**DOTT. VALERIO NOBILI**

Resp. UO Epatologia Osp. Pediatrico Bambino Gesù, Roma

## IL FEGATO GRASSO E L'OBESITÀ INFANTILE

A giugno del 2008 un noto giornale americano *The Washington Post* riportava che negli Stati Uniti più di sei milioni di bambini risultano essere affetti da una patologia epatica nota come "non-alcoholic fatty liver disease" NAFLD. La NAFLD in età pediatrica sta diventando in effetti un problema di crescente proporzione soprattutto nei bambini soprappeso o obesi dei paesi industrializzati (non solo in Nord America, ma anche in Europa ed Australia).

La steatosi epatica di origine non-alcolica o NAFLD, è quindi una patologia emergente che comprende un ampio spettro di condizioni epatiche; dalla semplice steatosi, alla steatoepatite con necro-infiammazione e fibrosi più o meno avanzata (condizione nota anche come steatoepatite non-alcolica (NASH, non-alcoholic steatohepatitis), fino alla cirrosi e, secondo alcune osservazioni, al carcinoma epatocellulare. Dal punto di vista anatomo-patologico la NAFLD assomiglia alla malattia epatica alcol-indotta, pur sviluppandosi in soggetti con consumo modesto (< 20 g/die) o nullo di alcolici. Stime di popolazione basate su criteri indiretti (es. elevazione delle transaminasi, fegato "brillante" all'ecografia, etc.) indicano che la prevalenza della NAFLD si aggira tra il 10-25% della popolazione generale, con ampie differenze in funzione dell'età e dell'etnia.

Questa patologia epatica è stata studiata inizialmente nell'adulto e non esistono allo stato attuale dati certi sulla possibilità di estrapolare le conoscenze della NAFLD dell'adulto e trasferirle in campo pediatrico, anche se già da qualche anno nel mondo si studia questo argomento. Ciò dipende in massima parte dal fatto che in molti casi esistono numerose differenze fra questa patologia nel bambino e quella riscontrata nel soggetto adulto.

In questa sede oggi intendiamo focalizzare la nostra attenzione esclusivamente sulle conoscenze attuali e sui maggiori risultati raggiunti nel bambino, in modo da poter fornire al pediatra curante strumenti utili ed efficaci alla comprensione, alla diagnosi e alla gestione terapeutica della NAFLD.



Associazione culturale ONLUS "Giuseppe Dossetti: i Valori - Sviluppo e Tutela dei Diritti"
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# La steatosi epatica nel bambino (NAFLD/NASH)

**Dr Valerio Nobili**
**Resp. Struttura Semplice**
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**Resp.Unita' di Ricerca**
**Prevenzione malattie endocrino-metaboliche**
**U.O.C. Epatologia**
**Ospedale Bambino Gesu'**
**nobili@opbg.net**

Nonalcoholic fatty liver disease (NAFLD) is a common disorder characterized by the accumulation of macrovesicular fat in hepatocytes. The condition of

HEPATOLOGY 2006

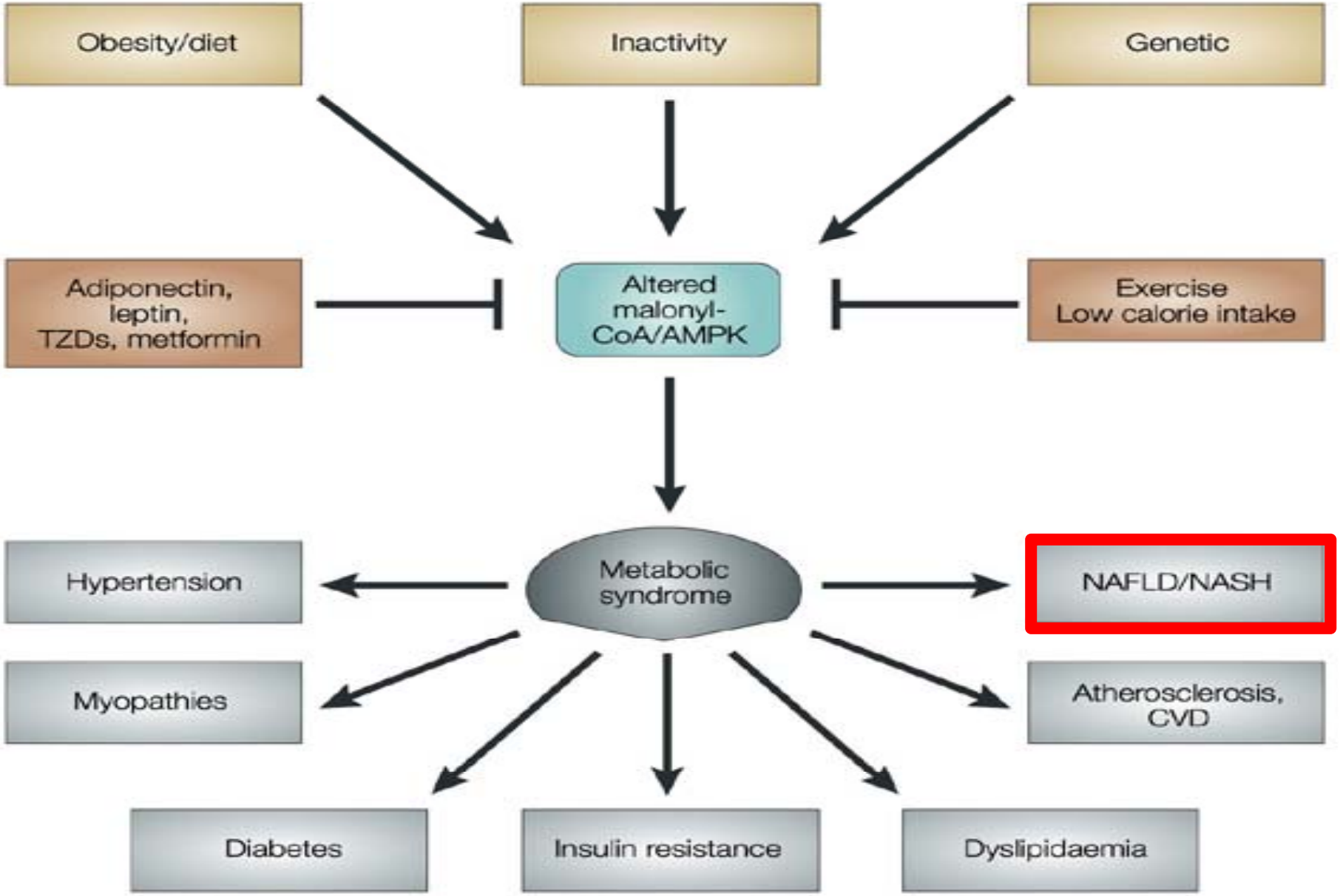


# NAFLD in Children: A Prospective Clinical-Pathological Study and Effect of Lifestyle Advice

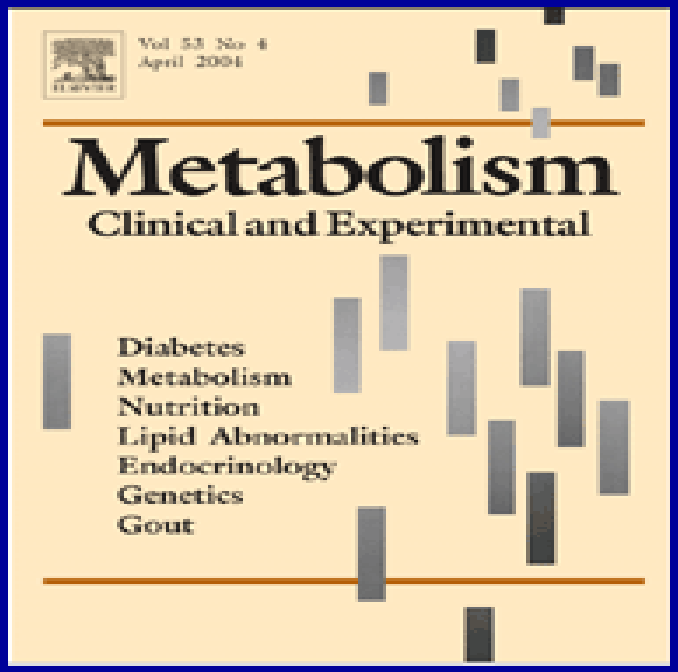
Valerio Nobili,[1] Matilde Marcellini,[1] Rita Devito,[2] Paolo Ciampalini,[3] Fiorella Piemonte,[4] Donatella Comparcola,[1] Maria Rita Sartorelli,[1] and Paul Angulo[5]

disease."[2] Within a few years, the first cases of pediatric NASH were reported.[3] NASH is currently defined as fatty liver disease in which there is also inflammation and varying degrees of hepatic fibrosis. In recent years, much


MS
NAFLD
NASH



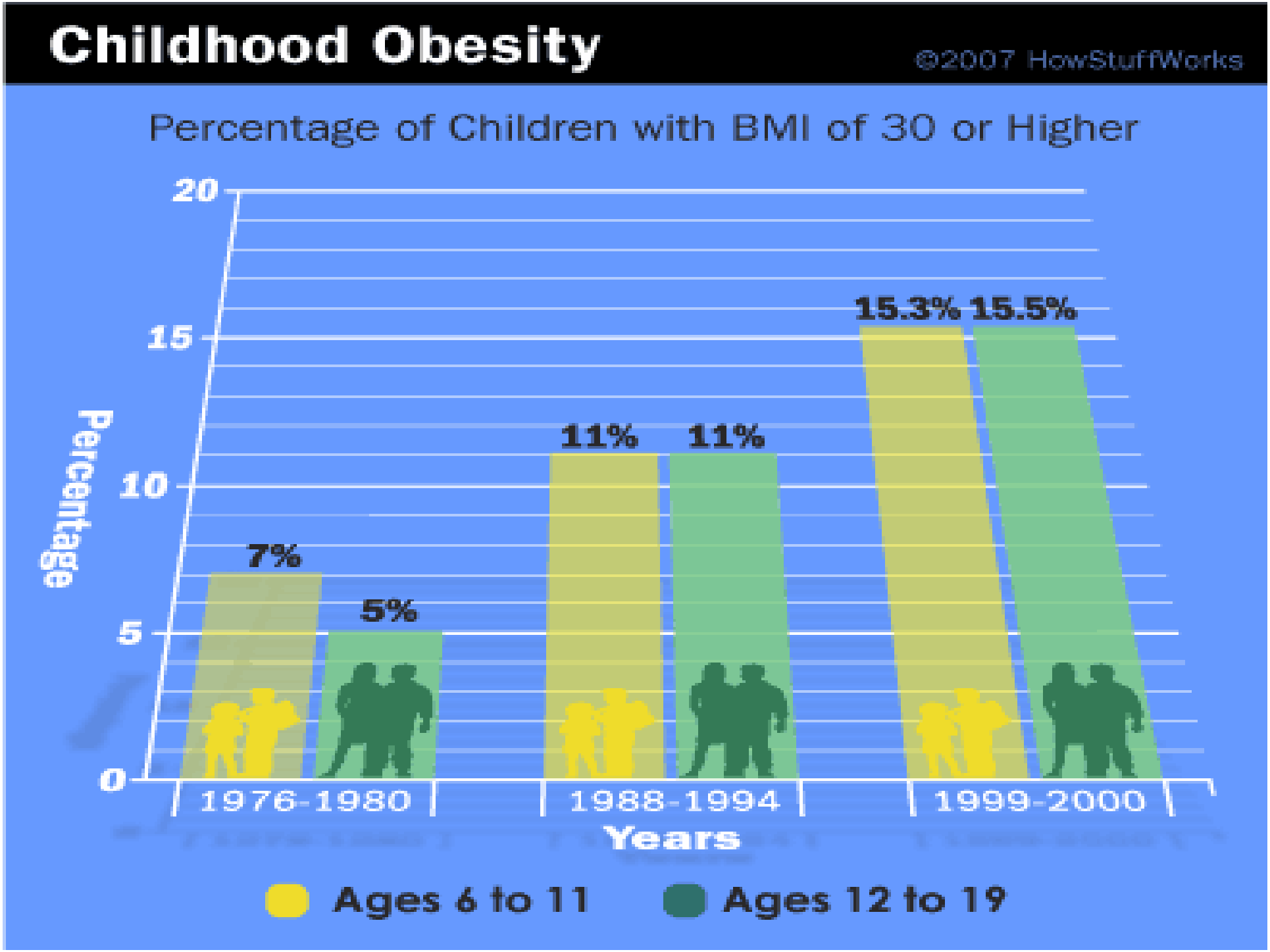

Nature Reviews | Drug Discovery

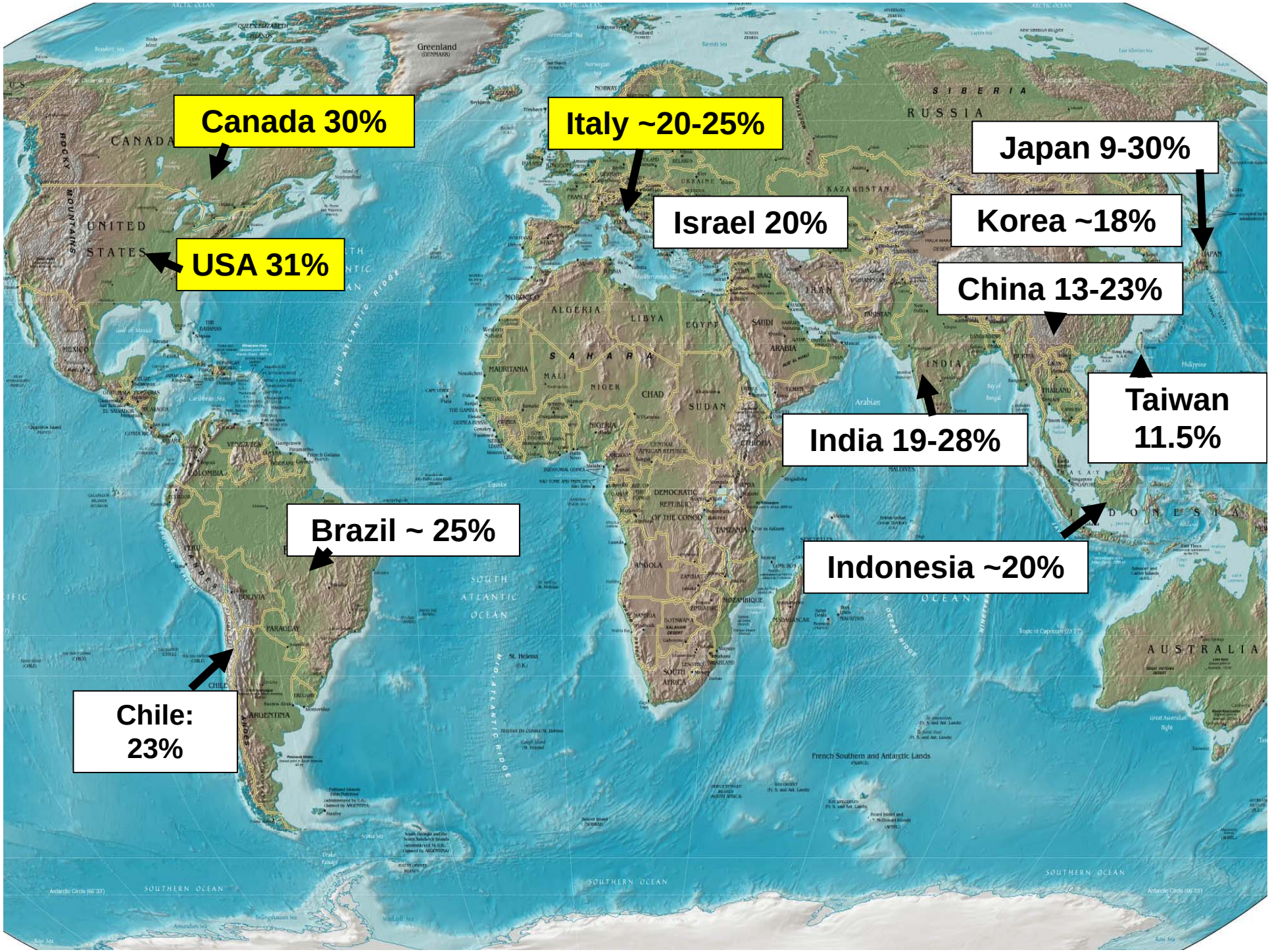



# METABOLISM 2010

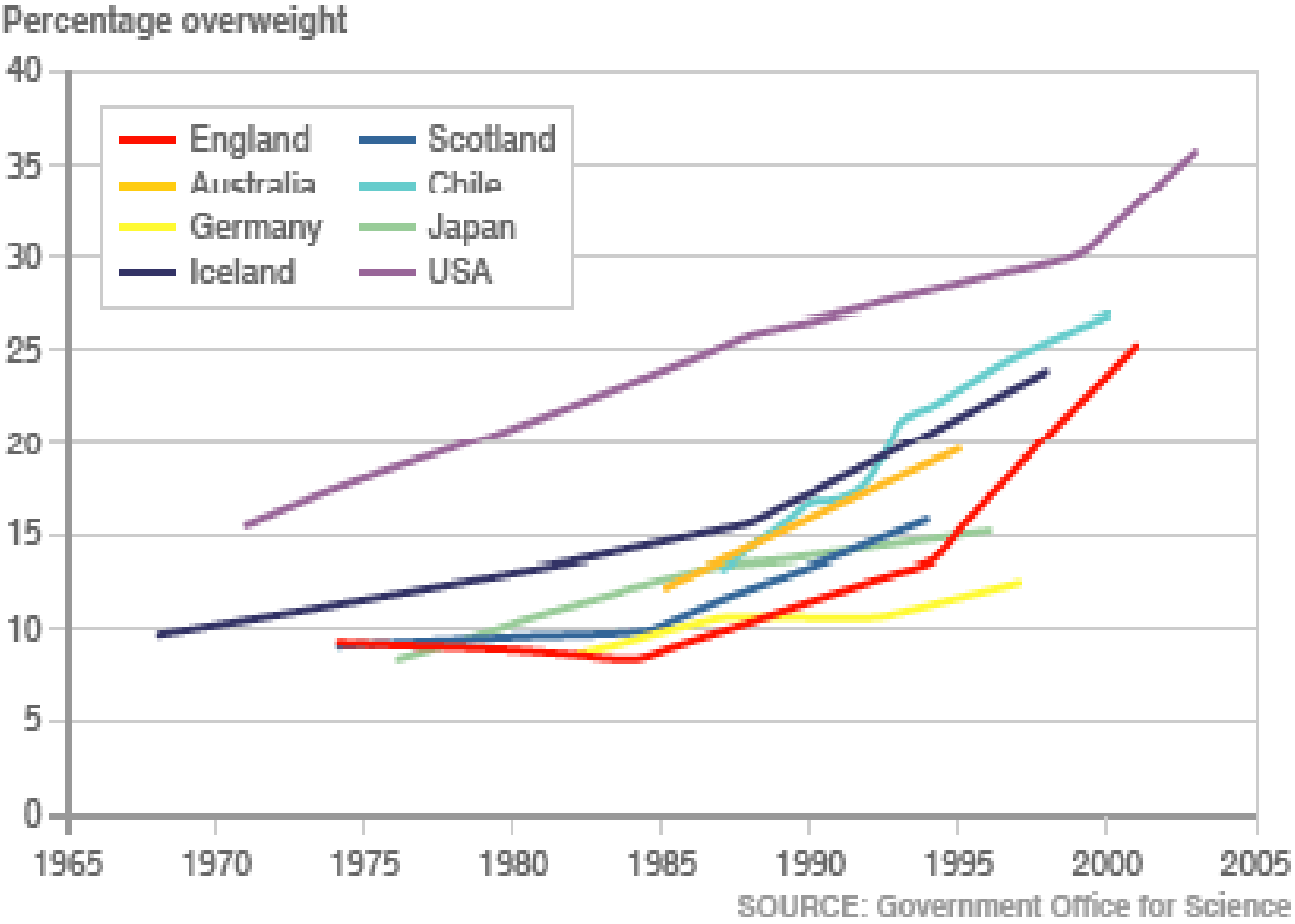
## Fatty liver and metabolic syndrome: a very burden for the future generations

[1]Valerio Nobili, MD, and [2]Carlo Agostoni, MD


Childhood Obesity
©2007 HowStuffWorks
Percentage of Children with BMI of 30 or Higher
20
15
10
5
0
Percentage
7%
5%
11%
11%
15.3%
15.5%
1976-1980
1988-1994
1999-2000
Years
Ages 6 to 11
Ages 12 to 19

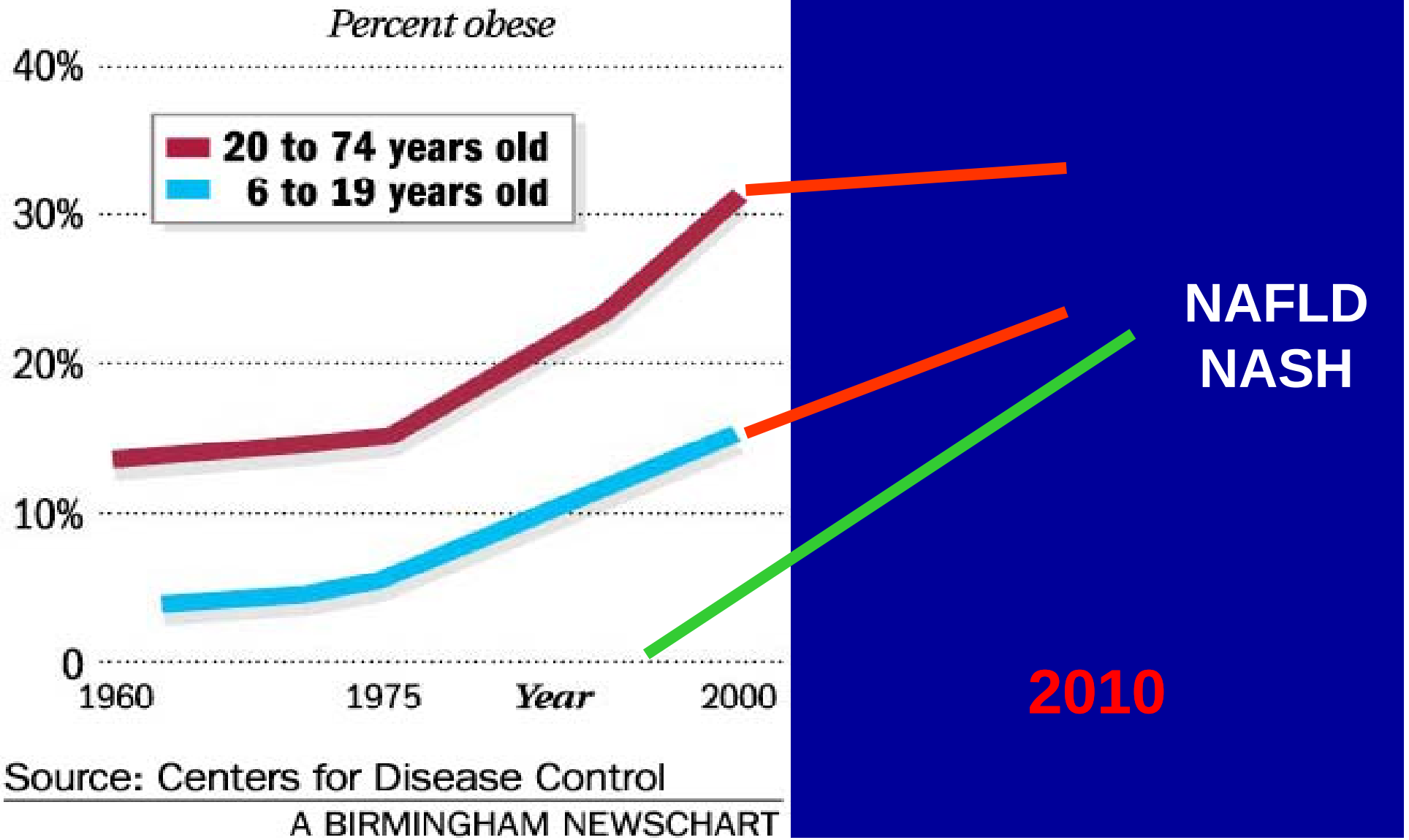

Canada 30%
Italy ~20-25%
Japan 9-30%
Israel 20%
Korea ~18%
USA 31%
China 13-23%
India 19-28%
Taiwan 11.5%
Brazil ~ 25%
Indonesia ~20%
Chile: 23%

# INCREASING NUMBER OF OVERWEIGHT CHILDREN AROUND THE WORLD



# An expanding problem

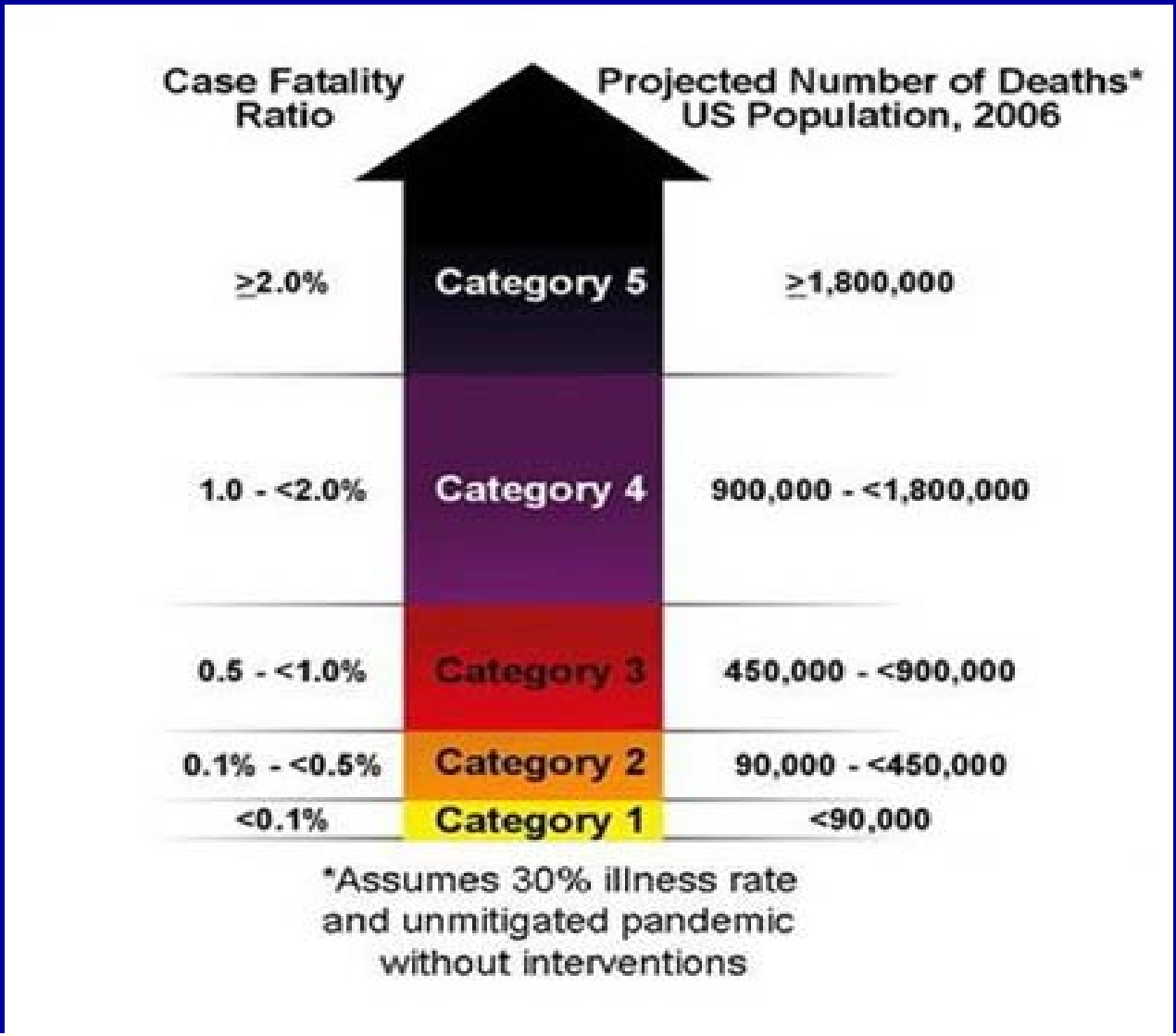
One quarter of children in the United States are obese.

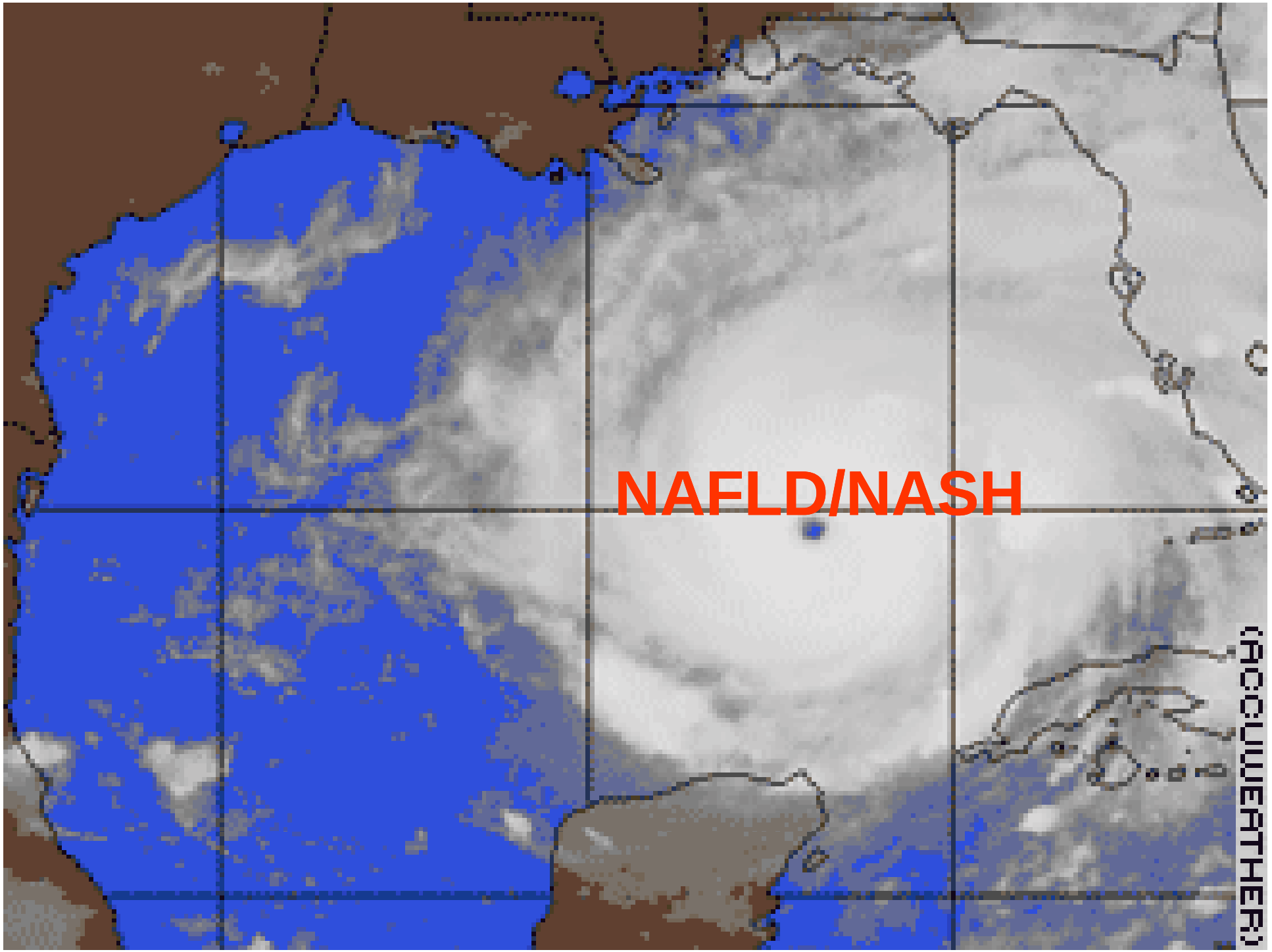



Source: Centers for Disease Control

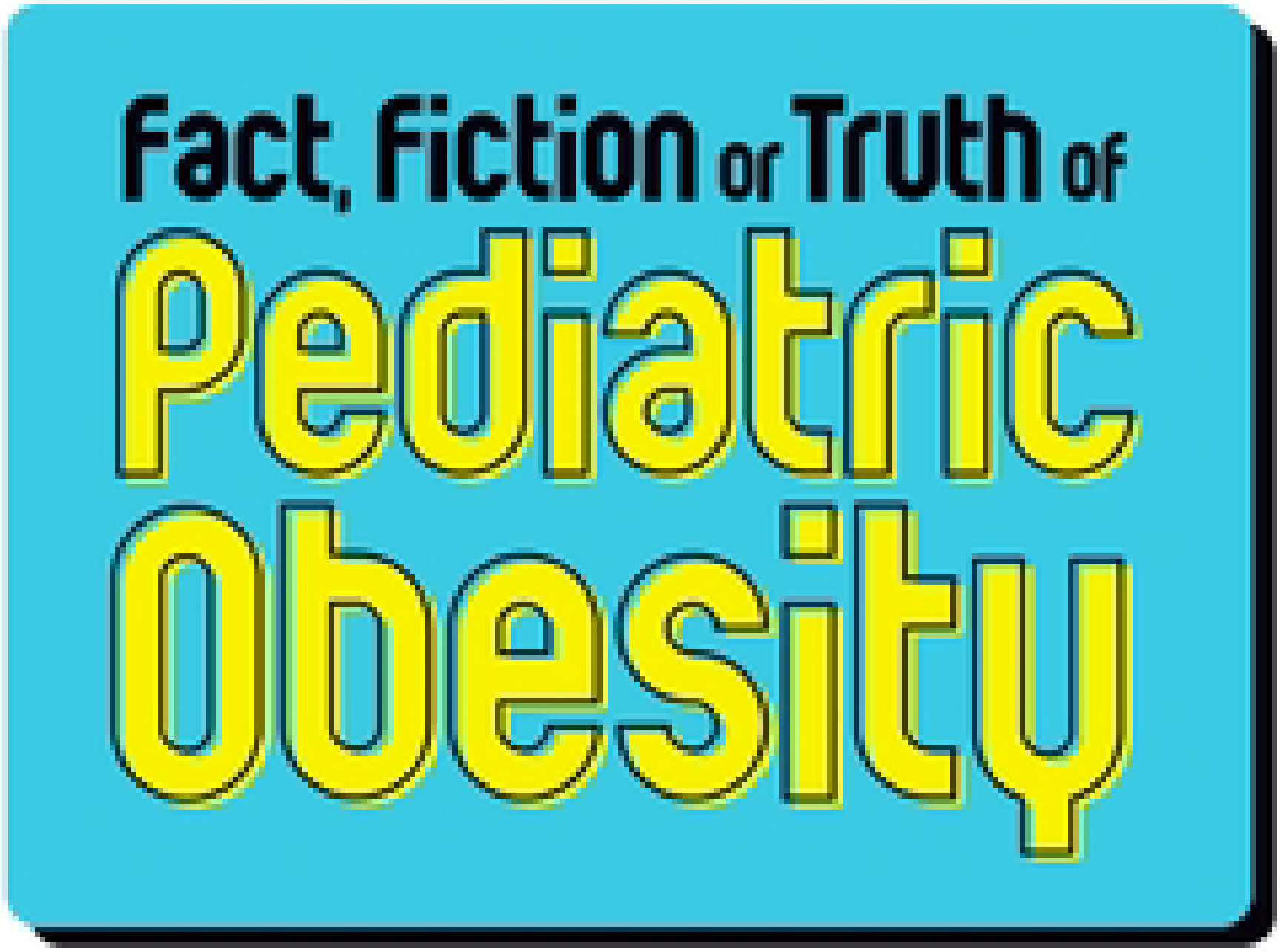
A BIRMINGHAM NEWSCHART

# PANDEMIX SEVERITY INDEX



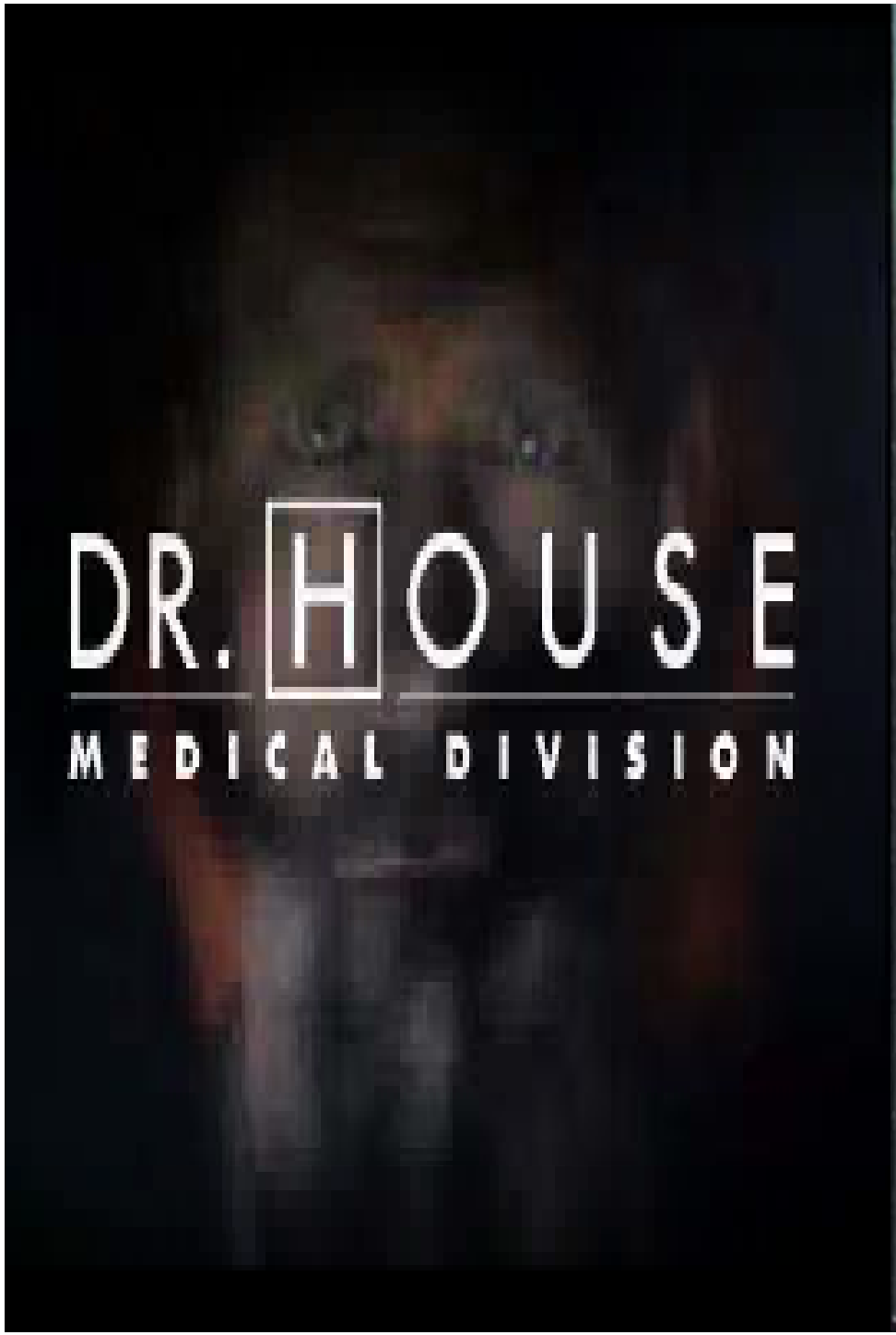

NAFLD/NASH
(ACCUWEATHER)

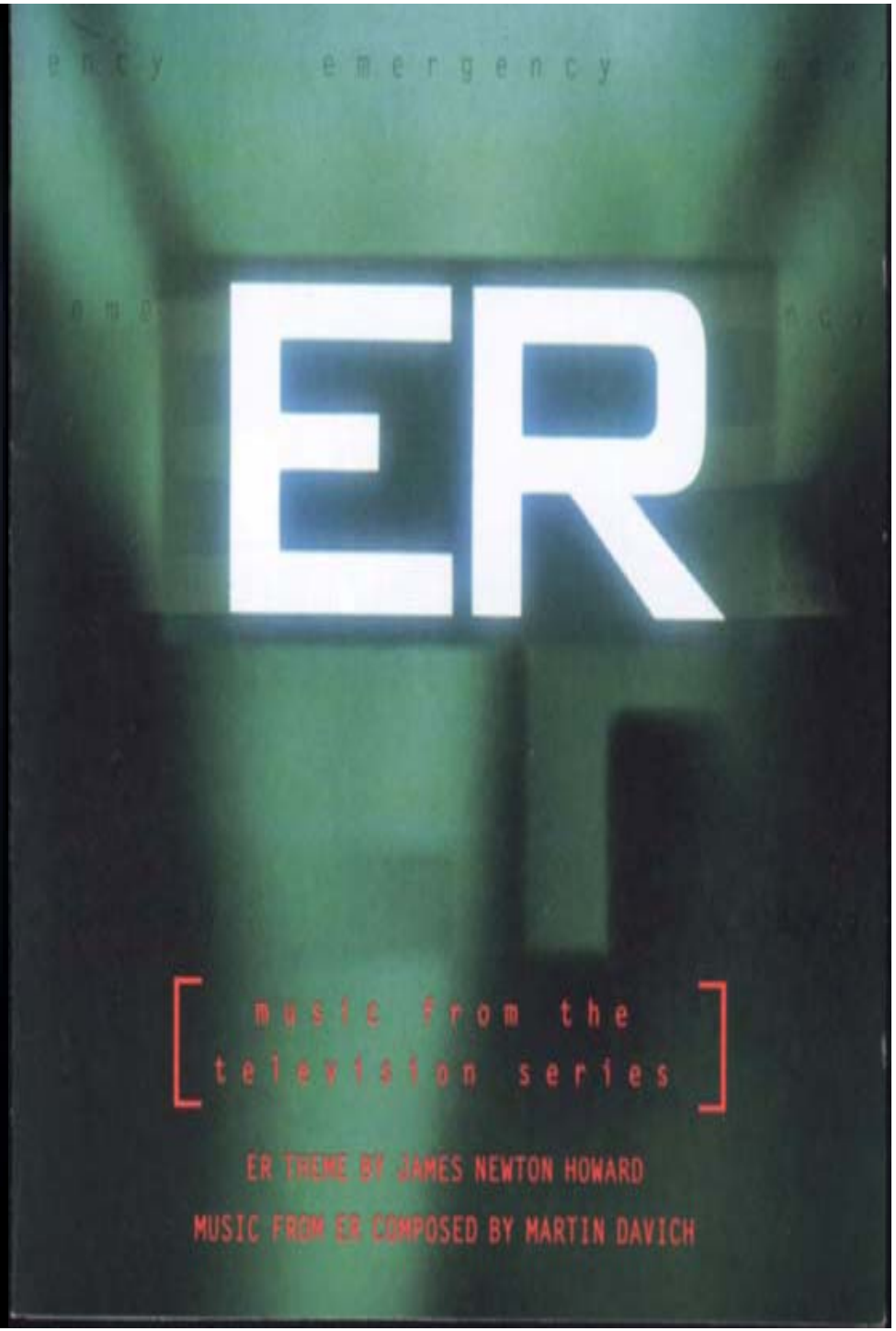



Fact, Fiction or Truth of
Pediatric
Obesity

"If even 1% of children with NAFLD in the USA progress to end-stage liver disease that would require liver tx, we shall need cadaver donor organs by more than 10-fold"

**Schwimmer J.B. Semin Liver Dis 2007**


DR. HOUSE
MEDICAL DIVISION

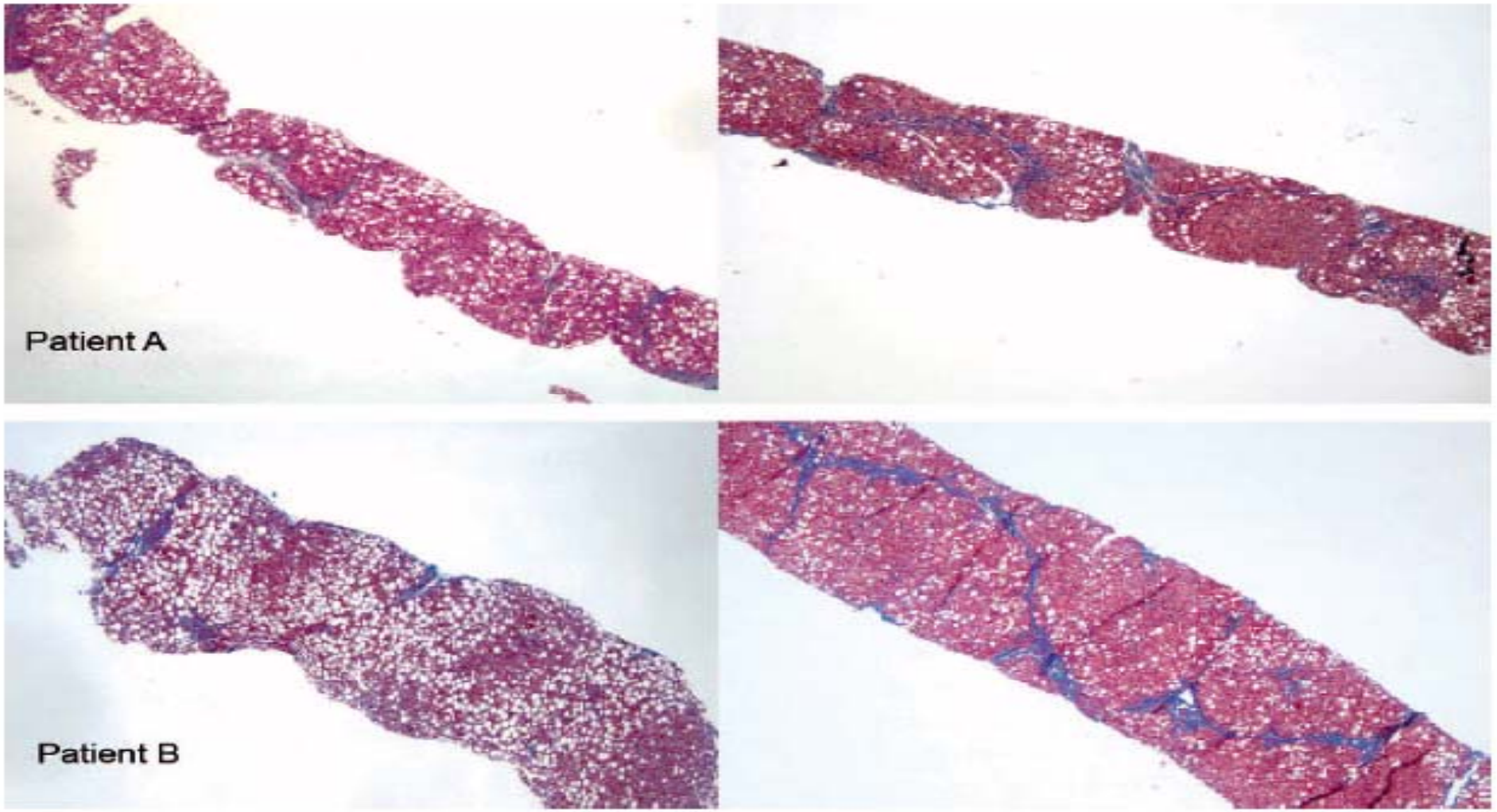

emergency
ER
music from the television series
ER THEME BY JAMES NEWTON HOWARD
MUSIC FROM ER COMPOSED BY MARTIN DAVICH

JPGN 2010



# Rapid Progression of NASH in Childhood

*Rohit Kohli, †Todd Boyd, *Kathleen Lake, *Kim Dietrich, *Lynda Nicholas,
*William F Balistreri, ‡Dawn Ebach, §Harohadli Shashidhar, and *Stavra A. Xanthakos






GUT

# The natural history of non-alcoholic fatty liver disease in children: a follow-up study for up to 20 years

A E Feldstein, P Charatcharoenwitthaya, S Treeprasertsuk, J T Benson, F B Enders and P Angulo

*Gut* 2009;58;1538-1544; originally published online 21 Jul 2009;
doi:10.1136/gut.2008.171280

fibrosis stage in four children. During follow-up, two children died and two underwent liver transplantation for decompensated cirrhosis. The observed survival free of liver transplantation was significantly shorter in the NAFLD cohort as compared to the expected survival in the general United States population of the same age and sex (log-rank test, $p<0.00001$), with a standardised mortality ratio of 13.6 (95% confidence interval, 3.8 to 34.8). NAFLD recurred in the allograft in the two cases transplanted, with one patient progressing to cirrhosis and requiring re-transplantation.



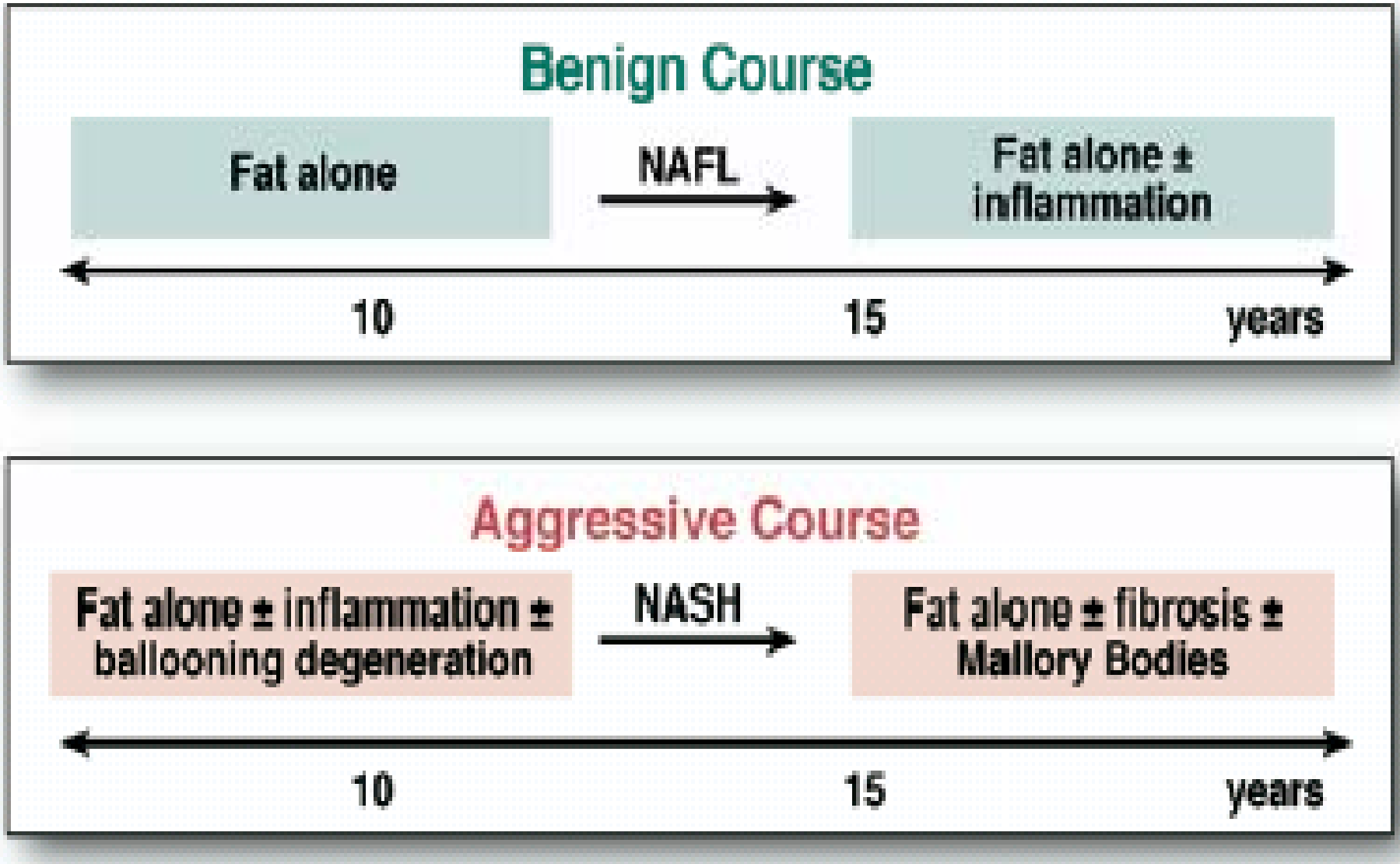

# Childhood NAFLD: a ticking time-bomb?

Valerio Nobili and Chris Day

*Gut* 2009;58;1442
doi:10.1136/gut.2009.184465

18 years, respectively. The main "take home" message therefore is that, contrary to generally accepted wisdom, the time from the first development of NAFLD to irreversible end-stage disease may be as short as 10–20 years rather than three or more decades. Accordingly, in the absence of effective pharmacological anti-fibrotic therapies, it is vitally important that children with NAFLD are diagnosed as early as possible to allow the opportunity for the appropriate lifestyle adjustments to be made aimed at arresting or reversing disease progression. For this

# Natural History Of NAFLD




Up to 23% may progress to cirrhosis; 5% risk of hepatocellular carcinoma

Preferiti Strumenti ?

titis Center, Cincinnati Children's Hospital ...

Cincinnati Children's
change the outcome

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# Steatohepatitis Center

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Steatohepatitis Center

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- How to Refer
- Meet the Team
- Contact Us

## About the Steatohepatitis Center

The Steatohepatitis Center within the Division of Gastroenterology, Hepatology and Nutrition at Cincinnati Children's Hospital Medical Center is a multidisciplinary clinic created to care for the unique needs of pediatric patients with non-alcoholic fatty liver disease (NAFLD) or non-alcoholic steatohepatitis (NASH).

The Steatohepatitis Center is led by a team of physicians with specific expertise and research interest in the area of NAFLD and pediatric obesity.

### Treating Children With Non-Alcoholic Fatty Liver Disease

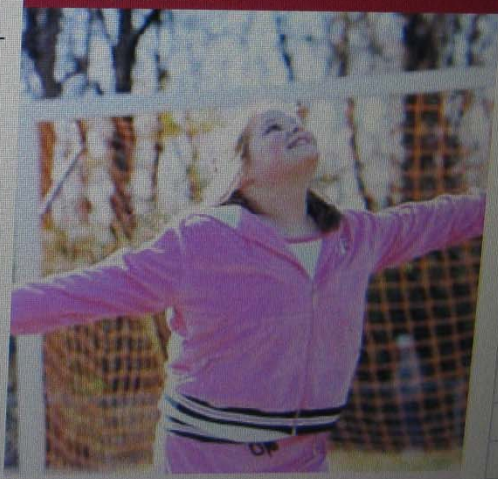
When someone is overweight or obese, too much fat can be stored in the liver. This can lead to a disease called non-alcoholic fatty liver disease, or NAFLD.

In some children and adults, the extra fat in the liver becomes a more severe problem, causing inflammation and scar tissue. When this happens, it is called non-alcoholic steatohepatitis, (pronounced stee-at-oh-hep-a-titus), or NASH. Over time, NASH can lead to severe scarring, called cirrhosis (sir-oh-sis). Cirrhosis can lead to liver failure and loss of liver function.

Besides obesity, other risk factors for NAFLD include many features of the metabolic syndrome, such as:

- Diabetes and insulin resistance

**Non-Alcoholic Fatty Liver Disease: A Growing Epidemic**



- With the growing obesity epidemic, NAFLD is now believed to be the most common liver disease worldwide, affecting up to 13% of children and one-third of adults.
- NASH affects 2-3% of all adults and children, but is found in approximately 25% of children who have fatty liver.

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Steatohepatitis Cent...

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  - Health Library
  - Health News
  - Healthy Living

## Health Information



### Illnesses & Conditions

Information on diseases and health concerns, including symptoms, treatment options, and prevention.

## Nonalcoholic Steatohepatitis (NASH)

healthwise
for every health decision

Overview

### What is nonalcoholic steatohepatitis (NASH)?

Nonalcoholic steatohepatitis (NASH) is liver inflammation caused by a buildup of fat in the liver. NASH is part of a group of liver diseases, known as nonalcoholic fatty liver disease, in which fat builds up in the liver and sometimes causes liver damage that gets worse over time (progressive liver damage).

Although the cause is not known, NASH seems to be related to certain other conditions, including obesity, high cholesterol and triglycerides, and diabetes.

- Overview
- Cause
- Symptoms
- What Happens
- What Increases Your Risk
- When to Call a Doctor
- Exams and Tests
- Treatment Overview

Internet

start SIP LAZIALE [modalit... Liver Center at UCSD... UCSD Medical Center ...


American Stroke Association
A Division of American Heart Association
American Heart Association
Learn and Live.
Don't supersize him.
Childhood obesity is a growing epidemic that increases heart disease. Requiring minimum standards for physical education, such as 150 minutes per week of physical education for elementary schools and 225 minutes for middle schools, gives children a fighting chance against obesity and heart disease. And, coordinated school health programs will ensure that children have sound minds and healthy bodies. You can prevent supersized children who suffer more health problems and grow into unhealthy, less productive and disabled adults. Don't miss your chance to shape a whole new generation of Americans and stop the nation's No. 1 killer—heart disease.
Heart disease. You're the Cure.



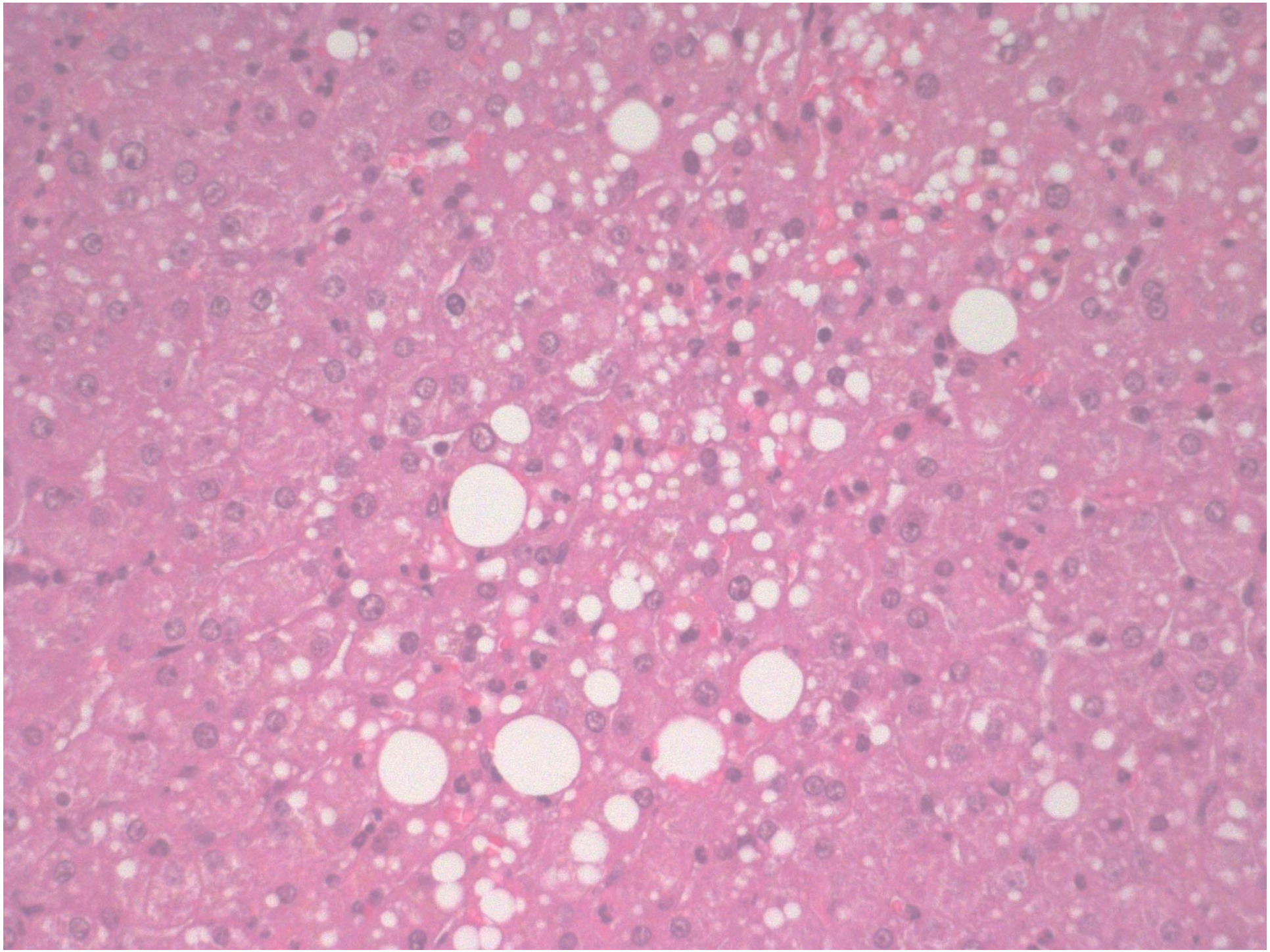

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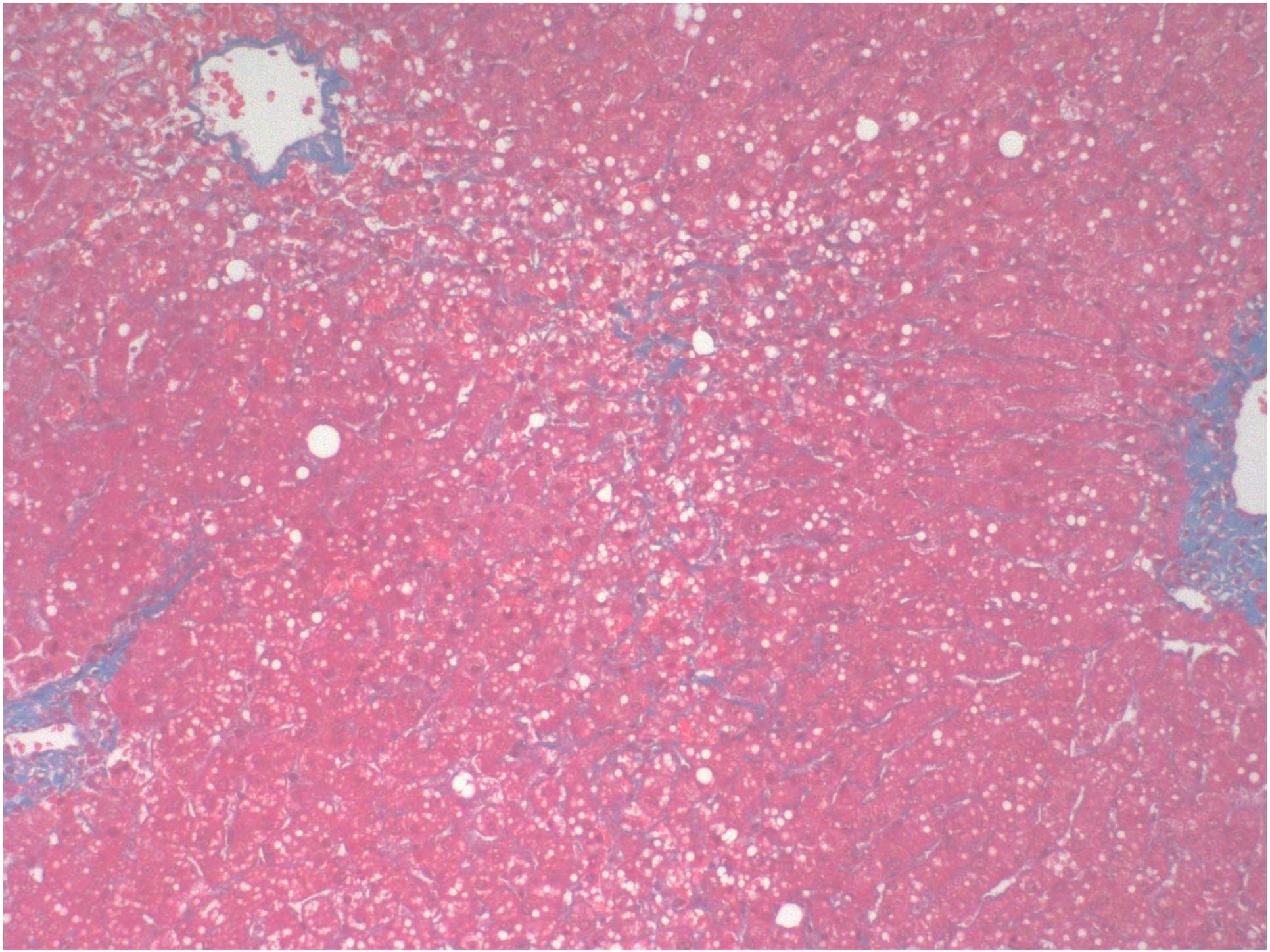
Pediatric Transplantation
DOI: 10.1111/j.1399-3046.2010.01324.x

Editorial

# Steatosis and fibrosis in paediatric liver transplant: Insidious graft's enemies – A call for clinical studies and research

PROOF





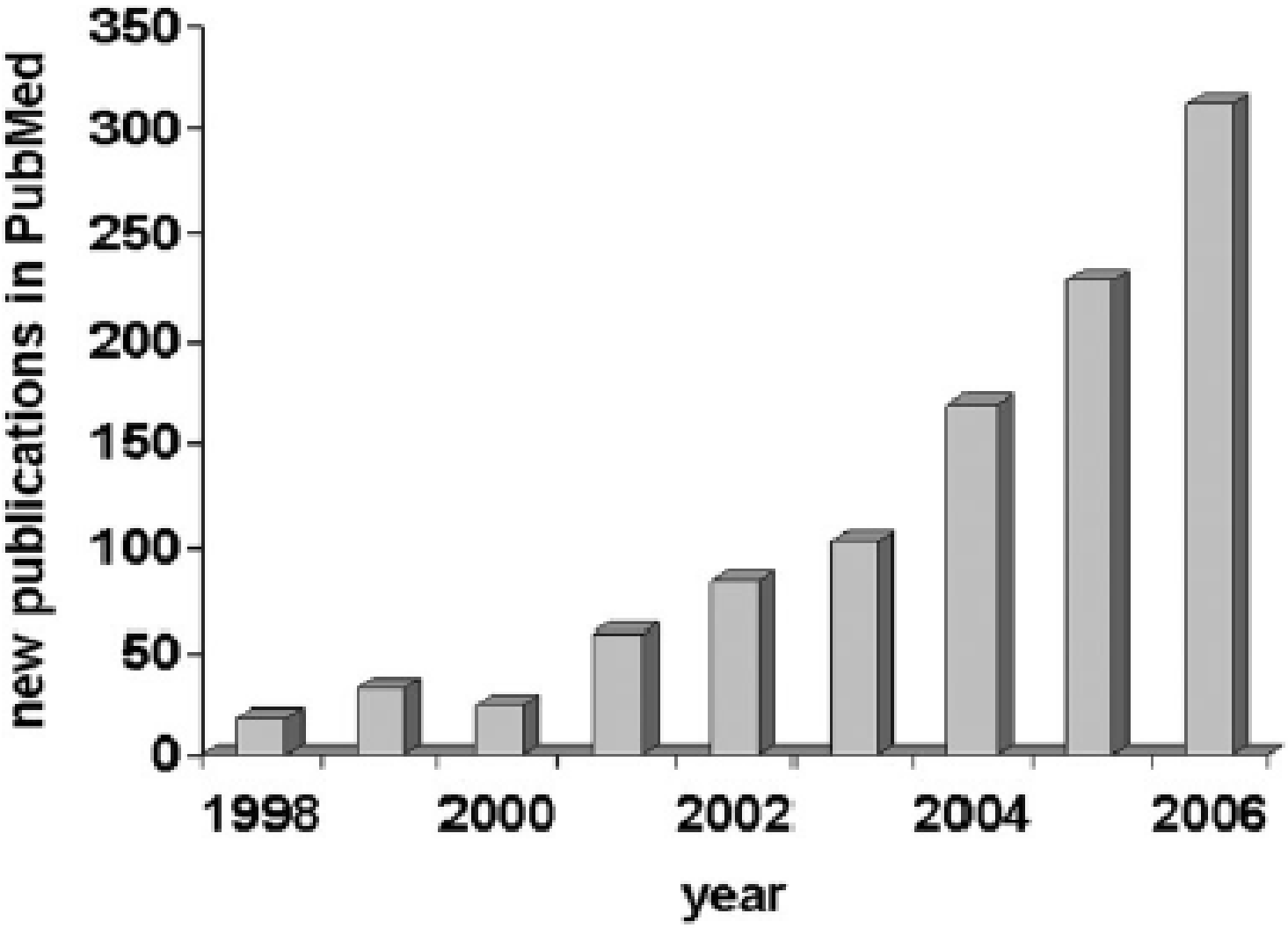
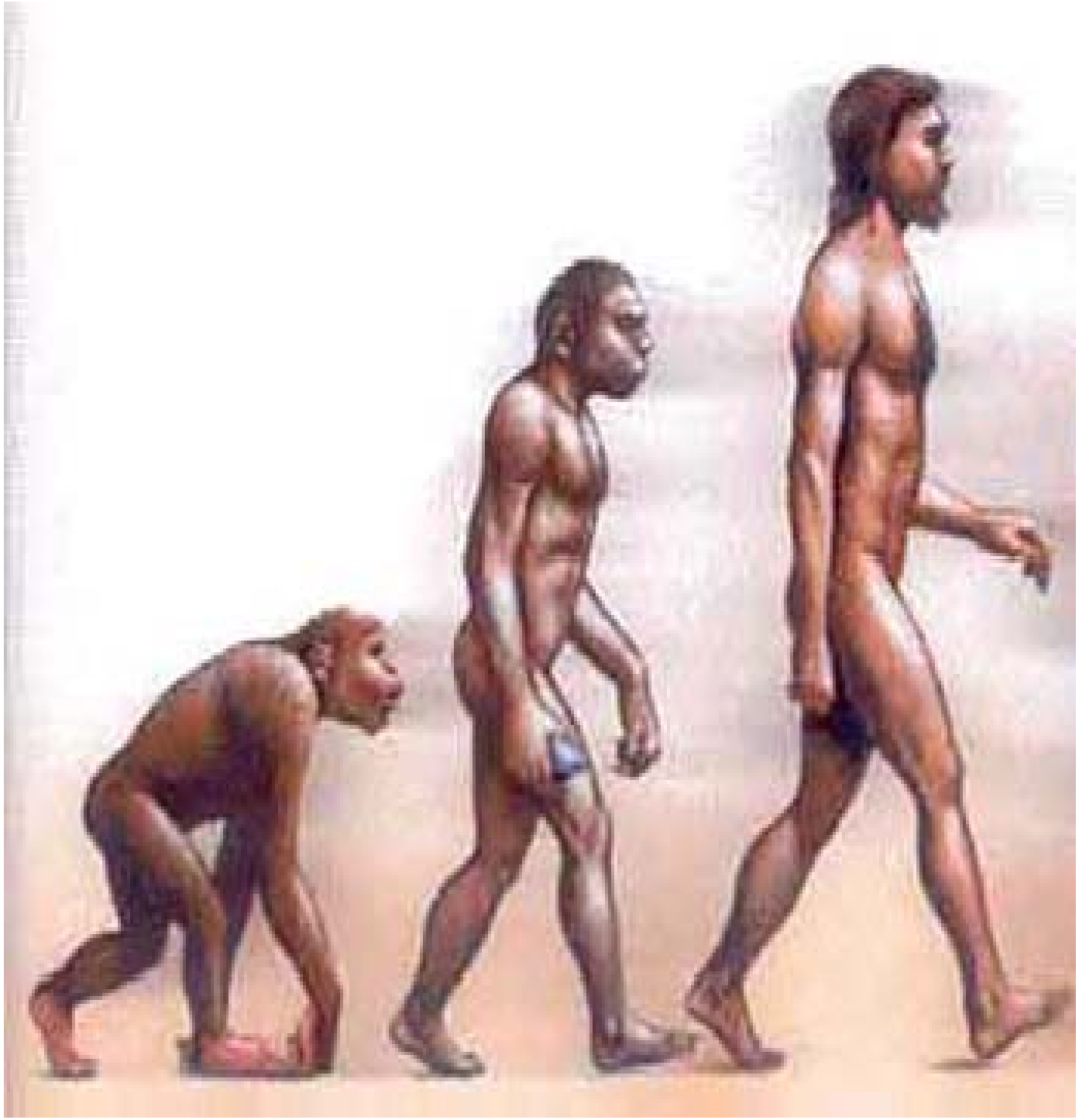
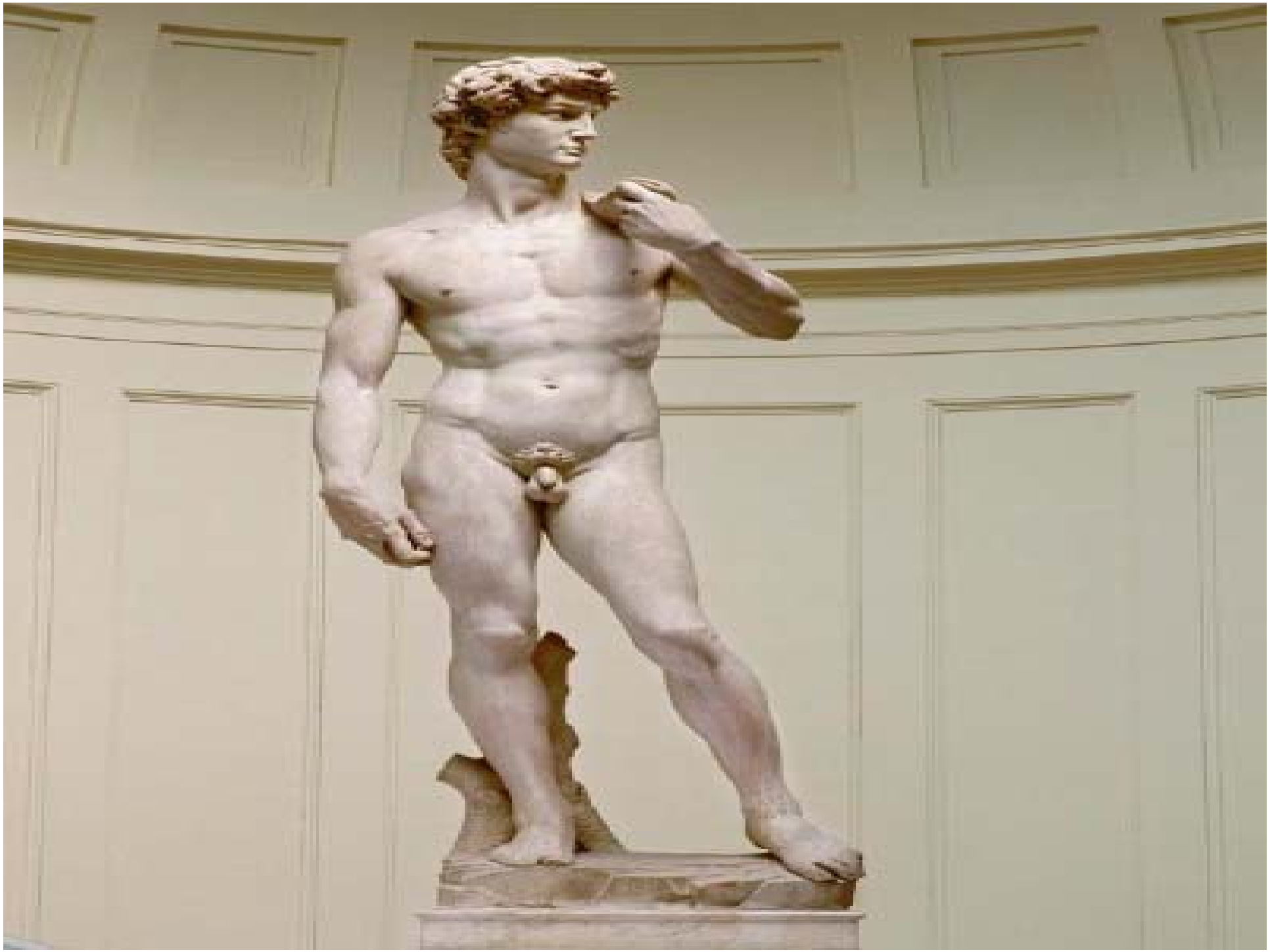
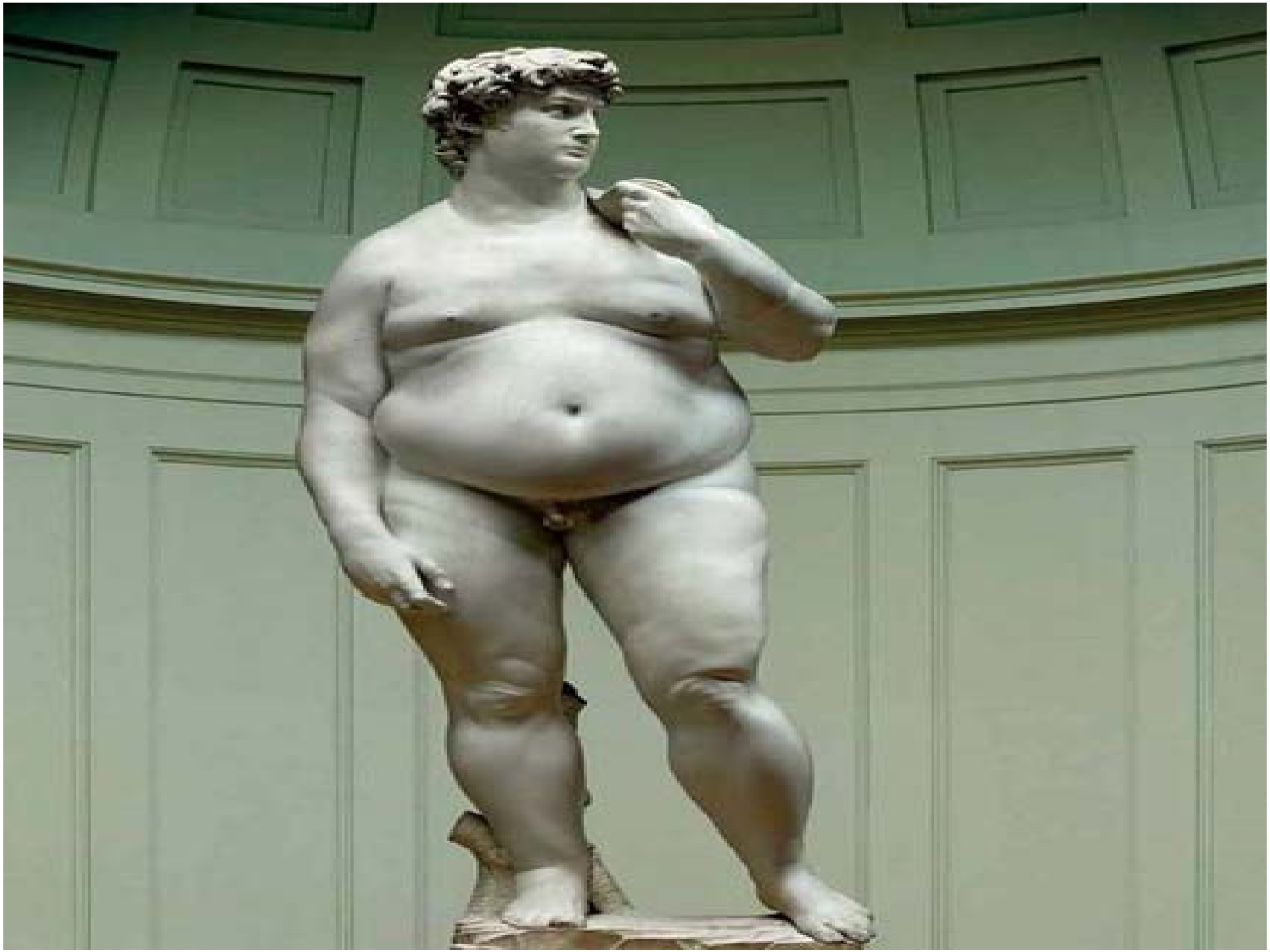



Fig. 1. Number of original publications per year, using the search terms NAFLD and NASH, is shown.

2010





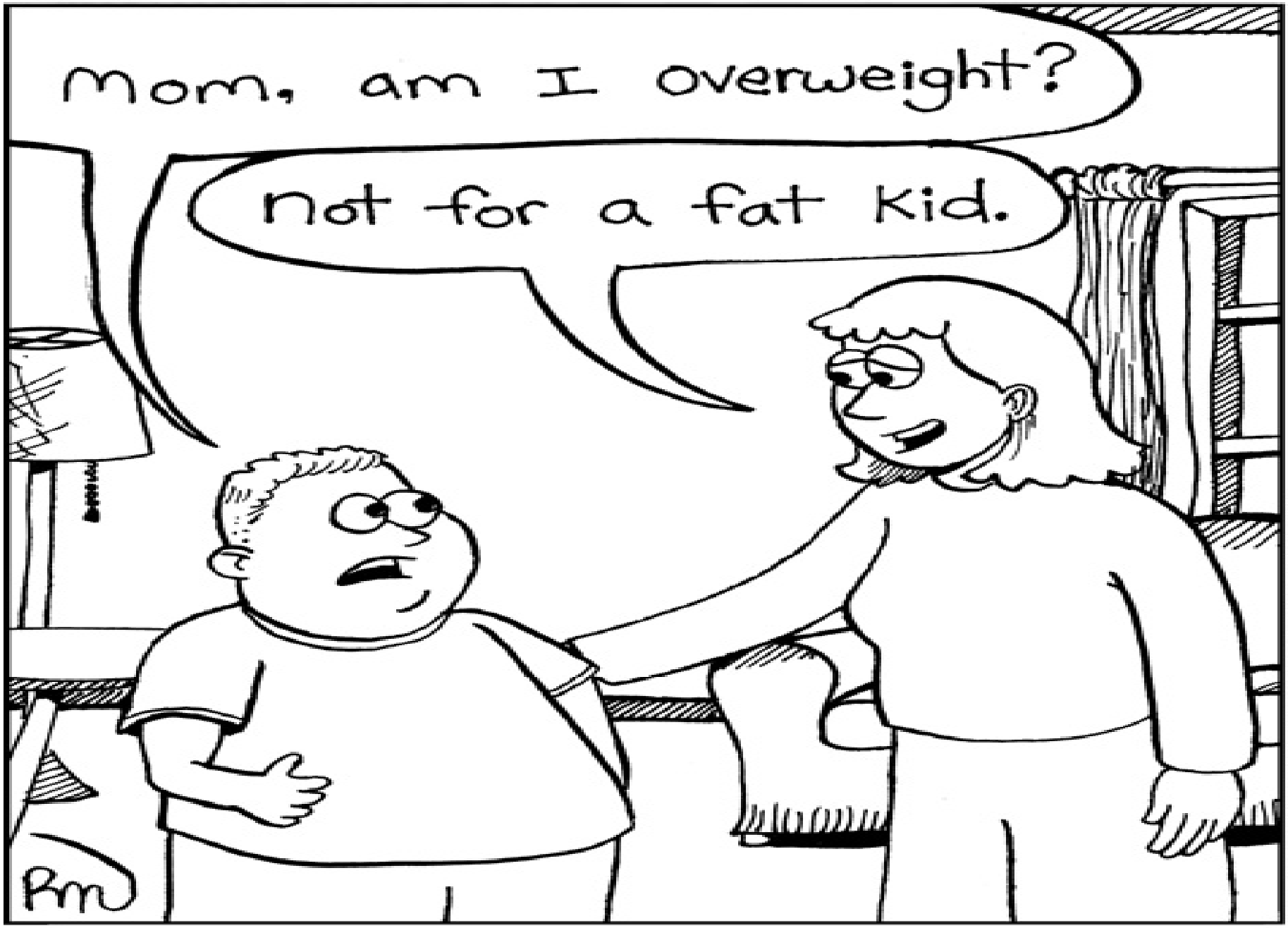





McDonald's
Coca-Cola



# At Random By Ryan Mason

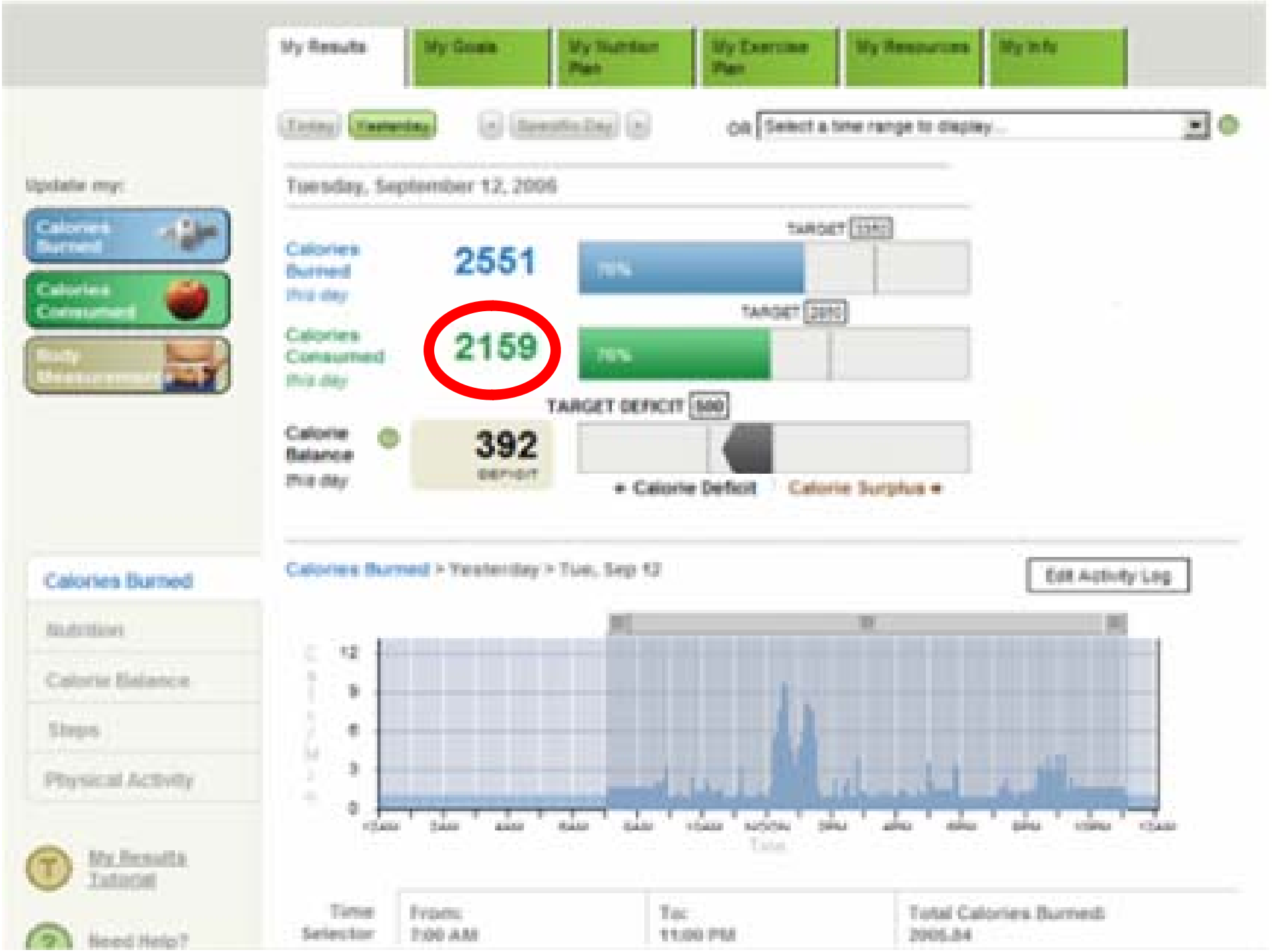





Killer Sofa.
Make Healthier Choices.
Eat healthy foods. Get more exercise.




bodybugg
FITNESS

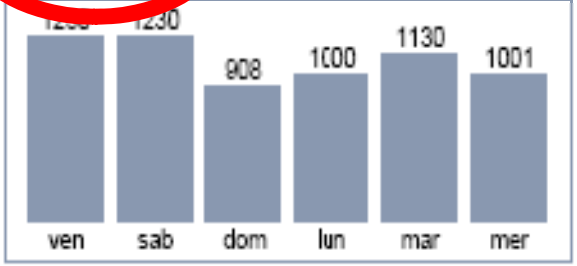

My Results
My Goals
My Nutrition Plan
My Exercise Plan
My Resources
My Info
Today
Yesterday
Specific Day
OR
Select a time range to display...
Update my:
Calories Burned
Calories Consumed
Body Measurements
Tuesday, September 12, 2006
Calories Burned
this day
2551
TARGET
76%
Calories Consumed
this day
2159
TARGET
76%
TARGET DEFICIT 500
Calorie Balance
this day
392
DEFICIT
Calorie Deficit
Calorie Surplus
Calories Burned
Nutrition
Calorie Balance
Steps
Physical Activity
Calories Burned > Yesterday > Tue, Sep 12
Edit Activity Log
12
9
6
3
0
Time
My Results Tutorial
Need Help?
Time Selector
From:
7:00 AM
To:
11:00 PM
Total Calories Burned:
2005.84

| Paziente | Età | Sesso | Peso | Altezza | Mano | Fumatore | BMI |
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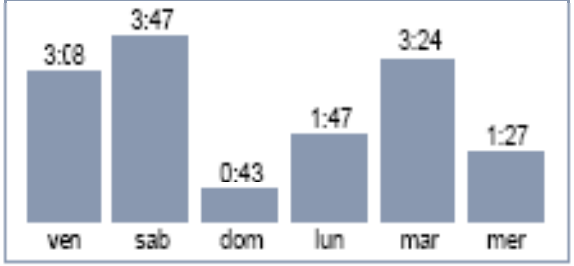
## Dispendio Energetico Totale

Media Die: 1083 cal
Totale: 6499



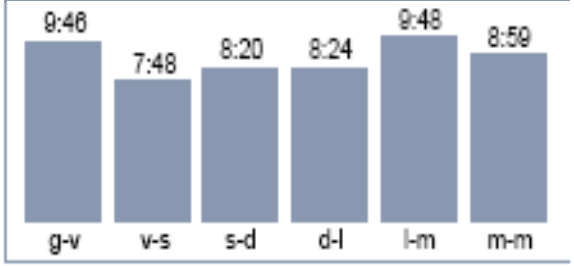

## Durata Attività Fisica (3.0 METs)

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Totale: 14 ore 18 min



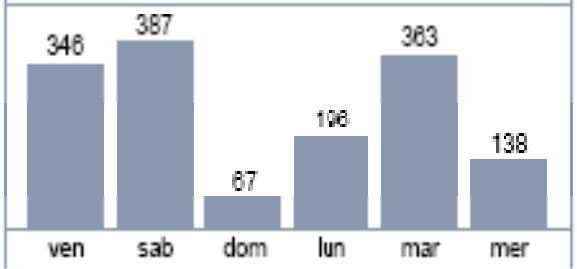

## Sdraiato (da mezzanotte a mezzanotte)

Media Die: 8:51
Totale: 2 giorni 5 ore 5 min



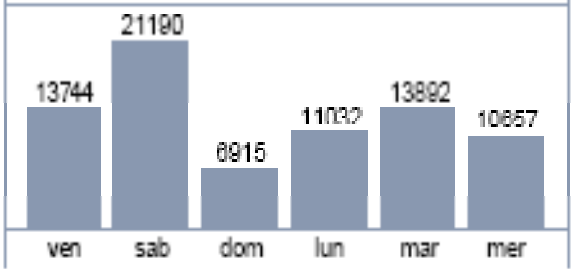

## Spesa Energetica Attiva (3.0 METs)

Media Die: 250 cal
Totale: 1497



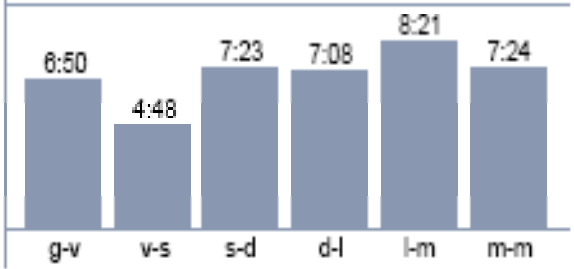

## Numero di Passi

Media Die: 12905 passi
Totale: 77430




## Durata Sonno (da mezzanotte a mezzanotte)

Media Die: 6:59
Totale: 1 giorno 17 ore 54 min



# Symptoms & signs in children

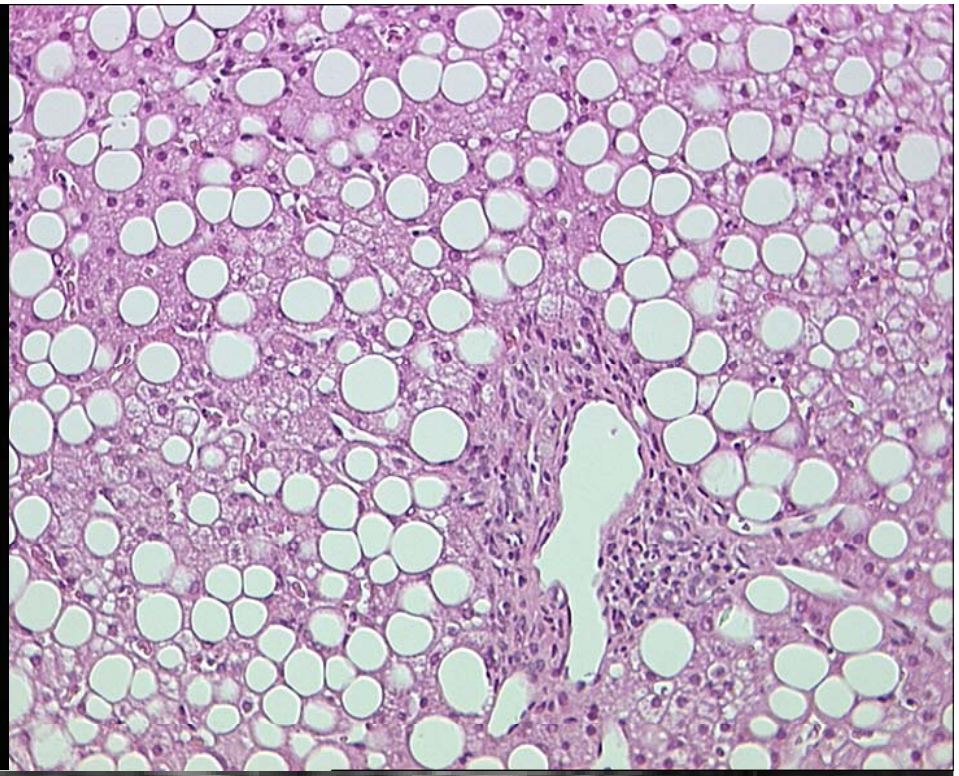
| | NAFLD (%) | NASH (%) |
|---|---|---|
| Asymptomatic | 60 | 55 |
| Fatigue | 30 | 45 |
| [illegible] | [illegible] | [illegible] |
| High ALT | 71 | 65 |
| Diabetes | 2 | 3 |
| Insulin Res. | 79 | 80 |
| Dyslipidemia | 11 | 12 |

STEATOSI EPATICA = 100%

1-2 x N


OSPEDALE PEDIATRICO BAMBINO GESU' - ROMA -
15:40:06 Tu 06/05/2008
SIEMENS
Abd
C5-2 3.5
FPS 17h
100
B
63
2D 60/1/17
MI 0.8 TIS 0.4 TIB 0.4 Tx 100%



Diffuse hyperechoic echotecture ("bright liver")

Increased liver echotexture
compared with the kidney

# NAS SCORE

Brunt and Kleiner. Design and validation of a Histological Scoring System for NAFLD. (Hepatology 2005;41:1313-1321)

NAS = 0-2 (not NASH) **STEATOSIS**

NAS = 3-4 (borderline) **INFLAMMATION**

NAS $\geq$ 5 (NASH) **BALLOONING**

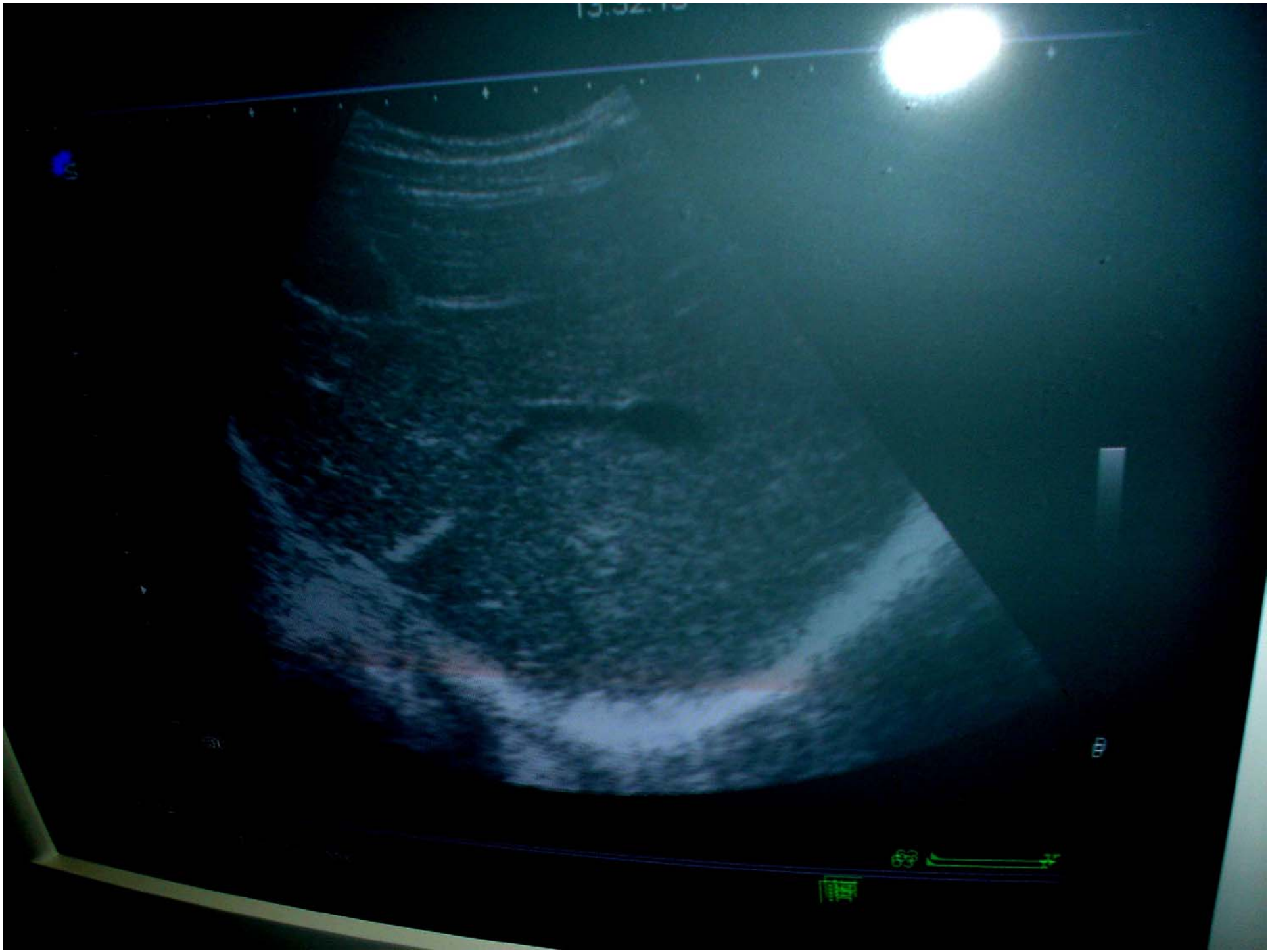


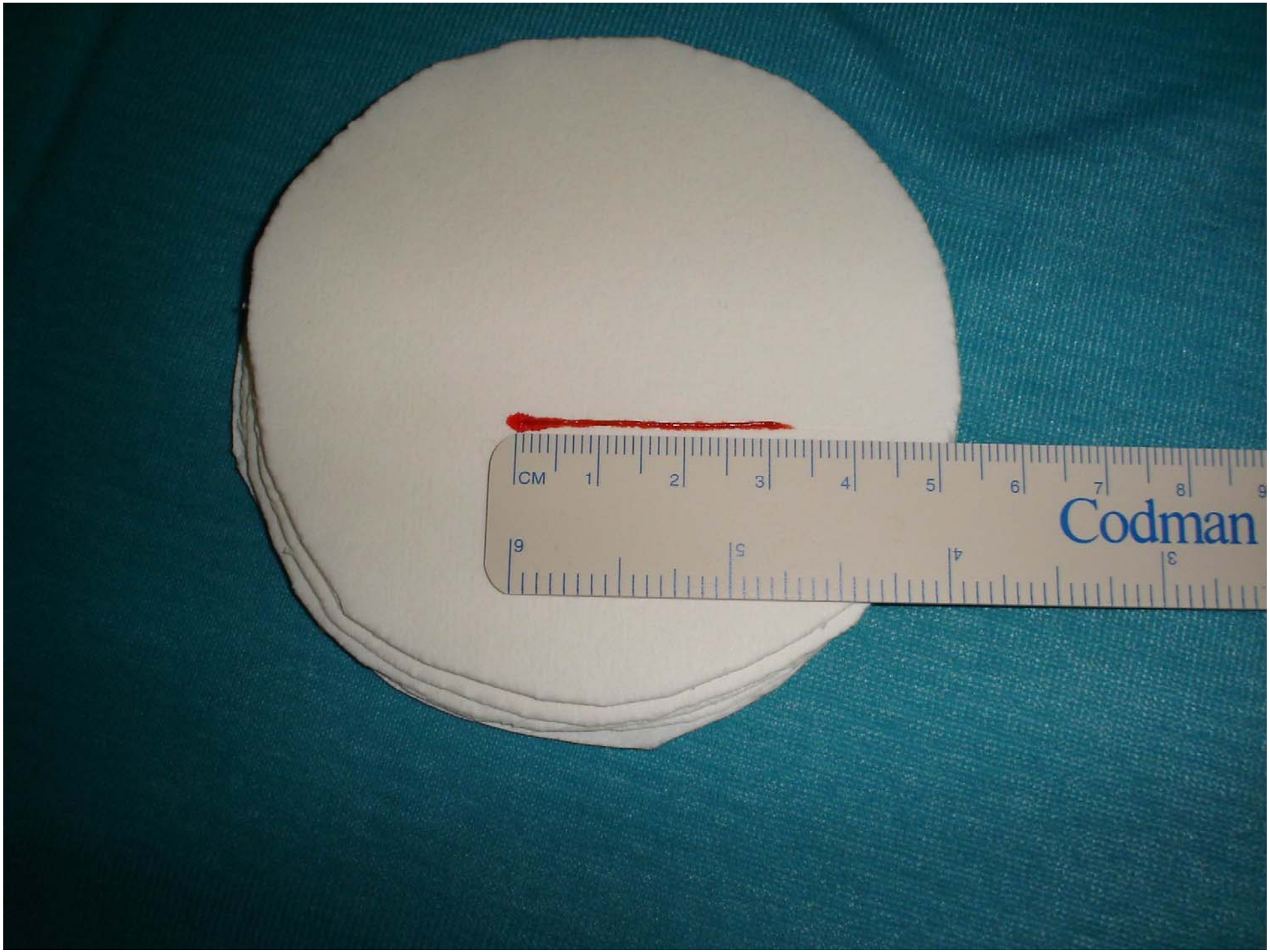
# Washington University in St. Louis



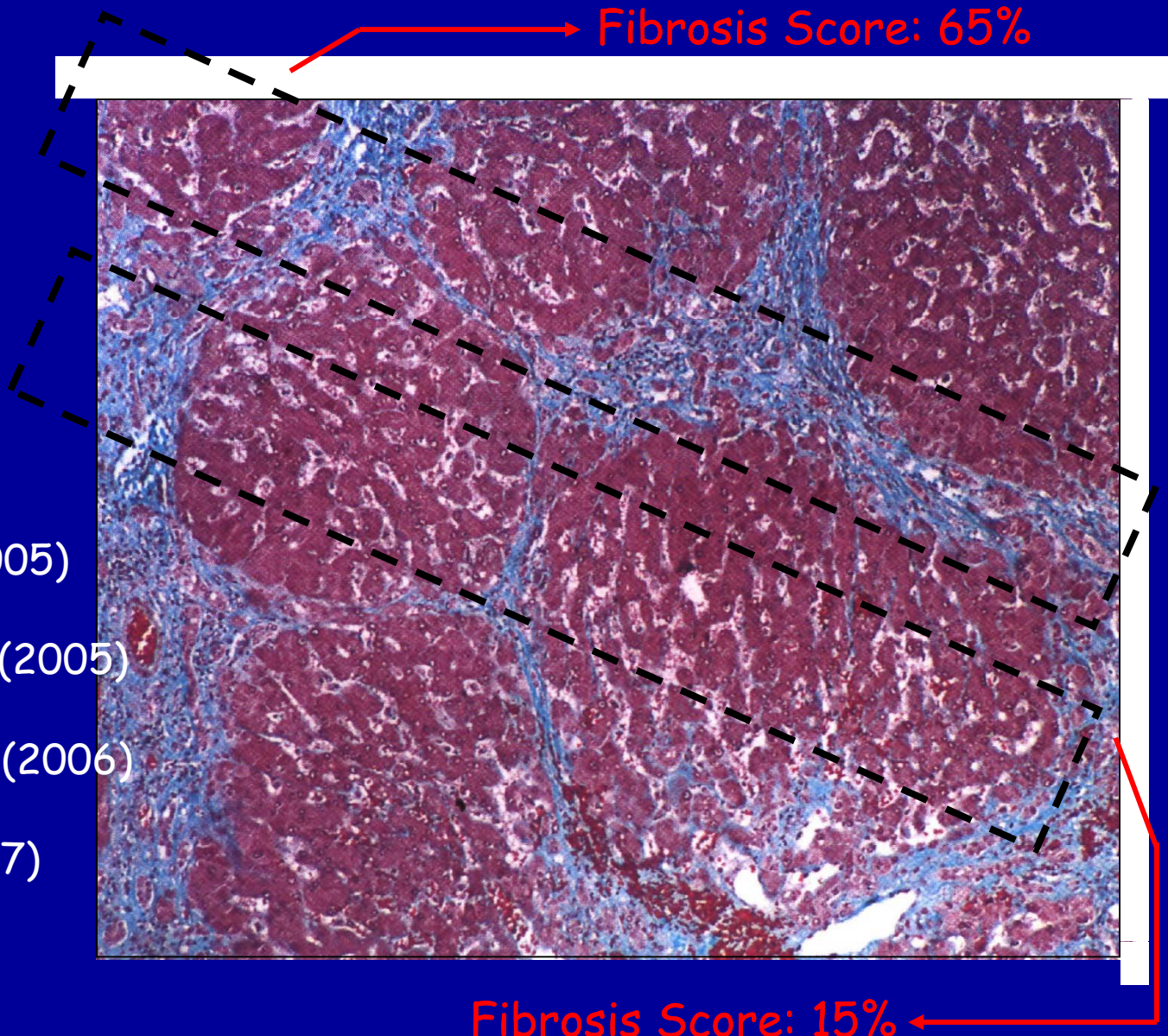

SIEMENS






CM
1
2
3
4
5
6
7
8
Codman

# Sampling Error of Liver Biopsy




Ratziu (2005)

Goldstein (2005)

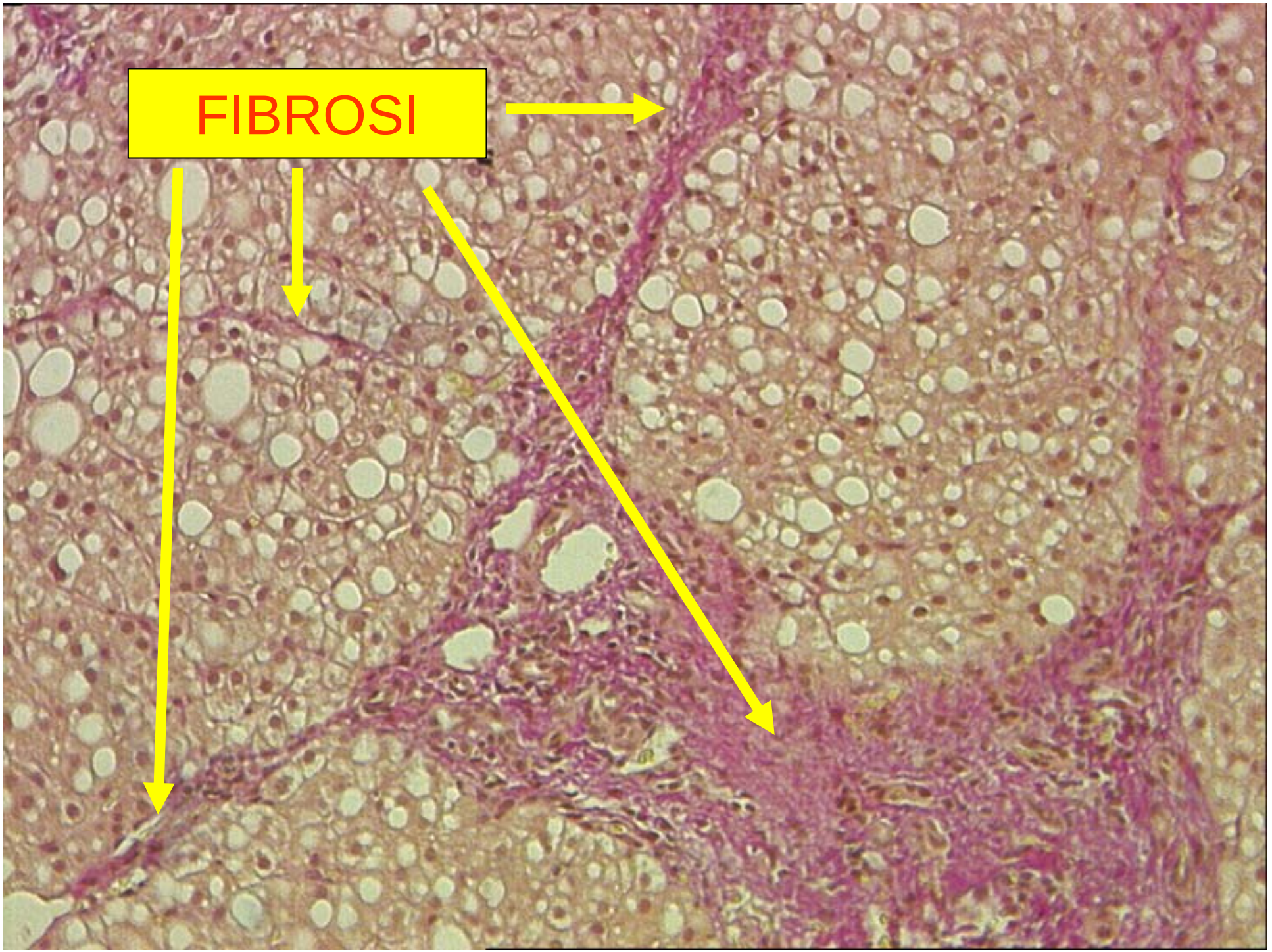
Merriman (2006)

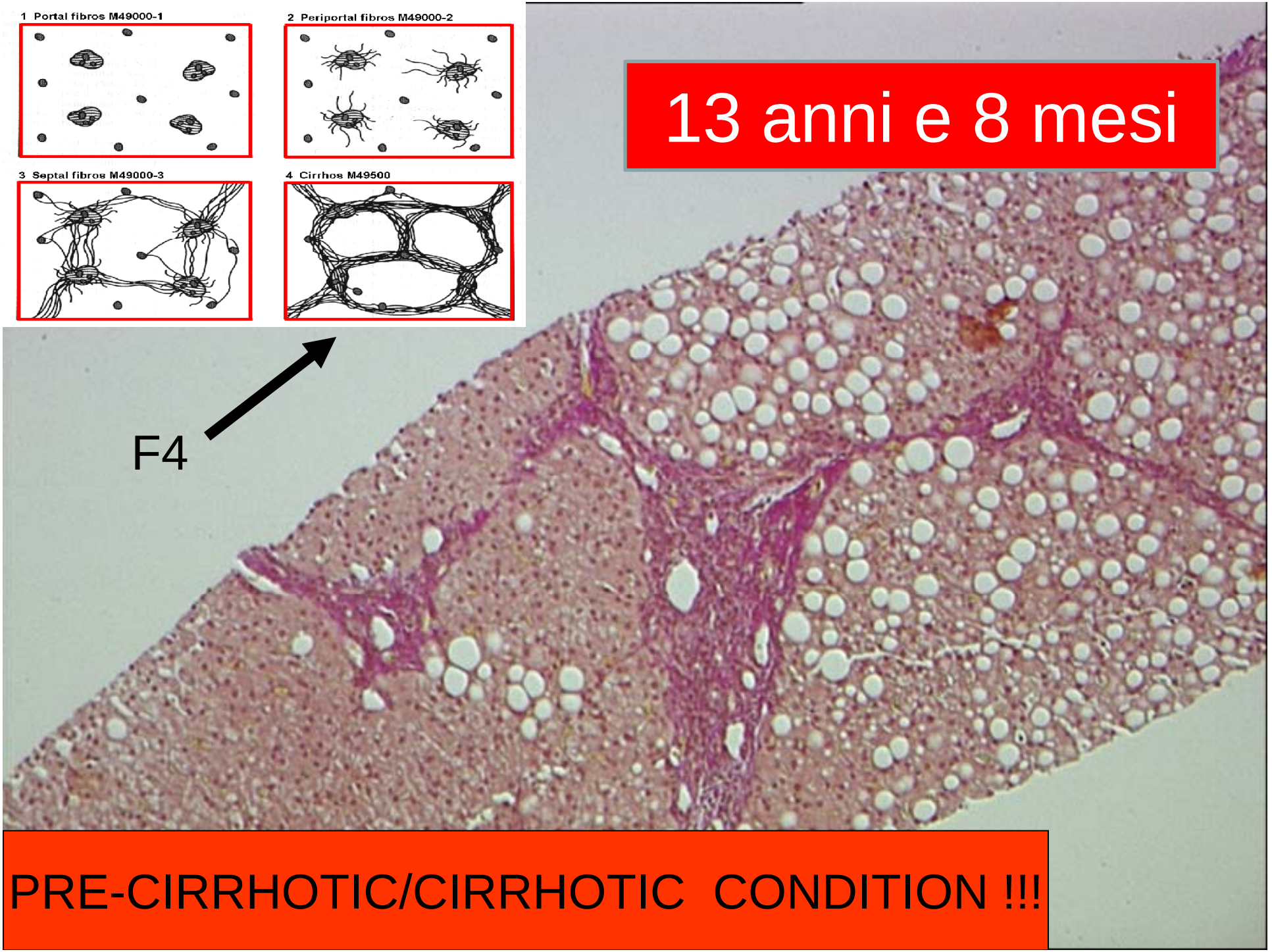
Arun (2007)

Courtesy of D. Schuppan and of A.McCollough






FIBROSI


1 Portal fibros M49000-1
2 Periportal fibros M49000-2
3 Septal fibros M49000-3
4 Cirrhos M49500
13 anni e 8 mesi
F4
PRE-CIRRHOTIC/CIRRHOTIC CONDITION !!!

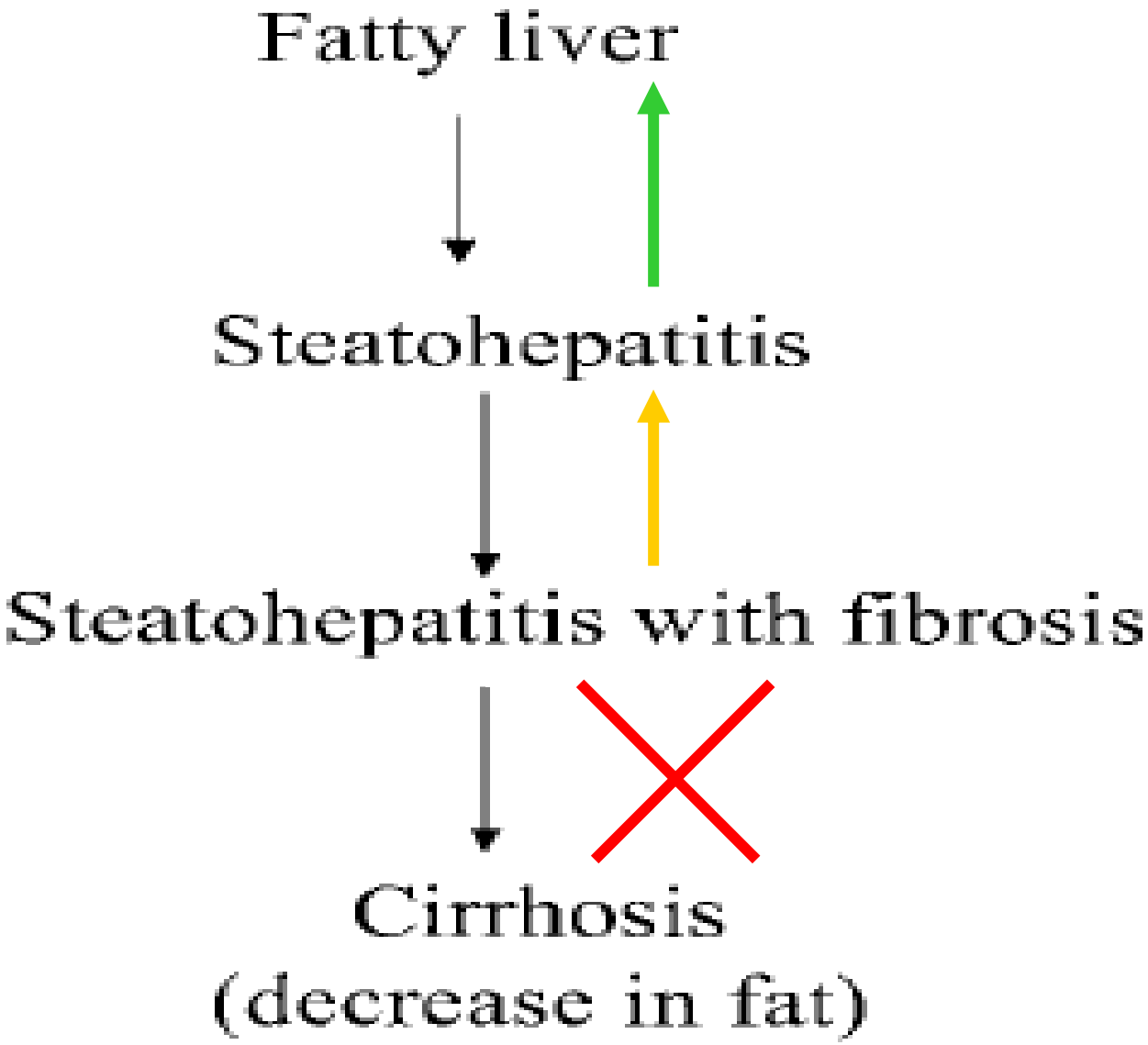



**Figure 2.** Stages in the progression of NAFLD.


4ft
3'4"
2'6"
170 lbs
205 lbs
210 lbs
223 lbs
R. Reynolds




GUT 2008;57(9):1283-7

# Waist circumference correlates with liver fibrosis in children with non-alcoholic steatohepatitis

M Manco,[1] G Bedogni,[2] M Marcellini,[1] R Devito,[3] P Ciampalini,[4] M R Sartorelli,[1] D Comparcola,[1] F Piemonte,[5] V Nobili[1]



BMC Medicine

BioMed Central

Research article

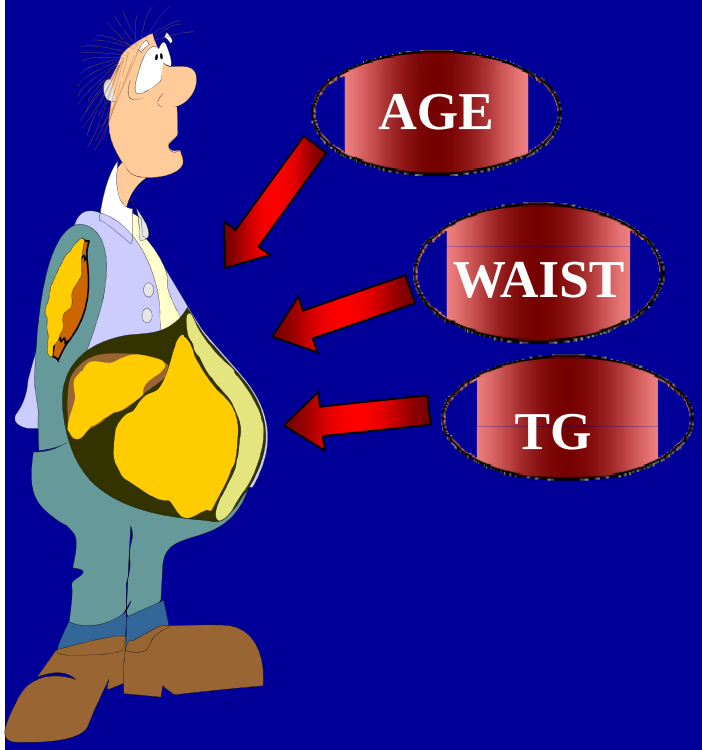
Open Access

# The pediatric NAFLD fibrosis index: a predictor of liver fibrosis in children with non-alcoholic fatty liver disease

Valerio Nobili*[1], Anna Alisi[1], Andrea Vania[2], Claudio Tiribelli[3], Andrea Pietrobattista[1] and Giorgio Bedogni[3]

# Pediatric NAFLD Fibrosis Index

- The index uses an algorithm based on age, waist circumference, and triglycerides with an accuracy of 0.84 (95%CI 0.81–0.87) in detecting fibrosis into the liver.




*Nobili et al, BMC Medicine, 2009*

# The pediatric NAFLD fibrosis index: THE PNFI

*Nobili V et al., BMC Gastroenterol., 2009*

| | | |
|---|---|---|
| Age (years) | 10 | -15,057 |
| Waist (cm) | 84 | 17,388 |
| Trygliceride s | 180 | 10,163 |
| Constant | ********** | -10,074 |
| Sum | ********** | 2,420 |

The PNFI is 9

PNFI ≤ 3 cut-point may be used to rule out liver fibrosis

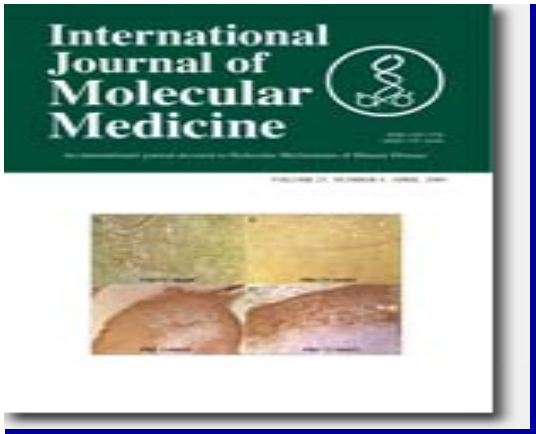
PNFI ≥ 9 cut-point may be used to rule in liver fibrosis




fimp Federazione Italiana Medici Pediatri

# VALIDAZIONE DEL PNFI A LIVELLO NAZIONALE

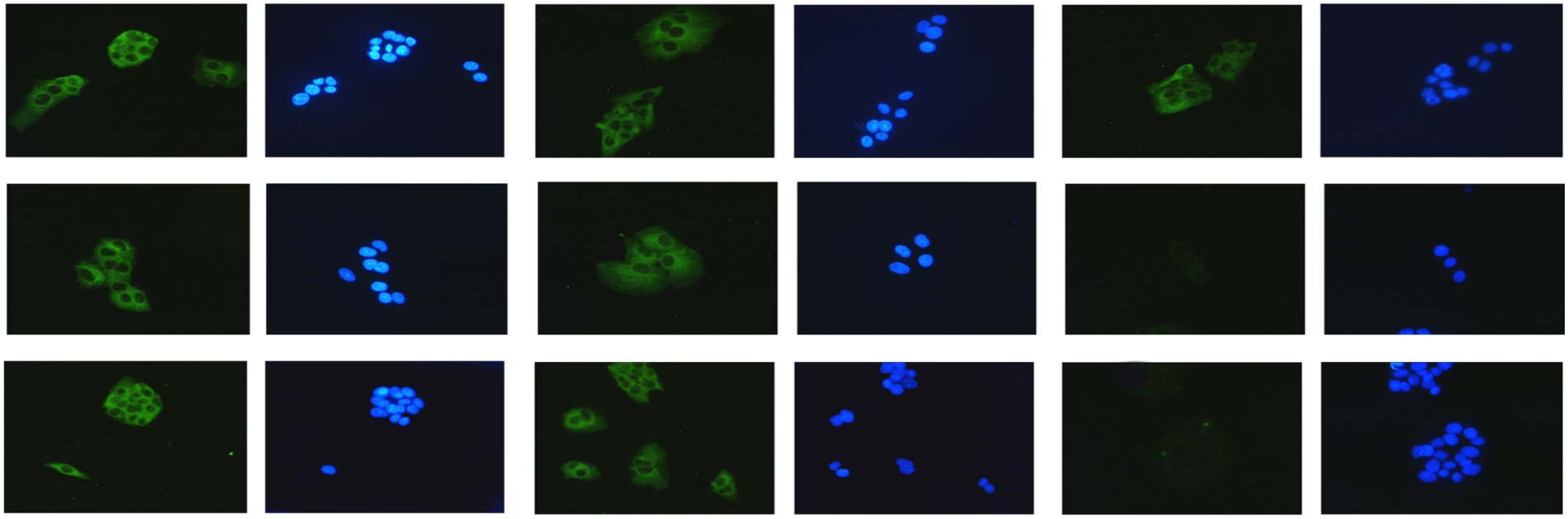





## Int J Mol Med 2009 ( In press)

**Glutathionylation of p65NF-kB correlates with proliferating/apoptotic hepatoma cells exposed to pro- and anti-oxidants**

Anna Alisi [1]*, Fiorella Piemonte [2], Anna Pastore [3], Nadia Panera[1], Chiara Passarelli [2], Giulia Tozzi [2], Stefania Petrini [2], Andrea Pietrobattista [1], GianFranco Bottazzo [4], Valerio Nobili [1]



# Aspetto degli epatociti isolati da ratti NASH con e senza terapia antiossidante



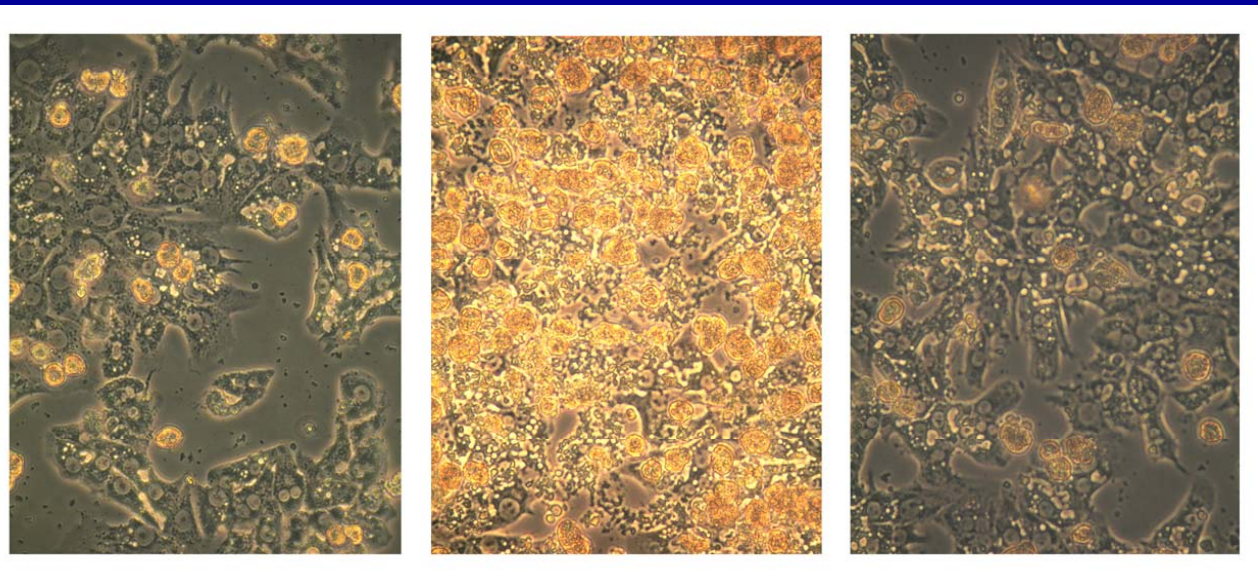
RATTO NORMALE



RATTO NASH

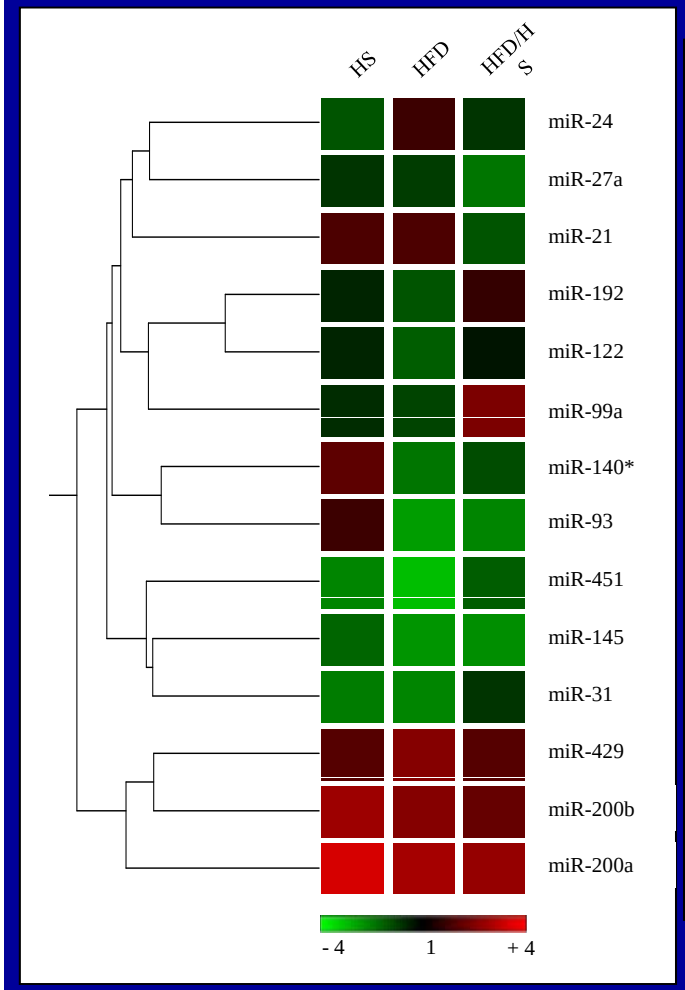


RATTO NASH
TERAPIA ANTIOSSIDANTE

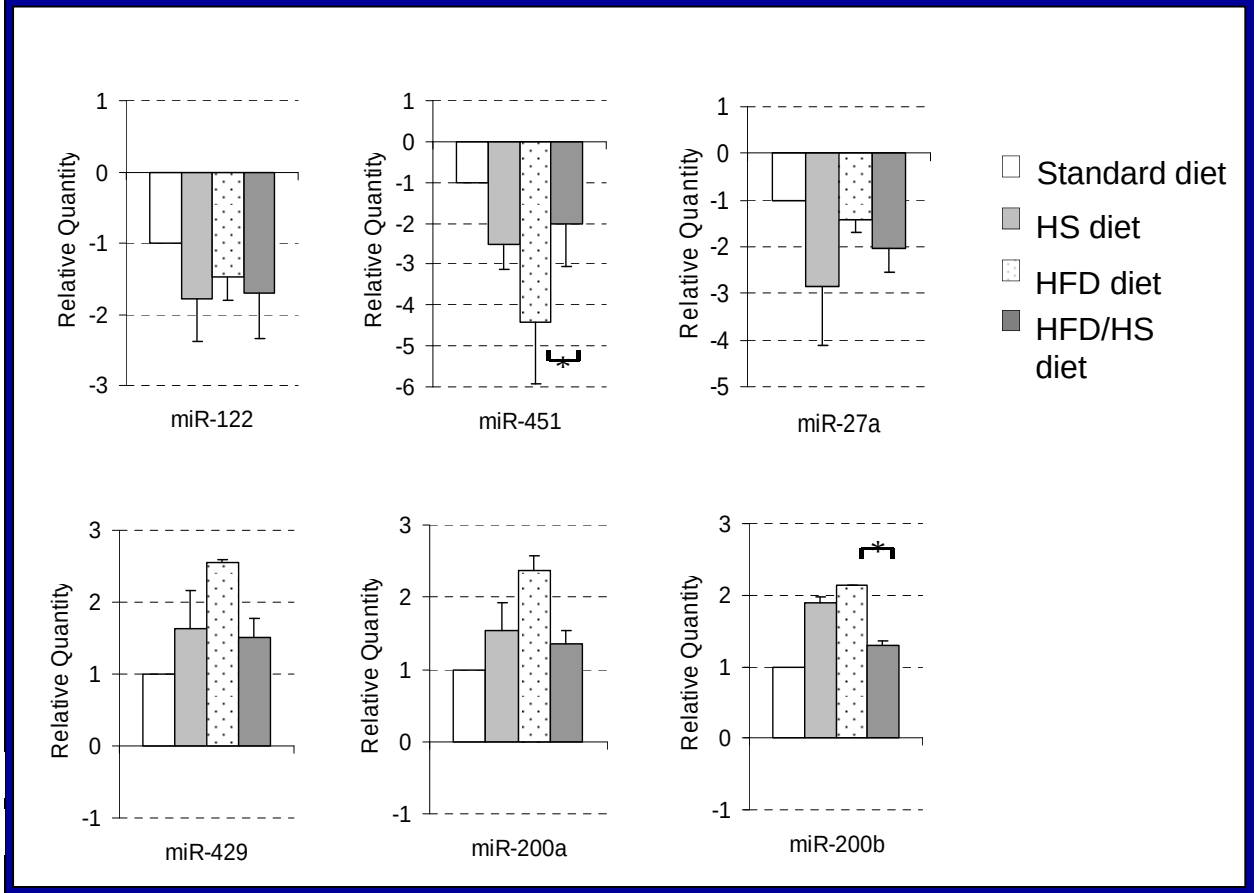


# MicroRNAome analysis to reveals novel molecular determinants in the pathogenesis of diet-induced NAFLD

Unsupervised hierarchical clustering of modulated miRNAs in different diet.

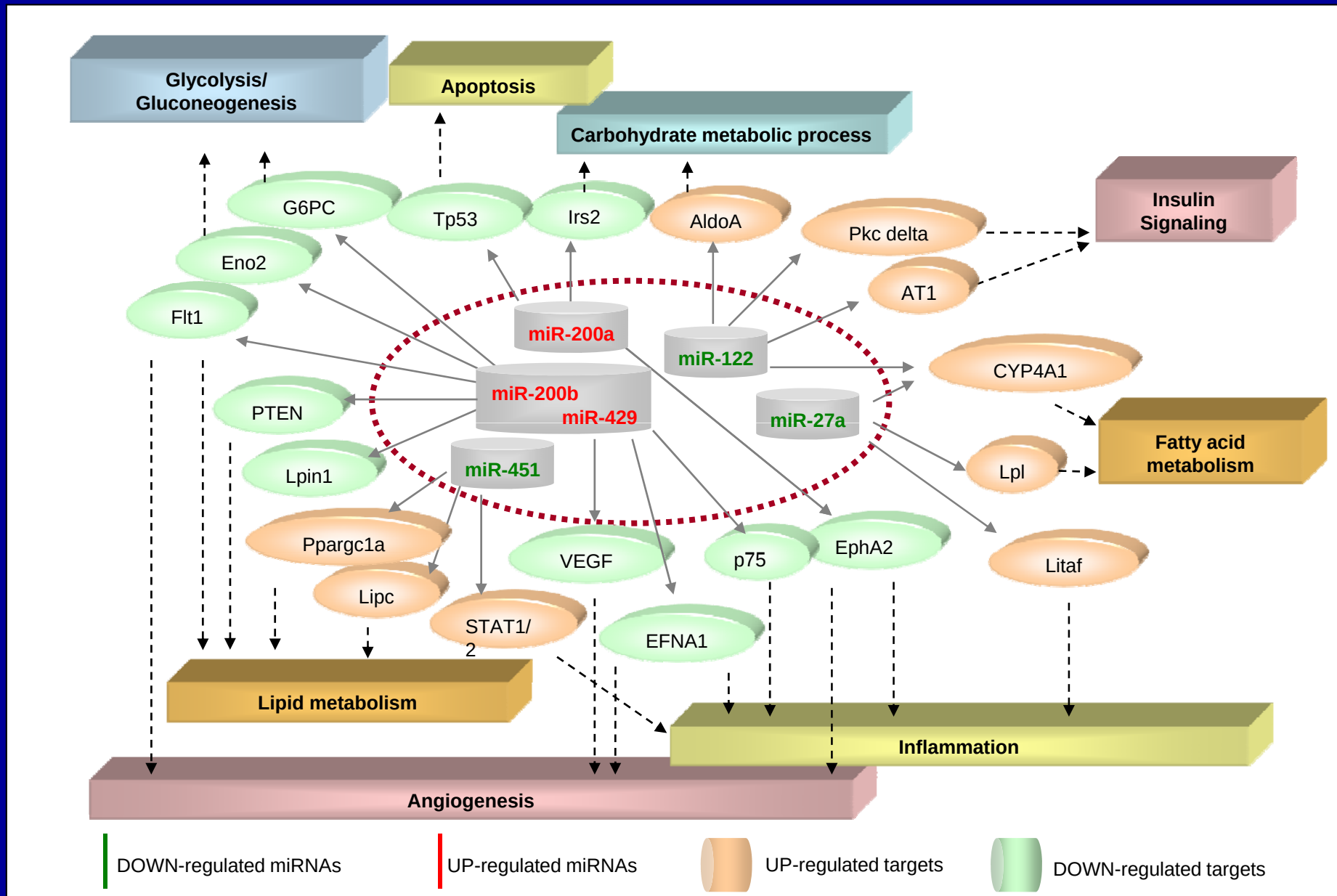



Real-time PCR validation of up and down-regulated miRNAs.



# Diagram of potential miRNA targets.

COURTESY BY Dr ALISI





# Collaborations

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Dr. Rita Devito
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Pr. Christopher P. Day

**Mayo Clinic, Rochester:**
Pr. Paul Angulo

# THANK YOU FOR YOUR ATTENTION

