

**IV CONVEGNO ITALO-BRASILIANO DI PEDIATRIA E NEONATOLOGIA
SALVADOR DE BAHIA
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Follow-up of pediatric chronic liver disease

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Italy

Chronic liver disease

- Cholestatic liver disease
- Viral liver disease
- Metabolic liver disease
- Iatrogenic liver disease
- Genetic liver disease
- Liver in systemic disease

Pediatric liver disease: epidemiology

- 15000 children/yrs hospitalized
- 1:2500 live birth
- 12.5% of liver transplantation

Pediatric liver disease

Cholestatic liver disease

- Biliary atresia

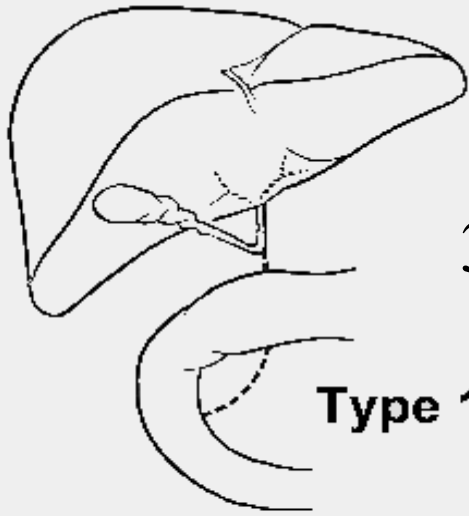
Metabolic disease

- Non alcoholic fatty liver disease (NAFLD)

Biliary Atresia: Epidemiology

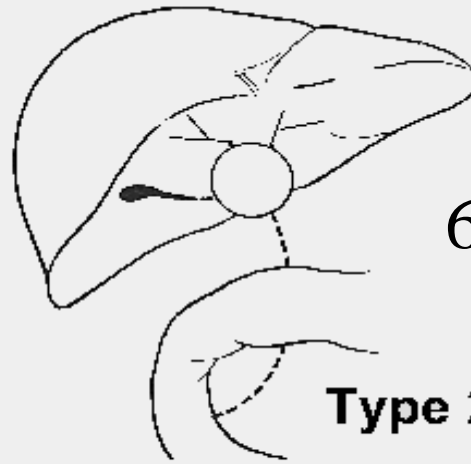
- The most common neonatal cholestasis disorder (1:18000 live birth)
- High morbidity and mortality with high health costs: (0.2% of total health care expenditure for 0.0006% of pediatric population in USA)

Anatomical type of biliary atresia



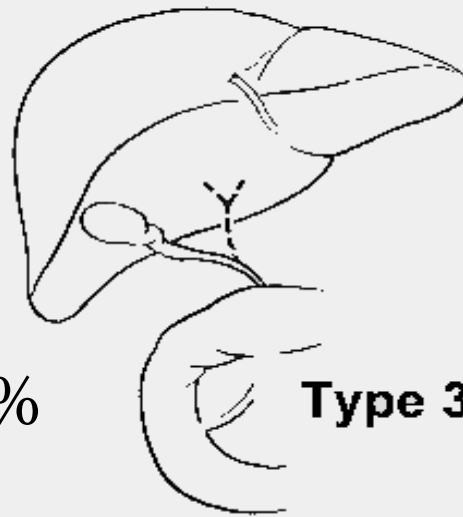
3%

Type 1



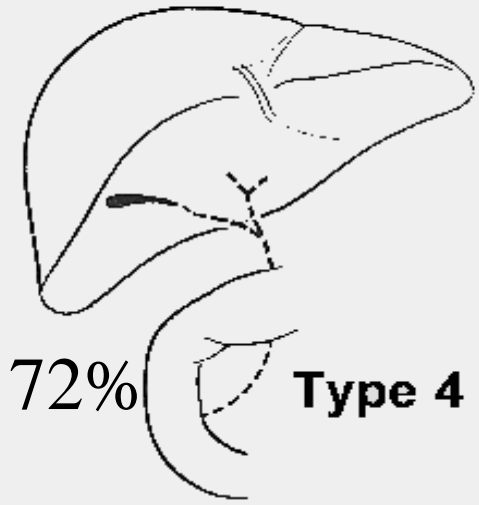
6%

Type 2



19%

Type 3



72%

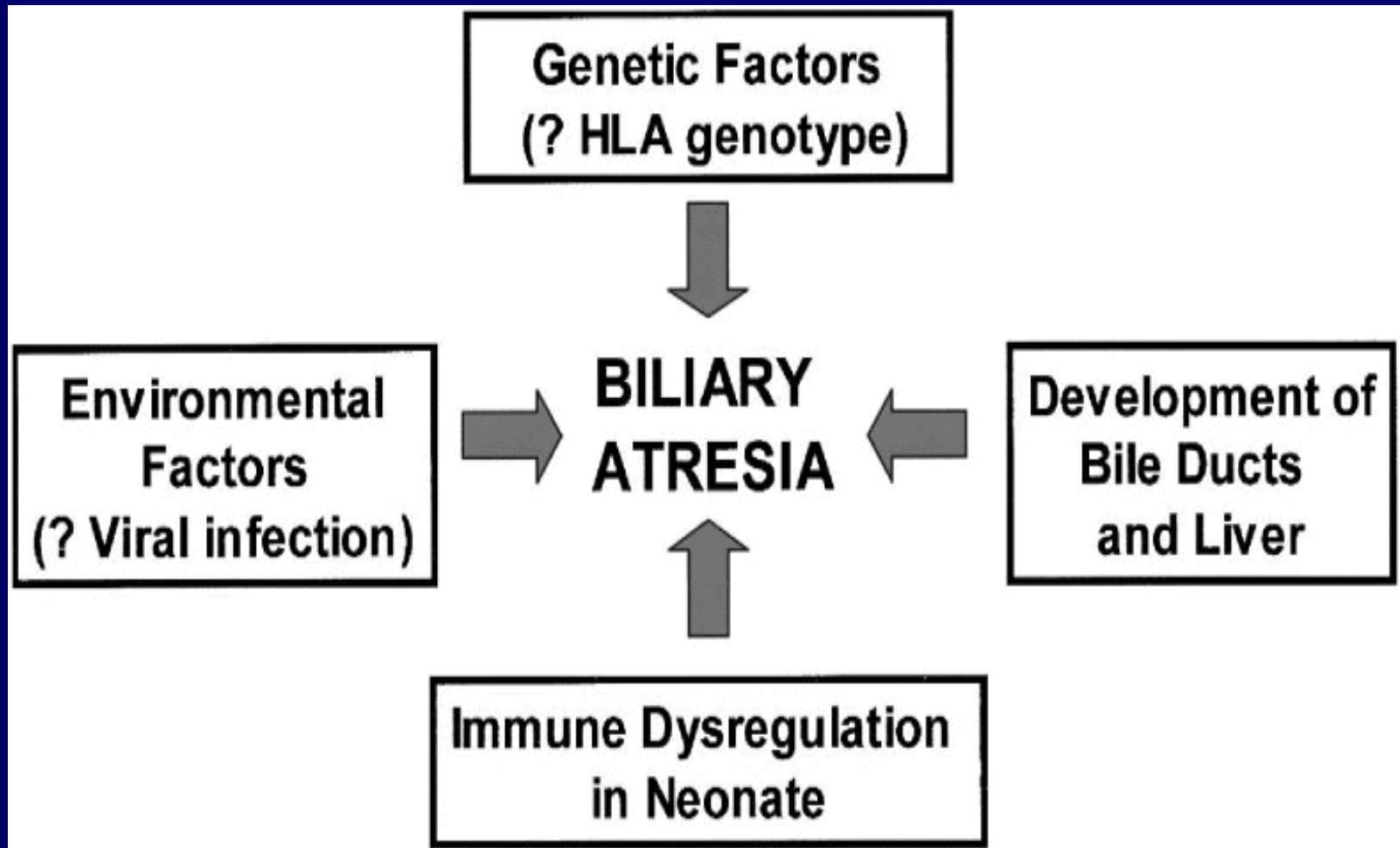
Type 4

Forms of Biliary Atresia

Fetal or embryonic form (8-12%):
hepatobiliary disease associated with polysplenia, cardiac defects, absence of retrohepatic inferior cava, situs inversus pre-duodenal portal vein, malrotation of the intestine

Perinatal or acquired form (>80%)

Biliary Atresia: Pathogenetic aspects



Management of Biliary Atresia

- Medical treatment: no effective (UDCA only after surgery)
- Kasai operation
- Liver transplantation

Kasai Procedure

Liver

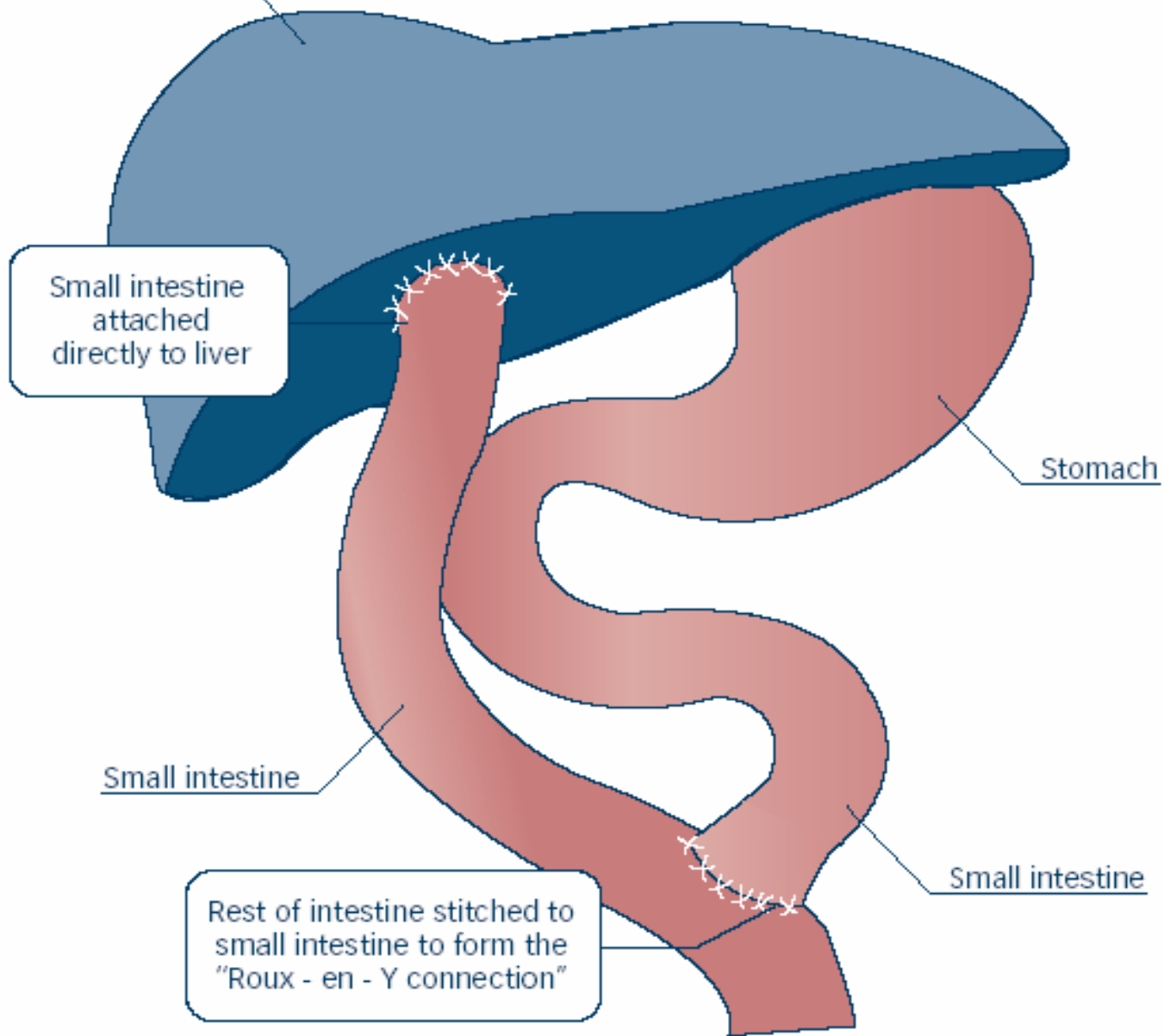
Small intestine attached directly to liver

Stomach

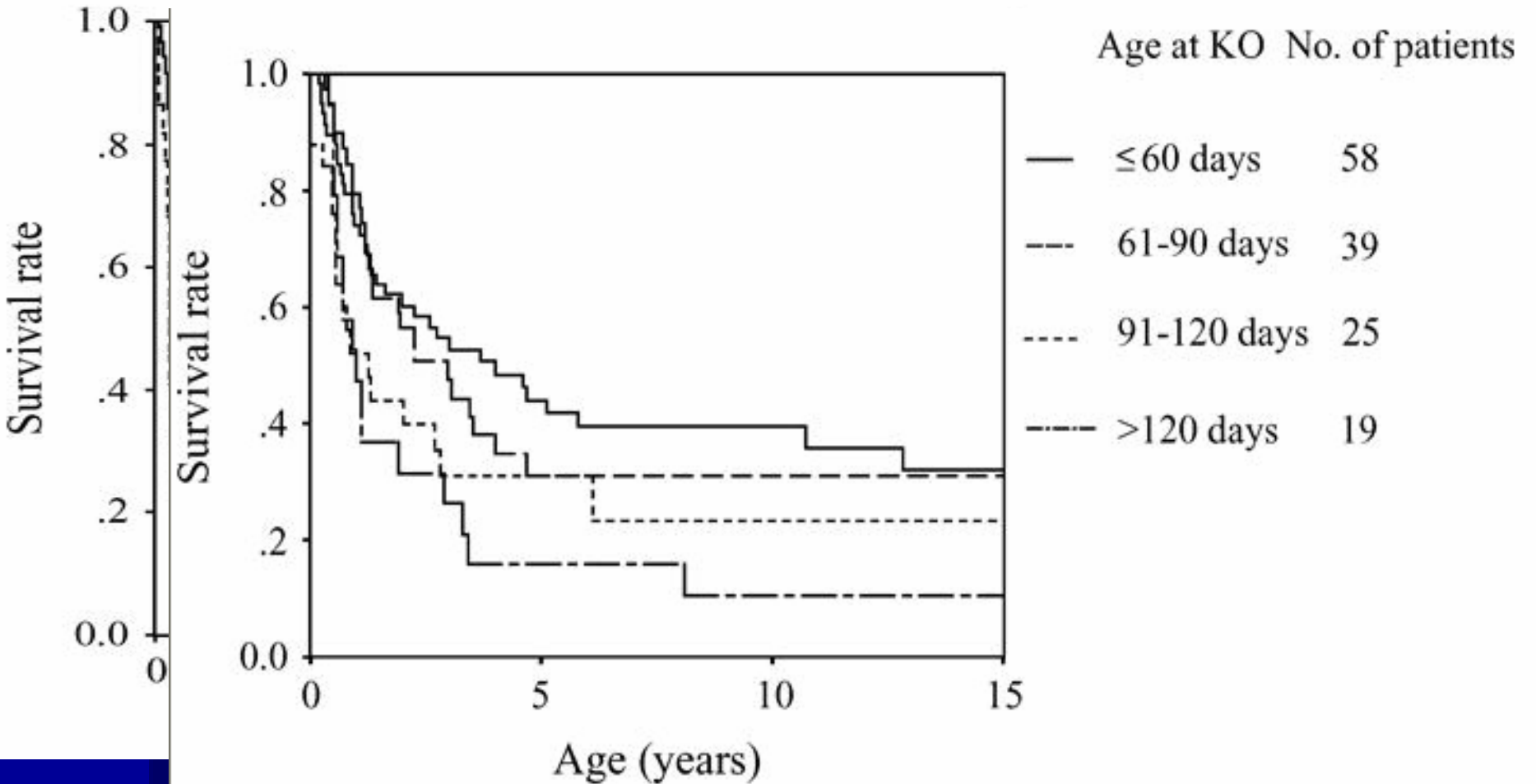
Small intestine

Rest of intestine stitched to small intestine to form the "Roux - en - Y connection"

Small intestine



Biliary Atresia and Kasai operation: survival rate (n=141)



Biliary Atresia and Kasai operation: risk factors (n=141)

Variable	RR	CI 95%	<i>P</i>
Year of Kasai operation			
1976–1980	3.1	>(1.8; 5.3)	<0.005
≥1980	1	–	
Age at Kasai operation (days)			
≤120	1	–	0.608
>120	1.2	(0.7; 2.4)	
Jaundice free after Kasai operation			
Yes	1	–	<0.005
No	3.4	(2.2; 5.4)	
Repeated cholangitis			
No	1	–	0.039
Yes	1.6	(1.1; 2.6)	

RR, risk ratio; CI, confidence interval.

Complications of Kasai operation

Early:

bacterial cholangitis

obstruction of the intestinal loop

Late:

portal hypertension

- variceal hemorrhage (40-60% at 5-10 yrs)

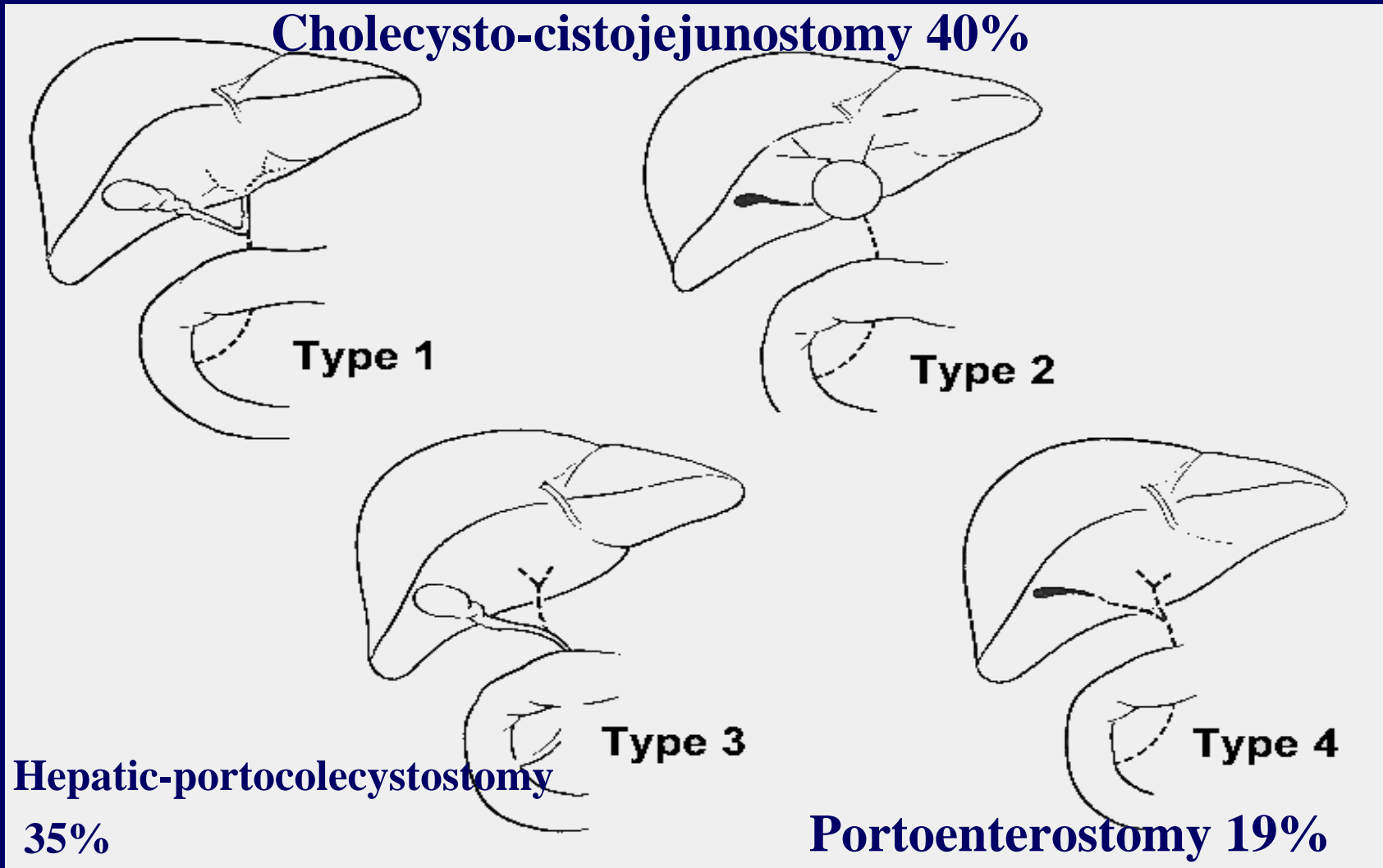
- ascites – SBP- pruritus

portosystemic encephalopathy

Factors shown to predict outcome after kasai

- Age at operation
- Experience of the surgeon
- Site of atresia of the extrahepatic duct
- Number and severity of cholangitis

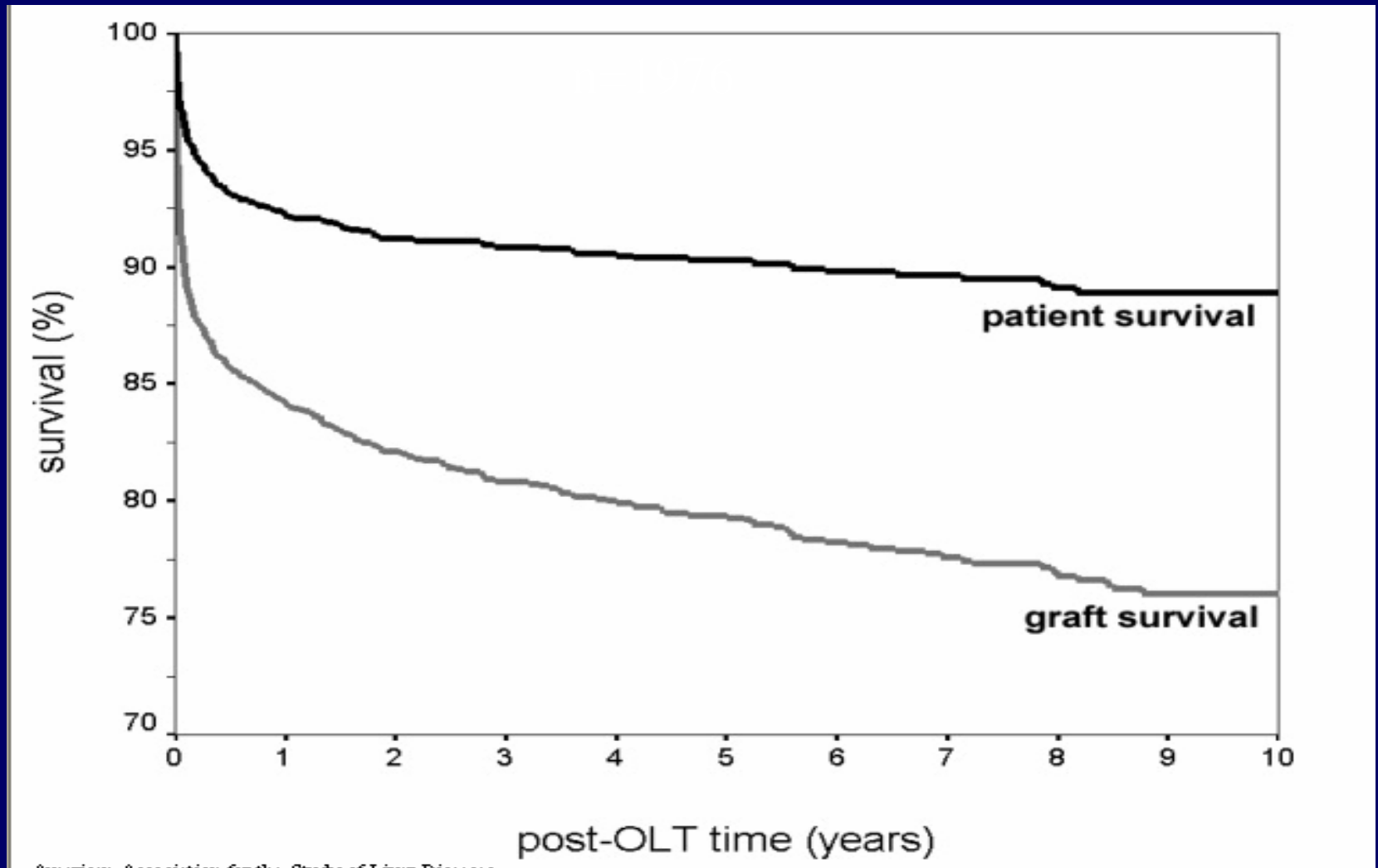
20 yrs survival after surgery with native liver according to type of biliary atresia (n=63)



Biliary atresia: Indication for Liver Transplantation

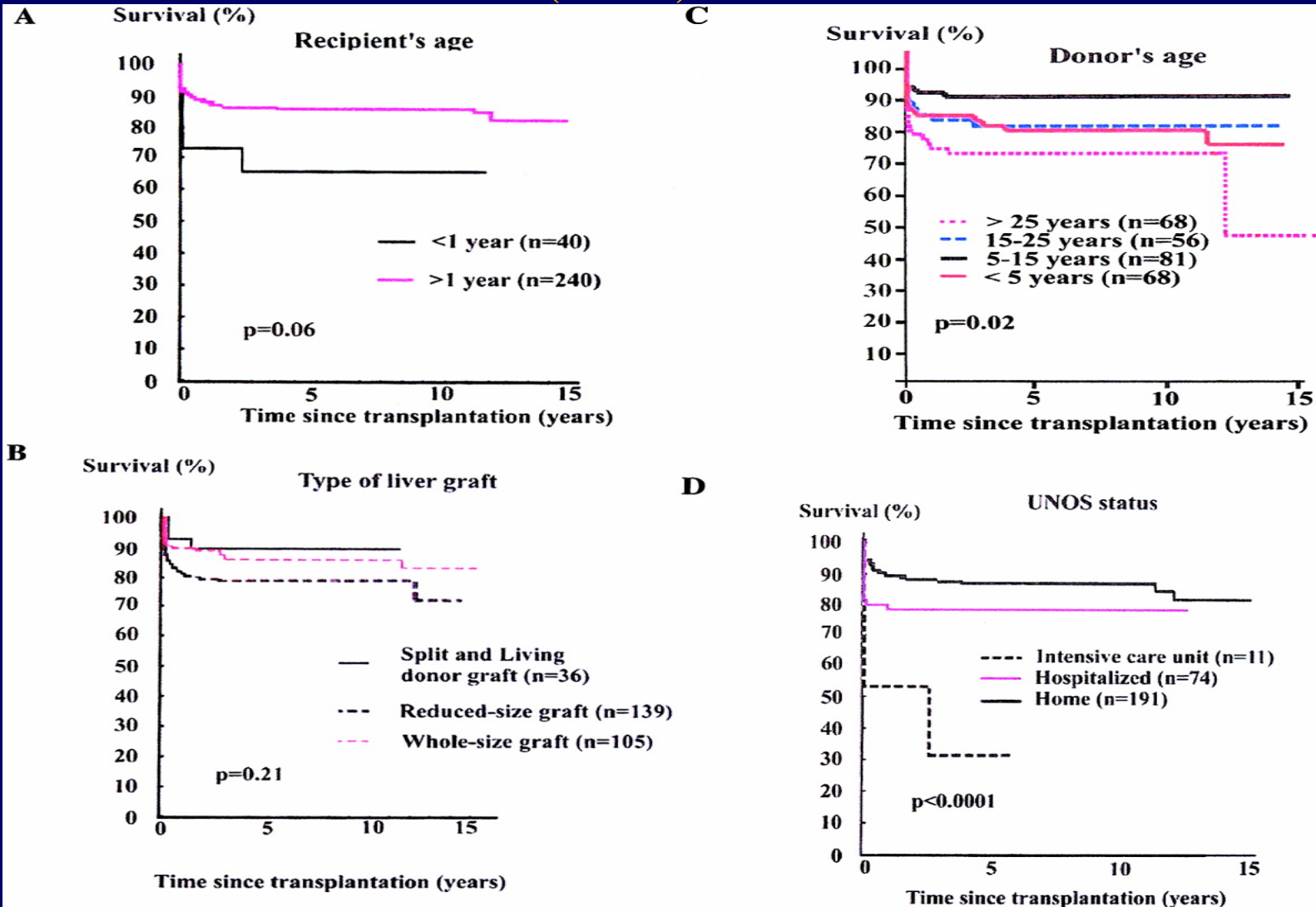
- Poor bile drainage after kasai
- End stage liver disease
- Intractable biliary tract infections

Biliary atresia: Actuarial survival rate after OLT (n=1976) (UNOS database)



Biliary atresia: survival rate after OLT

(n=280)



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NAFLD/NASH

NAFLD

Steatosis

Non specific
Inflammation

NASH

Necroinflammation+
Balloniform Degeneration

Fibrosis

Prevalence of NAFLD in children

NAFLD is likely the most common cause of liver disease in children

Non selected children

- Ultrasound study (Japan) 2,6 %
- Necroscopy study (USA) 17 %

Obese children

- Biochemical study (ALT evaluation) 23-77%

NAFLD: Causes

Insulin-resistance



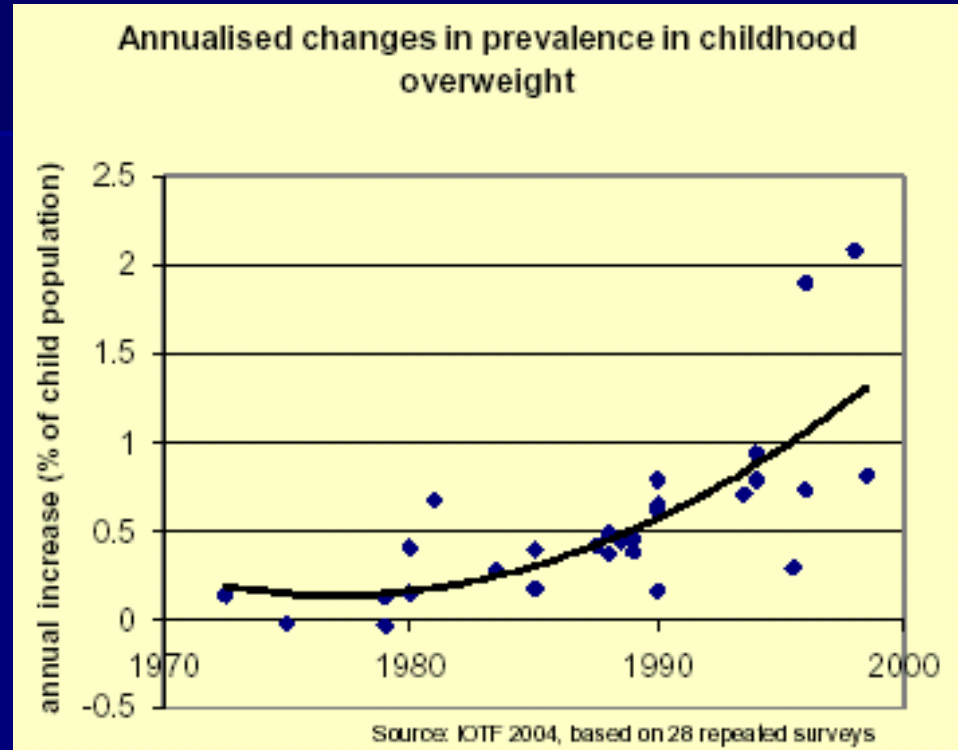
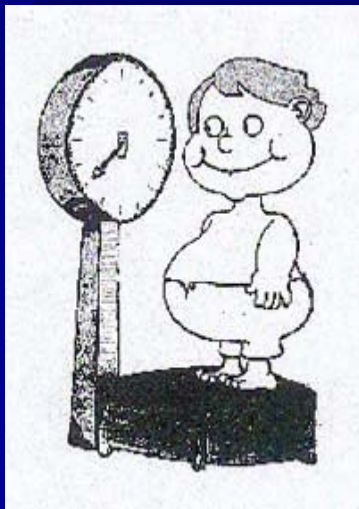
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graph TD; IR([Insulin-resistance]) --- O((Obesity)); IR --- D((Diabetes)); O --- D;
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Obesity

Diabetes

OBESITA' IN ETA' PEDIATRICA

Childhood obesity

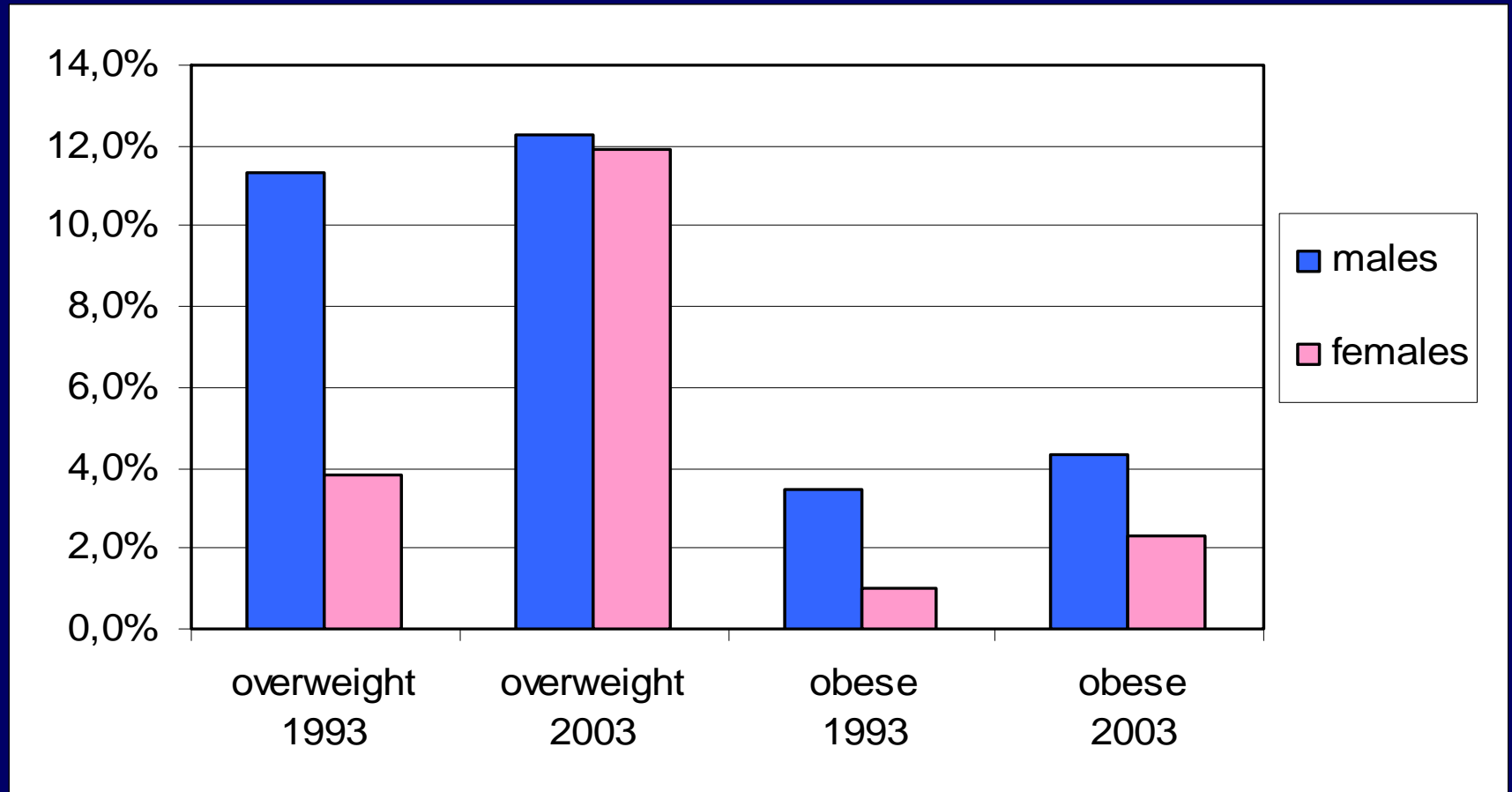


Obesity in Europe - 3 International Obesity TaskForce March 2005

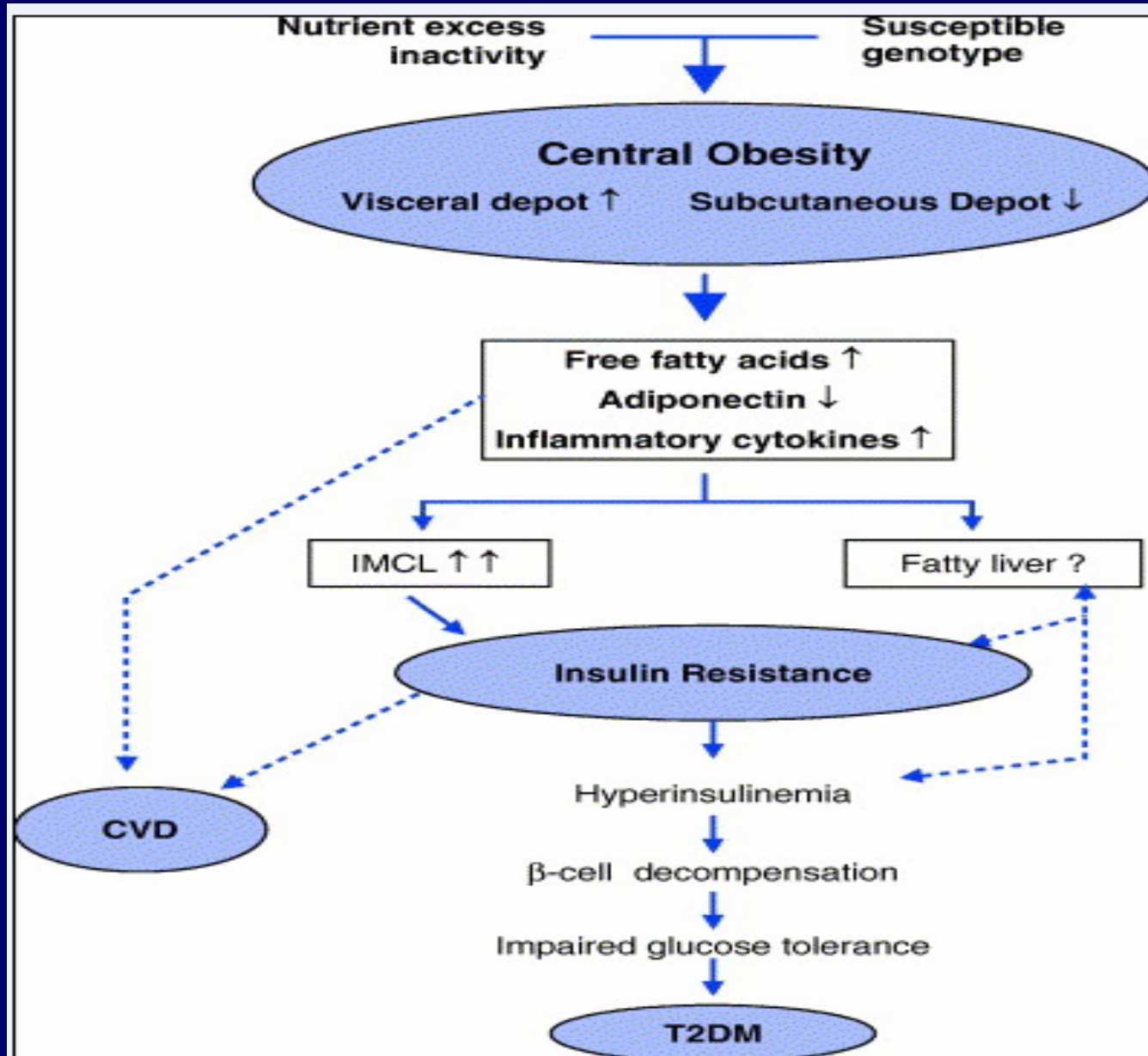
- Pandemia
- Tracking
- Morbidity

OBESITA' IN ITALIA

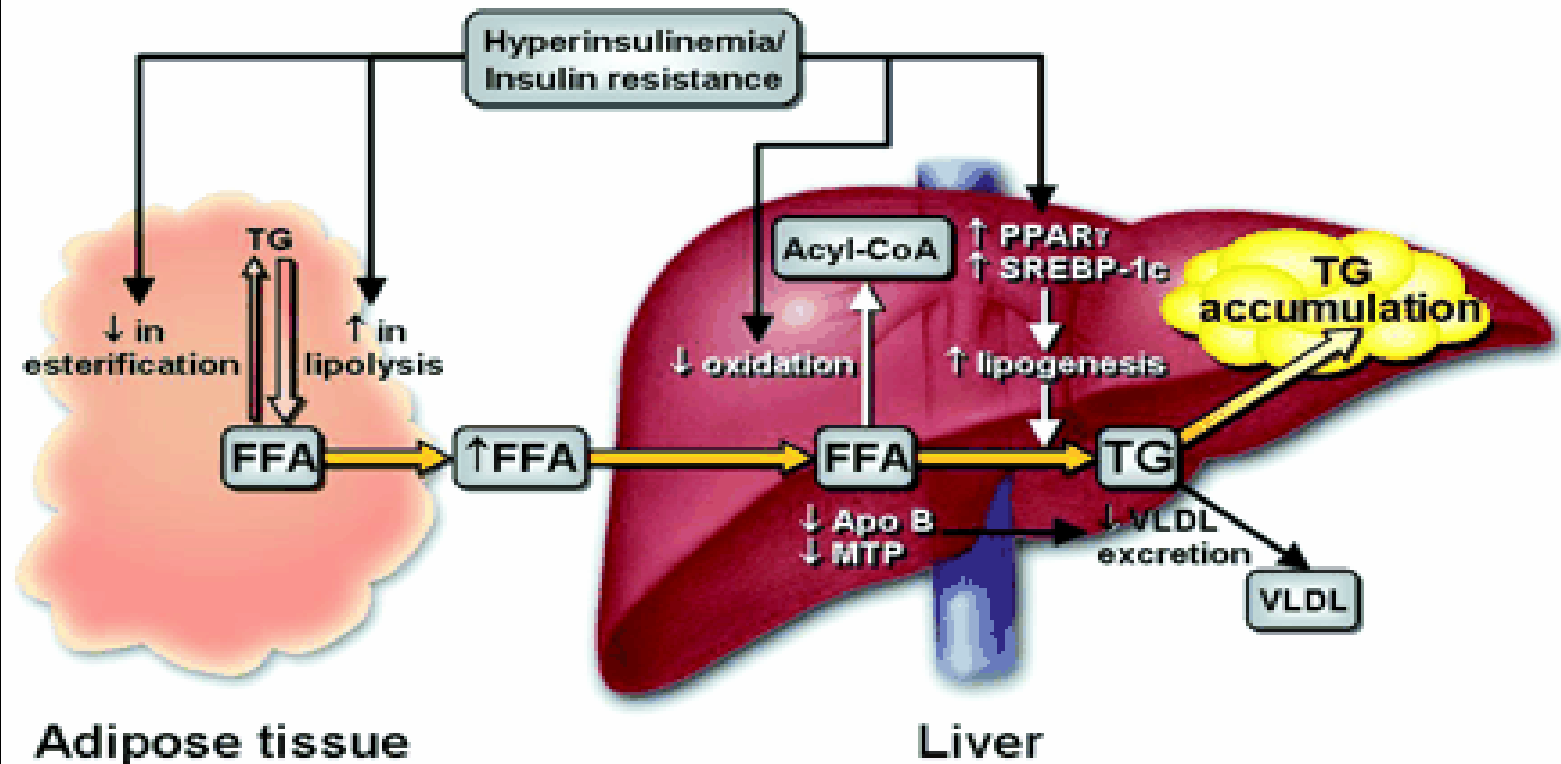
Prevalenza del sovrappeso e dell'obesità
in bambini italiani dai 2 ai 6 anni.



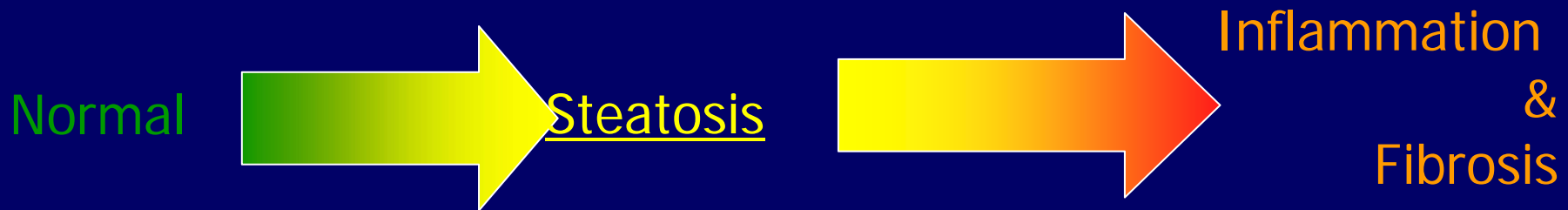
Mechanisms of obesity-related morbidities



NAFLD and Insulin Resistance



Two hits theory"



1° hit:

-hyperinsulinism

↑ FFA

↓ B-Oxidation FFA

↓ Export triglycerides

2° hit:

↑ Oxidative Stress (Fe, CYP2E1)

↑ Lipids Peroxidation

↑ TNFa

↑ TGFb

↑ Leptin

Categories of NAFLD: from Steatosis to NASH

- Type 1: Simple steatosis
- Type 2: Steatosis plus lobular inflammation
- Type 3 : Steatosis,lobular inflammation, ballooning degeneration
- Type 4: Steatosis, ballooning degeneration, Mallory bodies and or fibrosis

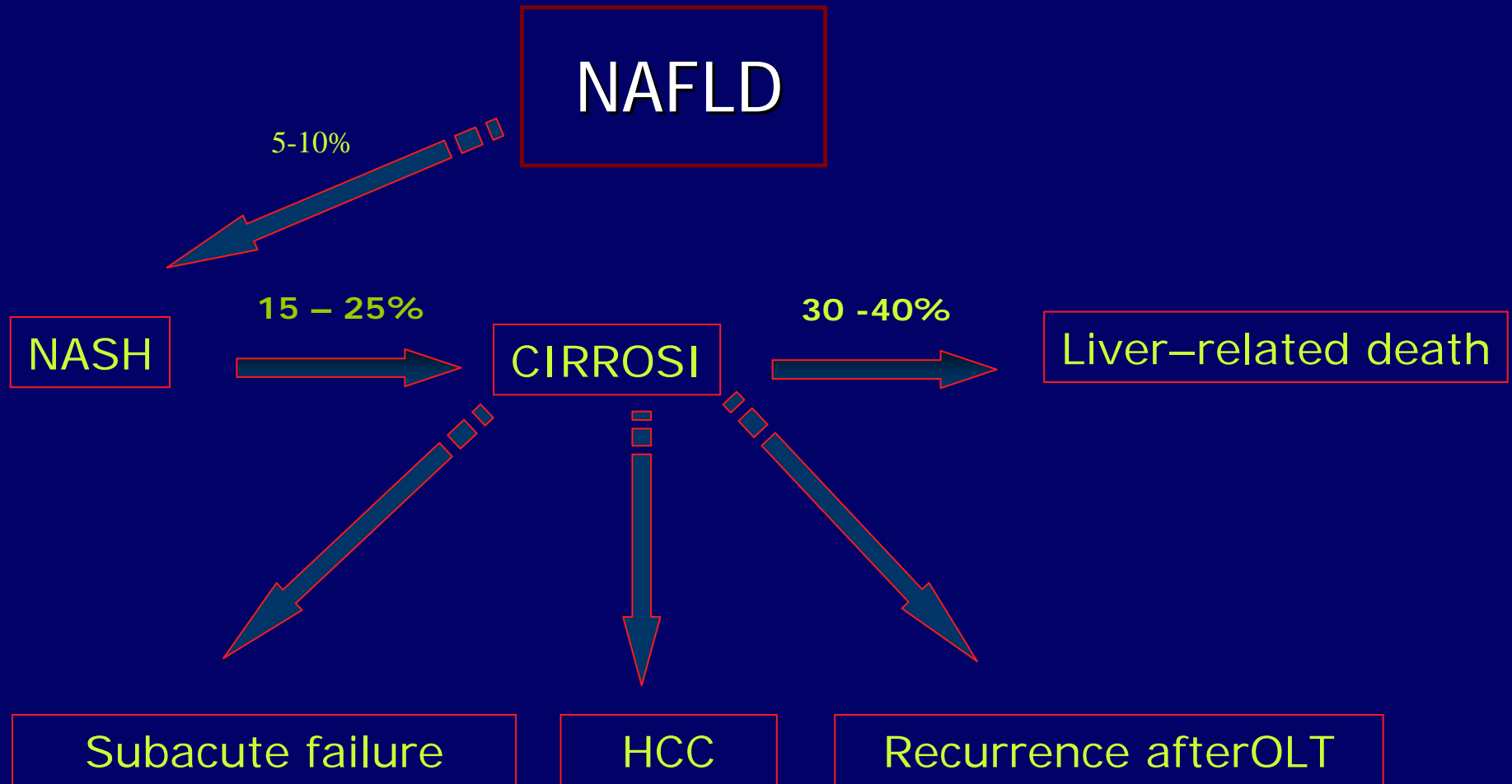
NASH Type: Definition

Adult	Type 1			Type 2		
Ballooning degeneration	+	+	-			-
Perisinusoidal fibrosis	-	+	+			-
Steatosis		+			+	
Portal inflammation		-		+	+	-
Portal fibrosis		-		-	+	+

Children

+, feature is present; -, feature is absent.

Natural history of NAFLD



NASH: predictors of fibrosis (n=144)

- Age > 45 anni
- BMI > 31,1 Kg/m² (M) e 32,3 Kg/m² (F)
- AST/ALT ratio > 1
- NIDDM

Independent predictors

Predictors of liver pathology outcome (Multivariate model) (n=43)

	Model	Variables	P value
Steatosis	< 0.0001	QUICKI	< .0001
		Age	< .0001
		Race	.0060
Inflammation, portal	0.0009	ALT	.0181
		Insulin	.0007
Fibrosis, perisinusoidal	< 0.0001	AST	.0003
		Insulin	.0003
		BMI Z score	.0004
Fibrosis, portal	0.0028	RUQ pain	.0031
		HOMA-IR	.0178

Management NAFLD

NASH require two hits:- fat accumulation in liver
- increased oxidative stress



Modify Lifestyle

- appropriate diet
- aerobic exercise

Pharmacological treatment

Fats, Oils & Sweets
USE SPARINGLY

KEY

- Fat (naturally occurring and added)
- ▼ Sugars (added)

These symbols show fats and added sugars in foods.

Milk, Yogurt & Cheese Group
2-3 SERVINGS



Meat, Poultry, Fish, Dry Beans, Eggs & Nuts Group
2-3 SERVINGS



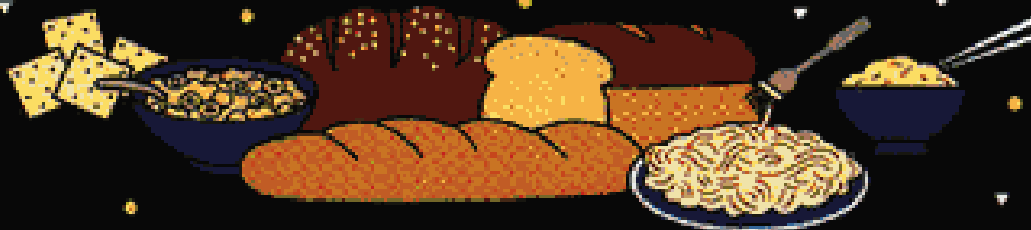
Vegetable Group
3-5 SERVINGS



Fruit Group
2-4 SERVINGS



Bread, Cereal, Rice & Pasta Group
6-11 SERVINGS



Bread, Cereal, Rice & Pasta Group
6-11 SERVINGS

PLAY EVERY DAY!

PLAY EVERY DAY!

CUT DOWN ON



- T.V. watching
- Video and computer games
- Sitting more than 30 minutes at a time

2-3 TIMES A WEEK

Leisure & Playtime



- Swinging
- Canoeing
- Tumbling
- Miniature golf

Strength & Flexibility



- Push-ups/pull-ups
- Martial arts
- Dancing
- Rope climbing

3-5 TIMES A WEEK

Aerobic Exercises (at least 20 minutes)



- Roller blading
- Biking
- Skateboarding
- Rope climbing
- Swimming
- Running



Recreational activities (at least 20 minutes)



- Volleyball
- Basketball
- Soccer
- Skiing
- Kickball
- Relay races

EVERYDAY

(as often as possible)



- Play outside
- Take the stairs instead of the elevator
- Help around the house or yard

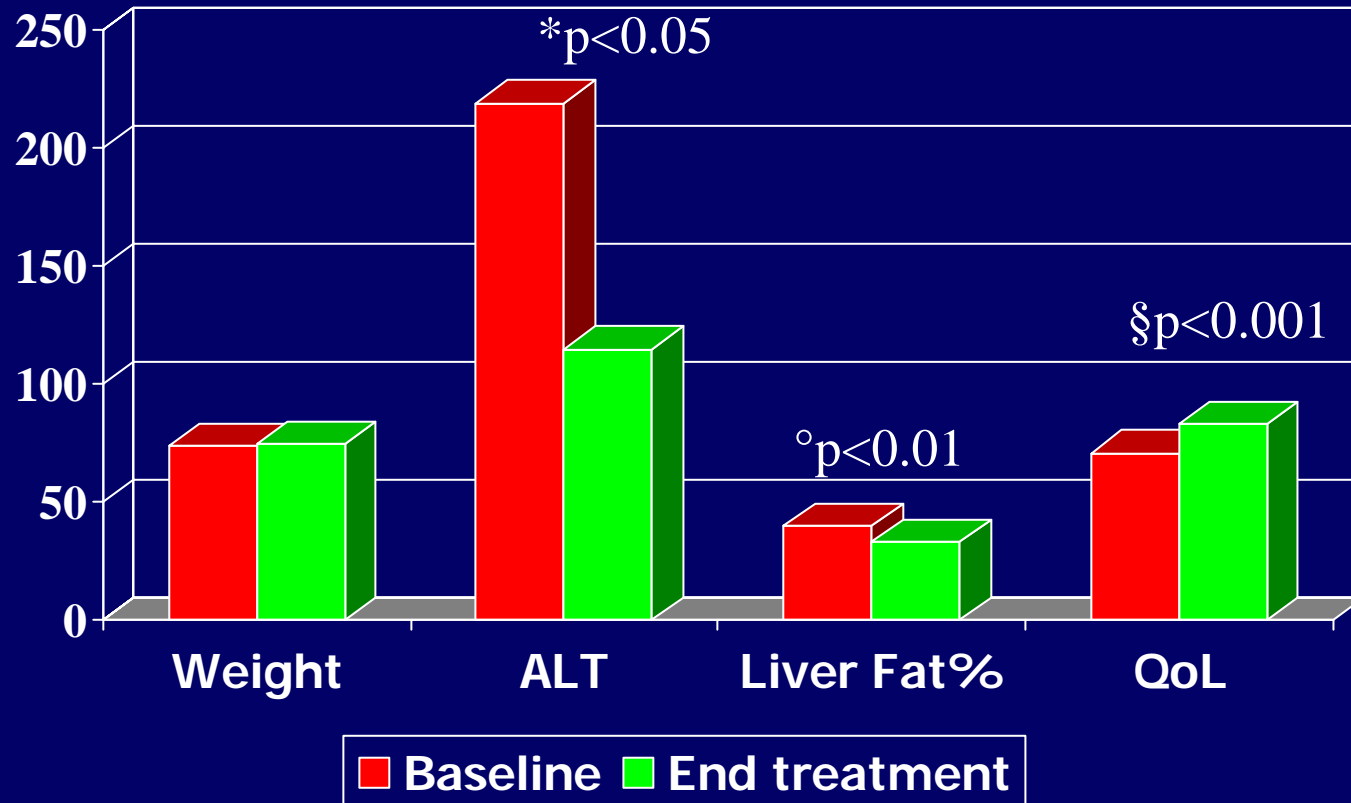
- Bathe your pet
- Pick up your toys
- Walk to the store
- Go for a walk



Pediatric trial treatment in NAFLD

Intervention	n	Entry criteria	Duration tpx mo.	Outcome
Vit. E Levine 00	11	Obese, ALT	4-10	Normal ALT- same BMI
UDCA Vairo 00	7	Obese,ALT	4	↔ ALT,US
Weight loss Vairo 94	7	Obese,ALT	2-6	Normal ALT, ↓↓ US
Weight loss Franzese 97	28	Obese,US	3-6	↓↓ US

Effect of 24 wks metformin (500 mg/bd) treatment for pediatric NASH (n=8)



Quicki: before 0.294, after 0.310 p<0.05

Schwimmer APT,2005

TONIC Trial: Treatment of Nonalcoholic fatty Liver Disease in Children (funded by NIDDKD)

- Tonic trial will enroll 180 nondiabetic boys and girls ages 8 to 15 yrs with NAFLD
- TREATMENT Schedule:
Metformin+ Vit E
VS
Placebo for 2 yrs