



con il patrocinio di



**PROGRESSI E NUOVE FRONTIERE IN**  
**GASTROENTEROLOGIA**  
**ED ENDOSCOPIA DIGESTIVA**



**BELLUNO**  
15-16 GIUGNO 2023

# Steatosi e Steato-Fibrosi Epatica

*Cosa c'è all'orizzonte?*

Paolo Montalto





EASL-EASD-EASO Clinical Practice Guidelines for the management of non-alcoholic fatty liver disease<sup>22</sup>

European Association for the Study of the Liver (EASL)<sup>21</sup>, European Association for the Study of Diabetes (EASD) and European Association for the Study of Obesity (EASO)

Journal of Hepatology 2016 vol. 64 | 1388-1402

**NAFLD**

- Excessive hepatic fat accumulation with IR
- Steatosis in >5% hepatocytes
- Exclusion of secondary causes and AFLD

**NAFL**

- Pure steatosis
- Steatosis and mild lobular inflammation

**NASH**

**HCC**

**EARLY**

F0/F1 Fibrosis

**FIBROTIC**

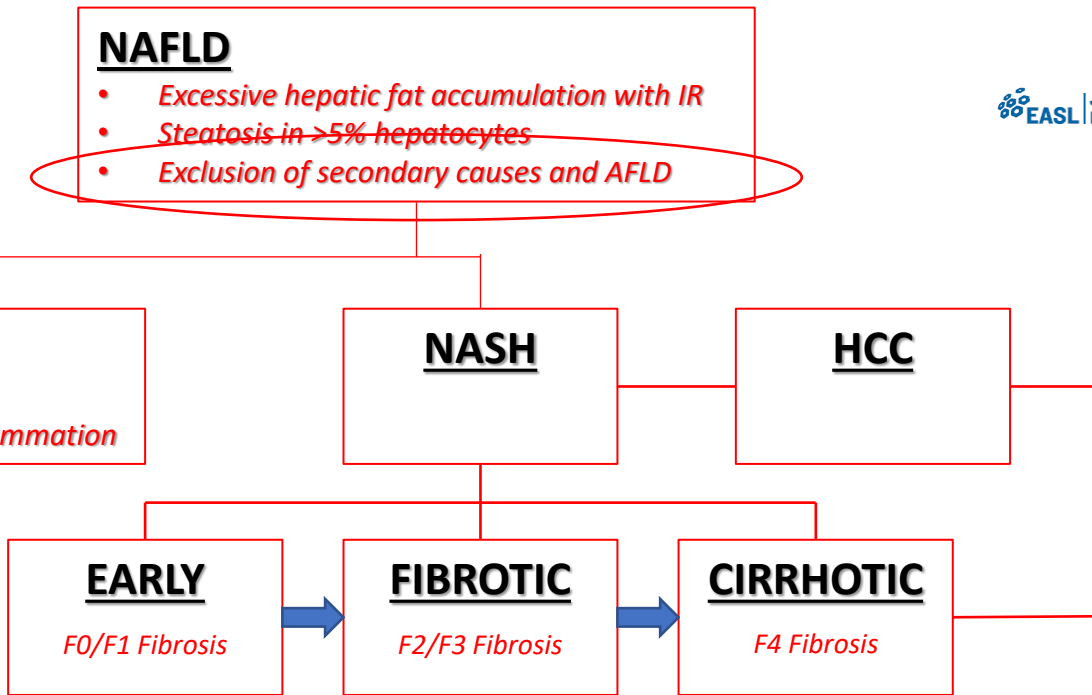
F2/F3 Fibrosis

**CIRRHOTIC**

F4 Fibrosis

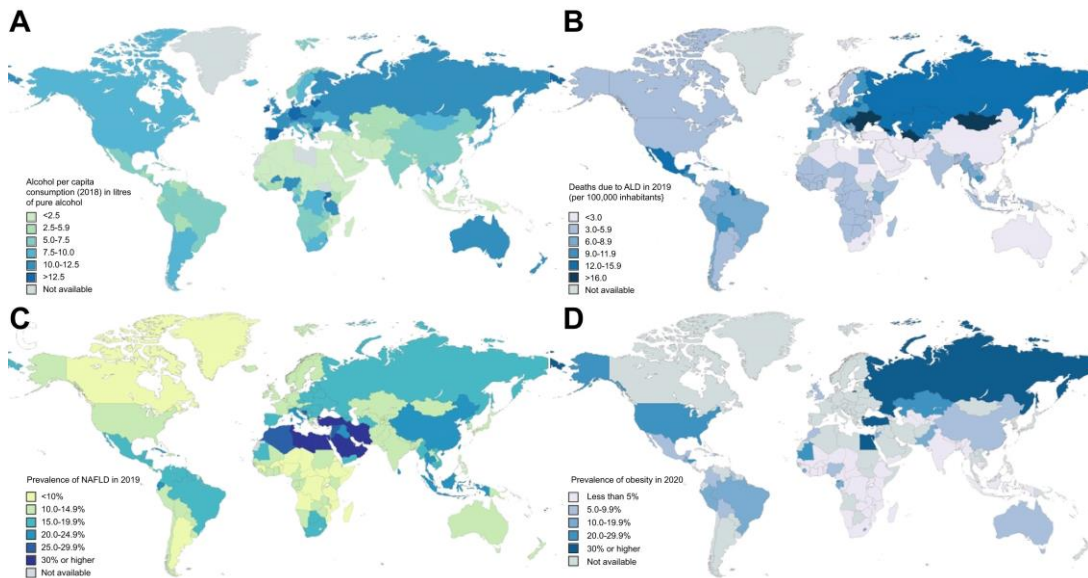
**Definizioni**

Definitive diagnosis of NASH requires a liver biopsy





## J Hepatol 2023: Global Burden of liver disease: 2023 update



- Prevalenza Globale NAFLD: 32,4%
- In progressivo aumento (parallelo a quello dei disturbi metabolici associati)
- Prima eziologia di trapianto epatico
- Alto impatto economico (destinato a crescita esponenziale)
- Incremento stimato dell'incidenza della NAFLD e delle sue complicanze (cirrosi scompensata, HCC, mortalità): x2-x3 nel 2030

(Estes C et al. 2018)

La principale minaccia per la salute globale (bambini e adolescenti) dei prossimi decenni





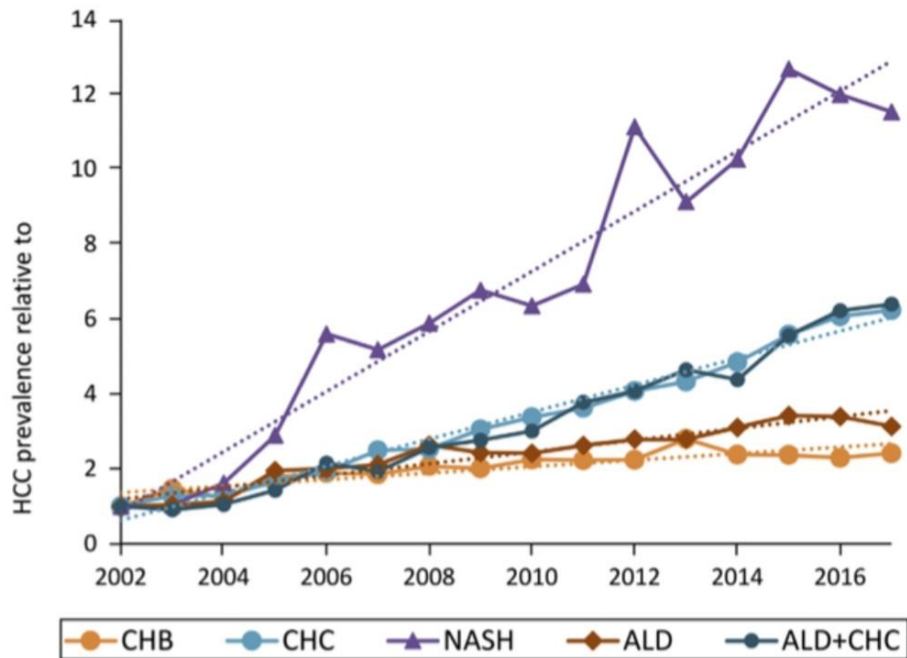
### Clinical Gastroenterology and Hepatology 2019;17:748–755

## Nonalcoholic Steatohepatitis Is the Fastest Growing Cause of Hepatocellular Carcinoma in Liver Transplant Candidates



Zobair Younossi,<sup>\*,†</sup> Maria Stepanova,<sup>§</sup> Janus P. Ong,<sup>||</sup> Ira M. Jacobson,<sup>¶</sup> Elisabetta Bugianesi,<sup>#</sup> Ajay Duseja,<sup>\*\*</sup> Yuichiro Eguchi,<sup>‡‡</sup> Vincent W. Wong,<sup>§§</sup> Francesco Negro,<sup>|||</sup> Yusuf Yilmaz,<sup>¶¶</sup> Manuel Romero-Gomez,<sup>##</sup> Jacob George,<sup>\*\*\*</sup> Aijaz Ahmed,<sup>†††</sup> Robert Wong,<sup>§§§</sup> Issah Younossi,<sup>§</sup> Mariam Ziayee,<sup>§</sup> and Arian Afendy,<sup>§</sup> on Behalf of the Global Nonalcoholic Steatohepatitis Council

Nonalcoholic steatohepatitis is the most rapidly growing cause of HCC among US patients listed for liver transplantation.





# American Journal of TRANSPLANTATION



Volume 20, Issue s1

Special Issue: OPTN/SRTR Annual Data Report 2018

Pages: 1-568  
January 2020



## OPTN/SRTR 2018 Annual Data Report: Liver

A. Kwong<sup>1</sup>, W. R. Kim<sup>1,2</sup>, J. R. Lake<sup>1,3</sup>, J. M. Smith<sup>1,4</sup>,  
D. P. Schladt<sup>2</sup>, M. A. Skeans<sup>2</sup>, S. M. Noreen<sup>5</sup>, J. Foutz<sup>5</sup>,  
E. Miller<sup>5</sup>, J. J. Snyder<sup>2,6</sup>, A. K. Israni<sup>2,6,7</sup>, B. L. Kasiske<sup>2,7</sup>

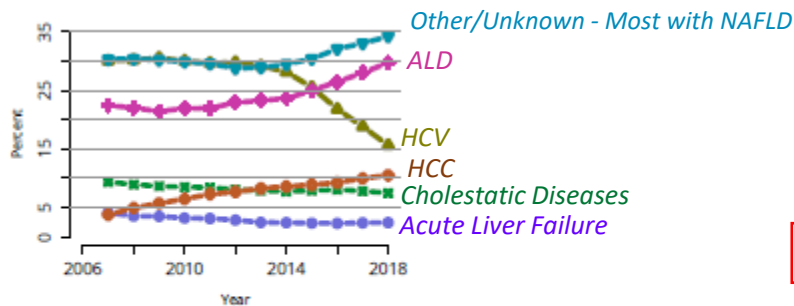


Figure LI 6. Distribution of adults waiting for liver transplant by diagnosis. Candidates waiting for transplant at any time in the given year. Candidates listed concurrently at multiple centers are counted once. Active and inactive patients are included. HCV, hepatitis C virus; ALD, alcoholic liver disease; Chol. disease, cholestatic disease; HCC, Hepatocellular carcinoma.

### NAFLD (Non-Alcoholic Fatty Liver Disease)

- principale causa di epatopatia cronica nel mondo occidentale
- manifestazione epatica della sindrome metabolica
- principale indicazione a trapianto di fegato (USA)



Rischio CV aumentato rischio?



**A new definition for metabolic dysfunction-associated fatty liver disease: An international expert consensus statement**

**NAFLD manifestazione epatica della sindrome metabolica**

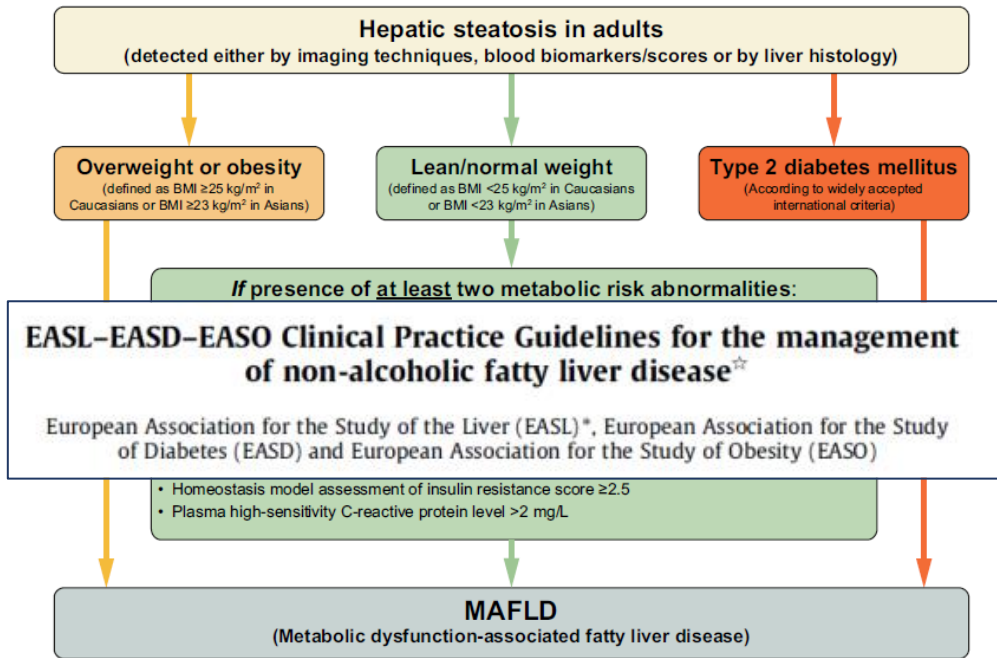
**NAFLD**

diagnosi di esclusione



**MAFLD**

diagnosi positiva





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Associazione Italiana  
Gastroenterologia e  
Dipartimento Digestivo



S.I.E.D.



GGE



fismad



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Comune di Belluno



Ospedale di Belluno

# PROGRESSI E NUOVE FRONTIERE IN GASTROENTEROLOGIA ED ENDOSCOPIA DIGESTIVA



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THE LANCET  
Gastroenterology & Hepatology

ARTICLES | VOLUME 8, ISSUE 1, P20-30, JANUARY 2023

Global prevalence of non-alcoholic fatty liver disease and non-alcoholic steatohepatitis in the overweight and obese population: a systematic review and meta-analysis

Jingxuan Quek \* • Kai En Chan \* • Zhen Yu Wong, MBBS \* • Caitlyn Tan • Bryan Tan • Wen Hui Lim • et al.

Show all authors • Show footnotes

«The global burden of NAFLD  
parallels the increase  
in obesity rate across the world»

Pooled analysis comprising 101 028 individuals:

NAFLD in overweight population 69-99%

NAHS in overweight population 33-50%

NAFLD in obese population 75-97%

NAHS in obese population 33-67%





DIABETES, VOL. 37, DECEMBER 1988

## Banting Lecture 1988

# Role of Insulin Resistance in Human Disease

GERALD M. REAVEN

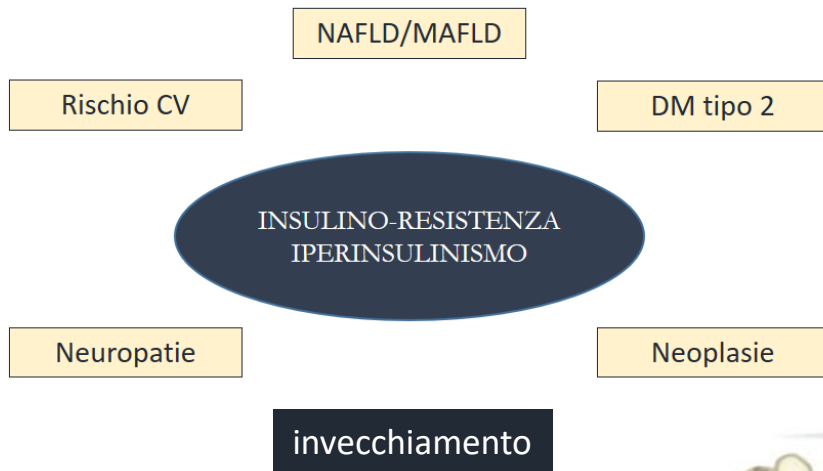
Resistance to insulin-stimulated glucose uptake is present in the majority of patients with impaired glucose tolerance (IGT) or non-insulin-dependent diabetes mellitus (NIDDM) and in ~25% of nonobese individuals with normal oral glucose tolerance. In these conditions, deterioration of glucose tolerance can only be prevented if the  $\beta$ -cell is able to increase its insulin secretory response and maintain a state of chronic hyperinsulinemia. When this goal cannot

**Insulino-resistenza:** per evitare lo sviluppo di iperglicemia deve incrementare la risposta secretoria insulinica da parte della beta-cellula, con lo sviluppo di uno stato di **iperinsulinismo cronico**.

- evento chiave non solo per lo sviluppo di **diabete mellito tipo 2**, ma di tutta una serie di affezioni (ipertrigliceridemia, ipercolesterolemia, ipertensione arteriosa) che la rendono **causa prevalente di rischio CV** («**Sindrome X**»)
- Obesità inizialmente non compresa nella definizione di Sindrome X (soggetti insulino-resistenti non obesi, soggetti obesi non insulino-resistenti)
- Importanza non solo dell'accumulo di grasso viscerale ma anche epatico ed ectopico (associazione di **obesità viscerale** e «**fegato grasso**»)



# INSULINO-RESISTENZA: substrato comune di molte patologie croniche



## nature medicine

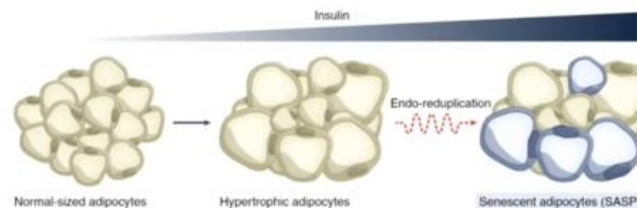
Article | Published: 04 October 2021

### Obesity and hyperinsulinemia drive adipocytes to activate a cell cycle program and senescence

[Qian Li](#), [Carolina E. Hagberg](#), [Helena Silva Cascales](#), [Shuai Lang](#), [Mervi T. Hyvönen](#), [Firoozeh Salehzadeh](#), [Ping Chen](#), [Ida Alexandersson](#), [Eleni Terezaki](#), [Matthew J. Harms](#), [Maria Kutschke](#), [Nahida Arifen](#), [Niels Krämer](#), [Myriam Aouadi](#), [Carole Knibbe](#), [Jeremie Boucher](#), [Anders Thorell](#) & [Kirsty L. Spalding](#)

*Nature Medicine* 27, 1941–1953 (2021) | [Cite this article](#)

14k Accesses | 30 Citations | 128 Altmetric | [Metrics](#)



*Adipocyte cell cycle progression associates with obesity and hyperinsulinemia, with a concomitant increase in cell size, nuclear size and nuclear DNA content. Chronic hyperinsulinemia in vitro or in humans, however, is associated with subsequent cell cycle exit, leading to a premature senescent transcriptomic and secretory profile in adipocytes*

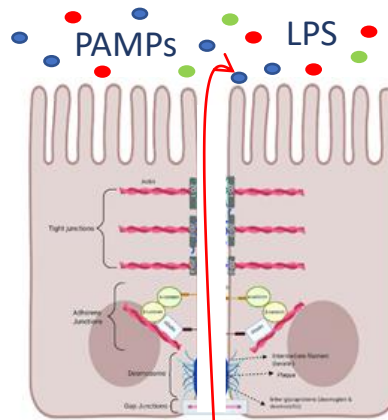


# THE MULTI-HIT PATHOGENESIS of NASH

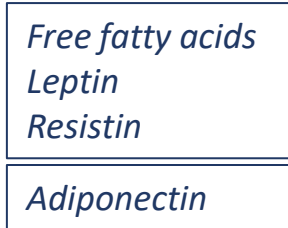
«Unhealthy» Diet  
Sedentary Lifestyle  
Genetic Factors

Gut Epithelia

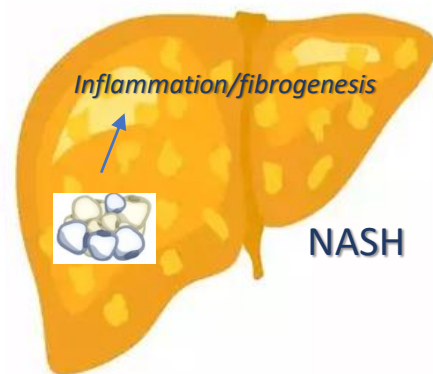
«Leaky» Tight Junctions



«expanded» inflamed visceral fat



dysbiosis



(Buzzetti E et al. 2016) (Marra F Svegliati Baroni G. 2018)



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Help Desk: <http://www.wjnet.com/esps/helpdesk.aspx>  
DOI: 10.3748/wjg.v23.i1.60

*World J Gastroenterol* 2017 January 7; 23(1): 60-75  
ISSN 1007-9327 (print) ISSN 2219-2840 (online)  
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ORIGINAL ARTICLE

Basic Study

## Sodium butyrate attenuates high-fat diet-induced steatohepatitis in mice by improving gut microbiota and gastrointestinal barrier

Da Zhou, Qin Pan, Feng-Zhi Xin, Rui-Nan Zhang, Chong-Xin He, Guang-Yu Chen, Chang Liu, Yuan-Wen Chen, Jian-Gao Fan

**frontiers**  
in Immunology

ORIGINAL RESEARCH

published: 11 June 2021

doi: 10.3389/fimmu.2021.678360

## Prebiotic Inulin and Sodium Butyrate Attenuate Obesity-Induced Intestinal Barrier Dysfunction by Induction of Antimicrobial Peptides

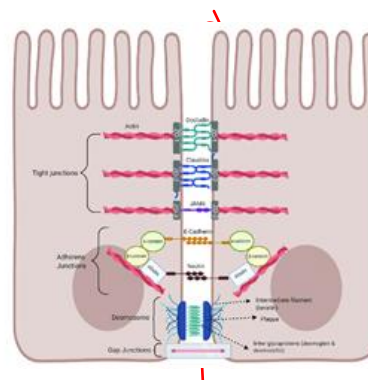
Julia Beisner<sup>1</sup>, Louisa Filipe Rosa<sup>1</sup>, Valentina Kaden-Volynets<sup>1</sup>, Iris Stolzer<sup>2</sup>, Claudia Günther<sup>2</sup> and Stephan C. Bischoff<sup>1\*</sup>

molecules

Review

## The Protective Role of Butyrate against Obesity and Obesity-Related Diseases

Serena Coppola<sup>1,2,\*</sup>, Carmen Avagliano<sup>3,\*</sup>, Antonio Calignano<sup>3</sup> and Roberto Berni Canani<sup>1,2,4,5,\*</sup>







metabolic syndrome

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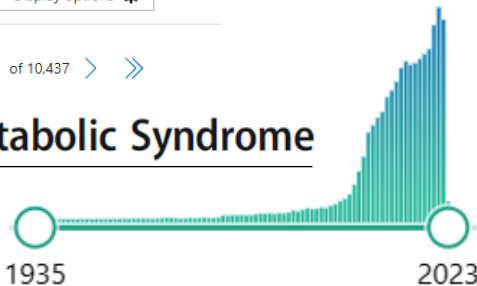
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104,364 results

Sorted by: Best match Page 1 of 10,437

## The Global Epidemic of the Metabolic Syndrome



### WHO 1999:

Presence of **insulin resistance** or glucose > 6.1 mmol/L (110 mg/dl), 2 h glucose > 7.8 mmol (140 mg/dl) (required) along with any two or more of the following:

1. **HDL cholesterol** < 0.9 mmol/L (35 mg/dl) in men, < 1.0 mmol/L (40 mg/dl) in women
2. **Triglycerides** > 1.7 mmol/L (150 mg/dl)
3. **Waist/hip ratio** > 0.9 (men) or > 0.85 (women) or BMI > 30 kg/m<sup>2</sup>
4. **Blood pressure** > 140/90 mmHg

- Il più grave pericolo per la salute pubblica nel mondo moderno (problema globale)
- Costi totali (diretti ed indiretti): trillions
- «**Present trend is not sustainable unless a magic cure is found (unlikely)** or concerted global governmental/ societal effort are made to change the lifestyle that is promoting it (high calorie-low fiber diet - fast food – and decrease in physical activity)»

*(Saklayen MG 2018)*

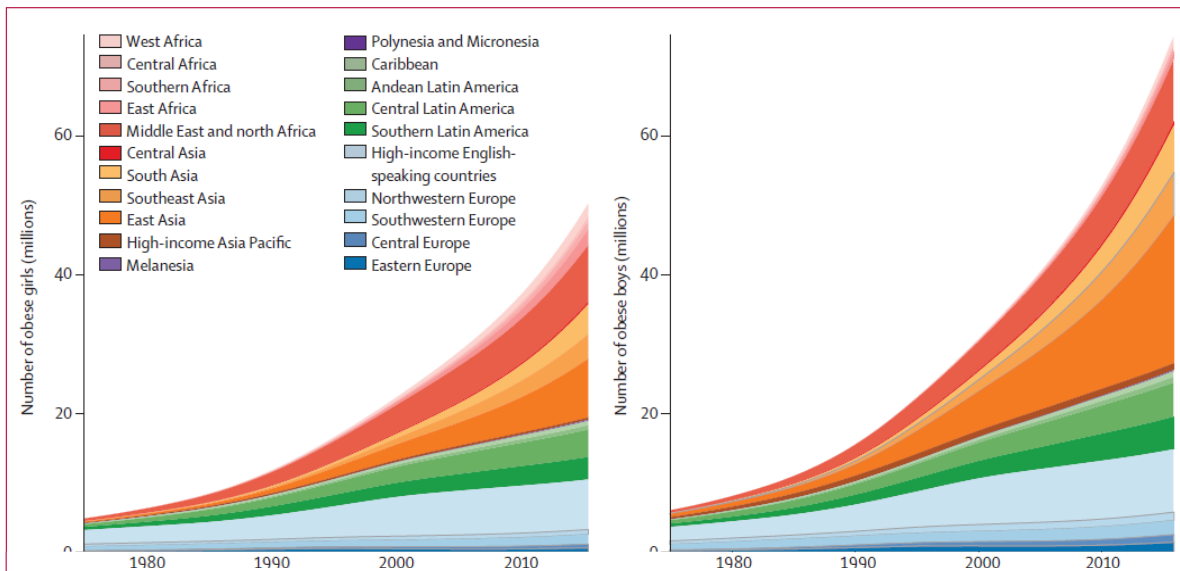


# Worldwide trends in body-mass index, underweight, overweight, and obesity from 1975 to 2016: a pooled analysis of 2416 population-based measurement studies in 128.9 million children, adolescents, and adults

Articles

NCD Risk Factor Collaboration (NCD-RisC)\*

Lancet 2017; 390: 2627-42



Trends in the number of children and adolescents (5-19 y.o) with obesity by region

US obesity rate:  
an unstoppable rise

- 1968: 15%
- 2008: 30%
- 2030: 50%
- 2102: 100%





## The Global Epidemic of the Metabolic Syndrome

*(Saklayen MG 2018)*

- Incidenza della SM va in parallelo a quella dell'obesità e del DM tipo 2; incremento 0.37%/anno nel periodo 1988-2010
- Dati CDC (US) 2017: 30.2 milioni (12.2%) di adulti  $\geq 18$  anni sono affetti da DM tipo 2
- Di questi ... 1 su 4 ... non lo sa !
- La prevalenza della SM e del Prediabete è circa di 3 volte maggiore (1/3 della popolazione adulta US)

*(National Center for Health Statistics – CDC – 2012)*



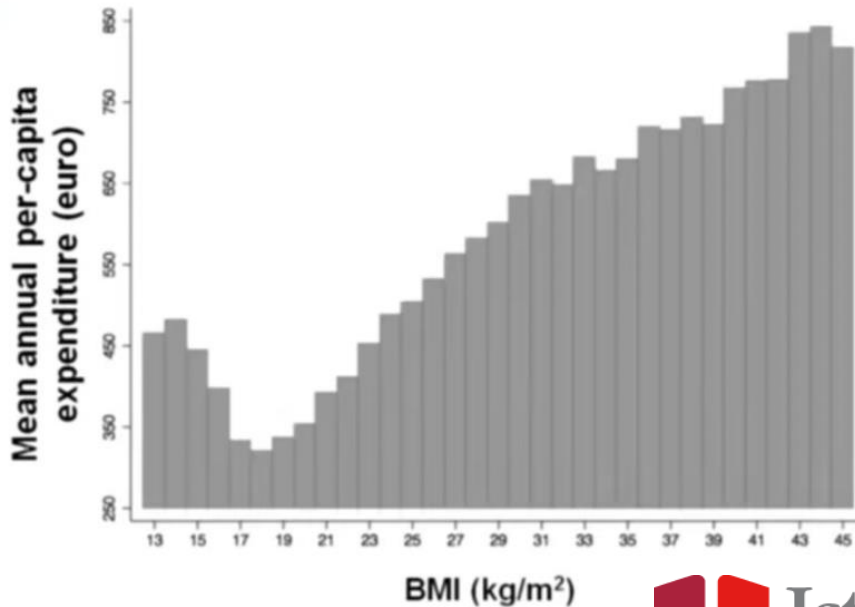
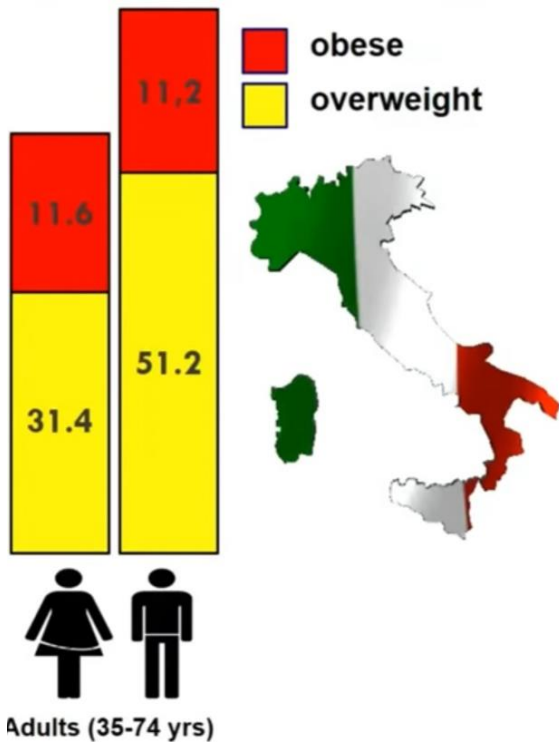
### ▪ Global Survey of Obesity (195 Countries) – 2015:

- 604 milioni di adulti obesi – 108 milioni di bambini obesi
- Prevalenza di Obesità raddoppiata dal 1980 in 73 Paesi; incrementata ovunque
- Dati ancora più eclatanti per incremento di prevalenza dell'obesità infantile
- Incremento più alto in giovani (25-29 anni) maschi in Paesi a basso indice socio-economico
- Bangladesh: percentuale di incremento più elevata per morte/disabilità correlate al BMI
- Turchia: riduzione della morbidità (-37.2%) e mortalità (-43.3%) correlate al BMI

*(2015 Obesity Collaboration GBD – NEJM 2017)*



# ITALIA: FATTORI DI RISCHIO PER LA SALUTE (OBESITA' E RISCHI CORRELATI) ISTAT 2016







Istituto Superiore di Sanità  
EpiCentro - L'epidemiologia per la sanità pubblica



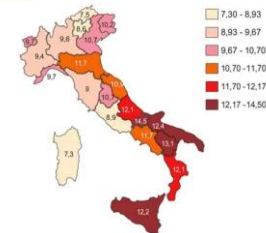
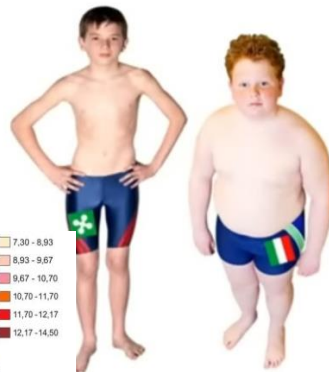
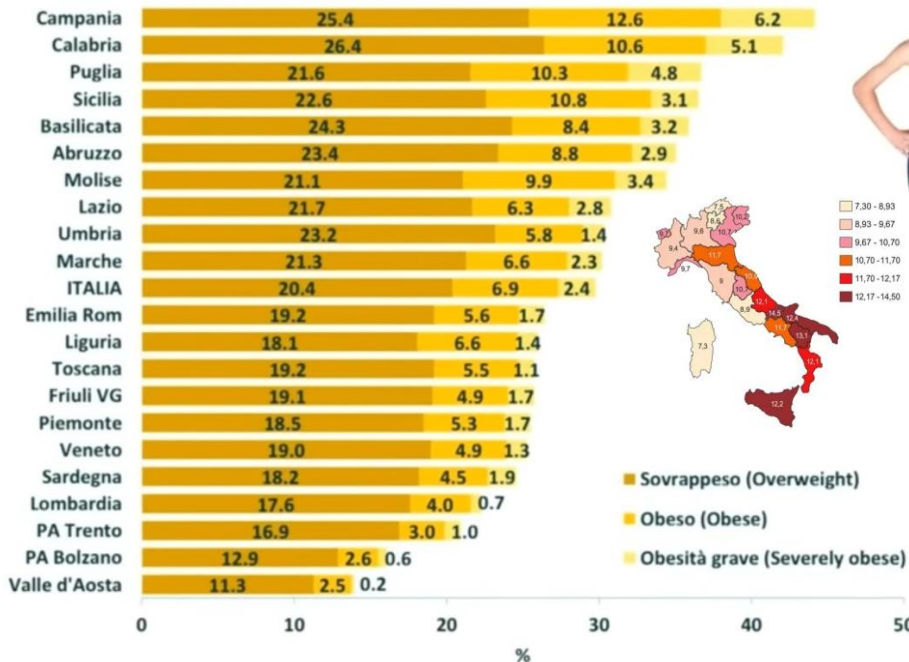
OKKio alla SALUTE

2007 →

*Sistema di sorveglianza su sovrappeso/obesità e fattori di rischio correlati nei bambini delle scuole primarie (6-10 anni)*

Nel 2019 il **20,4%** dei bambini è risultato in **sovrappeso** e il **9,4%** **obeso**, compresi i bambini **gravemente obesi** che da soli sono il **2,4%**, con una ampia variabilità regionale (prevalenza al SUD).

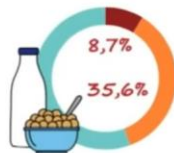
## 2019



(Infografica OKKIO alla Salute 2019)

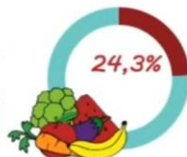


**CATTIVE ABITUDINI ALIMENTARI DEI BAMBINI**



**colazione**

Non fa colazione quotidianamente l'8,7% dei bambini. Fa una colazione non adeguata, ossia sbilanciata in termini di carboidrati e proteine, il 35,6% dei bambini.



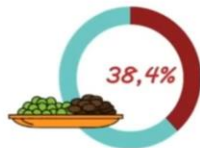
**consumo non quotidiano di frutta e/o verdura**

Il 24,3% consuma frutta e/o verdura meno di una volta al giorno.



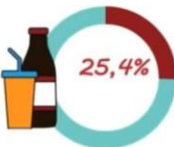
**merenda abbondante**

Il 55,2% dei bambini consuma una merenda di metà mattina abbondante e di conseguenza non adeguata.



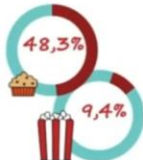
**news dal 2019 consumo di legumi**

I legumi sono consumati dal 38,4% dei bambini meno di una volta a settimana.



**consumo quotidiano di bevande zuccherate/gassate**

Il 25,4% consuma quotidianamente bibite zuccherate/gassate.



**news dal 2019 snack dolci e salati**

Il 48,3% dei bambini consuma snack dolci più di 3 giorni a settimana. Gli snack salati sono consumati più di tre giorni a settimana dal 9,4% dei bambini.

**ATTIVITÀ FISICA**

Il 20,3% dei bambini non ha svolto attività fisica il giorno precedente l'indagine.

20,3%



Il 73,6% dei bambini non si reca a scuola a piedi o in bicicletta.



**SEDENTARIETÀ**

43,5%

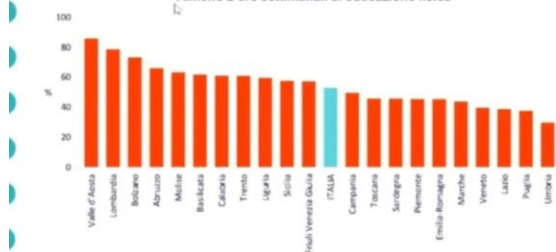
Il 43,5% dei bambini ha la TV nella propria camera da letto.

Il 44,5% dei bambini trascorre più di 2 ore al giorno davanti a TV e/o videogiochi/tablet/cellulare.

44,5%

Il 53,0% delle classi svolge almeno 2 ore di educazione fisica a settimana. Forte variabilità a livello regionale: dal 30% in Umbria all'86% in Valle d'Aosta.

**Almeno 2 ore settimanali di educazione fisica**





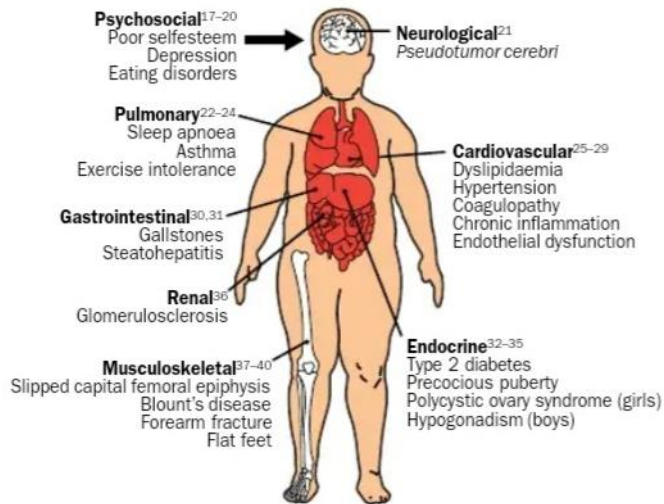
Lancet 2002, 360: 473-82

SEMINAR

Seminar

## Childhood obesity: public-health crisis, common sense cure

Cara B Ebbeling, Dorota B Pawlak, David S Ludwig



Complications of childhood obesity

## Years of Life Lost Due to Obesity

Kevin R. Fontaine, PhD

JAMA 2003;289(2):187-193

David T. Redden, PhD

Chenxi Wang, MD

Andrew O. Westfall, MS

David B. Allison, PhD

Il numero di YLL è molto maggiore per  
giovani/adolescenti rispetto ad adulti a parità  
di grado di sovrappeso/obesità

Un adolescente con obesità grave (BMI>45)  
ha un'aspettativa di vita di 13 anni minore  
rispetto ad un coetaneo non obeso



## Type 2 diabetes in adolescents and young adults

THE LANCET

Diabetes & Endocrinology

REVIEW | VOLUME 6, ISSUE 1, P69-80, JANUARY 2018

Nadia Lascar, James Brown, Helen Pattison, Anthony H Barnett, Clifford J Bailey, Srikanth Bellary

- La prevalenza del diabete tipo 2 negli adolescenti e nei giovani adulti è in drammatico aumento
- Analogamente al DM2 dell'adulto, fattori di rischio: familiarità, obesità, stile di vita sedentario
- Il **DM2 giovanile ha un fenotipo più aggressivo**: più lunga esposizione a iperinsulinismo → complicanze precoci
- Effetti negativi su qualità di vita ed esiti a lungo termine



- **Futura Catastrofe della Salute Pubblica**





ORIGINAL ARTICLE

## Long-Term Complications in Youth-Onset Type 2 Diabetes

TODAY Study Group\*

N ENGL J MED 385;5 NEJM.ORG JULY 29, 2021

**CONCLUSIONS**

Among participants who had onset of type 2 diabetes in youth, the risk of complications, including microvascular complications, increased steadily over time and affected most participants by the time of young adulthood. Complications were more common among participants of minority race and ethnic group and among those with hyperglycemia, hypertension, and dyslipidemia. (Funded by the National Institute of Diabetes and Digestive and Kidney Diseases and others; ClinicalTrials.gov numbers, NCT01364350 and NCT02310724.)

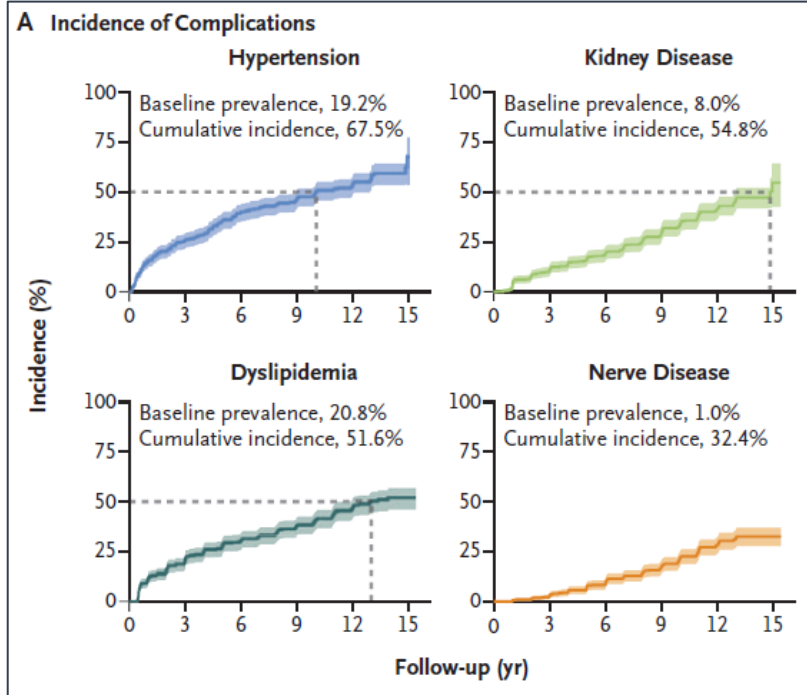
Age at Baseline: 10-17 yrs

After 13.4 ± 1.8 yrs:

**Mean Age:**  
**26.4 ± 2.8**

hypertension: 67%  
dyslipidemia: 51.6%  
diabetic nephropathy: 54,8%  
nerve disease: 32.4%  
retinal disease: 51%

*At least 1 complication occurred in 60.1% of the participants, and at least 2 complications occurred in 28.4%*



N Engl J Med 2021;385:416-26.

DOI: 10.1056/NEJMoa2100165

Copyright © 2021 Massachusetts Medical Society.



Burden, economic impact and research gaps:

Key findings from the Plain-European study on digestive diseases and cancers



# Burden of digestive diseases and priorities for digestive health research



New data are needed to raise political and public awareness of digestive diseases. The White Book 2 commissioned by UEG provides an international analysis on:

## 1 The burden of digestive diseases:

- Disease incidence, prevalence, mortality, Disability-Adjusted Life Years and trends on disease evolution
- Modifiable risk factors, including alcohol use, drug use, smoking and high BMI
- Socioeconomic factors that contribute to an unequal burden of digestive diseases

## 2 The economic impact of digestive diseases:

Measures of indirect and inpatient costs: estimated for 31 UEG member countries



## 3 The priority areas for digestive health research:

- Research priorities and preferences of UEG national society members
- Bibliometric analysis on the distribution of research activity in the field of digestive health
- Horizon 2020 funded research projects in digestive disease research



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# PROGRESSI E NUOVE FRONTIERE IN GASTROENTEROLOGIA ED ENDOSCOPIA DIGESTIVA



BELLUNO  
15-16 GIUGNO 2023

April 26, 2023 – European Parliament  
MEP Digestive Health Group

digestive  
health  
group.

Fostering Digestive  
Health for Better  
Quality of Life

ueg

Hosted by  
MEP Romana Jerković  
(S&D, Croatia)

**Bridging the gaps**  
A Pan-European study on digestive diseases across Europe

April 26, 2023 | 13:30 – 15:30 CEST  
European Parliament, Brussels

**“How can we turn this data into action?”**



**“Our efforts need to go beyond this room and beyond this meeting”**





## ACCUMULO DI DANNO MOLECOLARE INIZIA IN UTERO

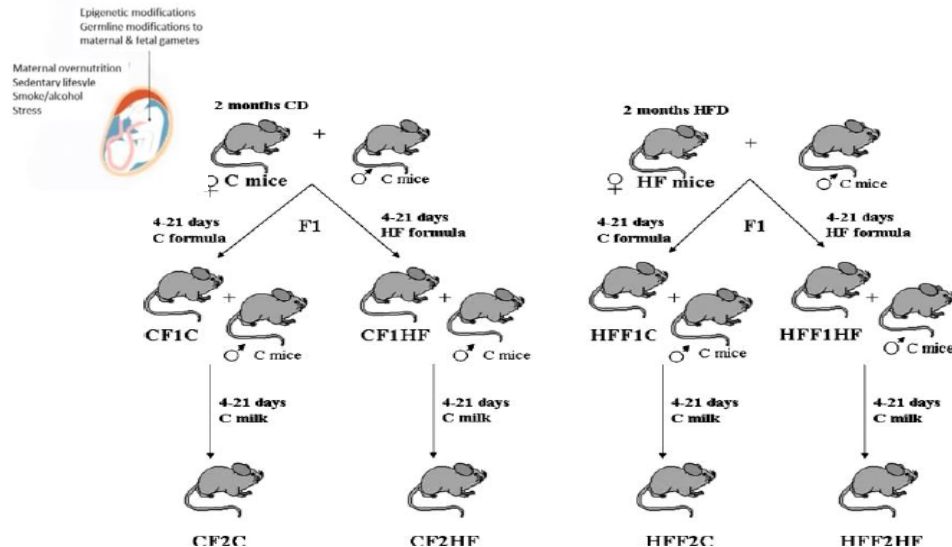
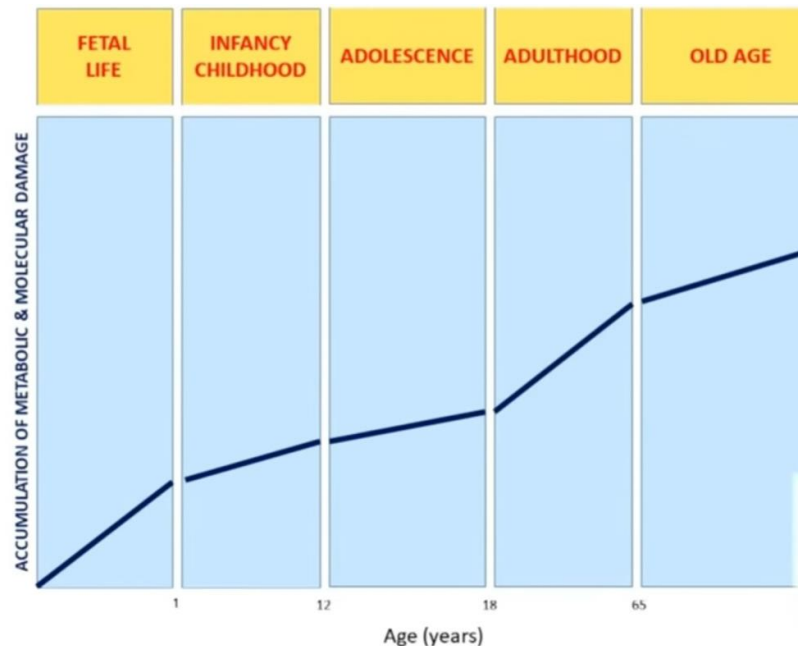


Fig. 1. First (F1) and second generation (F2) of mice production. F1 mice: CF1C, mice receiving a chow (C) diet in utero and during the suckling period; HFF1C, mice receiving a high-fat (HF) diet in utero and a C formula during the suckling period; CF1HF, mice receiving a C diet in utero and a HF formula during the suckling period; HFF1HF, mice receiving a HF diet both in utero and during the suckling period. F2 mice: all mice were fed on C milk by foster mothers and fed a C diet after 21 days of age. Mice were named from their progenitor mother: from CF1C (CF2C), from CF1HF (CF2HF), from HFF1C (HFF2C), and from HFF1HF (HFF2HF).

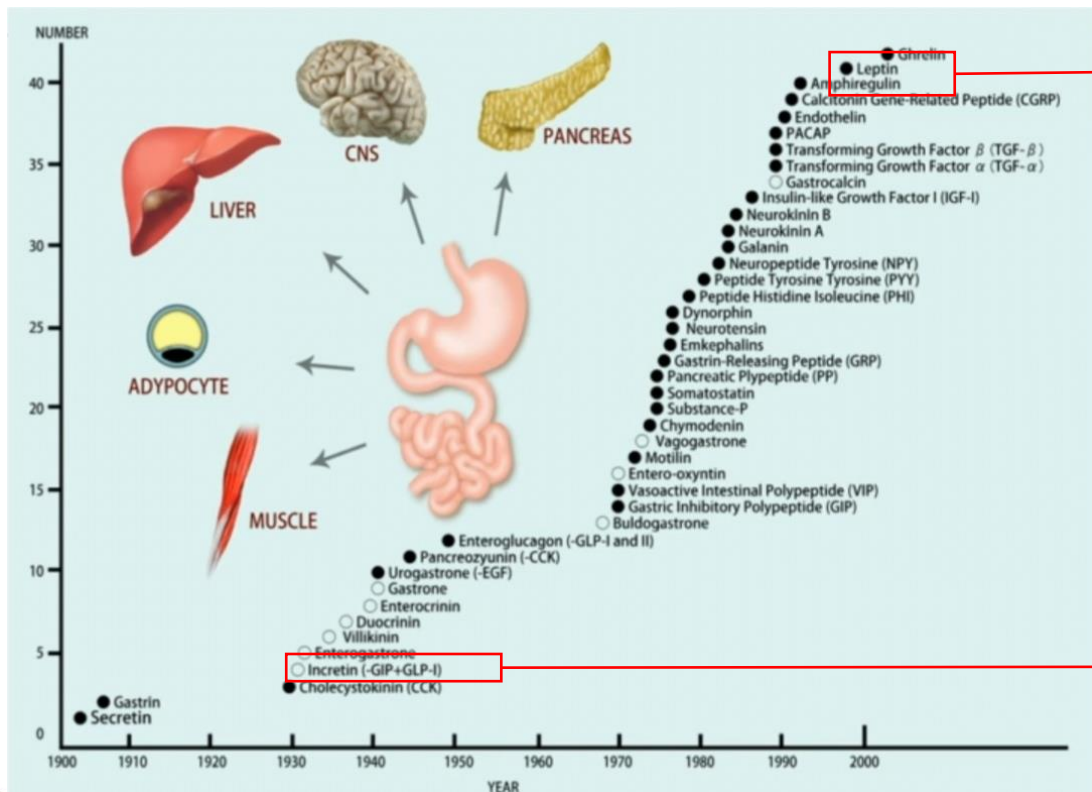
(Fontana L Nature 2014)

(Gniuli D. 2008)





## APPARATO DIGERENTE: GRANDE ORGANO ENDOCRINO

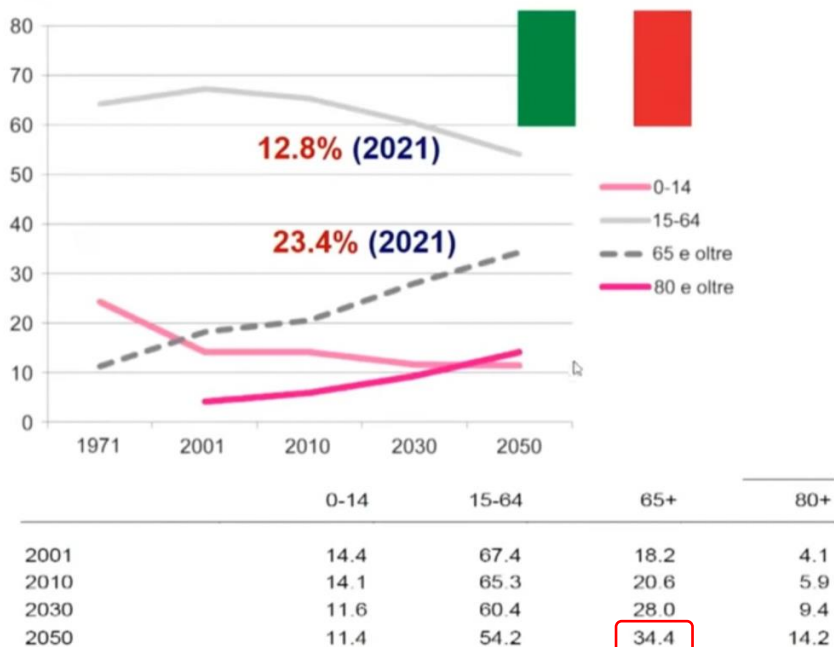


1994: somministrazione di **leptina** a topi deficienti geneticamente riduceva senso di fame e peso corporeo (Friedman)

Ancor prima della leptina una grande attenzione avevano avuto le **incretine**, in particolare uno, il **GLP-1** (glucagon-like peptide 1) che sembra avere un effetto opposto al diabete – quindi protettivo – al contrario del **GIP**, che sembrerebbe avere invece effetto opposto

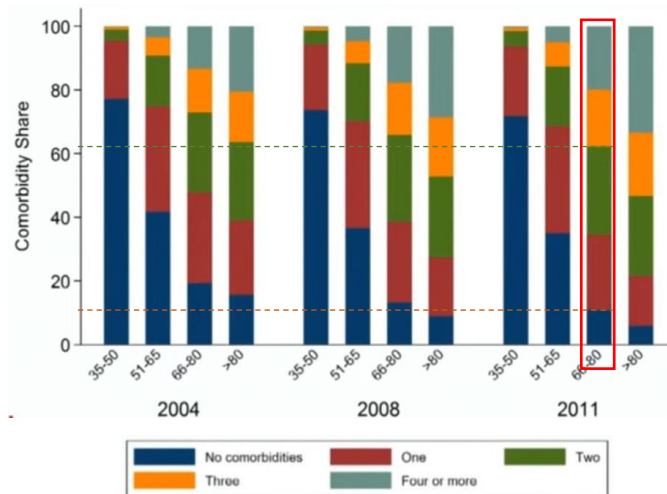


## ITALIA: TERZO POSTO AL MONDO PER POPOLAZIONE PIU' ANZIANA



(ISTAT)

## MA E' UNA LONGEVITA' SANA?



Atella et al., Aging Cell 2018

*la popolazione con età > 64 anni assorbe oltre il 60% della spesa farmacologica*



## SPESA SANITARIA: TOSCANA 2008-2022



### Dati Toscana (2008 – 2022)

#### Spesa Sanitaria Pubblica

##### 2008:

6.179 milioni di €

(circa il **70%** del budget di spesa complessivo della Regione)

##### 2022:

7741,5 milioni di €

(circa il **75%** del budget di spesa complessivo della Regione)

*(Documento di Economia e Finanza Regionale 2022 – Regione Toscana, Allegato A)*

*A questo incremento progressivo della spesa corrisponde un altrettanto progressivo e costante aumento delle criticità del sistema*

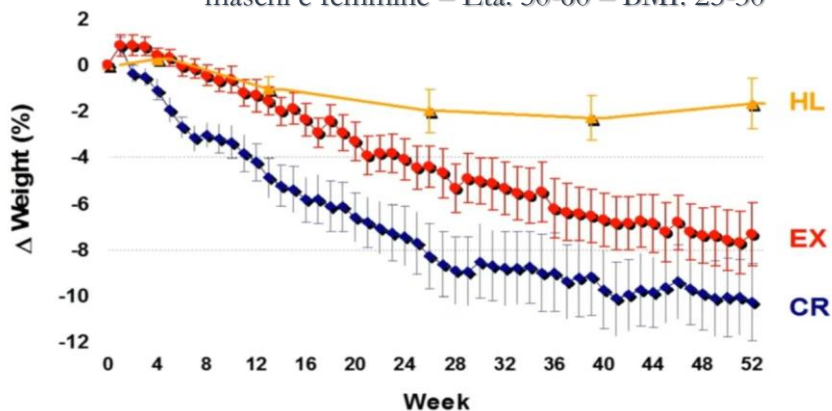
*Sono dati che mettono a rischio la sostenibilità stessa della nostra società e del nostro SSN, sempre più pronto a curare, controllare, assistere le malattie croniche e la disabilità ad esse conseguenti (sistema «reattivo») ma troppo poco attento alla prevenzione.*



## DIETA e STILE DI VITA: COSA POSSIAMO FARE IN PREVENZIONE PRIMARIA?

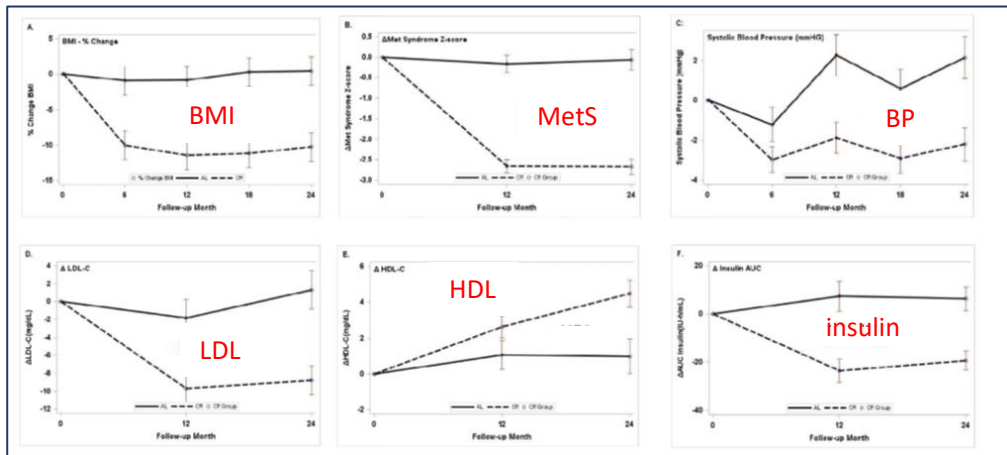
*1 ora di attività fisica – 72% HRmax – 6 giorni alla settimana*

maschi e femmine – Età: 50-60 – BMI: 25-30



(Racette S. J Gerontol 2006)

## RESTRIZIONE CALORICA e PARAMETRI DI RISCHIO METABOLICO

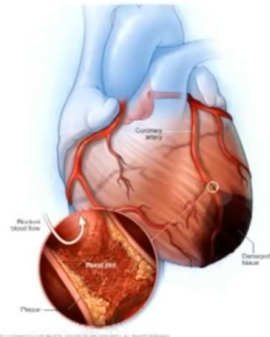
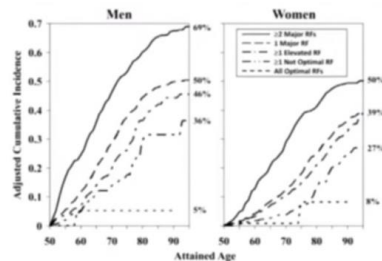


Kraus WE – CALERIE Investigators Lancet Diabetes Endocrinol 2019





## OPTIMAL CARDIOMETABOLIC RISK FACTORS AT AGE 50 IS ASSOCIATED WITH VERY LOW LIFETIME RISK FOR CVD AND MARKEDLY LONGER SURVIVAL



**Optimal risk factors** are defined as untreated T-CHOL <180 mg/dL (4.6 mmol/L), untreated BP <120/80 mmHg, nonsmoker & nondiabetic.

**Major risk factors** are defined as T-CHOL >240 mg/dL (6.2 mmol/L) or treated; SBP >160 mmHg, DBP >100 mmHg, or treated; smoker; or diabetic

Men			
Lifetime Risk for CVD (95% CI), %			
Risk Stratum*	To 75 y	To 95 y	Median Survival (IQR), y
Overall	35.0 (32.9–37.2)	51.7 (49.3–54.2)	30 (22–37)
All optimal risk factors	5.2 (0–12.2)	5.2 (0–12.2)	>39 (32–>45)
≥ 1 Not optimal risk factor	17.6 (10.9–24.4)	36.4 (23.1–49.6)	36 (29–42)
≥ 1 Elevated risk factor	26.0 (21.0–31.0)	45.5 (38.0–53.1)	35 (26–42)
1 Major risk factor	37.6 (33.8–41.5)	50.4 (46.2–54.5)	30 (23–36)
≥ 2 Major risk factors	53.2 (47.1–59.3)	68.9 (61.7–73.2)	28 (18–35)

FRAMINGHAM HEART STUDY. Lloyd-Jones et al., Circulation 2006

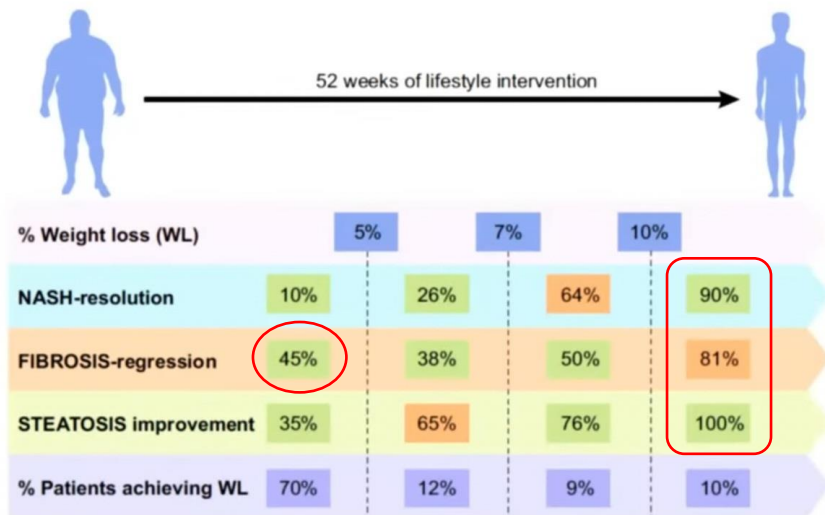


## DIETA e STILE DI VITA: COSA POSSIAMO FARE IN PREVENZIONE SECONDARIA?

### Weight Loss Through Lifestyle Modification Significantly Reduces Features of Nonalcoholic Steatohepatitis



Eduardo Vilar-Gomez,<sup>1,2</sup> Yadina Martinez-Perez,<sup>1</sup> Luis Calzadilla-Bertot,<sup>1</sup>  
Ana Torres-Gonzalez,<sup>1</sup> Bienvenido Gra-Oramas,<sup>3</sup> Licet Gonzalez-Fabian,<sup>3</sup> Scott L. Friedman,<sup>4</sup>  
Moises Diago,<sup>5</sup> and Manuel Romero-Gomez<sup>2</sup>

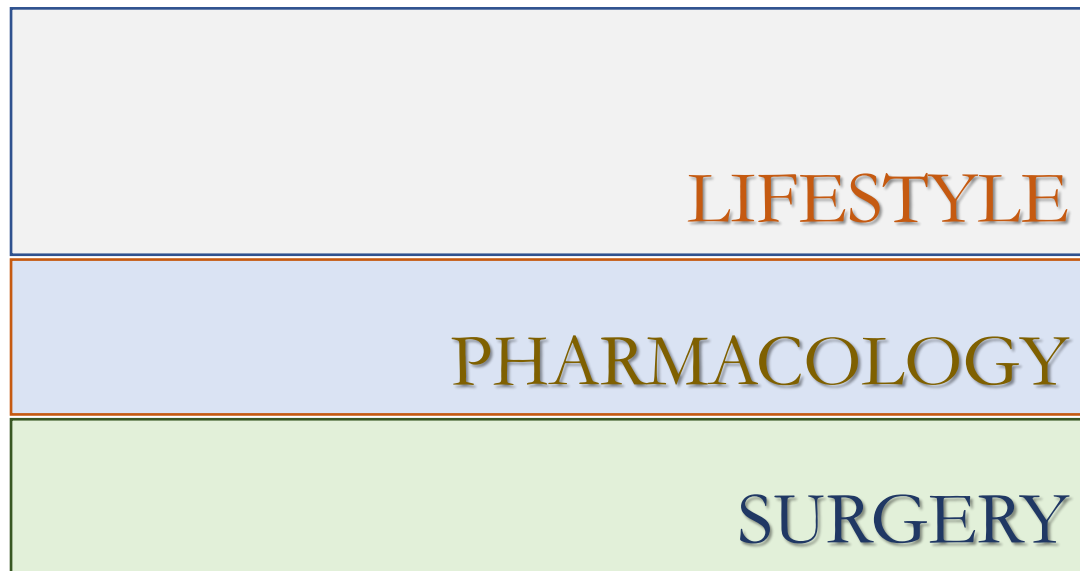


- 293 pazienti
- «Paired liver biopsies» in 261 pazienti



## TERAPIA

### Current of Guideline Recommendations for treatment of NASH



7-10% weight loss  
500-1000 daily calorie reduction  
Exercise

Pioglitazone  
Vitamin E

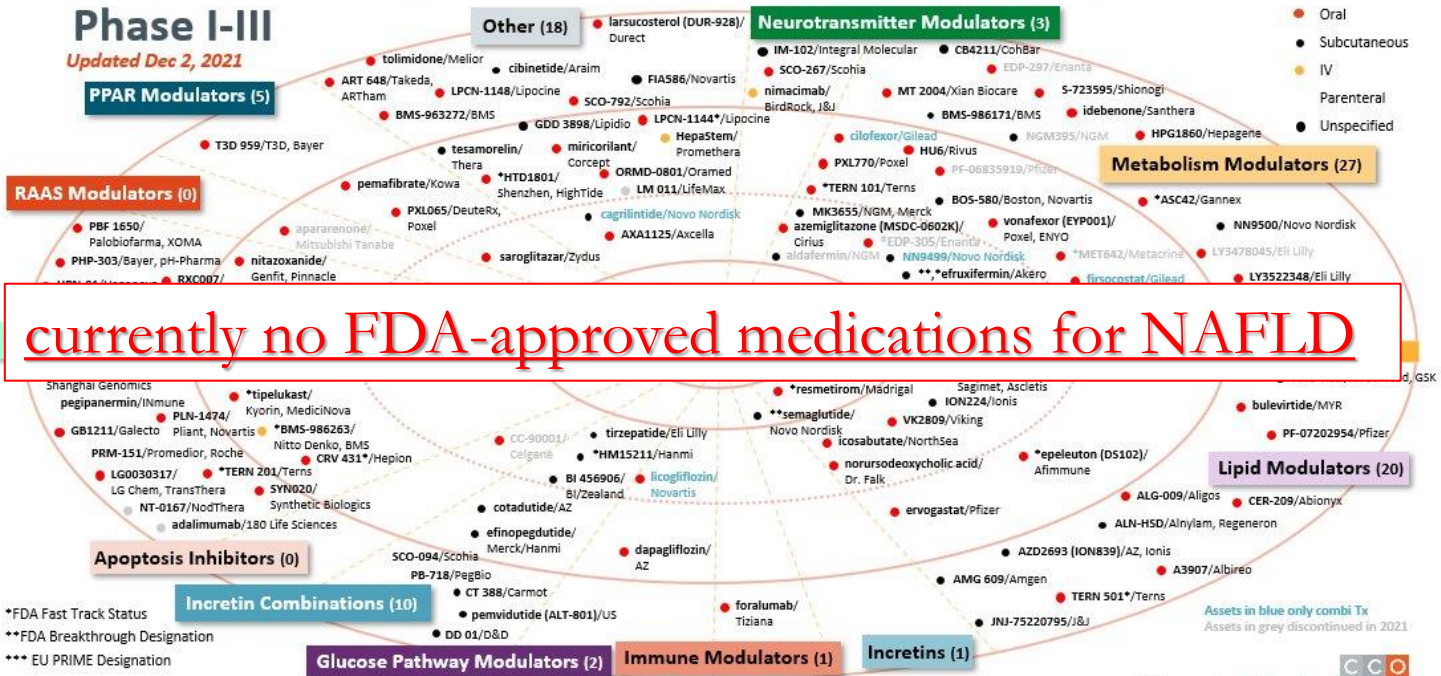
Bariatric Surgery / Endoscopy  
Liver Transplantation



# Agents in Development for NASH in US, EU, and Japan:

## Phase I-III

Updated Dec 2, 2021



Courtesy of Nina Brant, PhD

Slide credit: [clinicaloptions.com](http://clinicaloptions.com)







## TERAPIA

### The Global Epidemic of the Metabolic Syndrome

Risoluzione del DM dopo chirurgia bariatrica



**Adjustable  
Gastric Banding**

**38%**



**Roux-en-Y  
Gastric Bypass**

**84%**



**Biliopancreatic  
Diversion**

**98%**

(Buchwald H, JAMA 2004)



Diabetologia (2010) 53:2233–2240  
DOI 10.1007/s00125-010-1830-9

ARTICLE

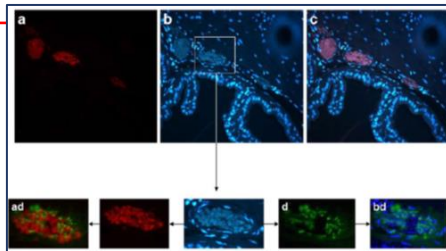
## Critical Role of the Duodenum in Causing Insulin-Resistance

### High-fat feeding stimulates endocrine, glucose-dependent insulinotropic polypeptide (GIP)-expressing cell hyperplasia in the duodenum of Wistar rats

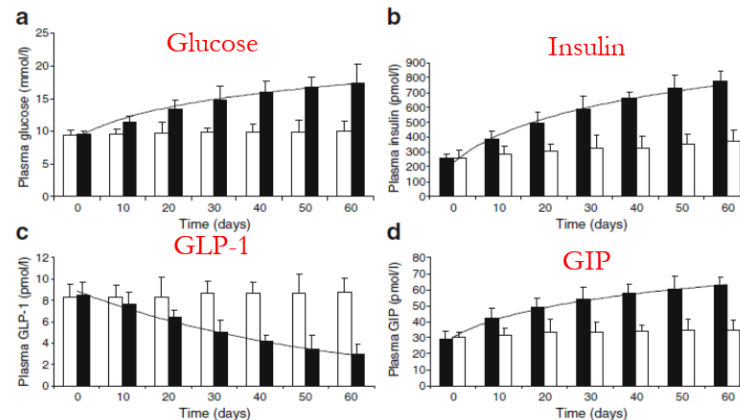
D. Gniuli • A. Calcagno • L. Dalla Libera • R. Calvani •  
L. Leccesi • M. E. Caristo • R. Vettor • M. Castagneto •  
G. Ghirlanda • G. Mingrone

- **duodeno** vero e proprio organo endocrino
- una dieta ad alto contenuto lipidico (HFD) stimola la proliferazione di cellule endocrine duodenali con iperproduzione di GIP → iperinsulinismo, insulino-resistenza e aumentato rischio di sviluppare diabete

- In risposta a OGTT i livelli circolanti di glucosio, insulina, e GIP incrementano, quelli di GLP-1 diminuiscono in modo esponenziale nel tempo in corso di HFD



Agglomerati di cellule con funzione endocrina a livello della mucosa duodenale, negative per GLP-1, positive per GIP

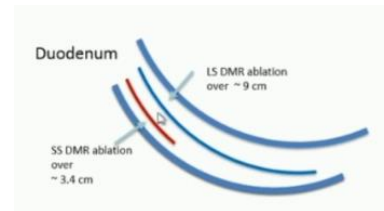




# Endoscopic Duodenal Mucosal Resurfacing for the Treatment of Type 2 Diabetes: 6-Month Interim Analysis From the First-in-Human Proof-of-Concept Study

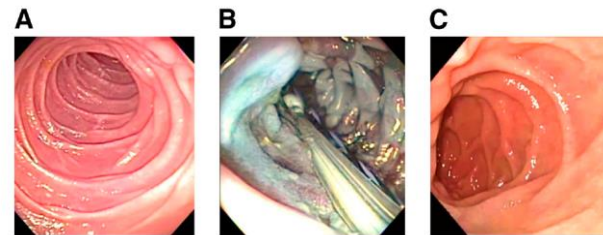
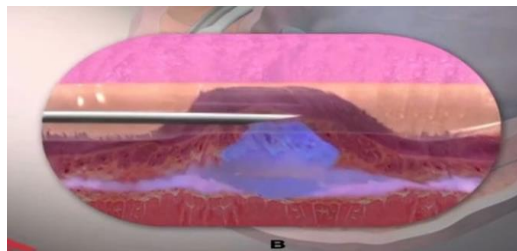
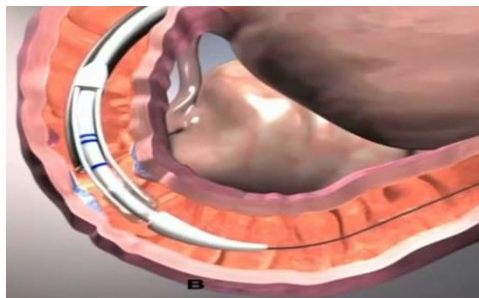
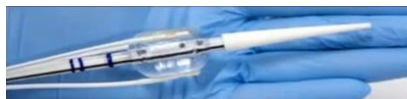
*Diabetes Care* 2016;39:2254–2261 | DOI: 10.2337/dc16-0383

Harith Rajagopalan,<sup>1</sup>  
Alan D. Cherrington,<sup>2</sup>  
Christopher C. Thompson,<sup>3</sup> Lee M. Kaplan,<sup>4</sup>  
Francesco Rubino,<sup>5</sup> Geltrude Mingrone,<sup>6</sup>  
Pablo Becerra,<sup>7</sup> Patricia Rodriguez,<sup>7</sup>  
Paulina Vignolo,<sup>7</sup> Jay Caplan,<sup>1</sup>  
Leonardo Rodriguez,<sup>7</sup> and  
Manoel P. Galvao Neto<sup>8,9</sup>



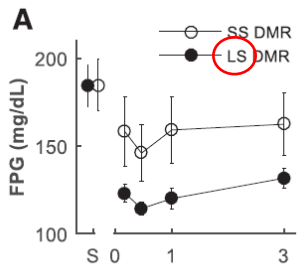
## OBJECTIVE

To assess procedural safety and glycemic indices at 6 months in a first-in-human study of duodenal mucosal resurfacing (DMR), a novel, minimally invasive, upper endoscopic procedure involving hydrothermal ablation of the duodenal mucosa, in patients with type 2 diabetes and HbA<sub>1c</sub> ≥7.5% (58 mmol/mol) on one or more oral antidiabetic agents.

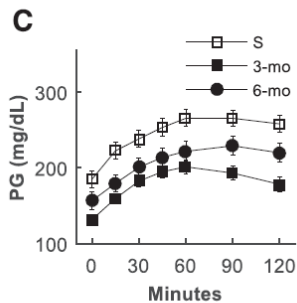
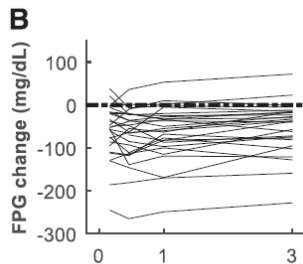




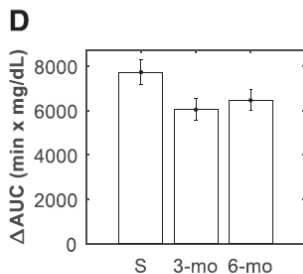
*Glicemia a digiuno*



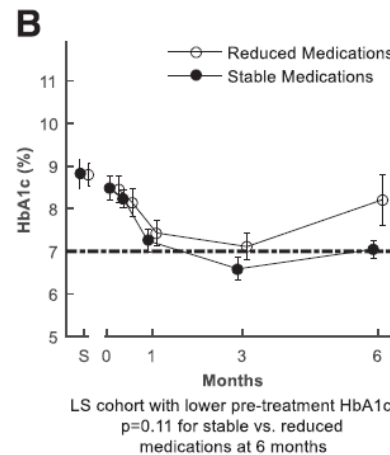
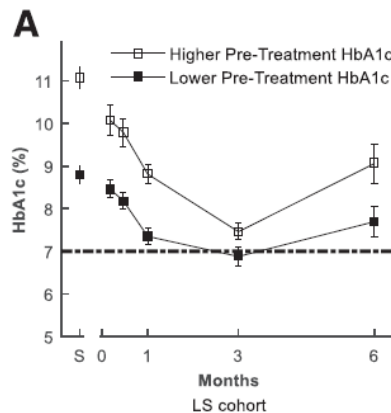
Efficacy cohort;  $p < 0.05$  for LS vs. SS at 1 and 3 months



LS cohort, change from screening;  
For PG(t=0):  $p < 0.001$  at 3-mo,  $p = 0.07$  at 6-mo  
For PG AUC:  $p < 0.001$  at 3-mo,  $p < 0.05$  at 6-mo



LS cohort, change from screening  
 $p < 0.01$  at 3-mo,  $p < 0.05$  at 6-mo



*Glicemia Post-Prandiale*





## Durable metabolic improvements 2 years after duodenal mucosal resurfacing (DMR) in patients with type 2 diabetes (REVITA-1 Study)

Annieke C.G. van Baar<sup>a</sup>, Jacques Devière<sup>b</sup>, David Hopkins<sup>c</sup>, Laurent Crenier<sup>d</sup>, Frits Holleman<sup>e</sup>, Manoel P. Galvão Neto<sup>f</sup>, Pablo Becerra<sup>g</sup>, Paulina Vignolo<sup>g</sup>, Leonardo Rodriguez Grunert<sup>g</sup>, Geltrude Mingrone<sup>h,i</sup>, Guido Costamagna<sup>h,j</sup>, Max Nieuwdorp<sup>k</sup>, Caterina Guidone<sup>l</sup>, Rehan J. Haidry<sup>m</sup>, Bu Hayee<sup>c</sup>, Cormac Magee<sup>m,n</sup>, Juan Carlos Lopez-Talavera<sup>o</sup>, Kelly White<sup>o</sup>, Vijeta Bhamhani<sup>o</sup>, Emily Cozzi<sup>o</sup>, Harith Rajagopalan<sup>o</sup>, Jacques J.G.H.M. Bergman<sup>a,\*</sup>



- Riduzione significativa dell'HbA1c - sostenuta nel F/U
- >50% dei pz. ha mantenuto o ridotto il regime terapeutico
- Miglioramento ALT, Colesterolo LDL, HDL, Trigliceridi
- Assenza Effetti Avversi

### ABSTRACT

**Aims:** Duodenal mucosal resurfacing (DMR) is an endoscopic procedure developed to improve metabolic parameters and restore insulin sensitivity in patients with diabetes. Here we report long-term DMR safety and efficacy from the REVITA-1 study.

**Materials and Methods:** REVITA-1 was a prospective, single-arm, open-label, multicenter study of DMR feasibility, safety, and efficacy in patients with type 2 diabetes (hemoglobin A1c [HbA1c] of 7.5–10.0% (58–86 mmol/mol)) on oral medication. Safety and glycemic (HbA1c), hepatic (alanine aminotransferase [ALT]), and cardiovascular (HDL, triglyceride [TG]/HDL ratio) efficacy parameters were assessed (*P* values presented for LS mean change). **Results:** Mean  $\pm$  SD HbA1c levels reduced from  $8.5 \pm 0.7\%$  ( $69.1 \pm 7.1$  mmol/mol) at baseline (*N* = 34) to  $7.5 \pm 0.8\%$  ( $58.9 \pm 8.8$  mmol/mol) at 6 months (*P* < 0.001); and this reduction was sustained through 24 months post-DMR ( $7.5 \pm 1.1\%$  [ $59.0 \pm 12.3$  mmol/mol], *P* < 0.001) while in greater than 50% of patients, glucose-lowering therapy was reduced or unchanged. ALT decreased from  $38.1 \pm 21.1$  U/L at baseline to  $32.5 \pm 22.1$  U/L at 24 months (*P* = 0.048). HDL and TG/HDL improved during 24-months of follow-up. No device- or procedure-related serious adverse events, unanticipated device effects, or hypoglycemic events were noted between 12 and 24 months post-DMR.

**Conclusions:** DMR is associated with durable improvements in insulin sensitivity and multiple downstream metabolic parameters through 24 months post-treatment in type 2 diabetes.

Clinical trial reg. no. NCT02413567, clinicaltrials.gov.

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# THE SHOWSTOPPER OBESITY DRUGS THAT HAVE STUNNED RESEARCHERS

| Nature | Vol 613 | 5 January 2023

- In 2000s the US FDA began approving drugs that mimicked GLP-1 as type 2 diabetes treatment
- By the mid-2010s one such drug, liraglutide, was capable of eliciting a loss in body weight of about 8% on average (5% more than placebo) – clinically relevant but not astonishing
- In early 2021 scientists were wowed by a phase III clinical trial investigating a new drug of the same type – semaglutide: this is a modified version of liraglutide, acts on the same pathways, but remains intact and active in the body for longer
- Those receiving weekly injection of semaglutide lost, on average, 14,9% of their body weight; those who received a placebo lost 2.4% on average



- Il più grave pericolo per la salute pubblica nel mondo moderno (problema globale)
- Costi totali (diretti ed indiretti): trillions
- «Present trend is not sustainable unless a magic cure is found (unlikely) or concerted global governmental/societal effort are made to change the lifestyle that is promoting it (high calorie-low fiber diet - fast food – and decrease in physical activity)»

*(Saklayen MG 2018)*

**MISSION: IMPOSSIBLE**

POPULATION







The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

*NEJM 2021; Mar 25;284(12):1113.1124*

## A Placebo-Controlled Trial of Subcutaneous Semaglutide in Nonalcoholic Steatohepatitis

P.N. Newsome, K. Buchholtz, K. Cusi, M. Linder, T. Okanoue, V. Ratziu, A.J. Sanyal, A.-S. Sejling, and S.A. Harrison, for the NN9931-4296 Investigators\*

### Conclusions:

This phase 2 trial involving patients with NASH showed that treatment with semaglutide resulted in a significantly higher percentage of patients with NASH resolution than placebo. However, the trial did not show a significant between-group difference in the percentage of patients with an improvement in fibrosis stage.





## CPG 2023 – Use of Available Medications

### Guidance Statements:

- There are currently no FDA-approved medications for the treatment of NAFLD, but drugs approved to treat associated comorbidities with potential benefit in NAFLD may be considered in the appropriate setting
- Semaglutide can be considered for its approved indications (T2DM/obesity) in patients with NASH as it confers cardiovascular benefit and improves NASH
- Pioglitazone improves NASH and can be considered for patients with NASH and T2DM
- Vitamin E can be considered in selected individuals as it improves NASH in some patients without diabetes
- Available data on semaglutide, pioglitazone, and Vitamin E do not demonstrate an antifibrotic benefit, and none has been carefully studied in cirrhotics
- Metformin, UDCA, statins, silimarin are well studied in NASH and should not be used as a treatment of NASH as they do not offer a meaningful histologic benefit



con il patrocinio di



**PROGRESSI E NUOVE FRONTIERE IN**  
**GASTROENTEROLOGIA**  
**ED ENDOSCOPIA DIGESTIVA**



**BELLUNO**  
15-16 GIUGNO 2023

# Steatosi e Steato-Fibrosi Epatica

*Cosa c'è all'orizzonte?*

Paolo Montalto





con il patrocinio di



Associazione Italiana  
Gastroenterologia e  
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**PROGRESSI E NUOVE FRONTIERE IN**  
**GASTROENTEROLOGIA**  
**ED ENDOSCOPIA DIGESTIVA**



**BELLUNO**  
15-16 GIUGNO 2023

# Steatosi e Steato-Fibrosi Epatica

*Cosa c'è all'orizzonte?*

