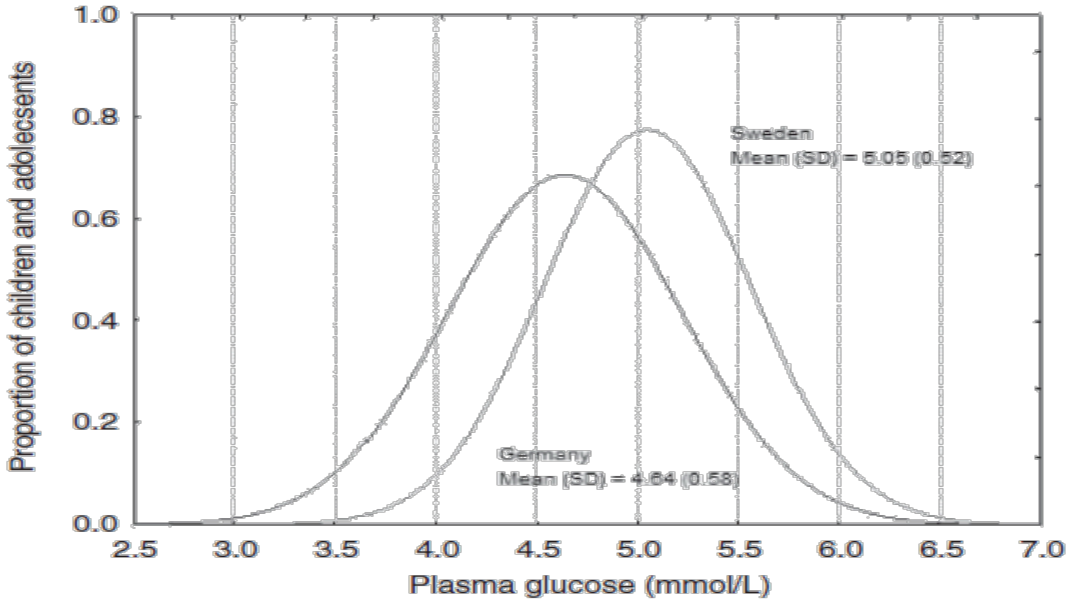


Figure 2. Distribution of fasting glucose among obese children and adolescents in Germany and Sweden.

Impaired fasting glucose prevalence in two nationwide cohorts of obese children and adolescents

International Journal of Obesity (2014) **38**, 40–45

Table 2. Incidence of Type 2 Diabetes Among the Two Baseline Age Cohorts J Clin Endocrinol Metab, April 2016, 101(4):1437–1444

		Baseline Age 5–11 Years				Baseline Age 12–19 Years			
Age at follow-Up, y	Category	No. of Cases	Person-Years	Incidence	Rate Ratio (95% CI)	No. of Cases	Person-Years	Incidence	Rate Ratio (95% CI)
10–14	Nonoverweight	2	7001.4	0.3	1.0				
	Overweight	31	6402.6	4.8	16.9 (4.1–70.8)				
	OHH or MSet-HH	8	1357.8	5.9	20.6 (4.4–97.1)				
	OIGT or MSet-IGT	19	353.4	53.8	188.2 (43.8–808.0)				
15–19	Nonoverweight	10	5660.0	1.8	1.0	3	4948.0	0.6	1.0
	Overweight	45	4851.5	9.3	5.3 (2.6–10.4)	25	5700.3	4.4	7.2 (2.2–24.0)
	OHH or MSet-HH	11	995.8	11.0	6.3 (2.7–14.7)	15	1906.8	7.9	13.0 (3.8–44.8)
	OIGT or MSet-IGT	10	221.9	45.1	25.5 (10.6–61.3)	24	781.1	30.7	50.7 (15.3–168.3)
20–24	Nonoverweight	21	4314.1	4.9	1.0	7	5222.1	1.3	1.0
	Overweight	56	3358.7	16.7	3.4 (2.1–5.7)	79	5638.9	14.0	10.5 (4.8–22.6)
	OHH or MSet-HH	21	749.0	28.0	5.8 (2.6–4.8)	33	2013.2	16.4	12.2 (5.4–27.6)
	OIGT or MSet-IGT	4	128.3	31.2	6.4 (2.2–18.7)	37	721.1	51.3	38.3 (17.1–85.9)
25–29	Nonoverweight	59	3370.5	17.5	1.0	45	4173.5	10.8	1.0
	Overweight	73	2274.2	32.1	1.8 (1.3–2.6)	113	3839.0	29.4	2.7 (1.9–3.9)
	OHH or MSet-HH	15	553.6	27.1	1.6 (0.9–2.7)	47	1362.1	34.5	3.2 (2.1–4.8)
	OIGT or MSet-IGT	6	73.1	82.1	4.7 (2.0–10.9)	38	344.9	110.2	10.2 (6.6–15.7)
30–34	Nonoverweight	58	2383.6	24.3	1.0	59	3209.3	18.4	1.0
	Overweight	66	1428.8	46.2	1.9 (1.3–2.7)	91	2493.3	36.5	2.0 (1.4–2.8)
	OHH or MSet-HH	16	399.4	40.1	1.6 (0.9–2.9)	36	947.9	38.0	2.1 (1.4–3.1)
	OIGT or MSet-IGT	5	45.8	109.1	4.5 (1.8–11.2)	16	150.1	106.6	5.8 (3.3–10.1)
35–39	Nonoverweight	56	1385.9	40.4	1.0	57	2177.2	26.2	1.0
	Overweight	38	730.2	52.0	1.3 (0.9–1.9)	63	1479.4	42.6	1.6 (1.1–2.3)
	OHH or MSet-HH	9	266.1	33.8	0.8 (0.4–1.7)	42	582.2	72.1	2.8 (1.8–4.1)
	OIGT or MSet-IGT	2	17.8	112.4	2.8 (0.7–11.4)	10	56.6	176.6	6.7 (3.4–13.2)
40–44	Nonoverweight					42	1162.5	36.1	1.0
	Overweight					50	674.1	74.2	2.1 (1.4–3.1)
	OHH or MSet-HH					20	325.1	61.5	1.7 (1.0–2.9)
	OIGT or MSet-IGT					1	10.0	99.5	2.8 (0.4–20.0)

Incidence is stratified into categories using baseline metabolic groups and age at follow-up and is shown in cases/1000 person-years.

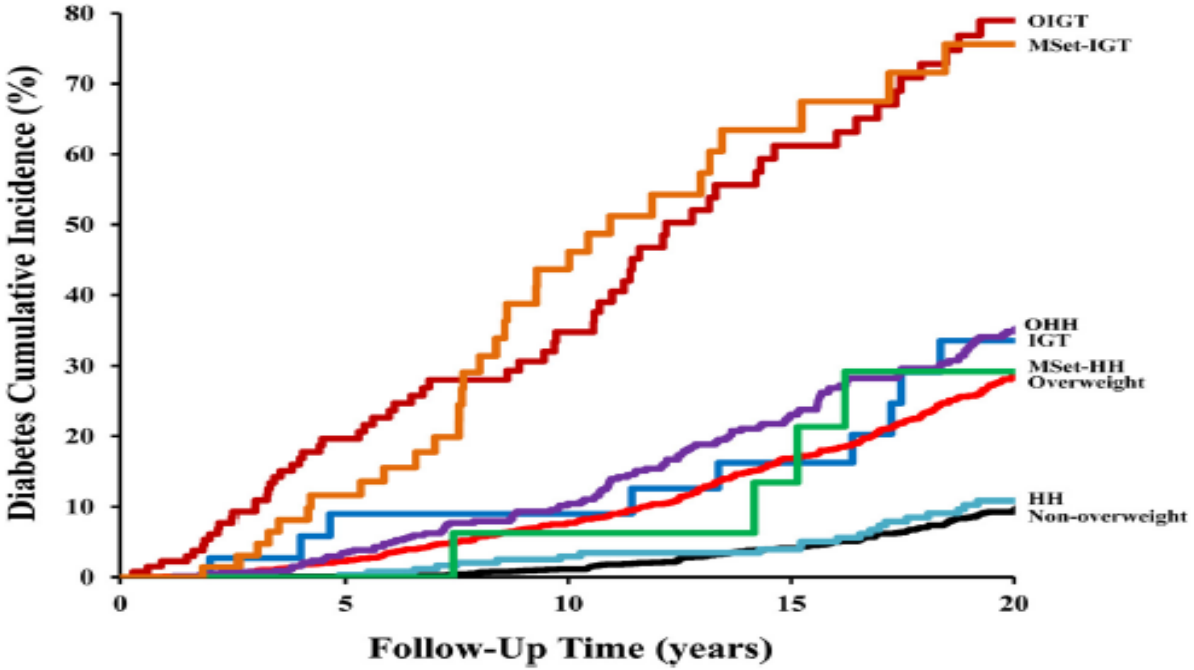


Figure 1. Twenty-year cumulative incidence of type 2 diabetes by baseline metabolic category.

L' obesità negli adolescenti rappresenta un fattore di rischio importante per diabete tipo 2.

La sua presenza sembra svelare ed amplificare una sottostante predisposizione genetica.

L' obesità riconosce una eziologia poligenica, amplificata da fattori culturali e sociali.

Curr Diab Rep. 2014 August ; 14(8): 508.

L' incremento del rischio di obesità tra i ragazzi che appartengono alle minoranze etniche può essere spiegato in parte da fattori comportamentali e disparità socio-economiche

- Ragazzini americani di origine messicana hanno un maggiore grado di obesità, sono più sedentari ed hanno una alimentazione "unhealthy" rispetto ai coetanei "bianchi"
- I ragazzi che frequentano scuole migliori (high socioeconomic school) fanno sport più regolarmente di quelli che frequentano "low socioeconomic school"
- I figli di genitori obesi passano ogni giorno più tempo davanti alla televisione
- I ragazzi che vivono con un solo genitore sono più in sovrappeso di quelli che vivono con due genitori

- In famiglie a basso tenore economico, l' obesità dei genitori e la depressione materna rappresentano fattori di rischio per obesità e sovrappeso
- Nelle famiglie ad elevato "income" ci sono diversi fattori predittivi:
  - una madre che lavora molte ore fuori casa
  - uno stile genitoriale "permissivo"

The risk factors of parental sedentary behaviour and overweight suggest children are exposed to an unhealthy home environment, which sets children on a trajectory to overweight and obesity. This is consistent with the findings of Zarnowiecki

2016 John Wiley & Sons Ltd, *Child: care, health and development*, **42**, 5, 603–624

Diabetogenic/obesogenic enviroment

Accelera lo sviluppo di diabete in quei soggetti giovani geneticamente predisposti

Ma quale è il peso relativo?

Genetica

Diabetogenic/obesogenic enviroment

gli studi di correlazione tra genetica e rischio di sviluppare diabete sono stati condotti prevalentemente sugli adulti

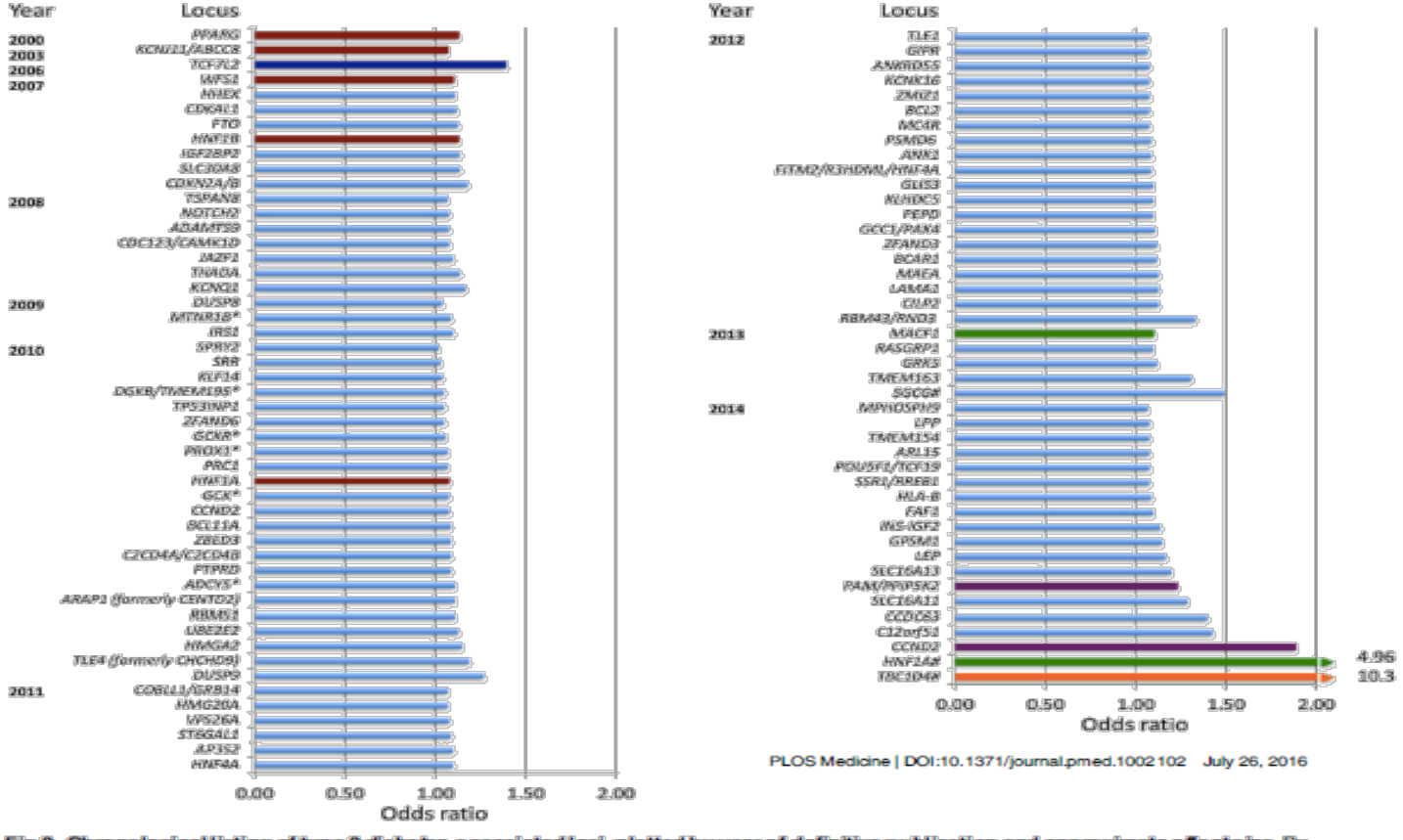


Fig 2. Chronological listing of type 2 diabetes-associated loci, plotted by year of definitive publication and approximate effect size. By

Gene-Lifestyle Interaction and Type 2 Diabetes: The EPIC InterAct Case-Cohort Study

PLOS Medicine May 2014 | Volume 11 | Issue 5

prospective EPIC study, a large European population-based cohort.[17] A GRS comprising 42 known loci was able to predict T2DM in this population. The C-statistic for the whole

A total of 340,234 participants of European descent were followed up for 3.99 million person-years (mean [range] follow-up of 11.7 [0–17.5] y), during which 12,403 verified incident cases of T2D were identified [1]. Individuals without stored blood

BMI (red: <25 kg/m^2; blue: 25 to <30 kg/m^2; black: ≥30 kg/m^2

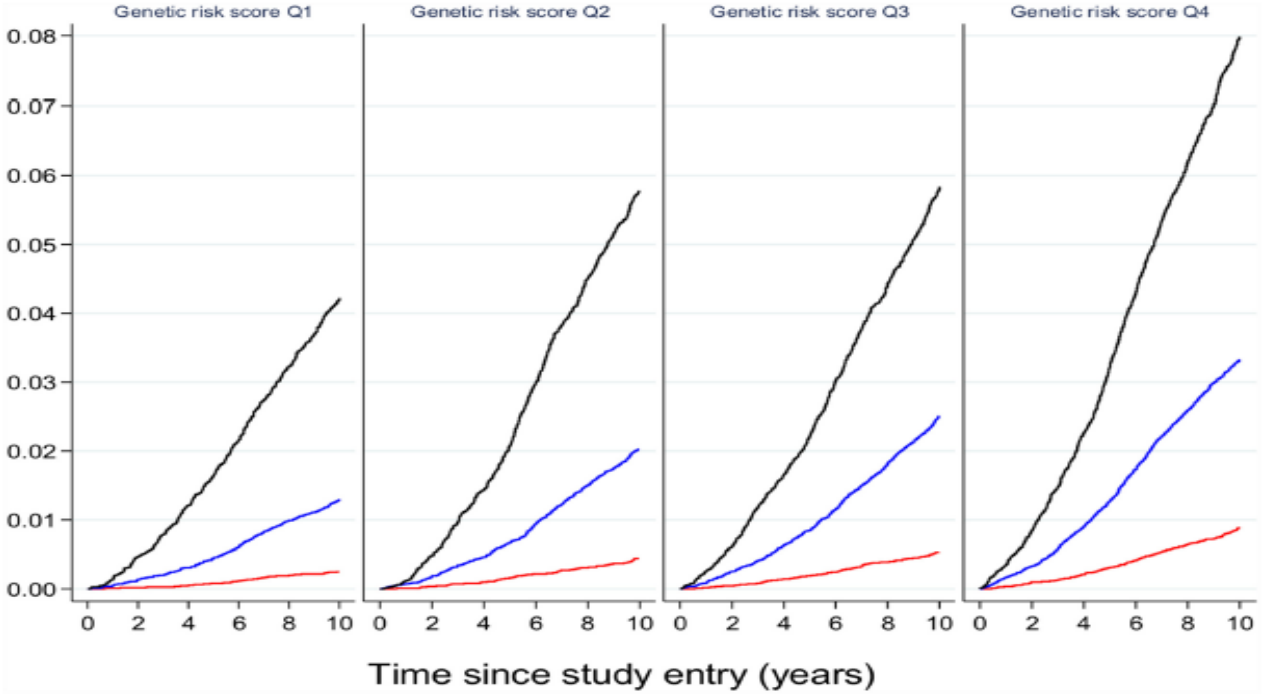
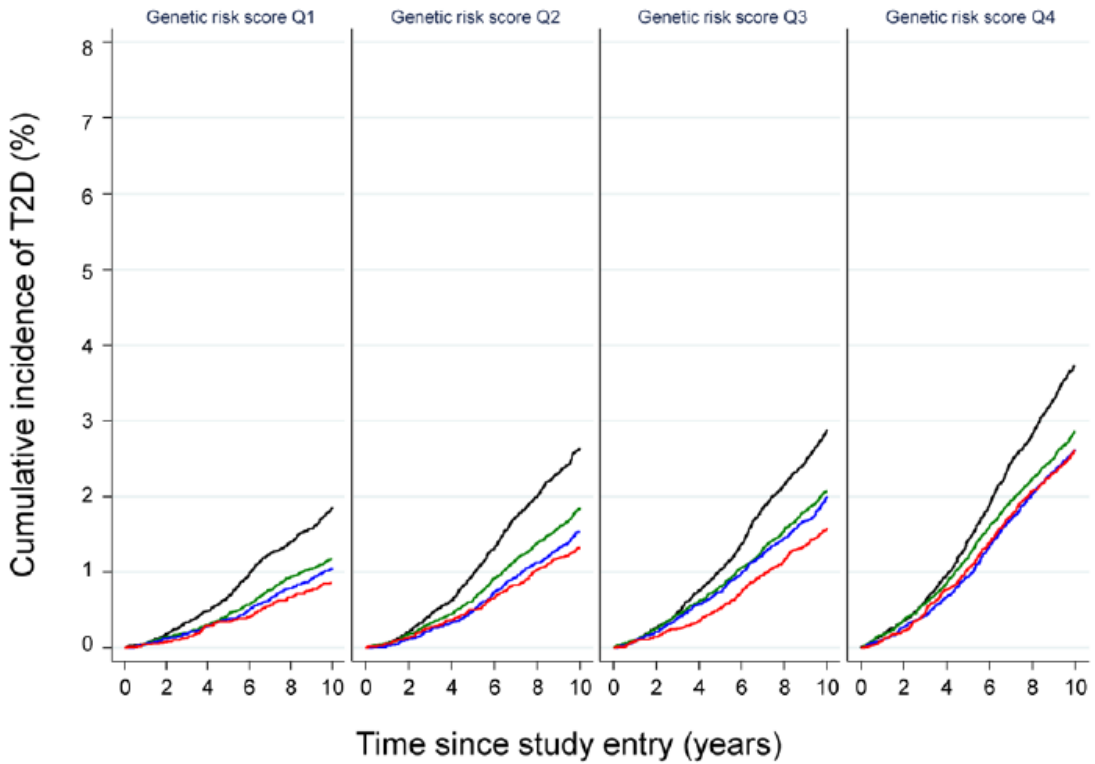


Fig 3. The relative effect of genetic risk and obesity on future type 2 diabetes. Participants in the EPIC-Interact study were stratified by quartiles of genetic risk and by strata of adiposity (obese in black, overweight in blue, and normal weight in red). The likelihood of developing type 2 diabetes is shown, indicating that obese participants with the lowest genetic burden have a higher absolute risk of diabetes than lean or overweight participants with the highest genetic burden. Image is from Langenberg et al. [19].

physical activity (red: active; blue: moderately active; green: moderately inactive; black: inactive)

Panel C: Absolute risk of T2D by genetic risk score and physical activity



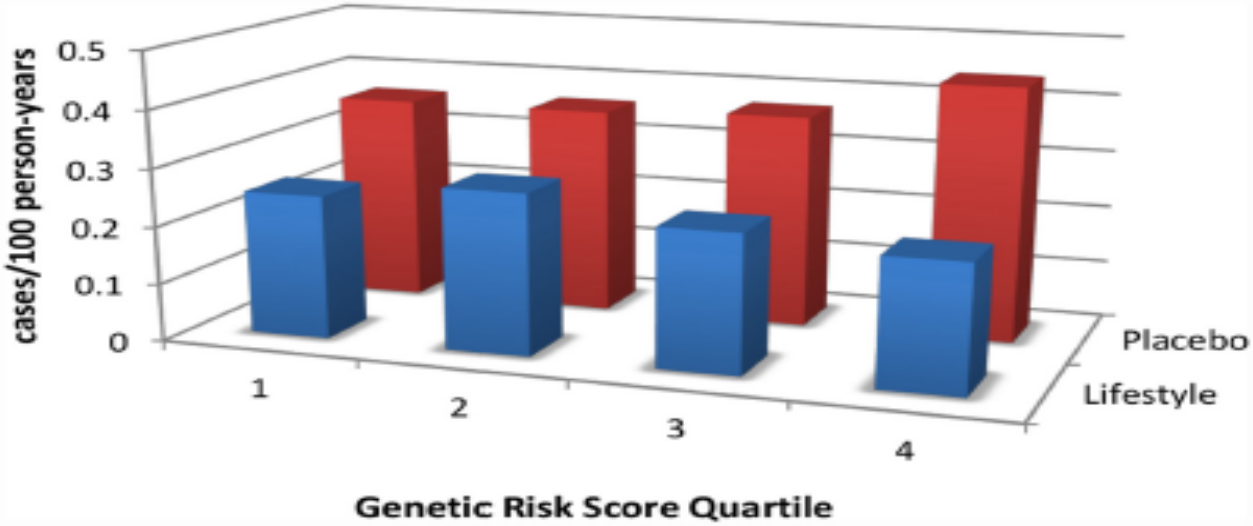


Fig 1. An intensive lifestyle intervention, as deployed in the U.S. Diabetes Prevention Program (DPP), is effective regardless of genetic risk score for type 2 diabetes. DPP participants were stratified by quartile of genetic risk constructed by adding risk alleles from 34 known type 2 diabetes-associated variants. Whereas the genetic risk score predicts diabetes incidence in the placebo arm (red bars), it does not do so in the lifestyle arm (blue bars); indeed, the intervention is highly effective in reducing diabetes incidence even in the quartile with the highest genetic risk. Data are from reference [11].

Lo studio EPIC mostra che il genetic risk score calcolato sui 42 loci presi in considerazione è fortemente associato al rischio di sviluppare diabete. Tuttavia il rischio assoluto di diabete tipo 2 è dominato da fattori MODIFICABILI, in particolar modo l'obesità

PLOS Medicine May 2014 | Volume 11 | Issue 5 |

Il peso delle comuni varianti genetiche riscontrabili nelle popolazioni è molto piccolo, ma potenziali eccezioni possono essere rappresentate da alcune varianti dotate di maggiore effetto e che possono essere specifiche per alcuni gruppi etnici

Nat Rev Endocrinol. 2014 April ; 10(4): 198–205.

Diabetogenic/obesogenic enviroment

Genetica

Family history of type 2 diabetes in 90%

Type 2 diabetes in nuclear family (60%) Type 2 diabetes in grandparents (30%)

La familiarità può essere spiegata non solo attraverso la trasmissione di varianti genetiche "a rischio", ma anche attraverso la trasmissione di modelli alimentari, culturali e sociali, che favoriscono lo sviluppo diabete ed obesità

Characteristics of Adolescents and Youth with Recent-Onset Type 2 Diabetes: The TODAY Cohort at Baseline

Characteristic	Female (n = 457)	Male (n = 247)	*P* value
Size at on-time birth (within 2 wk of due date)			<0.01
Small (<500 g)	9.9%	7.3%	
Normal (2500–4000 g)	76.8%	67.9%	
Large (>4000 g)	13.3%	24.8%	
Mother had gestational diabetes with participant	29.8%	40.1%	<0.01

Short- and long-term consequences for offspring exposed to maternal diabetes: a review

THE JOURNAL OF MATERNAL-FETAL & NEONATAL MEDICINE, 2017

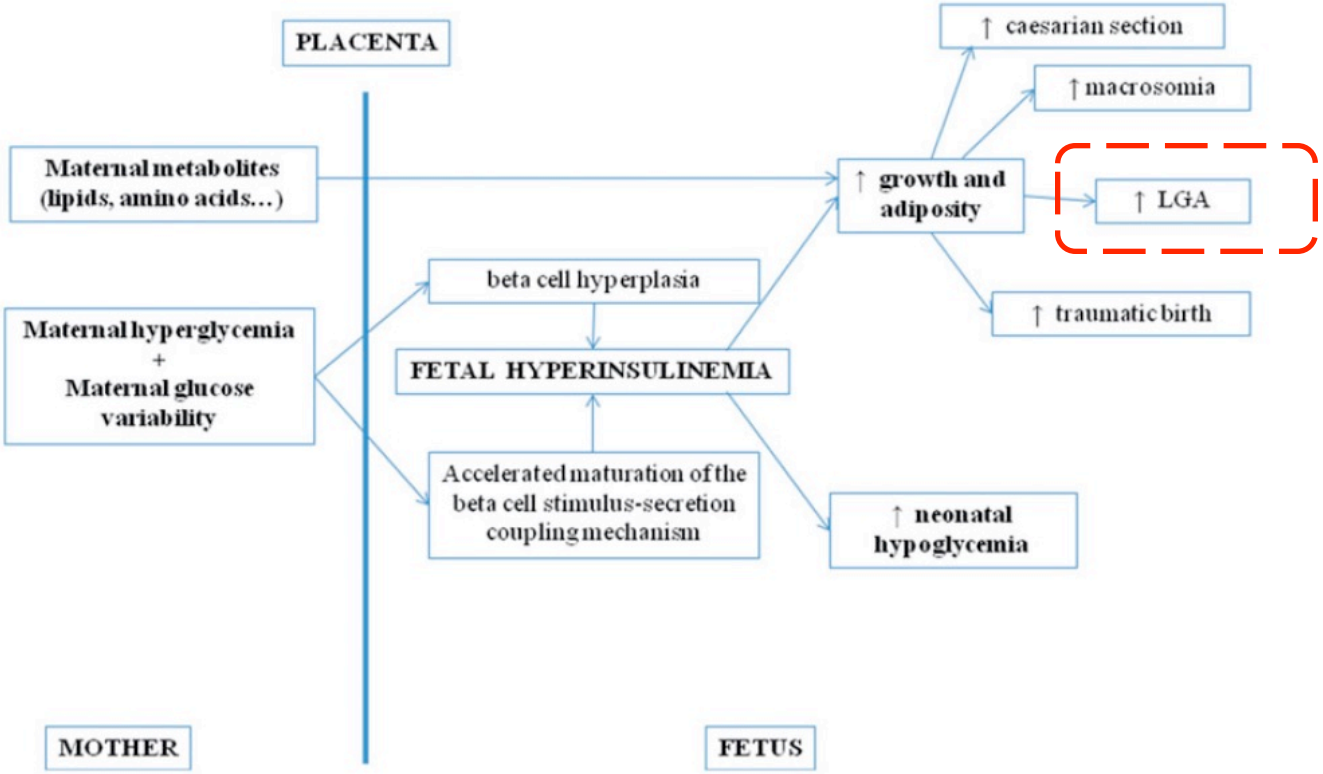


Figure 1. Short-term consequences of maternal diabetes in the offspring.

Association of Maternal Body Mass Index, Excessive Weight Gain, and Gestational Diabetes Mellitus With Large-for-Gestational-Age Births

Characteristic	White	Black	Hispanic	Asian or Pacific Islander	All Races
Total	347,693	127,555	166,100	19,048	660,396

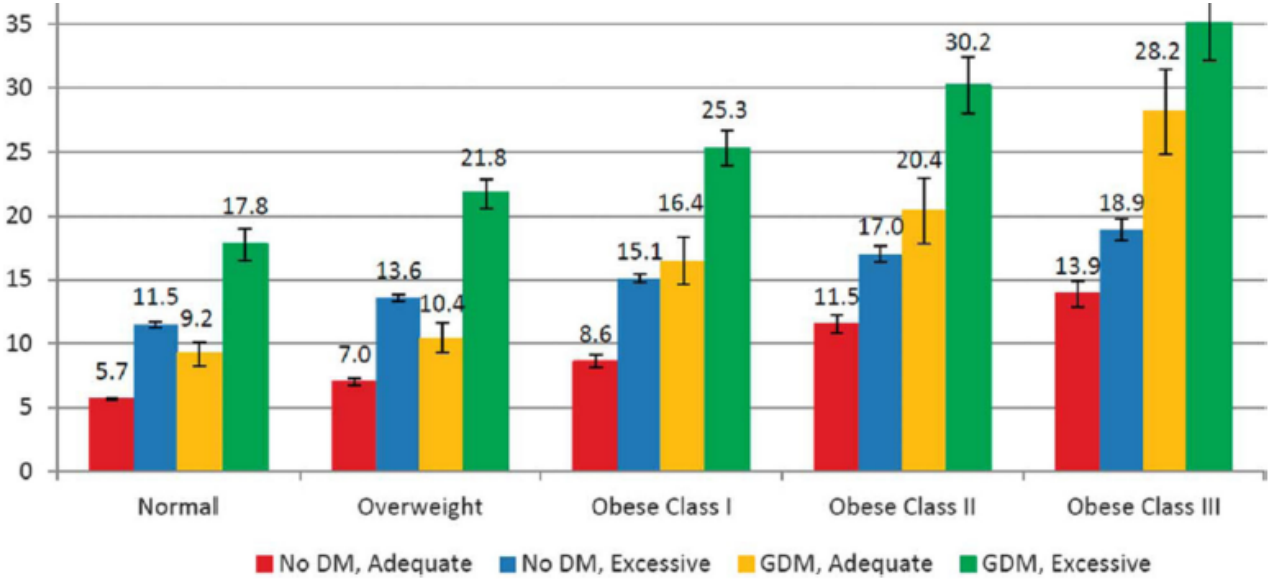


Fig. 1.
Prevalence of large for gestational age at the 90th percentile or greater by body mass index, gestational diabetes mellitus status, and gestational weight gain for births of gestational age at 37–41 weeks. DM, diabetes mellitus; GDM, gestational diabetes mellitus.
Kim. Contributions to Large-for-Gestational-Age Births. Obstet Gynecol 2014.

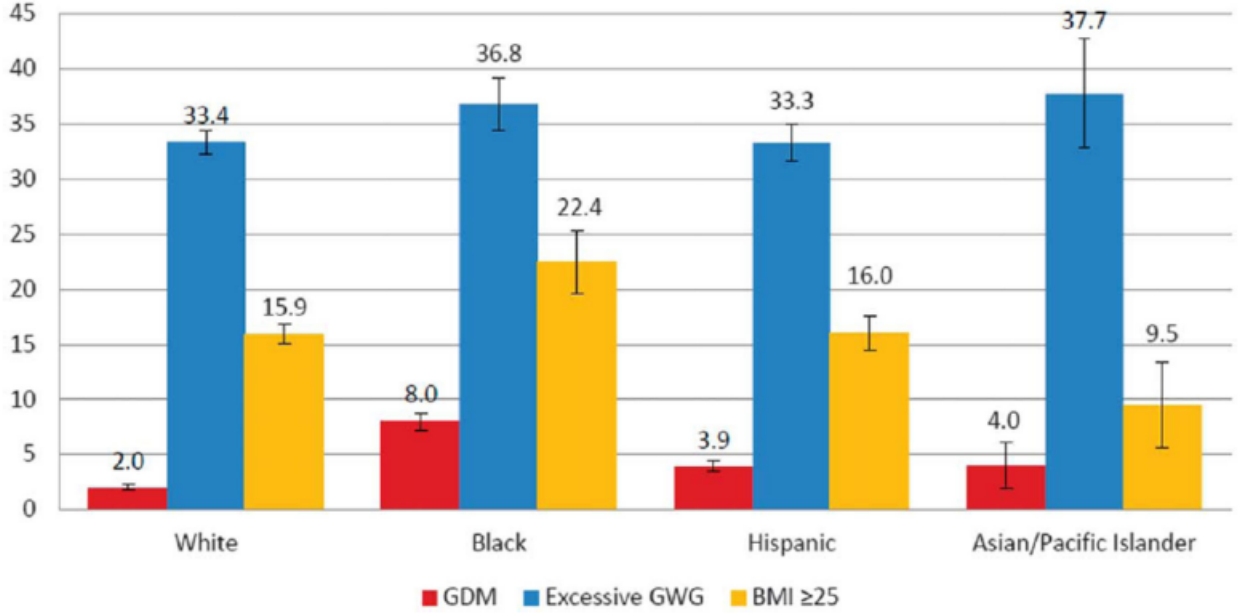
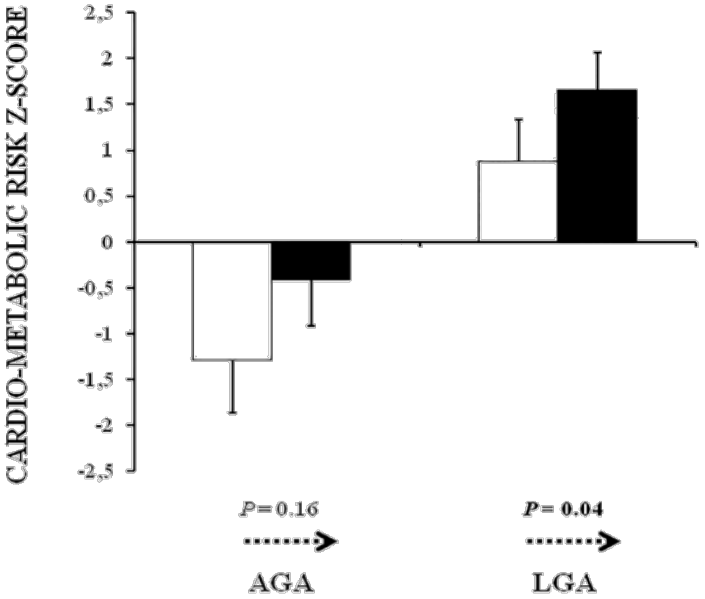


Fig. 2.

Population-attributable fractions and 95% confidence intervals (CIs) of large for gestational age at the 90th percentile or greater, stratified by race or ethnicity. Adjusted for age, parity, nativity, and the other exposure groups. GDM, gestational diabetes mellitus; GWG, gestational weight gain; BMI, body mass index.

Kim. Contributions to Large-for-Gestational-Age Births. Obstet Gynecol 2014.

Nascere Large For Gestational Age sembra incrementare il rischio di sindrome metabolica



PLOS ONE August 2014 | Volume 9 | Issue 8

Prothrombotic State, Cardiovascular, and Metabolic Syndrome Risk Factors in Prepubertal Children Born Large for Gestational Age

DIABETES CARE, VOLUME 33, NUMBER 11, NOVEMBER 2010

Table 1—*Characteristics, anthropometric indices, and indices of the prothrombotic state and insulin resistance, components of the IGFs-axis, lipid profile, and adipocytokines (means ± SD) at prepuberty of children born LGA (birth weight ≥95th percentile) or AGA (birth weight 10th–90th percentile)*

Characteristics and parameters	LGA group	AGA group	*P* value
n	31	33	—
Age (years)	6.5 ± 0.5	6.4 ± 0.6	ns
Body weight (kg)	32 ± 8	24 ± 6	<0.01
Body height (cm)	126 ± 8	119 ± 9	0.08
Waist circumference *z* score	0.80 ± 0.98	0.06 ± 1.3	0.05
BMI *z* score	0.80 ± 0.80	−0.20 ± 0.8	<0.001
Systolic BP *z* score	0.49 ± 0.41	0.41 ± 0.43	ns
Diastolic BP *z* score	0.71 ± 0.35	0.51 ± 0.5	ns
Prothrombin time (s)	13.29 ± 0.53	13.2 ± 0.52	ns
APTT (s)	37.04 ± 22	38.64 ± 24	ns
Fibrinogen (μmol/l)	7.67 ± 0.9	10.05 ± 2.3	≤0.0001
Antithrombin III (%)	104 ± 50	107 ± 69	ns
Protein C (%)	99 ± 11	97 ± 18	ns
Protein S (%)	69 ± 24	70 ± 19	ns
Fasting glucose (mmol/l)	5.1 ± 0.5	4.9 ± 0.6	ns
Fasting insulin (pmol/l)	48.6 ± 20.1	27 ± 24.3	<0.01
FGIR	0.11 ± 0.05	0.25 ± 0.11	≤0.0001
HOMA-IR	1.5 ± 0.6	0.8 ± 0.7	<0.01
IGF-1 (μg/l)	189 ± 115	140 ± 84	0.06
IGFBP-1 (μg/l)	84 ± 33	88 ± 31	ns
IGFBP-3 (mg/l)	2.6 ± 1.1	3.9 ± 0.8	≤0.0001
t cholesterol (mmol/l)	4.53 ± 0.6	4.45 ± 0.6	ns
HDL (mmol/l)	1.41 ± 0.2	1.45 ± 0.2	ns
Triglycerides (mmol/l)	0.65 ± 0.1	0.71 ± 0.2	ns
Lipoprotein(a) (μmol/l)	0.09 ± 0.1	0.3 ± 0.2	<0.001
Adiponectin (mg/l)	16.3 ± 6	14.7 ± 5	ns
Leptin (μg/l)	52 ± 23	31 ± 19	≤0.01
Visfatin (μg/l)	13.3 ± 6	13 ± 5	ns

APTT, activated partial thromboplastin time; FGIR, fasting glucose-to-insulin ratio; ns, not significant ($P > 0.05$).

Association of preterm birth and small for gestational age with metabolic outcomes in children and adolescents: A population-based cohort study from Taiwan

Pediatrics and Neonatology (2017) xx, 1–7

In this study, we analyzed the data from 37,119 preterm infants, 3386 SGA infants, and 162,020 matched controls

CI = 1.57–6.87). There was a 2.49-fold increased risk of type 2 DM (HR = 2.49, 95% CI = 1.98–3.14), a 1.80-fold risk

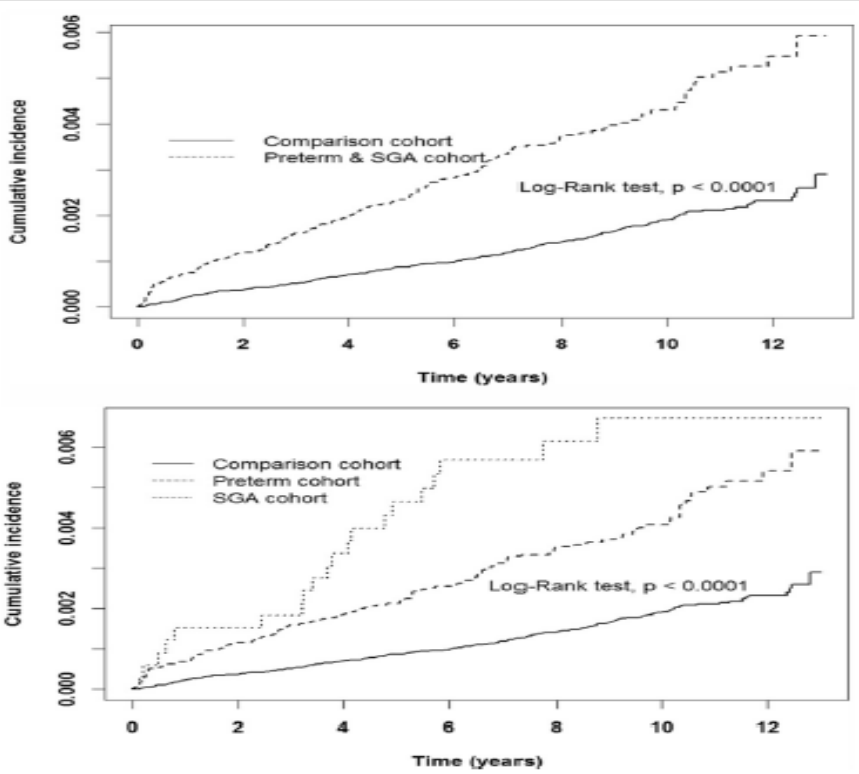
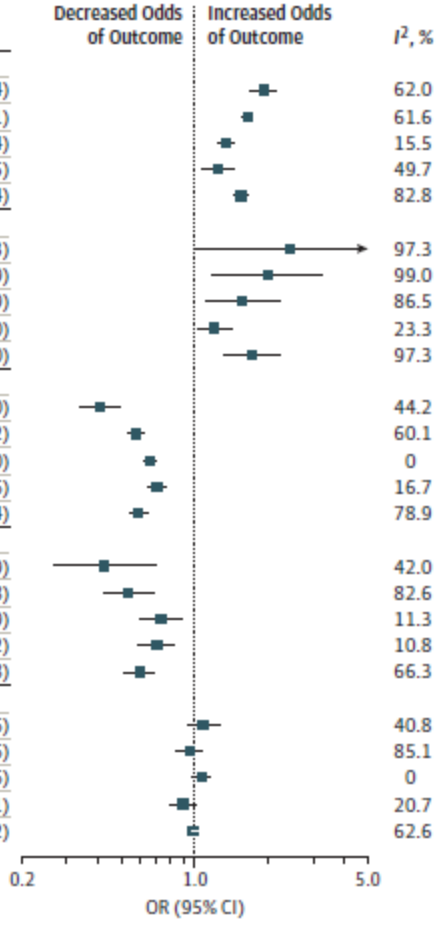


Figure 1 Cumulative incidence in being metabolic disease for cohorts of comparison and preterm & small for gestational age (SGA) (upper panel); and for cohorts of comparison, preterm, and SGA (lower panel).

Figure 2. Summary of Pooled Odds Ratios (ORs) for the Association Between Gestational Weight Gain Below and Above Guidelines With Adverse Outcomes

A Below recommended gestational weight gain

Outcomes by BMI category	Studies, No.	Women, No.	OR (95% CI)	I^2, %
SGA	11	1019805		
<18.5	9	28551	1.89 (1.67-2.14)	62.0
18.5-24.9	9	162331	1.63 (1.54-1.71)	61.6
25-29.9	9	27634	1.34 (1.24-1.44)	15.5
≥30	9	31526	1.24 (1.06-1.45)	49.7
Overall			1.53 (1.44-1.64)	82.8
Preterm birth	4	360833		
<18.5	4	19941	2.41 (1.01-5.73)	97.3
18.5-24.9	4	79537	1.96 (1.17-3.29)	99.0
25-29.9	4	6681	1.55 (1.10-2.19)	86.5
≥30	4	8598	1.20 (1.03-1.40)	23.3
Overall			1.70 (1.32-2.20)	97.3
LGA	13	1041399		
<18.5	9	29596	0.41 (0.34-0.50)	44.2
18.5-24.9	11	166212	0.58 (0.54-0.62)	60.1
25-29.9	11	27899	0.66 (0.62-0.70)	0
≥30	12	31675	0.70 (0.64-0.76)	16.7
Overall			0.59 (0.55-0.64)	78.9
Macrosomia	11	241665		
<18.5	7	15617	0.43 (0.27-0.69)	42.0
18.5-24.9	9	59503	0.54 (0.43-0.68)	82.6
25-29.9	9	4935	0.73 (0.60-0.89)	11.3
≥30	9	4740	0.70 (0.59-0.82)	10.8
Overall			0.60 (0.52-0.68)	66.3
Cesarean delivery	8	218207		
<18.5	7	15645	1.08 (0.94-1.26)	40.8
18.5-24.9	7	59100	0.95 (0.84-1.06)	85.1
25-29.9	7	2186	1.07 (0.98-1.16)	0
≥30	7	4336	0.89 (0.79-1.01)	20.7
Overall			0.98 (0.96-1.02)	62.6



B Above recommended gestational weight gain

JAMA. 2017;317(21):2207-2225.

Offspring

Diabetologia (2016) 59:1396–1399

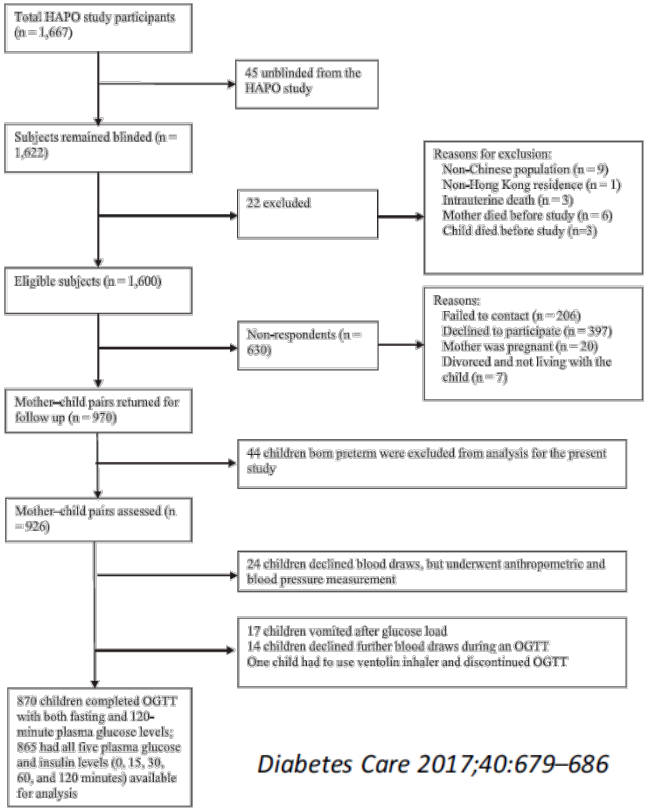
While the long-term maternal metabolic risk after GDM has long been well established, the long-term risks for the offspring are less well explored. Elegantly performed animal studies have demonstrated that offspring of mothers with GDM are at increased risk of GDM, diabetes, obesity, cardiovascular disease and structural hypothalamic changes [18, 19]. Furthermore, these animal studies have documented that normalisation of maternal blood glucose levels during pregnancy prevents these negative outcomes. While studies in adult offspring are limited, several human studies exist in children from different populations, involving a mix of different maternal diabetes types [20–22]. The results of these studies are in line with the animal studies, the majority finding increased risk of diabetes and obesity in children exposed to maternal diabetes.

L' iperglicemia materna
aumenta nella prole il rischio di diabete
tipo 2, obesità,
sindrome metabolica

Table 1. Long-t

Reference				Findings
Dabelea et al. [29]				iabetes significantly spring born after the loped diabetes than in before the mother was with diabetes (OR 3.7)
Stride et al. [30]	MODY due to mutation of HNF1α	211 subjects with a mutation in HNF-1α gene	–	Age at diagnosis of diabetes was significantly younger when the mother was diagnosed before pregnancy compared with when the mother was diagnosed after pregnancy (15.5 ± 5.4 versus 27.5 ± 13.1 years, $p < .0001$)
Clausen et al. [31]	GDM and type 1 diabetes	168 offspring of women with diet-treated GDM; 160 offspring of women with type 1 diabetes; 128 offspring from background population	~22 years	Two-fold risk of overweight in offspring of women with diet-treated GDM or type 1 diabetes compared with a background population, and the risk of metabolic syndrome was 4 and 2.5 times higher, respectively
Clausen et al. [33]	GDM and type 1 diabetes	168 offspring of women with diet-treated GDM; 160 offspring of women with type 1 diabetes; 128 offspring from a background population	~27 years	Adjusted ORs for type 2 diabetes or prediabetes (impaired glucose tolerance or impaired fasting glucose) of 7.76 (95% CI 2.58–23.39) in offspring of diet-treated GDM women, and 4.02 (95% CI 1.31–12.33) in offspring of type 1 diabetic women, by comparison with offspring from a background population
Vlachova et al. [34]	Type 1 diabetes	278 offspring of women with type 1 diabetes; 303 control offspring	~17 years	The prevalence of metabolic syndrome was higher in offspring of women with type 1 diabetes than in controls (2.8% versus 0.7%; $p = .054$), and so was the prevalence of prediabetes (impaired glucose tolerance or impaired fasting glucose) (15.4% versus 8.1%; $p = .011$)

OR: odds ratios; MODY: maturity-onset diabetes of the young; HNF: hepatocyte nuclear factor; GDM: gestational diabetes mellitus.



Diabetes Care 2017;40:679–686

Figure 1—Flowchart of HAPO study participants from the Hong Kong field center and eligible subjects in the follow-up study.

Table 1—Characteristics and cardiometabolic outcomes at 7 years of age between the offspring of mothers with normal glucose tolerance and mothers with GDM

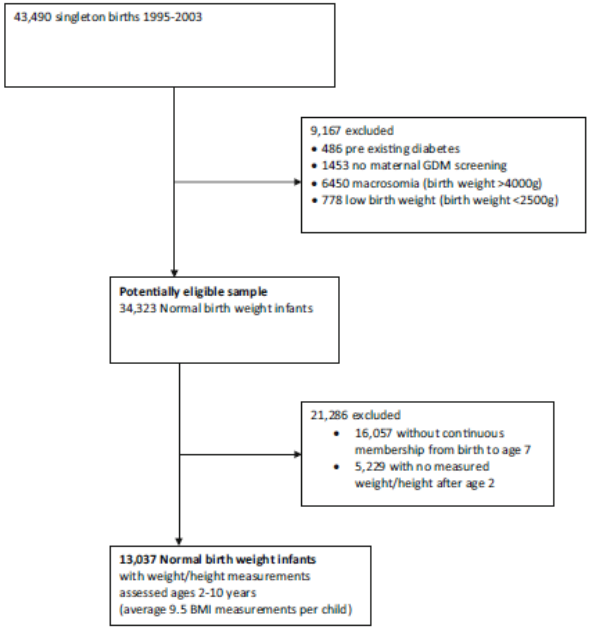
	Offspring		
	Mothers with NGT (n = 794)	Mothers with GDM (n = 132)	P value
Anthropometry			
Children's age (years), median (interquartile range)	7.0 (6.7–7.2)	6.9 (6.6–7.2)	0.03
BMI (kg/m^2)*	15.0 ± 2.3	15.3 ± 2.1	0.04
BMI percentile	42.6 ± 31.1	50.9 ± 32.0	0.01
Obesity (BMI ≥95th percentile)	67 (8.4)	9 (6.8)	0.53
Overweight or obesity (BMI ≥85th percentile)			
Overall	121 (15.3)	30 (22.7)	0.03
Boys	73 (17.2)	13 (22.8)	0.30
Girls	48 (13.0)	17 (22.7)	0.03
Waist-to-hip ratio*	0.84 ± 0.05	0.84 ± 0.04	0.64
Sum of skinfold thickness (mm)*			
Overall	35.8 ± 17.4	38.7 ± 15.7	0.07
Boys	35.2 ± 18.2	35.6 ± 15.4	0.71
Girls	36.4 ± 16.5	41.0 ± 15.5	0.03
Glycemia and insulin			
PG (mmol/L)			
Fasting	4.57 ± 0.35	4.64 ± 0.49	0.12
15 min	7.03 ± 1.16	7.20 ± 1.30	0.14
30 min	7.54 ± 1.49	7.99 ± 1.58	0.002
60 min	5.87 ± 1.51	6.30 ± 1.66	0.004
120 min	5.29 ± 0.97	5.39 ± 0.96	0.26
AUC(G)			
Overall	732 ± 118	768 ± 121	0.002
Boys	731 ± 118	769 ± 115	0.03
Girls	734 ± 119	766 ± 127	0.04
Children's glycemic status†			
IFG and/or IGT	13 (1.7)	5 (3.9)	0.04
DM	0 (0)	1 (0.8)	0.04
Fasting plasma insulin (mIU/L)	4.07 ± 5.33	3.77 ± 3.57	0.53
Fasting C-peptide (μg/L)	0.38 ± 0.43	0.32 ± 0.37	0.14
Matsuda ISI	16.2 ± 8.9	15.0 ± 8.3	0.14
HOMA-BCF	77.6 ± 72.8	71.4 ± 65.2	0.38
Insulinogenic index at 30 min	81.0 ± 94.2	67.8 ± 65.0	0.05
Oral disposition index	7.98 ± 9.43	6.62 ± 5.95	0.04
Lipid profile			
Total cholesterol (mmol/L)	4.47 ± 0.74	4.52 ± 0.68	0.41
HDL cholesterol (mmol/L)	1.66 ± 0.35	1.65 ± 0.31	0.73
LDL cholesterol (mmol/L)	2.47 ± 0.64	2.53 ± 0.61	0.33
Triglyceride (mmol/L)	0.74 ± 0.33	0.78 ± 0.34	0.24
Dyslipidemia‡	63 (8.2)	11 (8.4)	0.94
BP (mmHg)			
SBP*	102 ± 8.9	104 ± 8.7	0.01
DBP*	62 ± 7.9	63 ± 8.1	0.06
SBP at age-, sex-, and height-specific percentile	60 ± 24	66 ± 22	0.01
DBP at age-, sex-, and height-specific percentile	60 ± 22	64 ± 22	0.02
Hypertension (BP ≥95th percentile)	63 (8.0)	11 (8.3)	0.89
Prehypertension (BP 90th to <95th percentile)	50 (6.3)	11 (8.3)	0.51

Data are mean ± SD or n (%), unless otherwise indicated. BCF, β-cell function; DBP, diastolic blood pressure; NGT, normal glucose tolerance; SBP, systolic blood pressure. *Between-group comparison by ANCOVA after adjustment for age and/or sex as appropriate. †χ^2 test based on the rate of abnormal glucose tolerance. ‡Triglyceride ≥1.7 mmol/L or LDL cholesterol ≥3.4 mmol/L.

In Utero Exposure to Maternal Hyperglycemia Increases Childhood Cardiometabolic Risk in Offspring

Impact of Maternal Glucose and Gestational Weight Gain on Child Obesity over the First Decade of Life in Normal Birth Weight Infants

Matern Child Health J (2016) 20:1559–1568



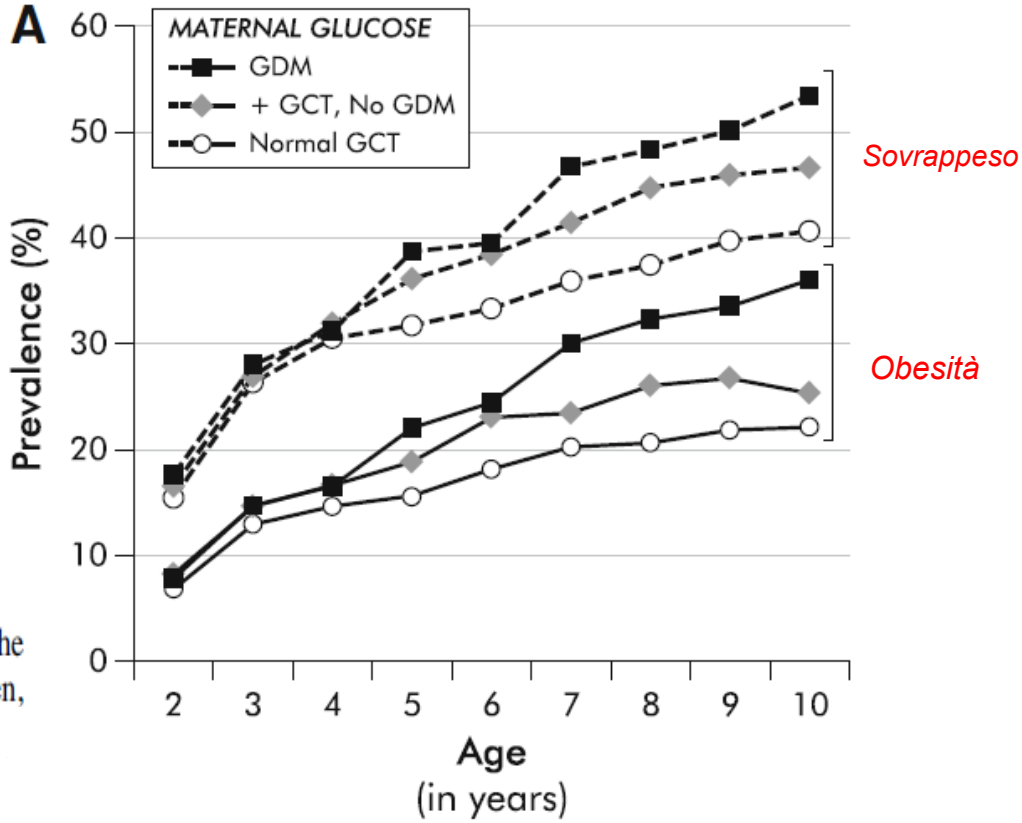
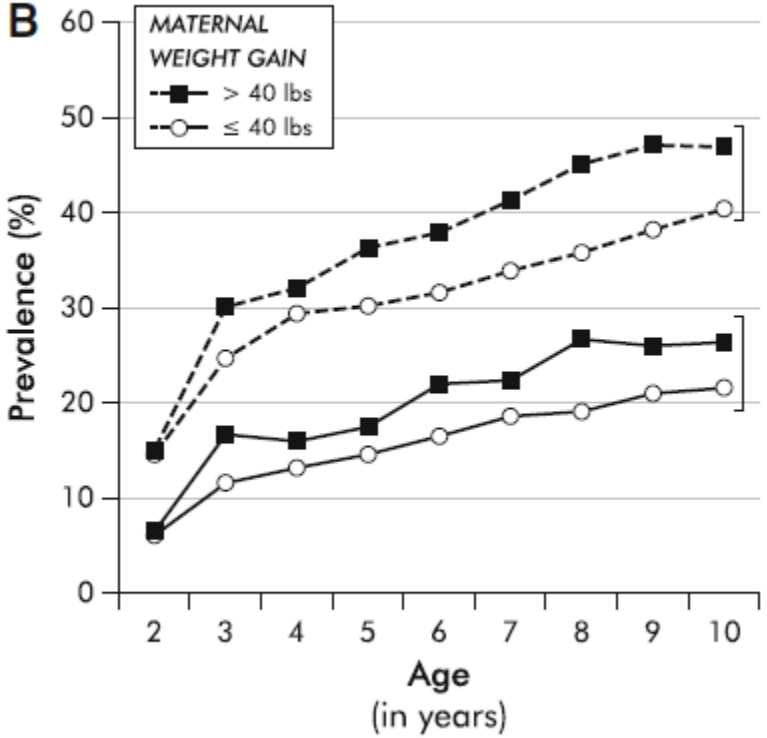


Fig. 2 Childhood overweight and obesity prevalences (%) across the first decade of life among 13,037 normal birth weight children, stratified by maternal glucose (a)



Sovrappeso

Obesità

Il diabete gestazionale così come l'eccessivo incremento di peso durante la gravidanza aumentano il rischio di obesità e sovrappeso nella prole

- Diabete mellito materno (gestazionale e precedente la gravidanza)
- Obesità materna
- Eccessivo incremento di peso durante la gravidanza
- Inadeguato incremento di peso durante la gravidanza
- LGA
- SGA

rappresentano ognuno fattori
che aumentano il rischio nella prole di

- Precoce obesità
- Diabete tipo 2 (sindrome metabolica)

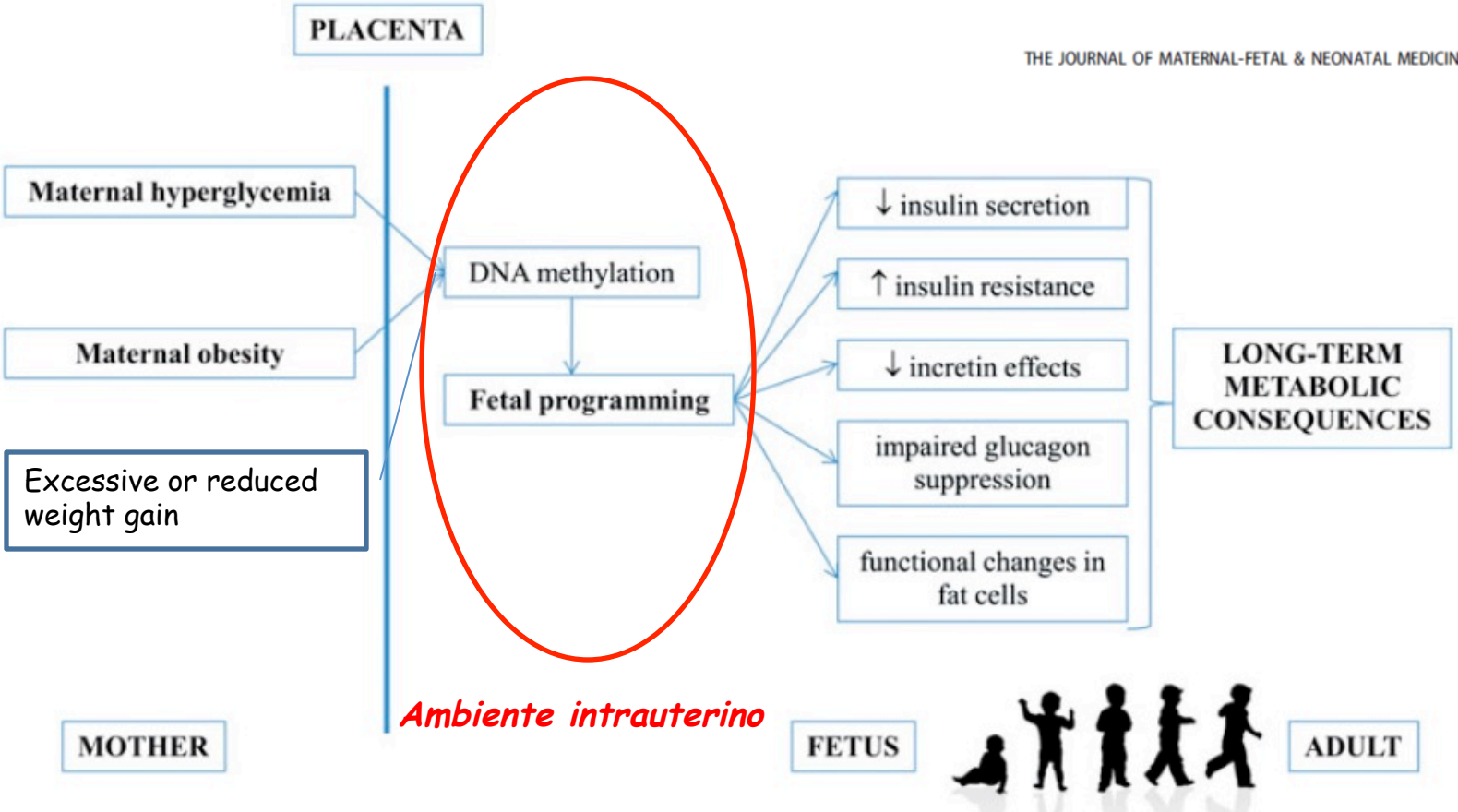
Developmental Origins of Health and Disease (DOHaD) hypotesis

Epigenetica: cambiamento ereditabile nella espressione genetica, non determinato da sottostanti modificazioni della sequenza di DNA

Cambiamento del fenotipo ma non del genotipo

Metilazione del DNA o metilazione degli istoni

Developmental Origins of Health and Disease (DOHaD) hypotesis



- Modificazioni presenti negli spermatozoi e negli ovociti dei genitori e mantenute attraverso le divisioni mitotiche nelle cellule somatiche del feto
- I marker epigenetici sono "parent-of-origin-specific"
- L' imprinting genetico è un processo dinamico
- I marker epigenetici possono essere trasmessi da una generazione all'altra
- Correlazione con il sesso del feto

A great deal of evidence supports the notion that early life exposure to maternal obesity alters the nuclear epigenome of the exposed offspring and may promote metabolic disease [57].

(GDM). The risk of developing T2DM later in life is 7 to 8-fold higher in women with GDM and their offspring, and is associated with several epigenetic modifications.[66,67]

investigation of the effects of *in utero* undernutrition in humans [42]. Women (F1) whose mothers (F0) were exposed to famine during the periconceptual period later had offspring (F2) with birth weights lower than those of offspring of women not exposed to famine *in utero*.


Condizioni economiche
Abitudini alimentari
Attività fisica
Obesità
Etnia
Ambiente intrauterino
Obesità materna
LGA
SGA
Peso acquisito durante la gravidanza


GRAZIE