"Transgenerational Transmission of Obesity and Liver Disease:

The Flood is coming!

Jude A. Oben MDPhD, FRCP, AGAF, FAASLD;
Sigma Xi Fellow; Experimental Hepatologist, KCL;
Consultant Gastro-Hepatologist, GSTT

Oui!

Si,Sim!

YES!!

对 – duì

是 | shì

What's in a name?

Is it?

i) NAFLD

ii) MAFLD

iii) DLD

iv) Who gives a %^&$#!?

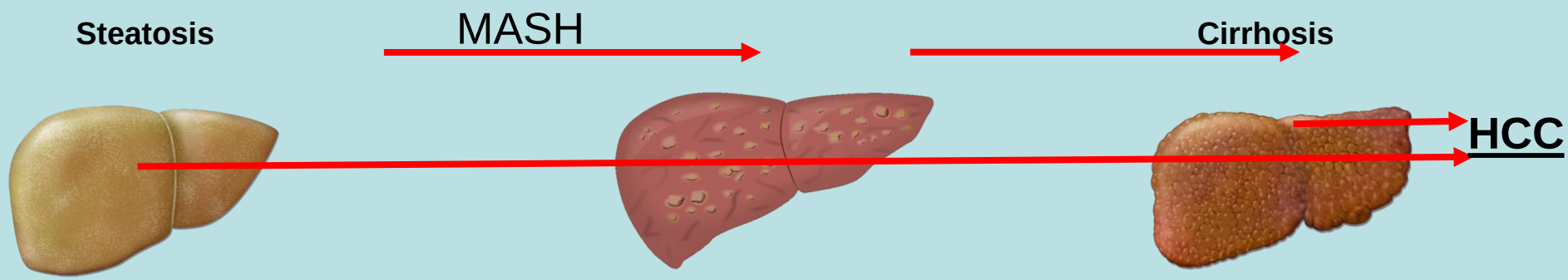
Do we care, Should we care?

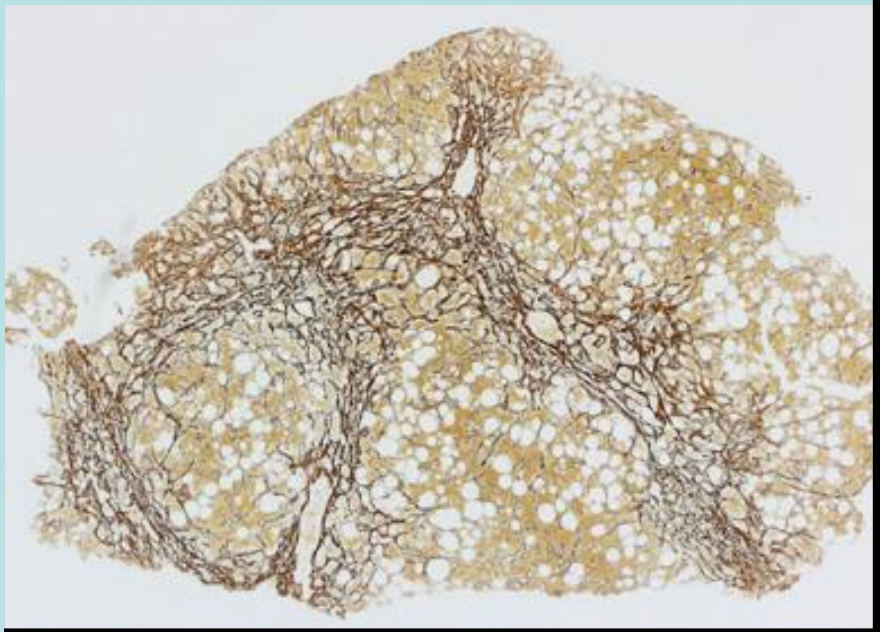
What is NAFLD/MASLD or DLD?

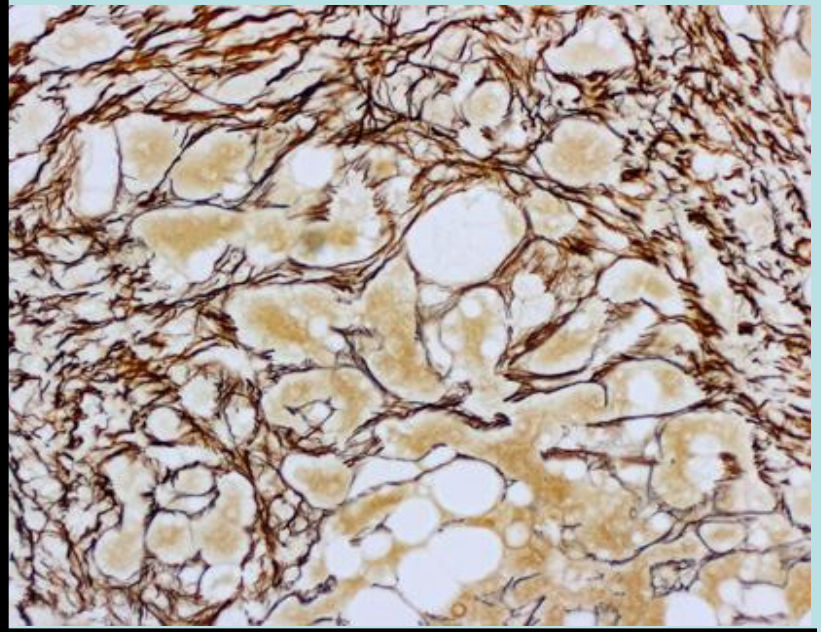
- Metabolic Dysfunction-Associated Steatotic Liver Disease **or DLD**
  - Ranges from steatosis to MASH- Cirrhosis and HCC

Since Steatosis to HCC: Not simple!!

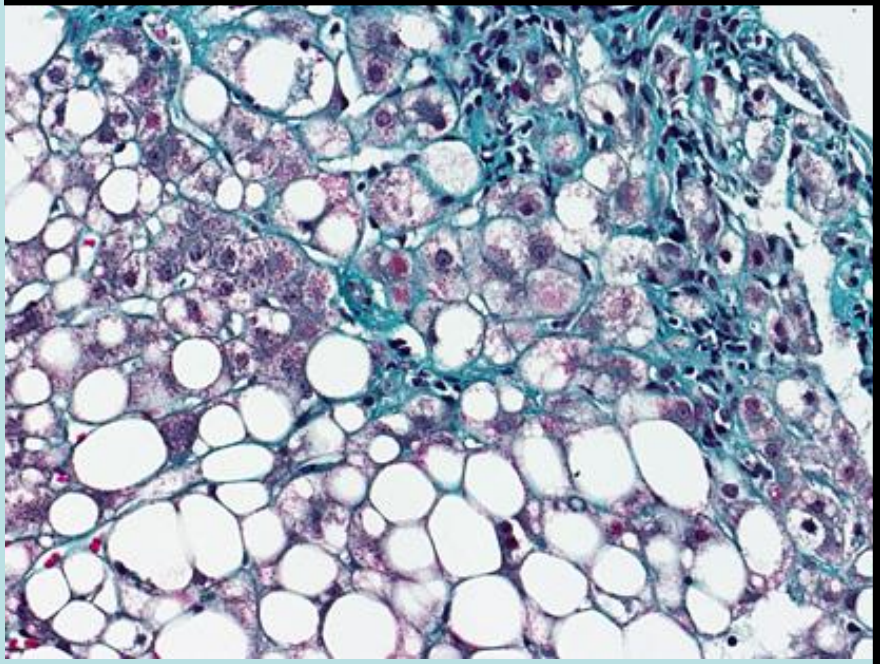
Steatosis	Steatosis/inflammation	Fibrosis	Cirrhosis

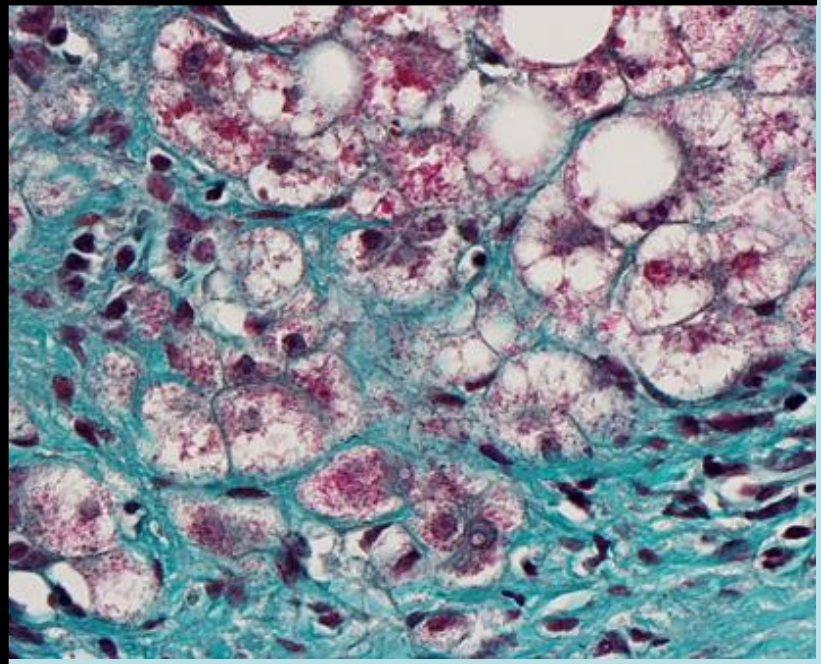


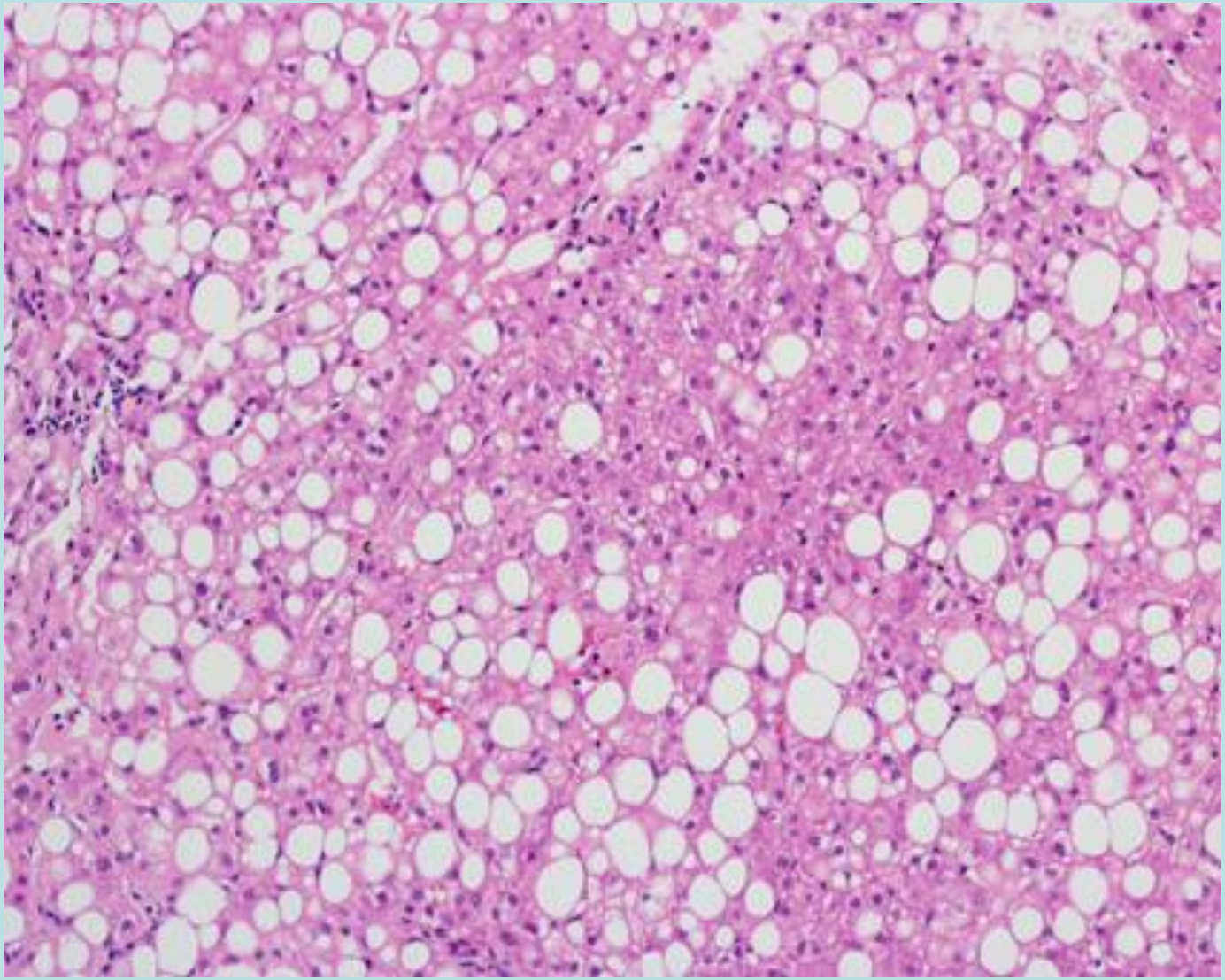




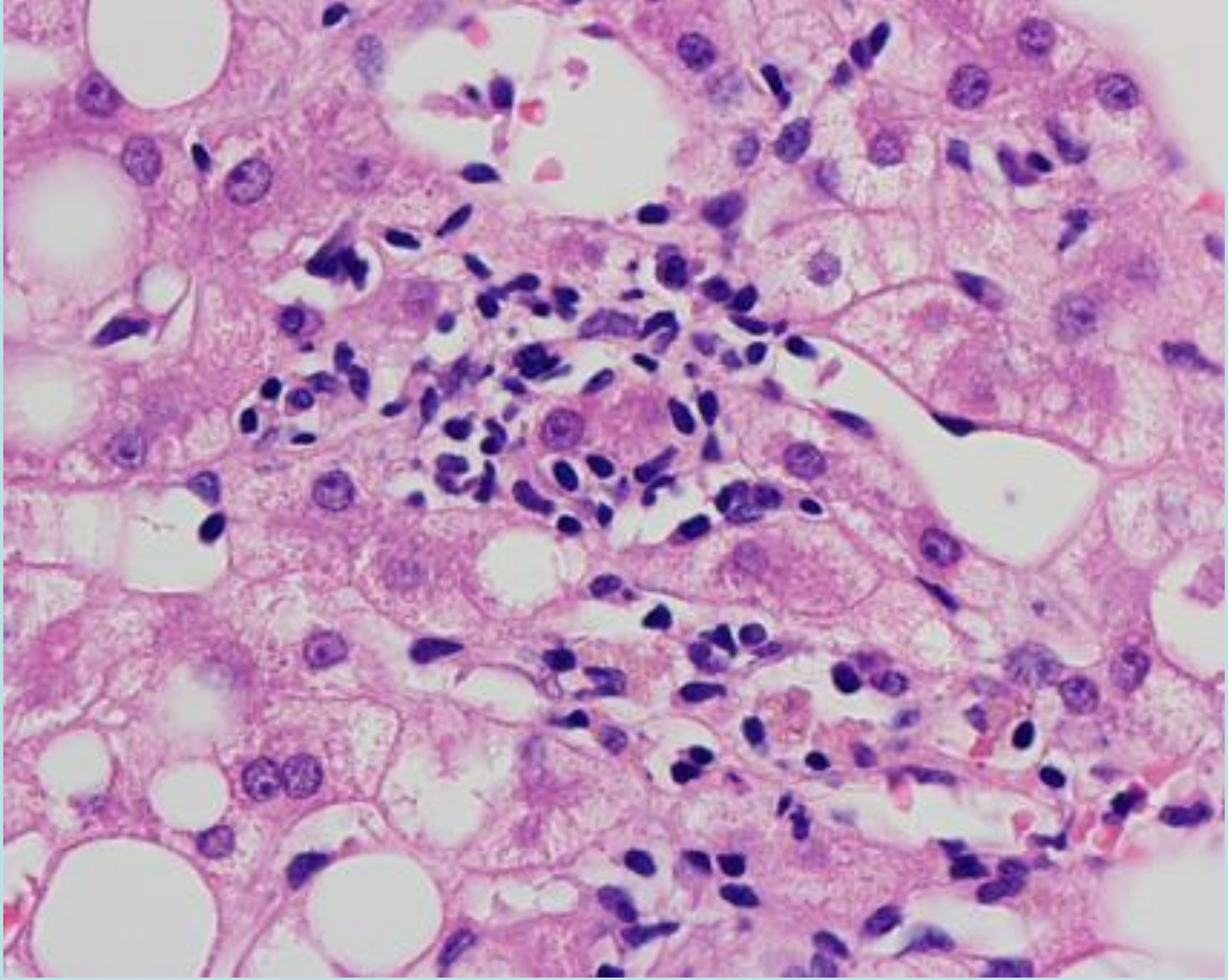
Cirrhosis







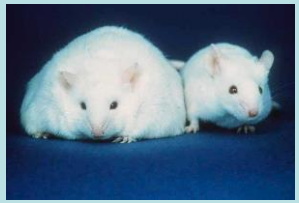
Macrovesicular steatosis.

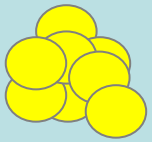


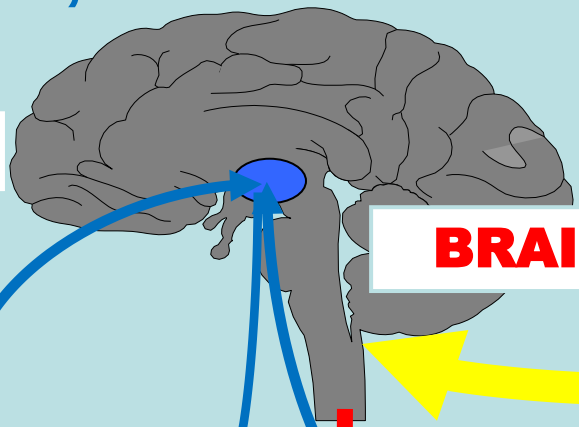
Lobular inflammation,

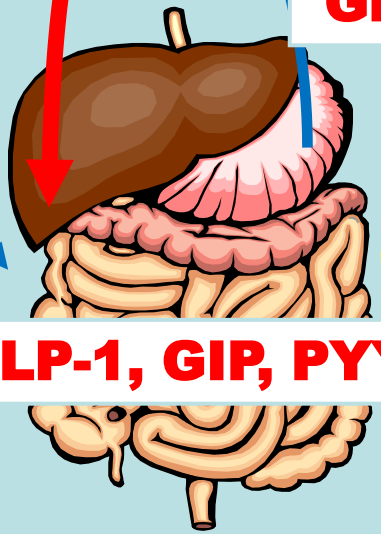
Ballooning.

GUT HORMONES AND APPETITE REGULATION: THE GOOD, The Bad and The Ugly?









Hypothalamus

BRAINSTEM

Leptin, Insulin

AFFERENTS:

VAGAL

Brain-Gut - Microbiota

Efferents

Ghrelin

GLP-1, GIP, PYY

DLD…Are we making progress:

Yes, LOTS!!

Translational Science: ***Metabolomics,*** **Microbiota, Mechanisms.**

Therapeutics: Metabolic Endoscopy – IGB, ESG

Pharmaceutics: GLP-1, GIP Ags etc

Case

Mr ZK 77♂, “lean”, Retired tailor.
Presented in the ED with Melaena.

Background

No UGI complaints, No NSAIDS,
No LDRF, No Etoh.
Allegedly Previously F&W

Diagnosis: MASLD/DLD

77♂ Cirrhotic:

Decompensated

What to do?

- **DM, 43 ♂, *motor cycle courier***

Problem:

- **Abnormal LFT's - ↑ALT**

- ***Background:***

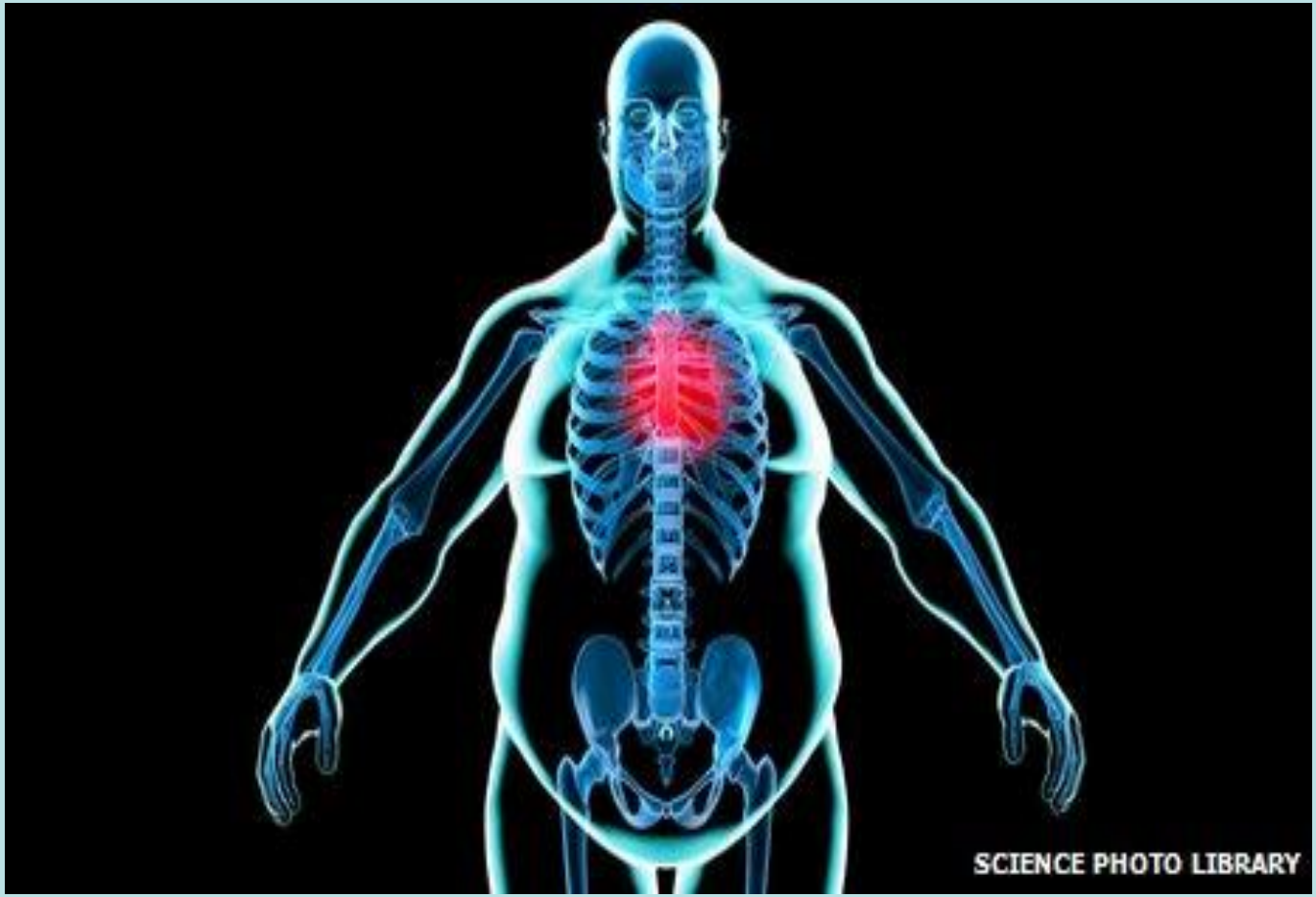
- **Obesity – Wt 150kg, BMI 47kg/m^2, WC – 125cm**
- **Hypertensive**

- **Daily Cannabis smoker,** 3-4 jnts/day

- **Ix**
- Confirmed deranged LFTs, -ve Liver Database –ve
- US – Fatty infiltration
- **Liver Biopsy – "Bridging Fibrosis" F3/4 Fibrosis**

So…..,

“It’s not in your bones…..!!”



But more…….

Or…...

“Dog walking – a modern approach”

Few people are aware there is a clear link between obesity and liver cirrhosis

Q: What are the underlying causes and mechanisms of DLD?

Obesity – T2DM – Insulin Resistance

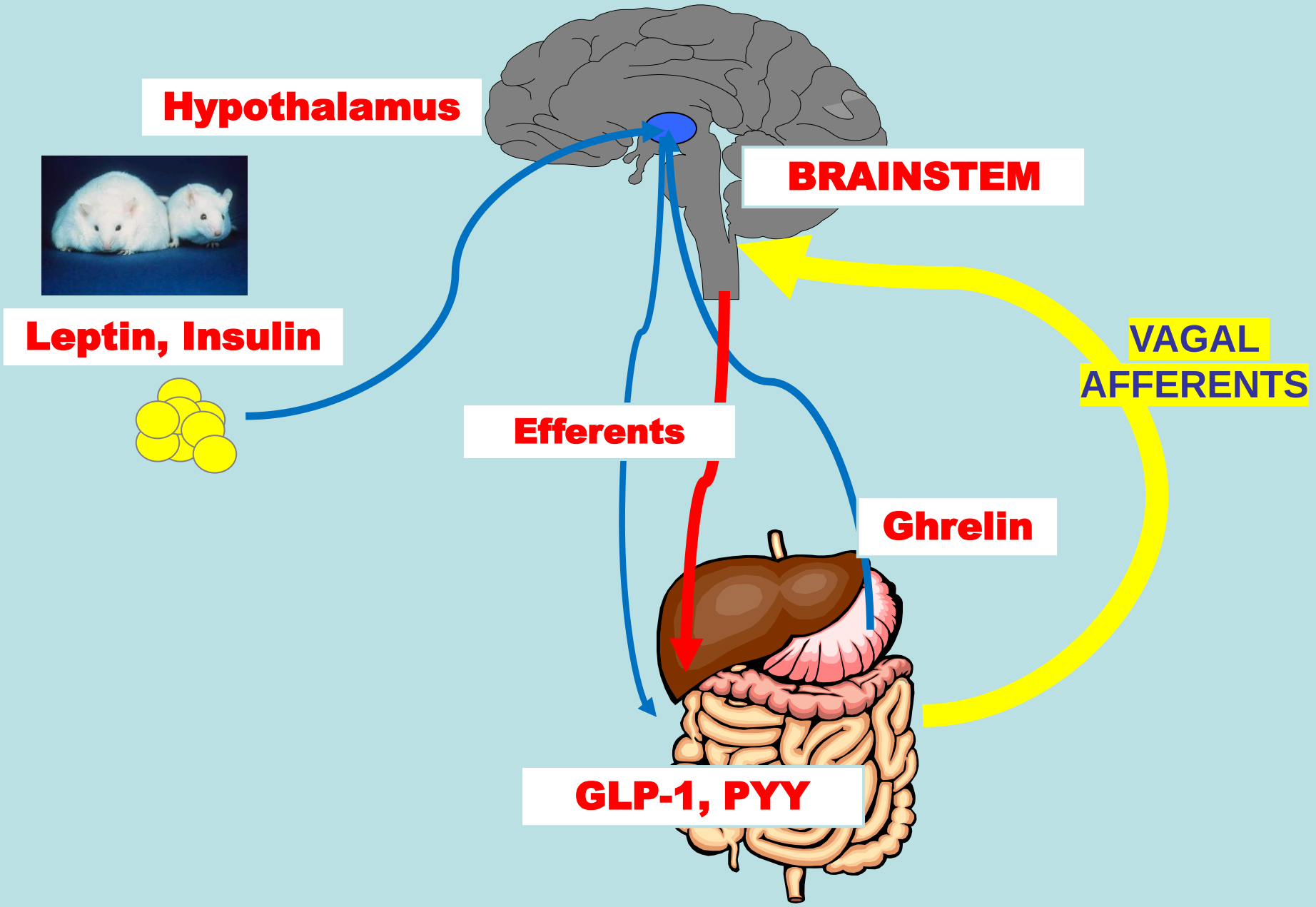
Genetics

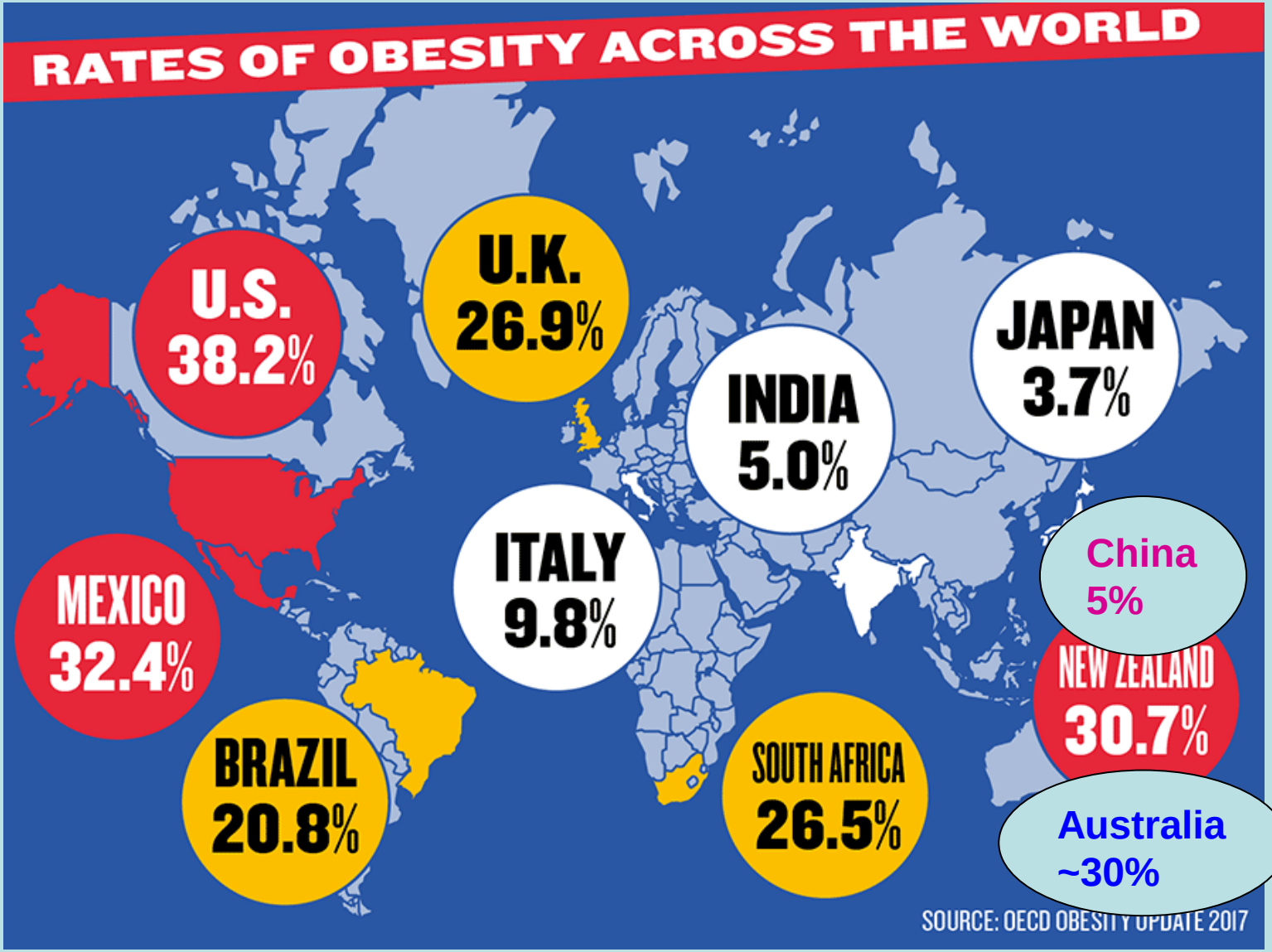
Epigenetics

Microbiota

Hypothalamic Control

GUT HORMONES AND APPETITE REGULATION: THE GOOD?

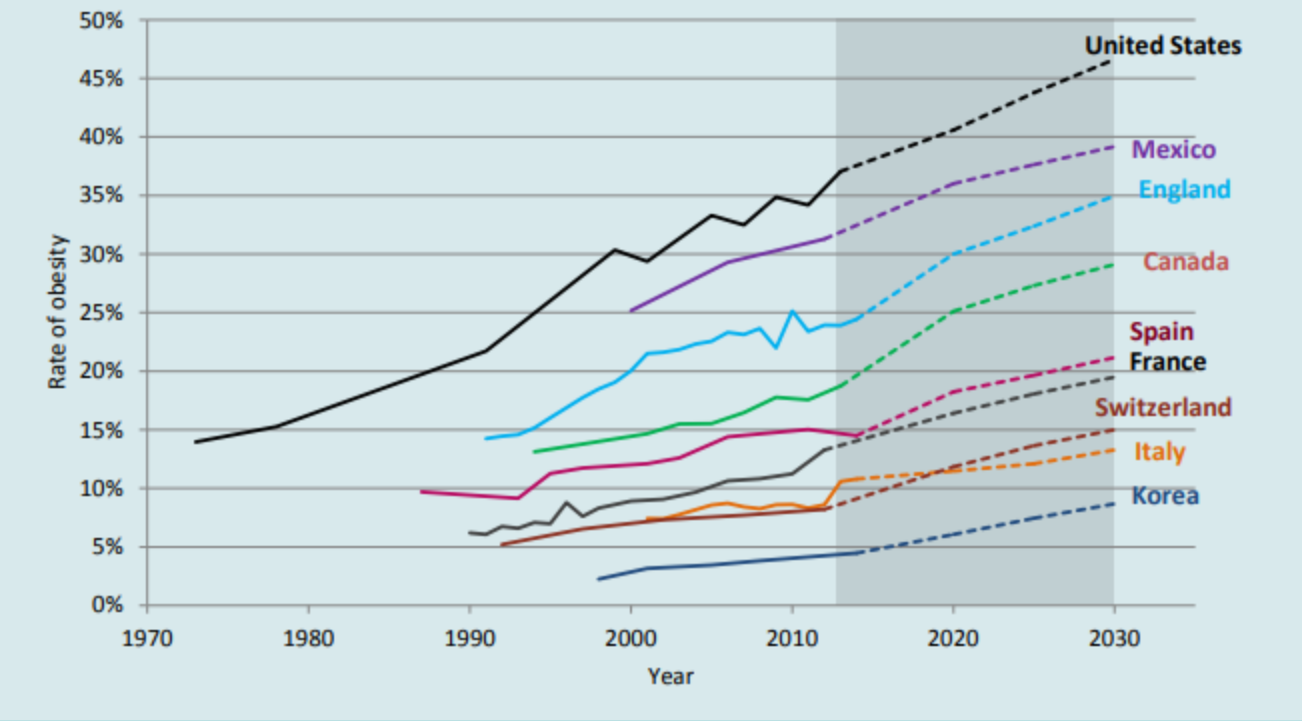




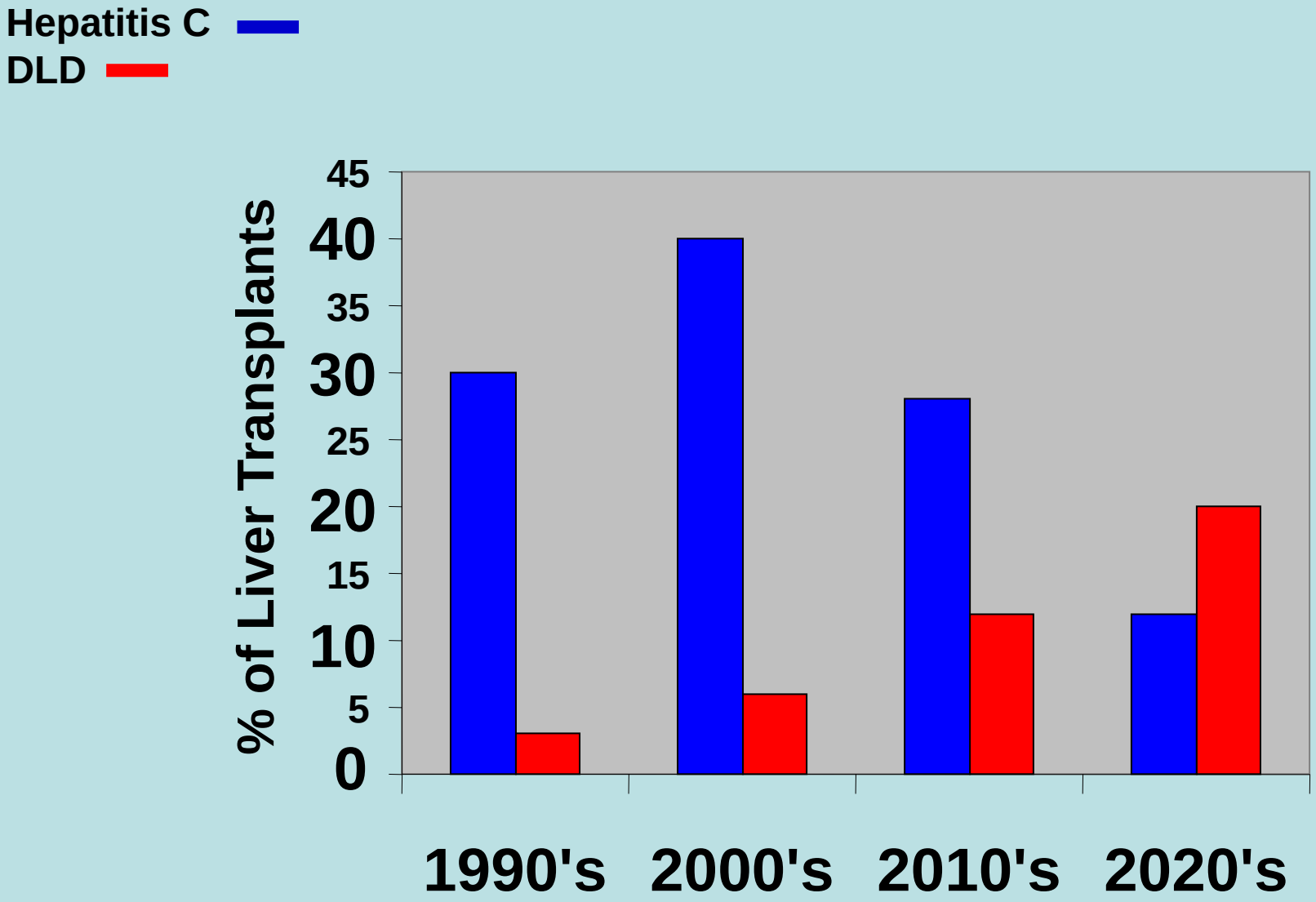
World Population 8bn:

India = 1.2; China 1.4; USA 0.33; Russia 0.14; Mexico 0.13; Brazil 0.21

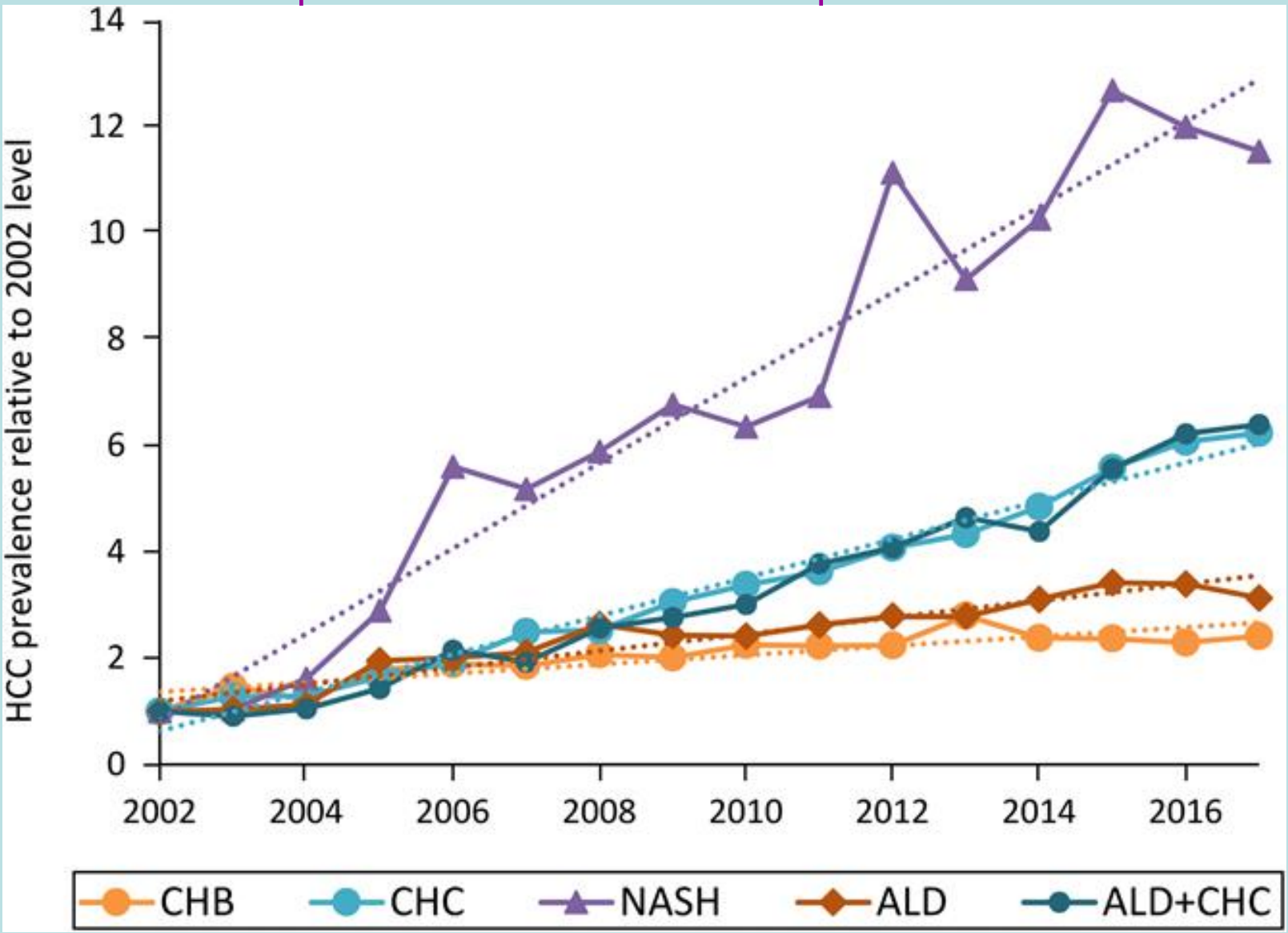
Projected Obesity Rates upto 2030



Projected numbers of liver transplants for Hepatitis C and DLD/MASLD

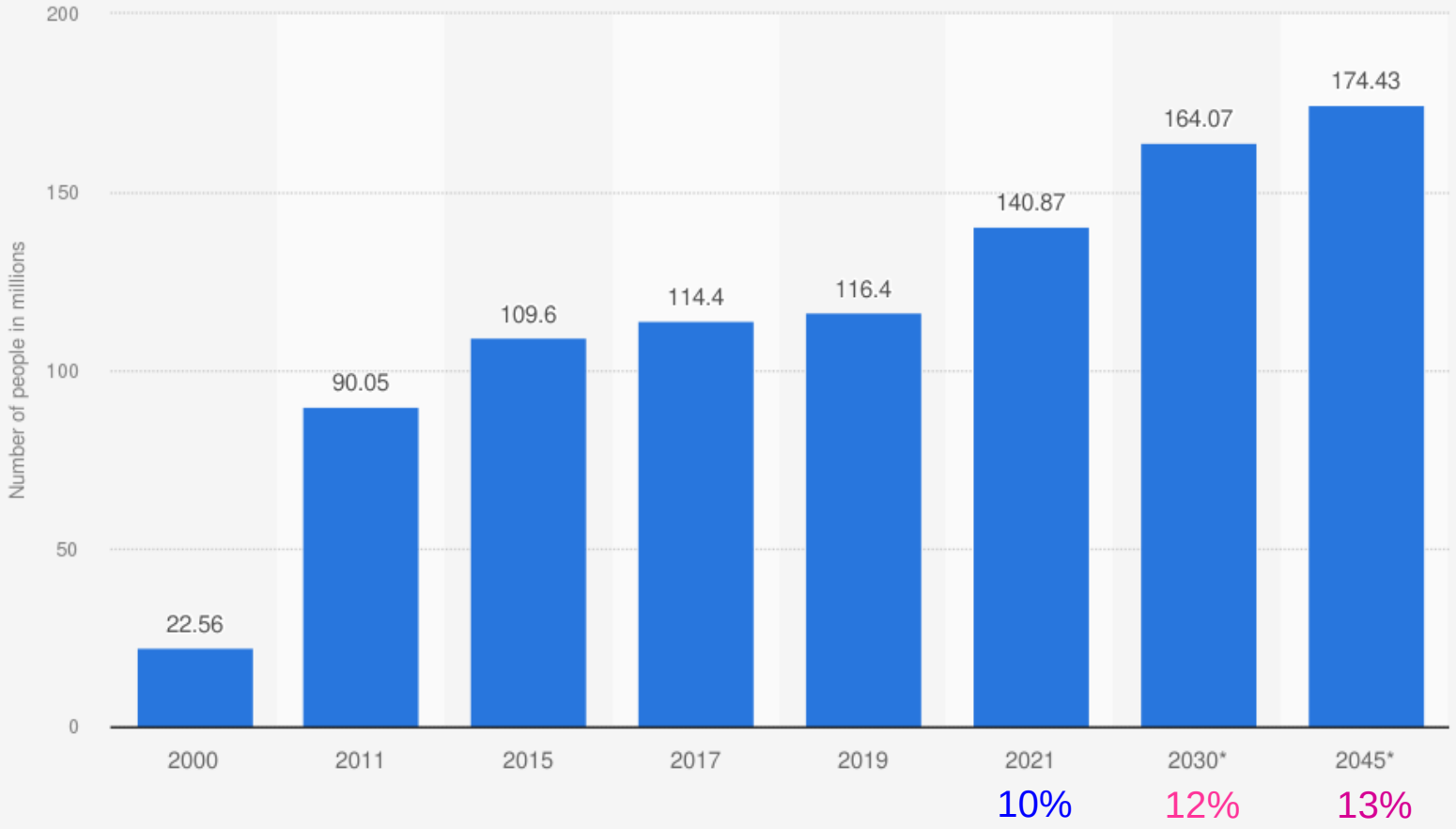


DLD/MASH is the most rapidly growing cause of HCC among US patients listed for liver transplantation.



Prevalence of HCC in waiting list candidates by aetiology relative to that in 2002. *Dotted lines* represent linear trends. Younossi et al, 2019, Hepatology 69, 2672-2682

Estimated number of people with diabetes mellitus in China from 2000 to 2021 with forecasts until 2045 (in millions)



Source
International Diabetes Federation
© Statista 2023

Additional Information:
China; 2000 to 2021; 20-79 years

Prevalence of Liver Fibrosis in T2DM in Primary Care: Unlinked Anonymous Analysis with HbA1c

Fibrosis-4 (FIB-4) Index for Liver Fibrosis	Number of T2DM patients with stage of Liver Fibrosis (%)
Total Number of Patient numbers = 582	
<1.45 **F0/F1**	**338 (58%)**
≥1.45–3.25 **F2, F3**	**211 (36%)**
>3.25 **F4**	**33 (6%)**

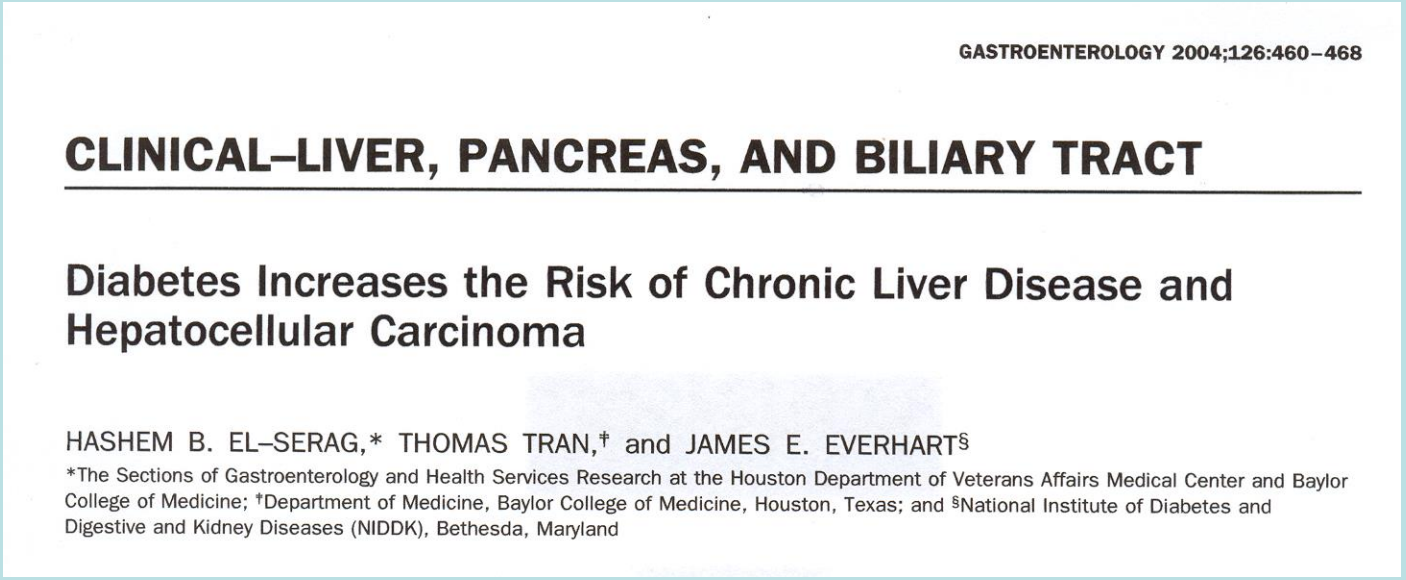
Alarming levels of severe liver fibrosis and cirrhosis in type 2 diabetes mellitus patients from primary care–an unlinked anonymous analysis Yong H, Brady S, Wierzbicki A & Oben ; Gut 72 (Suppl 3), A26-A27

- **American Diabetes Association: – June ‘23:**

- **Screen All Patients With Type 2 Diabetes for DLD!**

- **Fib-4: as a primary assessment of Diabetic liver disease.**

T2DM “through NAFLD” causes primary liver cancer



GASTROENTEROLOGY 2004;126:460–468

CLINICAL–LIVER, PANCREAS, AND BILIARY TRACT

Diabetes Increases the Risk of Chronic Liver Disease and Hepatocellular Carcinoma

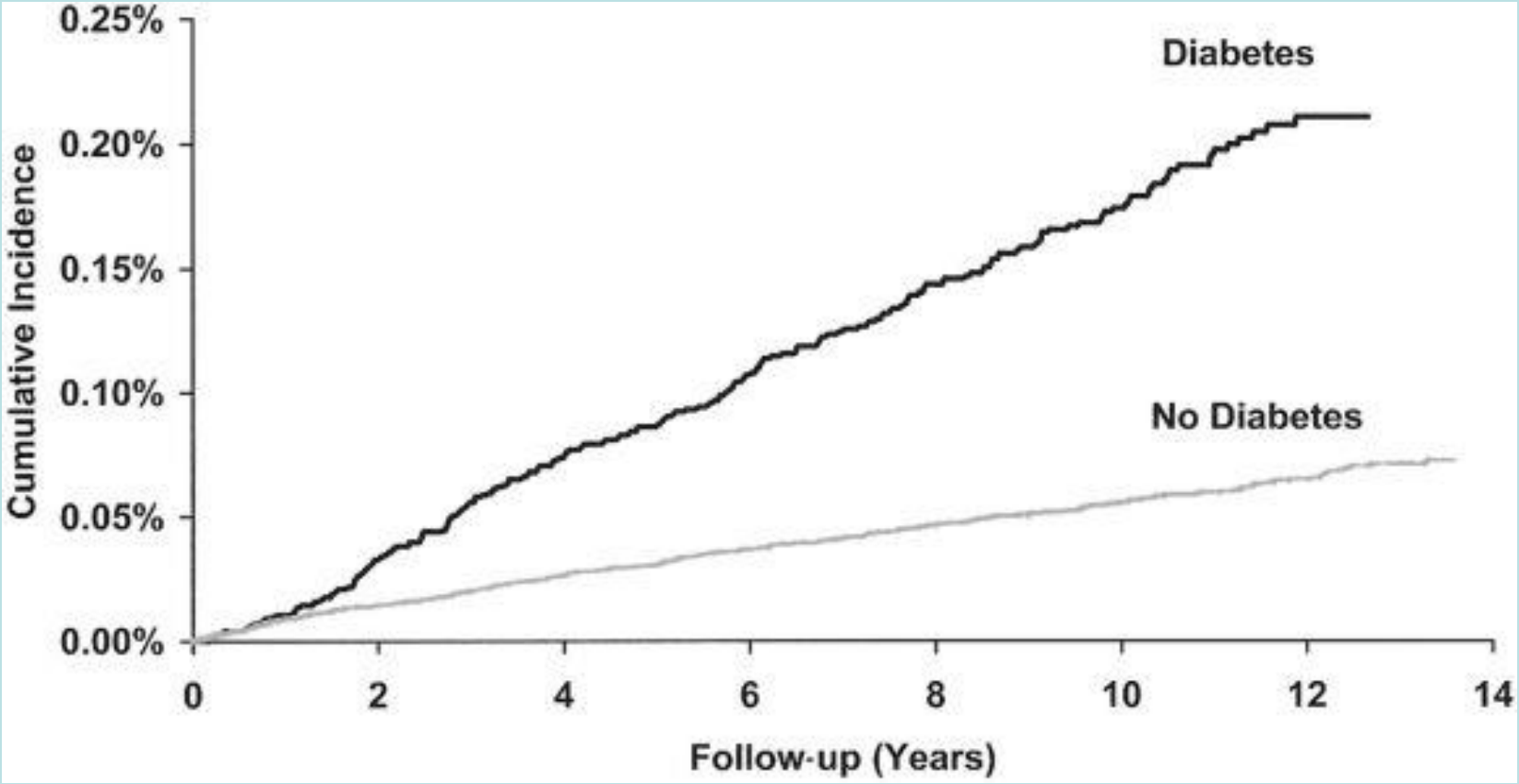
HASHEM B. EL–SERAG,* THOMAS TRAN,† and JAMES E. EVERHART§

*The Sections of Gastroenterology and Health Services Research at the Houston Department of Veterans Affairs Medical Center and Baylor College of Medicine; †Department of Medicine, Baylor College of Medicine, Houston, Texas; and §National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), Bethesda, Maryland

Gastroenterology Feb ‘04

1,000,000 patients study

Cumulative incidence of HCC

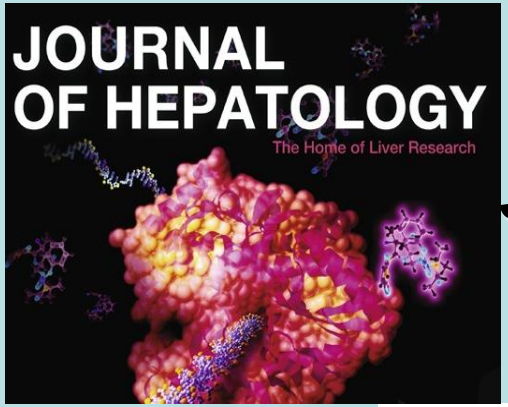


1,000,000 patients:
HCC rates in T2DM > Controls

Any insights into rising trend?

Yes: Transgenerational Transmission

Maternal OBESITY is involved in programming the development of NAFLD



June 2010, Vol 52, p913-920

Editorial p786

Research Article

EASL JOURNAL OF HEPATOLOGY

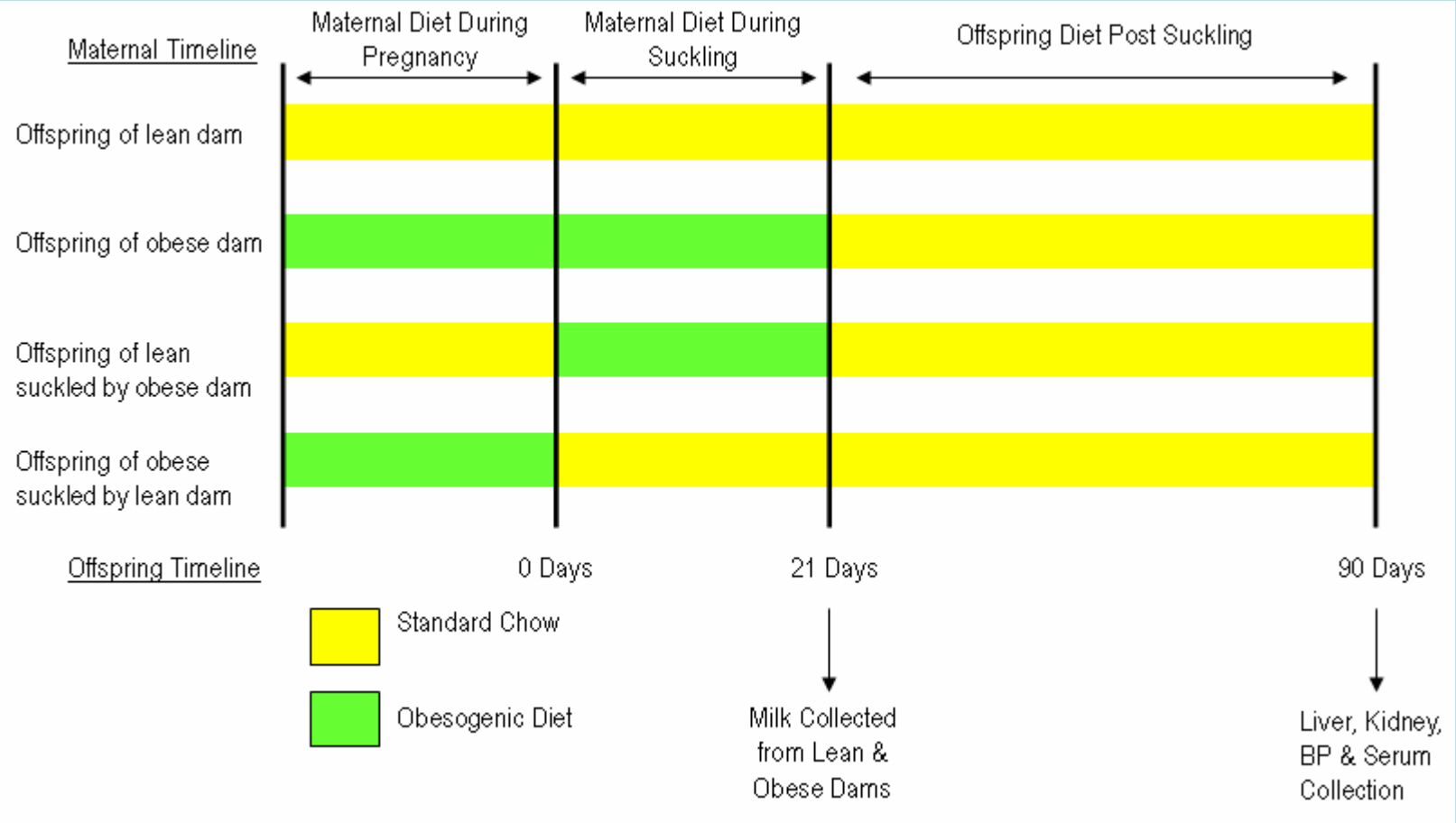
Maternal obesity during pregnancy and lactation programs the development of offspring non-alcoholic fatty liver disease in mice☆

Jude A. Oben[1,2,*], Angelina Mouralidarane[1,3], Anne-Maj Samuelsson[3], Phillippa J. Matthews[3], Maelle L. Morgan[1], Chad Mckee[1], Junpei Soeda[1], Denise S. Fernandez-Twinn[4], Malgorzata S. Martin-Gronert[4], Susan E. Ozanne[4], Barbara Sigala[1], Marco Novelli[5], Lucilla Poston[3], Paul D. Taylor[3]

[1]*University College London, Centre for Hepatology, Royal Free Hospital, London, UK;* [2]*Guy's and St. Thomas' Hospital, Department of Gastroenterology, London, UK;* [3]*King's College London, Division of Reproduction & Endocrinology, London, UK;* [4]*Metabolic Research Laboratories, University of Cambridge, Institute of Metabolic Science, Cambridge, UK;* [5]*University College London, Department of Pathology, London, UK*

See Editorial, pages 786–787

Cross-Fostering Breeding Protocol



Food intake increased in offsprings of obese suckled by an obese dam

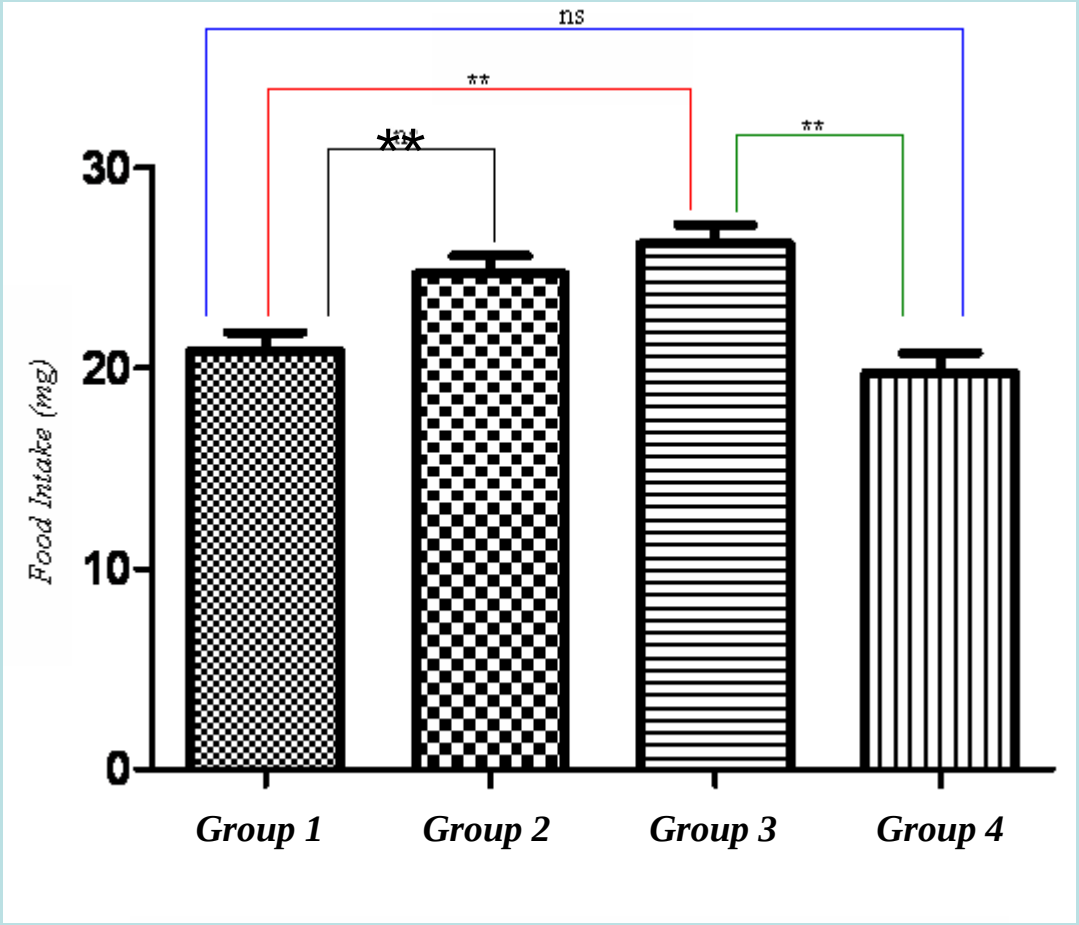
Key

Group 1: Offspring of lean suckled by lean dam

Group 2: Offspring of obese suckled by obese dam

Group 3: Offspring of lean suckled by obese dam

Group 4: Offspring of obese suckled by lean dam



Food Intake Measurements at 3 Months Postpartum:

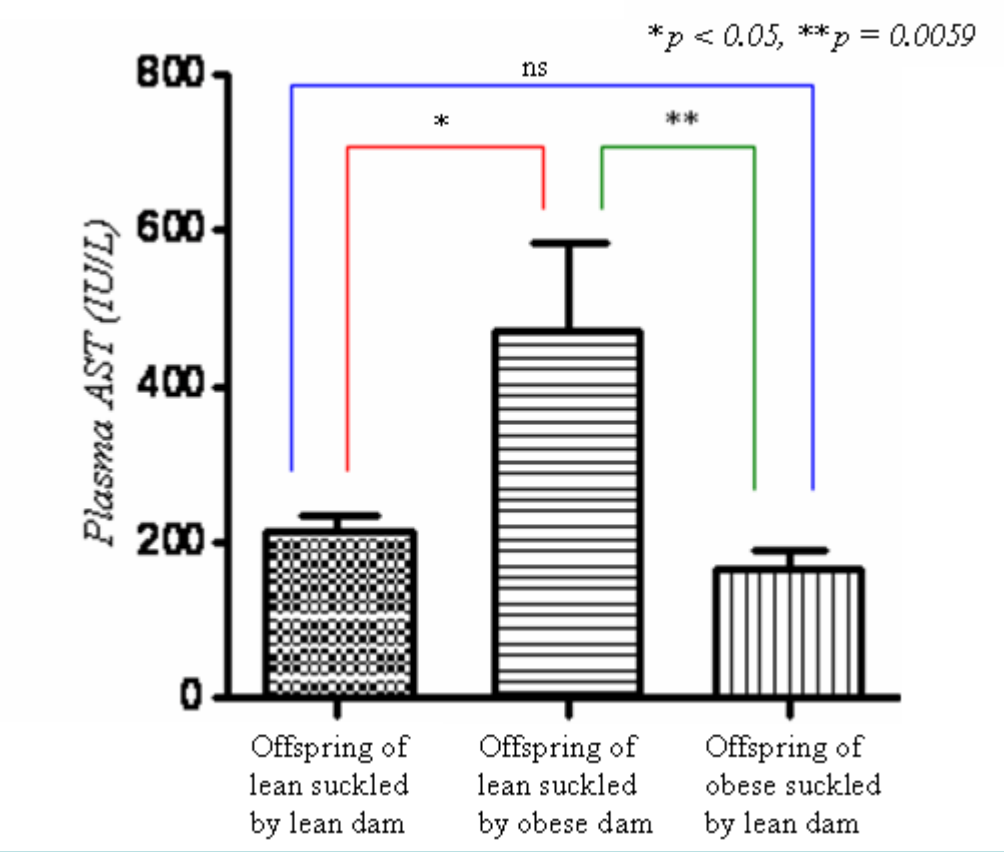
Group 1 v. Group 2 – Group 2 significantly greater p<0.001

*Group 1 v. Group 3 – Group 3 significantly greater, ** p < 0.001*

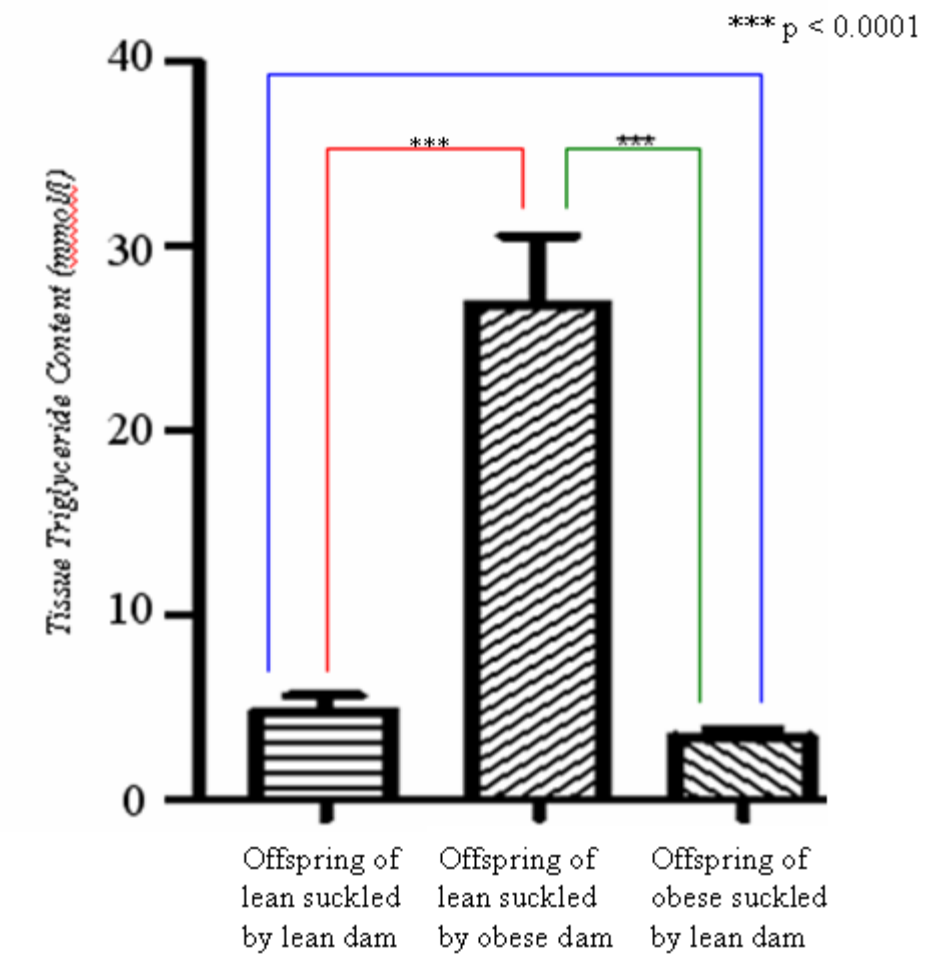
Group 1 v. Group 4 – not significant

*Group 3 v. Group 4 – Group 3 significantly greater, ** pP < 0.001.*

Plasma AST increased in offsprings of lean suckled by an obese dam



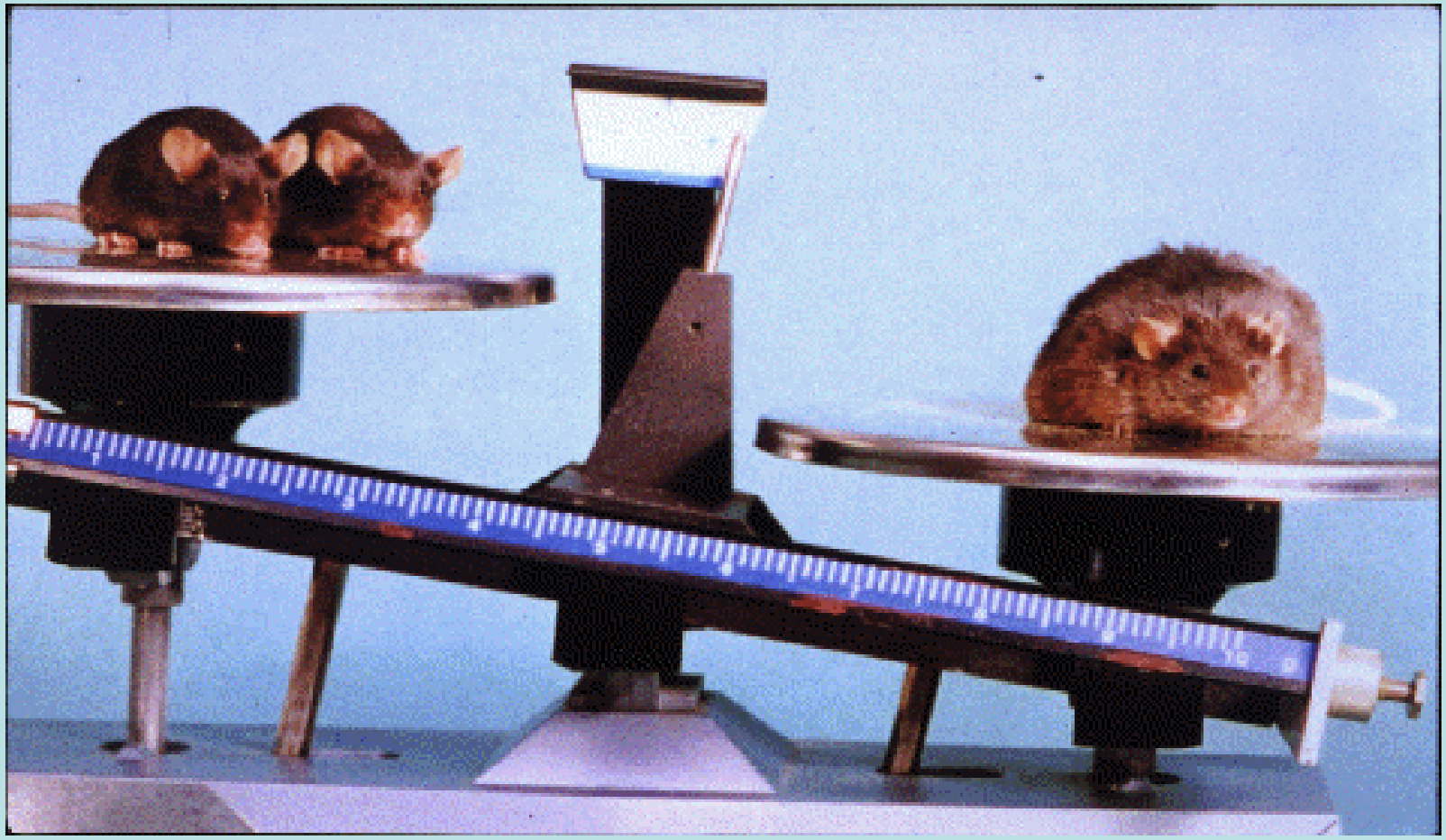
Liver tissue triglyceride increased in offsprings of lean suckled by obese dam



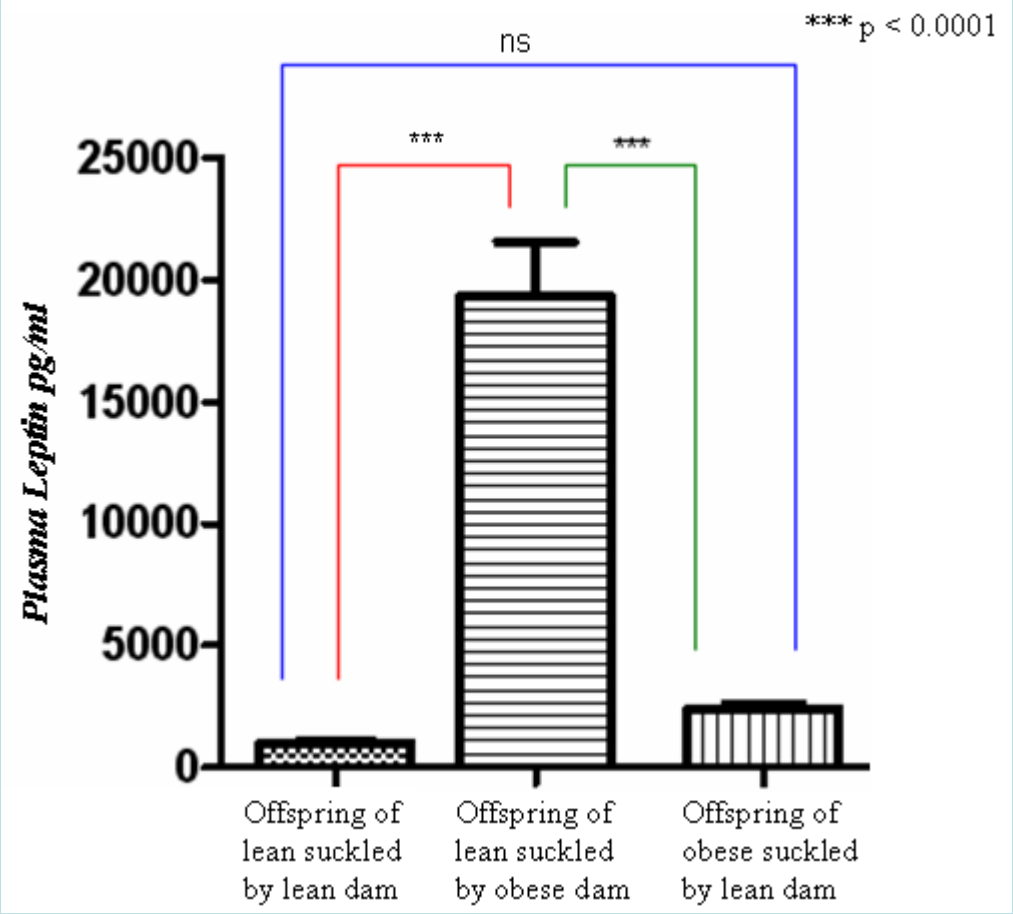
Mechanistically?

Lean

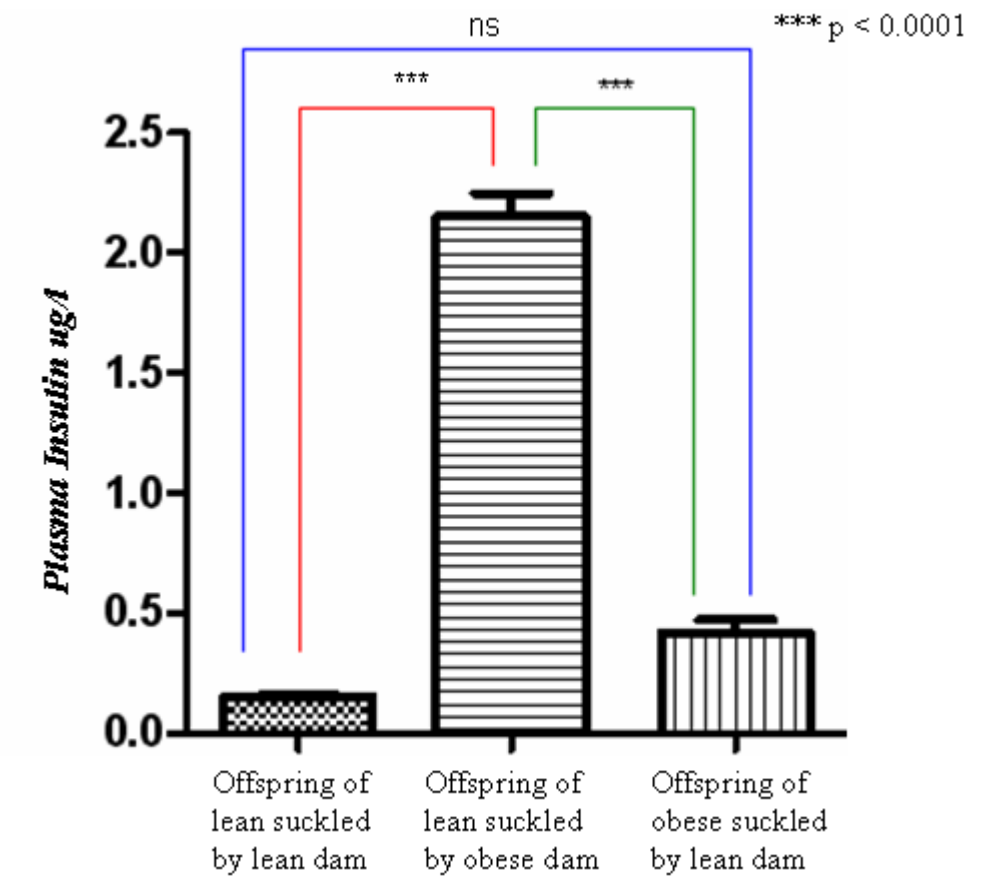
ob/ob – No leptin



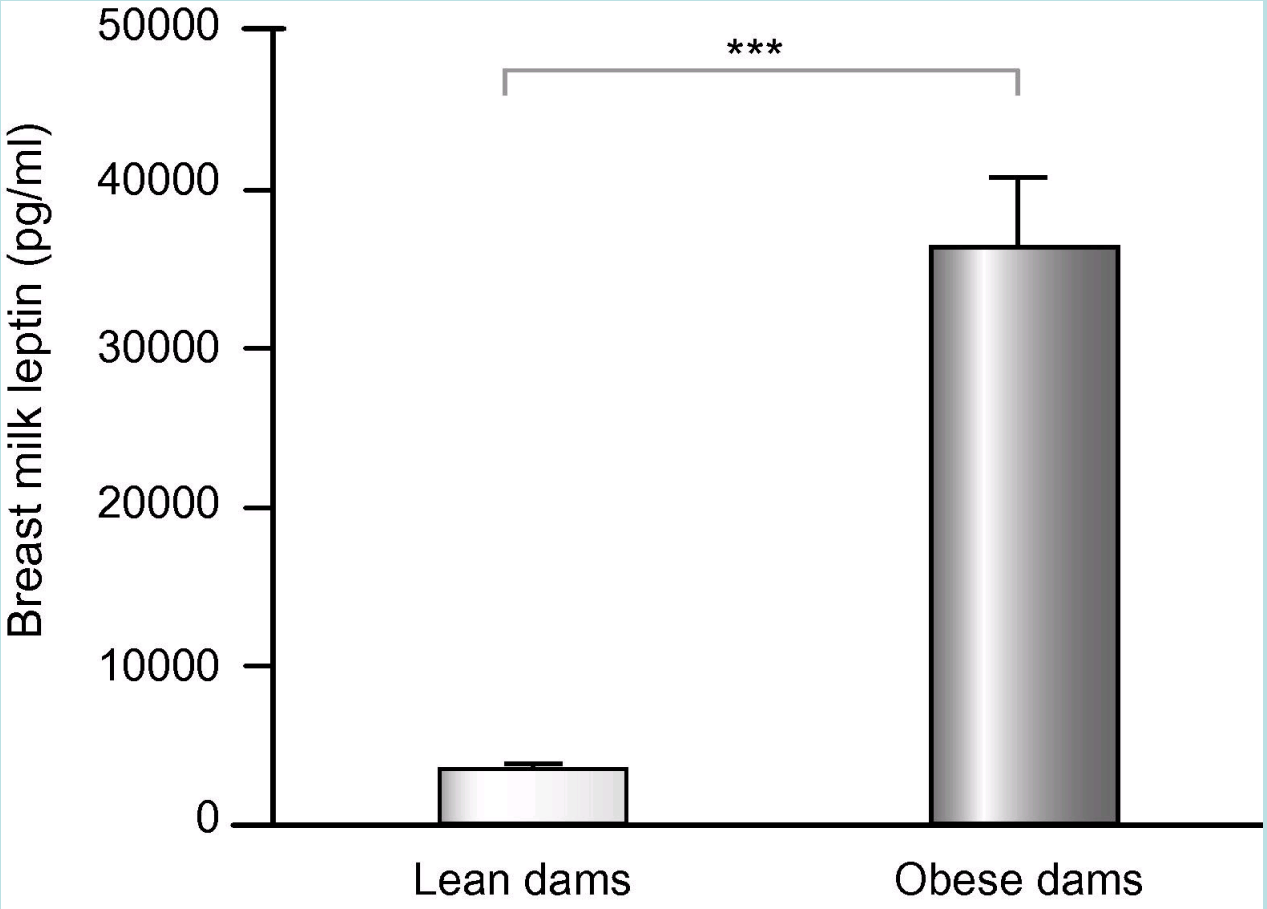
Plasma Leptin increased in offspring of lean suckled by an obese dam



Plasma Insulin increased in offspring of lean suckled by an obese dam



Breast Milk Leptin



Is it really just leptin - TBD!

To confirm involvement of DP in NAFLD: new more physiologically relevant model

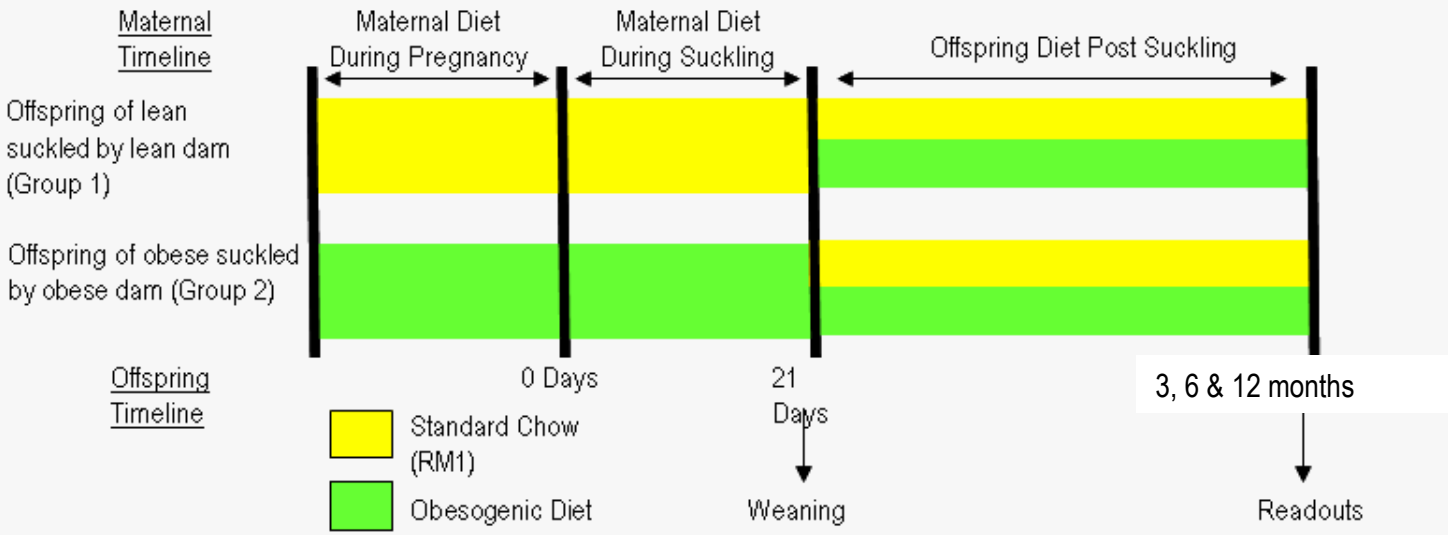
Maternal obesity programs offspring non-alcoholic fatty liver disease by innate immune dysfunction in mice.

Mouralidarane…….Oben.

Hepatology, 58, 128; Plus editorial pp4-5

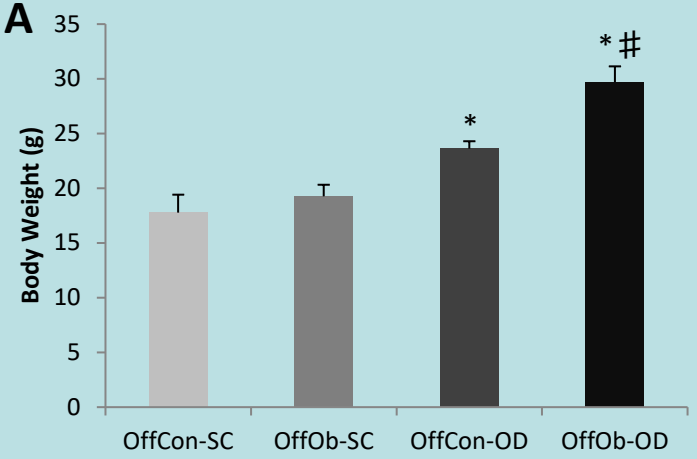
Aim

Programming Model



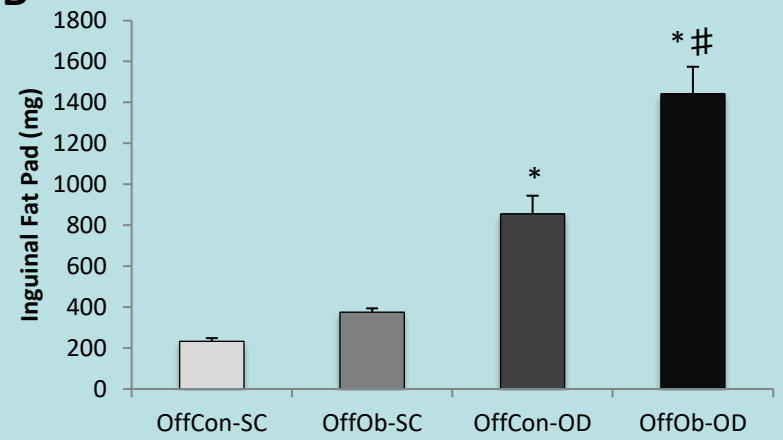
Statistically……

A



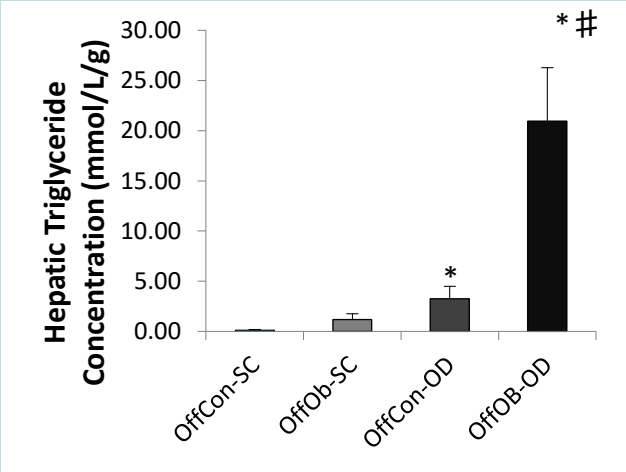
Source of Variation	% of Variation	P value
Interaction	7.16	0.0082
Maternal	13.83	0.0092
Post-weaning	64.00	< 0.0001

B



Source of Variation	% of Variation	P value
Interaction	9.27	0.0032
Maternal	5.24	0.0175
Post-weaning	72.65	< 0.0001

C



Source of Variation	% of Variation	P value
Interaction	21.61	0.0053
Maternal	27.48	0.0025
Post-weaning	41.08	0.0006

Obese phenotype ↑↑ in Offspring of Obese Dams weaned onto Obesogenic diet

Is it of relevance to humans?

Developmental Programming & NAFLD
- human evidence??

HEPATOLOGY
Official Journal of the American Association for the Study of Liver Diseases

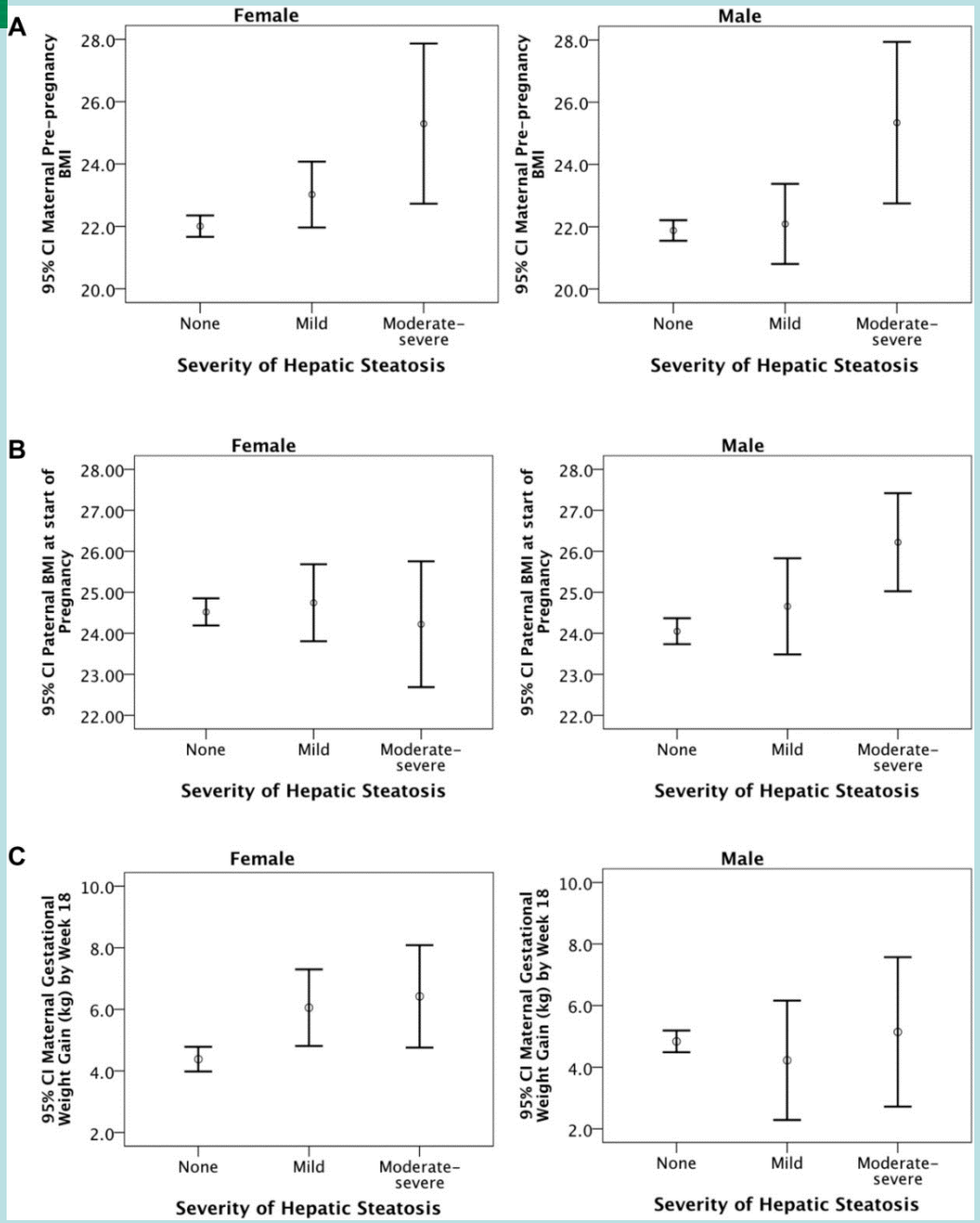
2018

Ayonride et al (2018); Sex differences between parental pregnancy characteristics and non-alcoholic fatty liver disease in adolescents. Hepatology 67:108-122. doi: 10.1002/hep.29347.

Western Australian Cohort Study:
Parental pregnancy and NAFLD in 1,170 adolescents aged 17yrs.

NAFLD diagnosed by USS in 15%.

**Higher maternal pre-preg BMI ($p < 0.001$), higher maternal weight gain by 18/36 gestation ($p < 0.001$) associated with NAFLD.

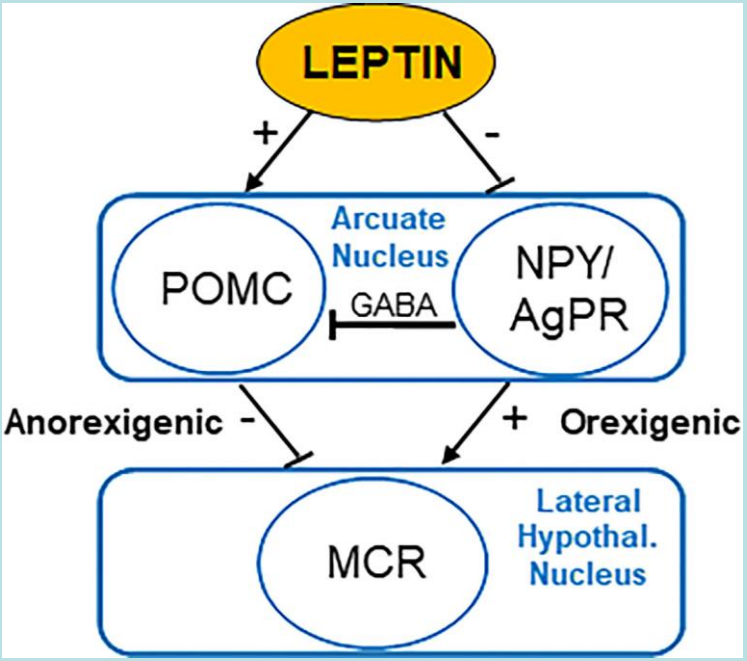


Leptin and NPY

- Leptin crosses BBB + ?Induces Lep resistance.

- **Ordinarily, Lep reduces NPY,**
- **NPY is pro-fibrogenic, appetite and hyperphagia**

- **?Therapeutically Bypass Leptin and target NPY**



Or is it the Microbiota and Dysbiosis? If so…..

Maternal microbiota transference at birth - t0,

Or via breast milk and skin at suckling?

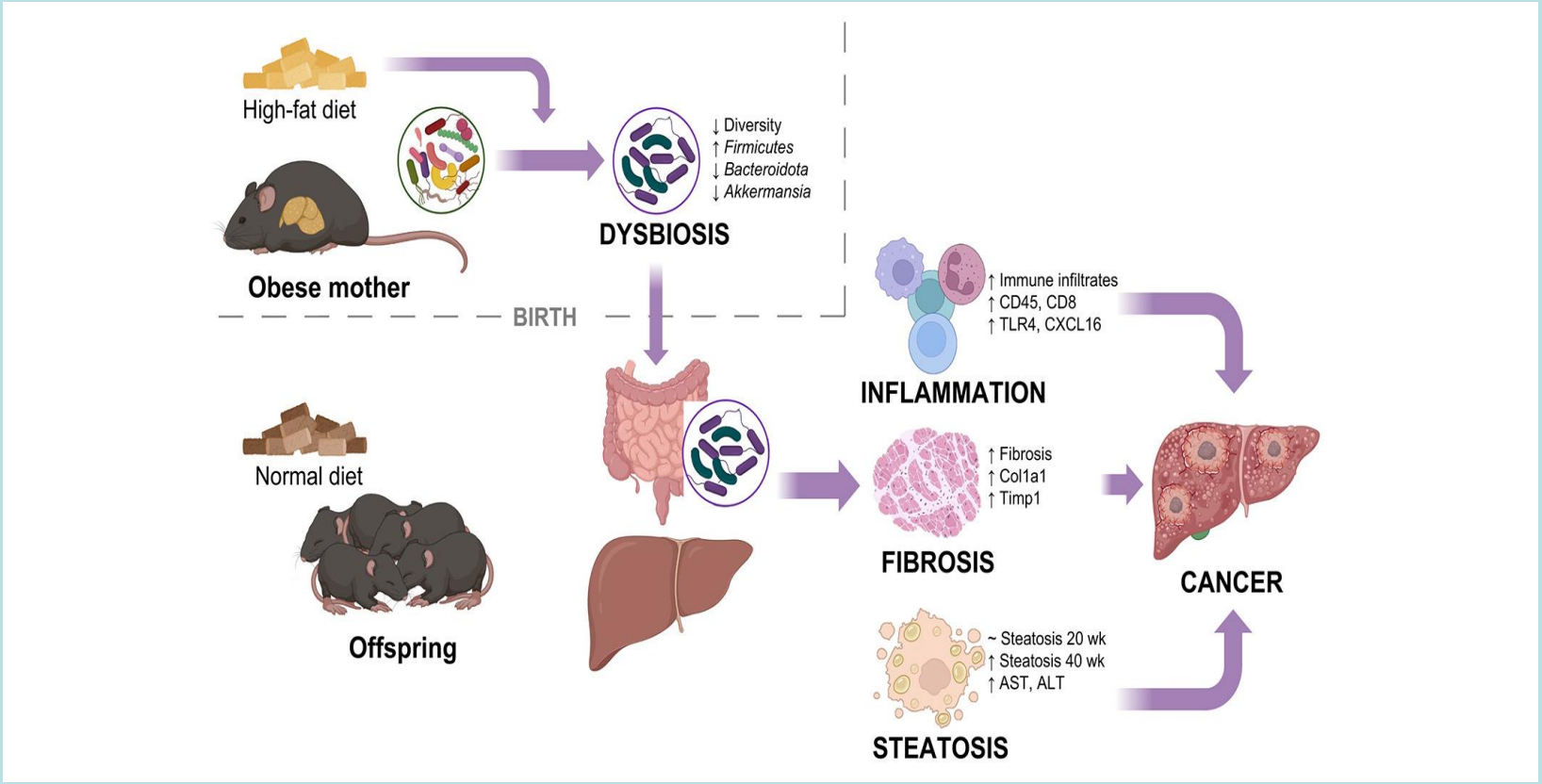
nature COMMUNICATIONS

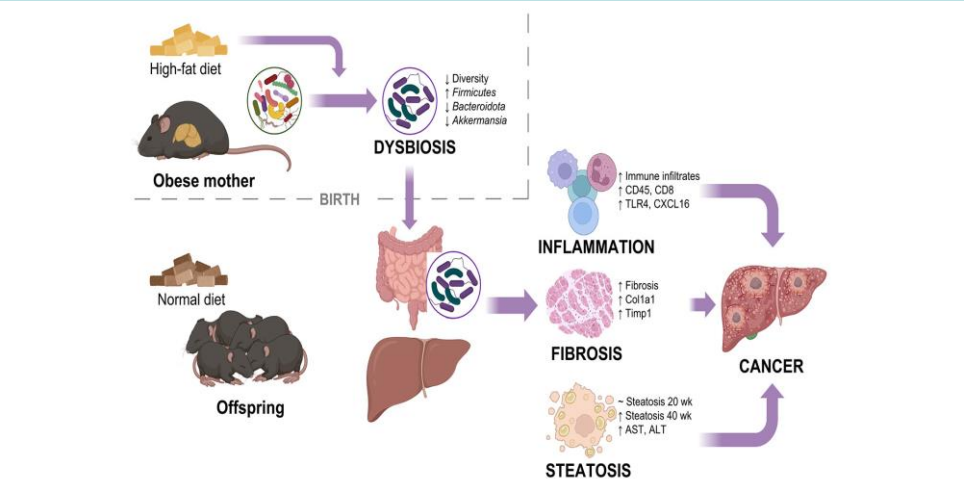
The gut microbiota in infants of obese mothers increases inflammation and susceptibility to NAFLD.

Soderborg T et al, 2018;
Nat Commun. 2018; 9: 4462; doi: 10.1038/s41467-018-06929-0

Conclusion:
Functional evidence supporting a causative role of maternal obesity-associated infant dysbiosis in childhood obesity and NAFLD.

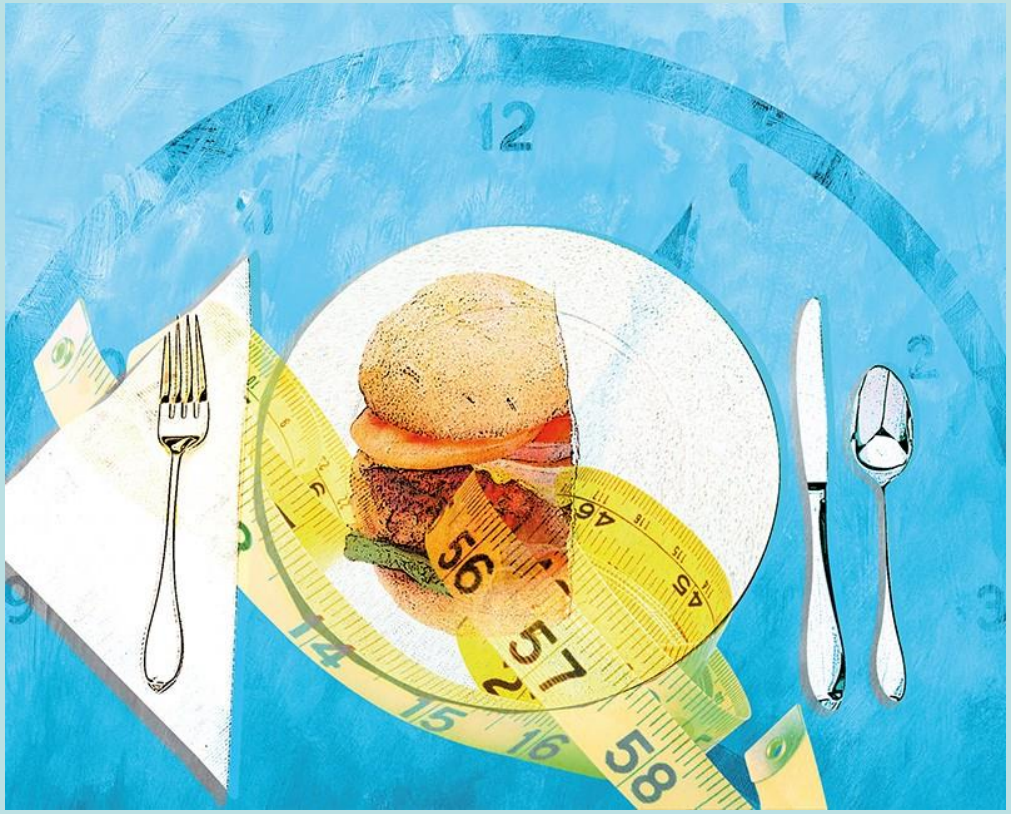
Moeckli et al (2024); Maternal obesity increases the risk of hepatocellular carcinoma through the transmission of an altered gut microbiome





- Obese mothers transmit an altered microbiome to their offspring which persists until adulthood.
- Maternal obesity increased steatosis, fibrosis and liver inflammation in offspring.
- Offspring of obese mothers are at a higher risk of developing liver cancer.
- Co-housing offspring of obese and lean mothers restores the gut microbiome and normalizes the liver cancer risk.
- Abundance of *Erysipelotrichaceae* and *Lachnospiraceae* bacteria correlate with tumor load, *Akkermansiaceae* with liver inflammation.

The microbiota's guide to weight gain



Microbial products and activity

- Microbiota products
- TLR4 angonists

Thank you for your attention!

Obesity Action

Raise Awareness

Support Science

Need More data

www.obesityac.org Charity No 1147991