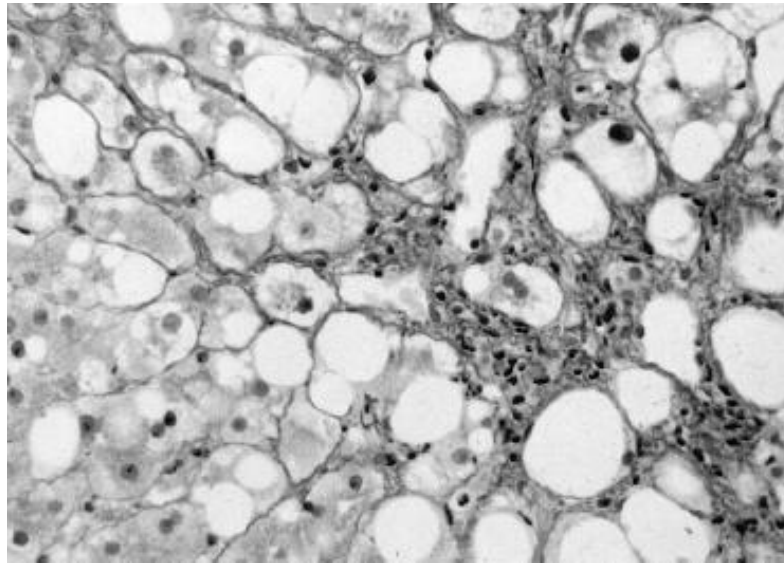


Alcoholic liver disease

Role of nutrition as risk factor and
therapeutic options



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Risk factors for ALD

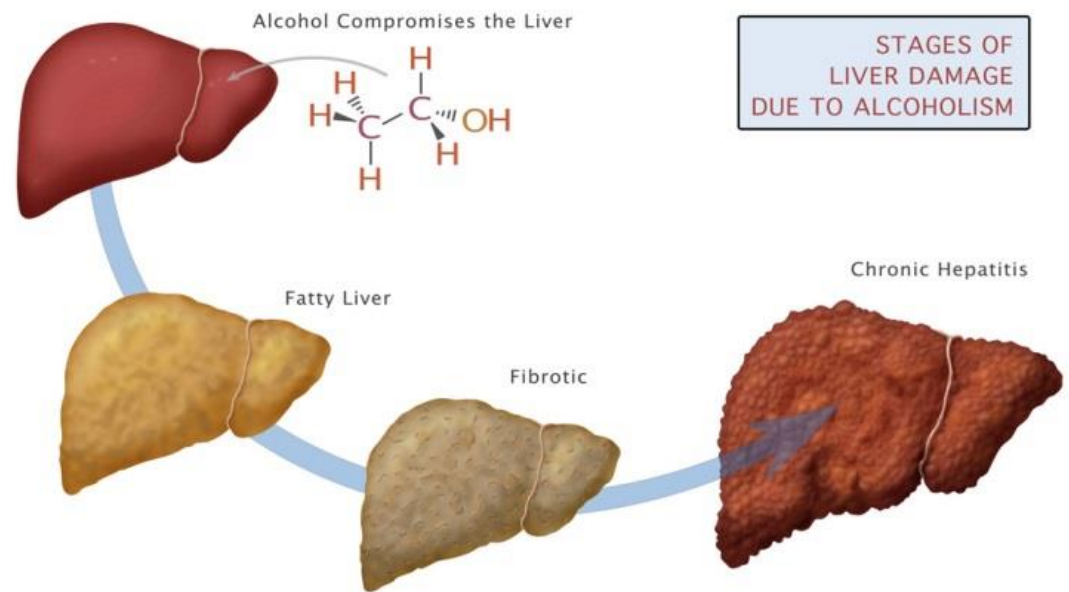
➤ Other risk factors

- ➔ **nutritional status**
- ➔ **gender (female)**
- ➔ **overweight >10 yrs**
- ➔ **genetic factors**
- ➔ **ethnic differences**

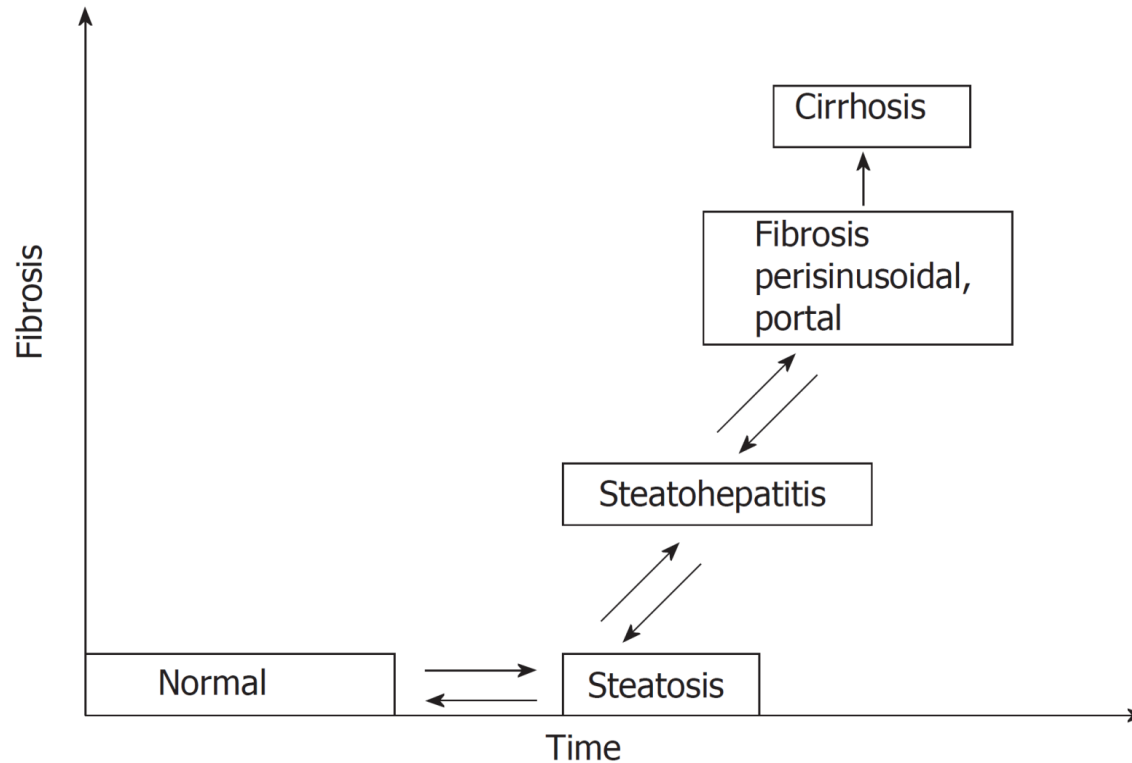
	Overweight Patients	Nonoverweight Patients	<i>P</i>
Number of patients	172	1,432	
Presence of cirrhosis (%)	103 (60)	505 (35)	<.001
Females (%)	41 (24)	366 (26)	NS
Age (y)	56 ± 9	46 ± 12	<.001
Total duration of alcohol abuse (y)	26 ± 12	22 ± 13	<.01
Alcohol intake over the last 5 years (g/d)	121 ± 73	117 ± 78	NS
BMI from minimum weight in the last 10 years	29 ± 2	21 ± 3	<.001
BMI 1 year before hospitalization	31 ± 4	22 ± 4	<.001
Midarm fat area expressed as a percent of the standard value of the age- and sex-specific 50th percentile at admission	103 ± 58	54 ± 36	<.001
Midarm muscle area expressed as a percent of the standard value of the age- and sex-specific 50th percentile at admission	105 ± 21	80 ± 26	<.001
Presence of ascites at admission (%)	62 (36)	316 (22)	<.001

Alcoholic liver disease (ALD)

- Major health issue
- No FDA-approved treatments
- Treating complications remains the mainstay of therapy



Overview: Chronic changes in liver disease



Of heavy long-term drinkers:

- 90 % fatty liver
- 10-30 % alcoholic hepatitis
- 8-20 % cirrhosis

In the 80s...

...nutrition was seen as primary cause of liver injury in ALD.

➤ „Although, experimentally, malnutrition may not be essential for the development of alcoholic hepatitis, clinically, it appears to precede the development of the liver injury, which suggests an interaction“.

	Severity of Disease			
	None	Mild	Moderate	Severe
Anorexia [†]	9.5	46.2	63.0	65.7
Weight loss ^{**} , [†]	9.5	36.8	27.1	16.2 ^{**}
Fever	0	18.0	26.2	19.2
Hepatomegaly	0	85.9	97.1	88.9
Splenomegaly [†]	4.8	24.5	38.6	46.2
Infection	0	5.2	16.8	8.1
Pancreatitis	4.8	13.6	10.3	10.1
Gastrointestinal bleeding	0	10.4	7.5	14.1

† p < 0.005

** increasing incidence of ascites

Nowadays...

...it is accepted that ALD can develop in well-nourished individuals.

➤ **Causative factor:**



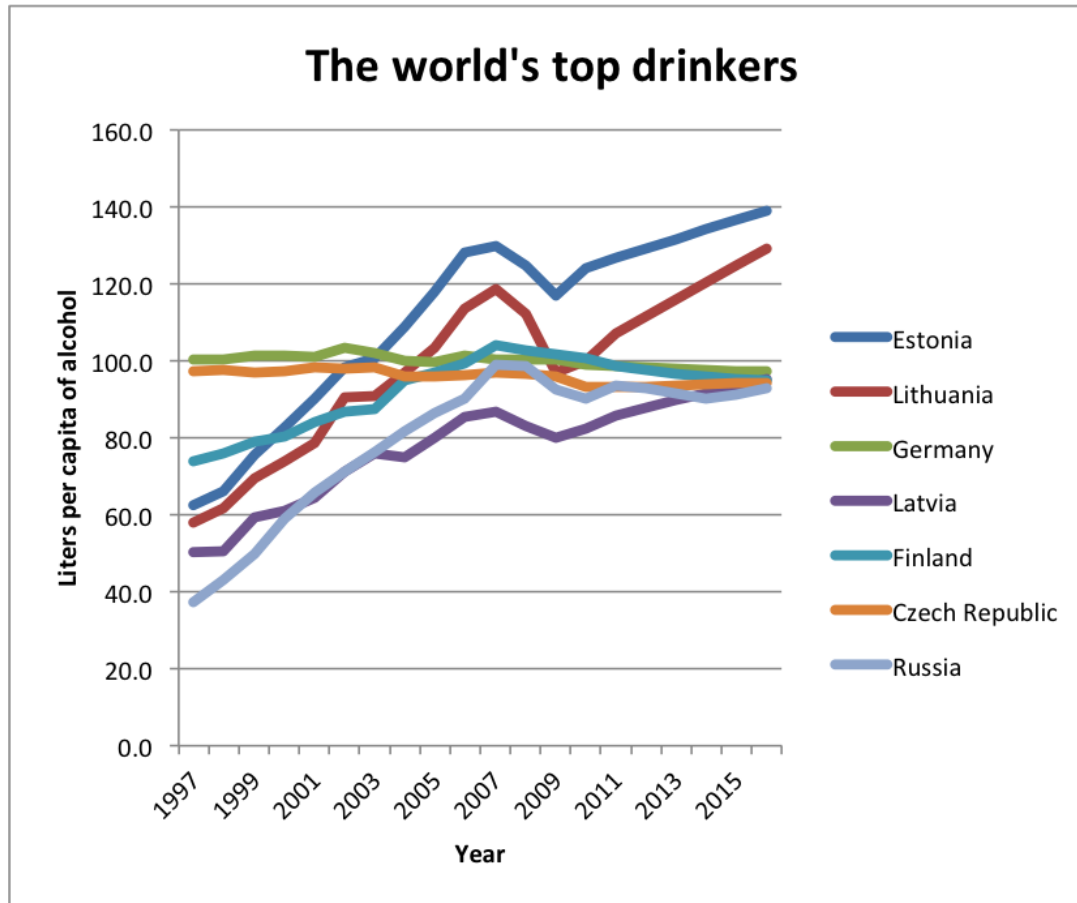
Critical „threshold“

Threshold for alcohol intake, which must be reached:

- **Daily intake of alcohol for 10-12 years**
- **Doses in excess of:**
 - ➔ **40-80 g/day for males**
 - ➔ **20-40 g/day for females**

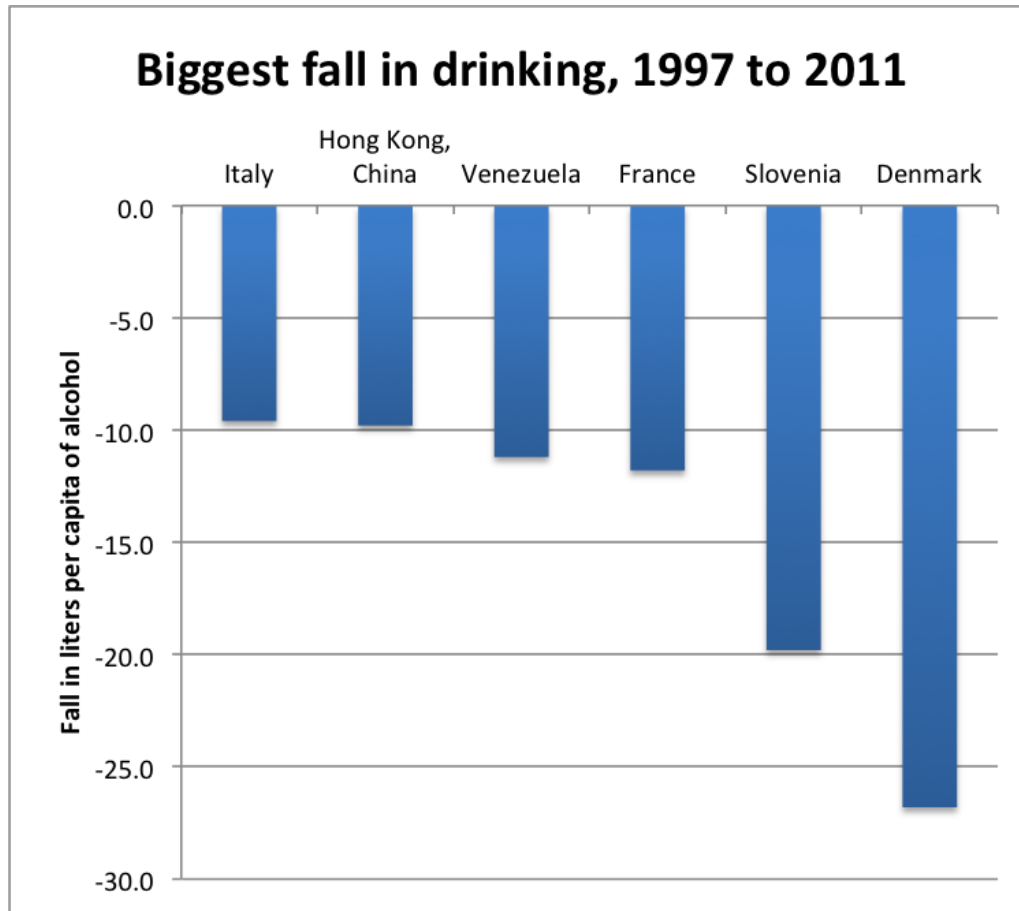


Alcoholic «front runners»



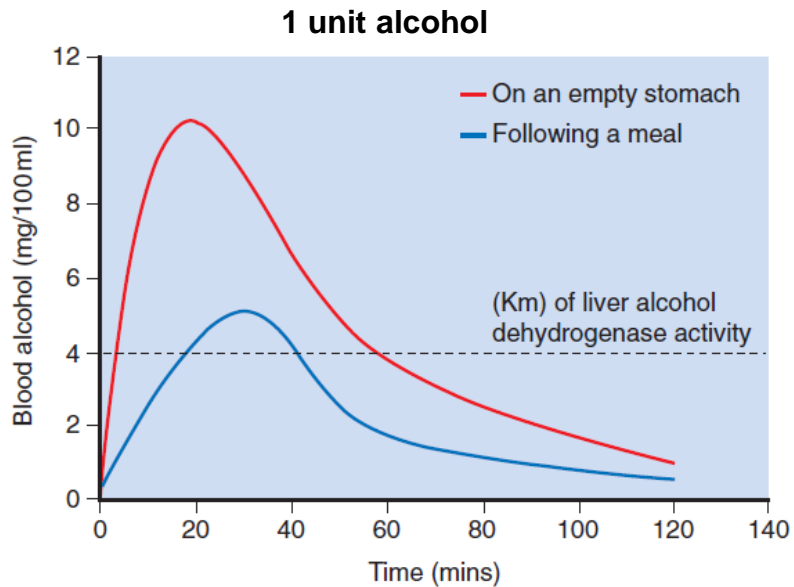
<https://epianalysis.wordpress.com/2012/02/28/alcohol/>

Slovenia: a good example



- Slovenia on second position
- Big fall despite proximity to other Eastern European nations with large increases
- Social support and alcoholic policy

Critical drinking pattern



Increased prevalence in alcohol related liver disease

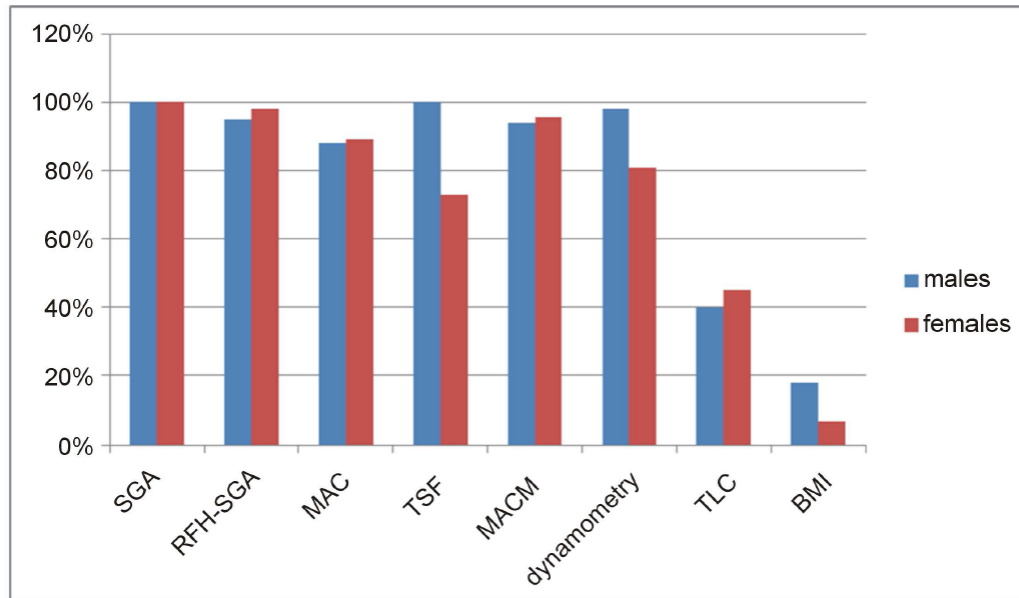
- Drinking alcohol outside mealtimes
- Drinking multiple different alcoholic beverages

Bellentani et al. Gut 1997;41:845-850

Stewart SF,+ Day CP. Alcohol and the Liver in Sherlock's Diseases of the Biliary System

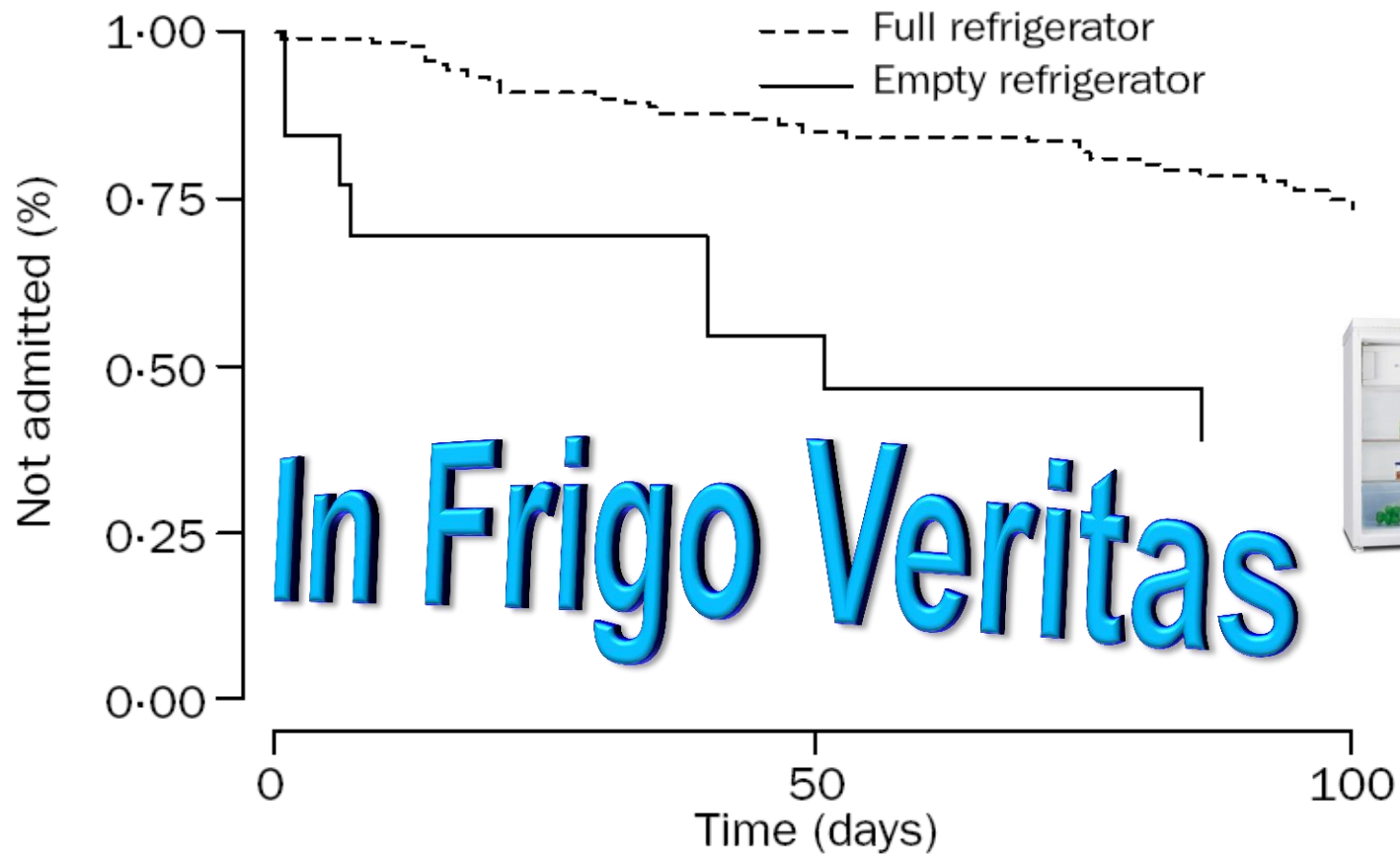
Malnutrition in ALD

➤ **Prevalence: 20-90%** (65 % viral hepatitis)



- **n = 60**
- **Patients with end stage liver disease prior to liver transplantation**
- **Comparison of different nutritional assessments**

➤ **Most frequent complication in liver disease and cirrhosis**



Ausmass des Problems

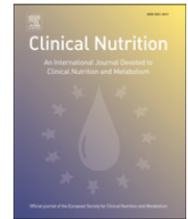
Clinical Nutrition 29 (2010) 38–41



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Clinical Nutrition

journal homepage: <http://www.elsevier.com/locate/cnu>



Original Article

Prevalence of undernutrition on admission to Swiss hospitals

Reinhard Imoberdorf^{a,*}, Remy Meier^b, Peter Krebs^c, Paul J. Hangartner^d, Bernhard Hess^e, Max Stäubli^f, Daniel Wegmann^g, Maya Rühlin^a, Peter E. Ballmer^a

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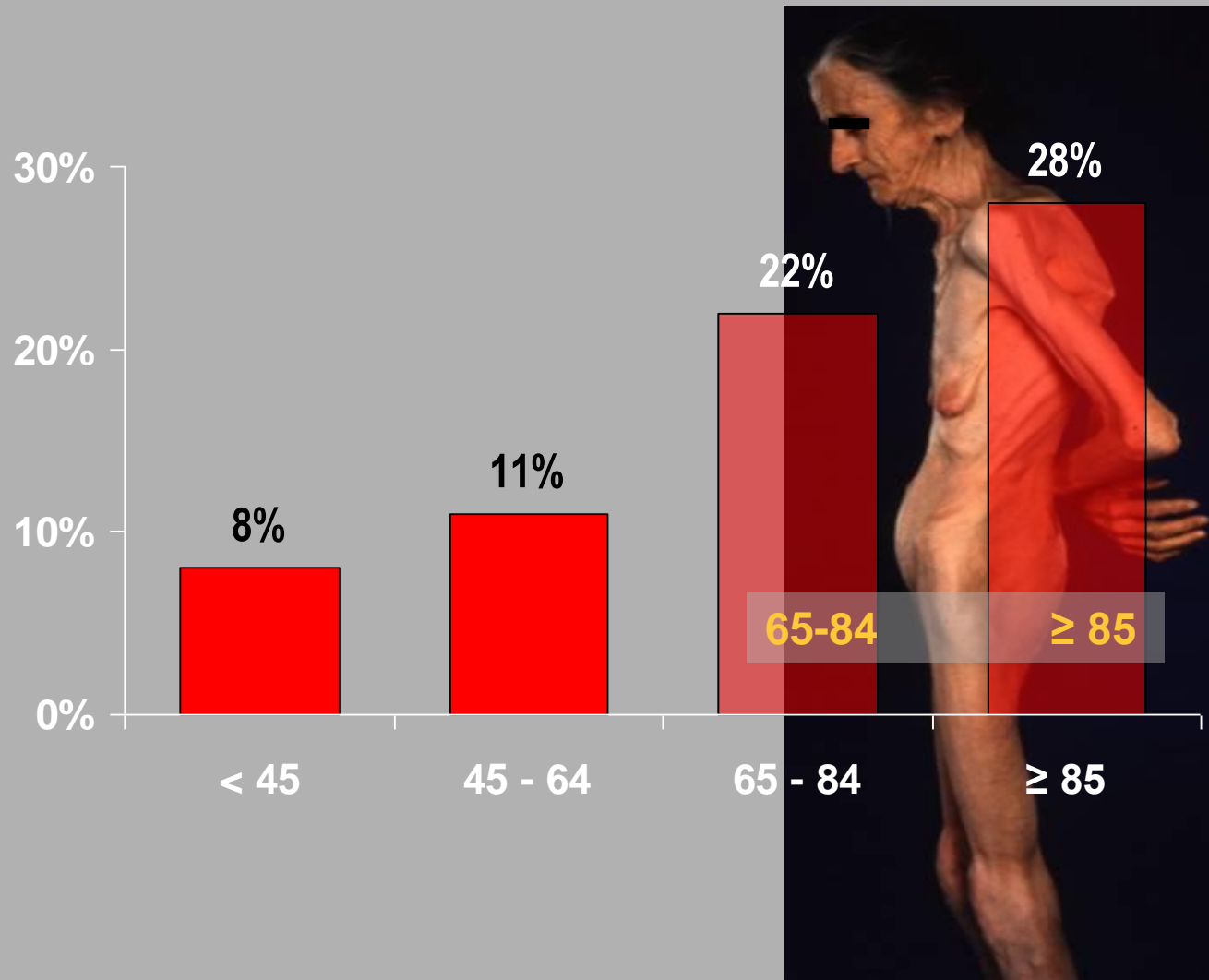
^e Spital Zimmerberg, CH-8810 Horgen, Switzerland

^f Spital Zollikerberg, CH-8125 Zollikerberg, Switzerland

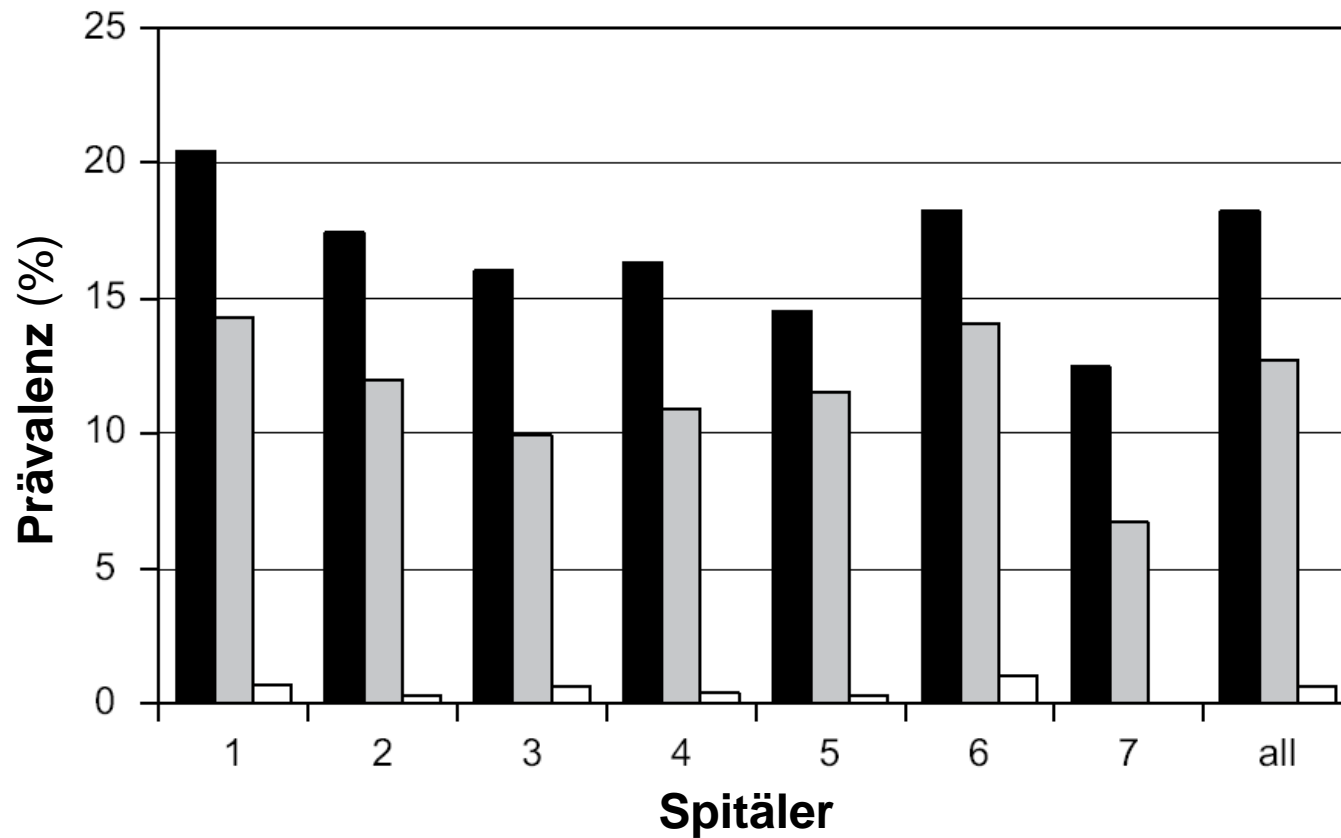
^g Kantonsspital Nidwalden, CH-6370 Stans, Switzerland

7 Hospitals, 32'837 Patients

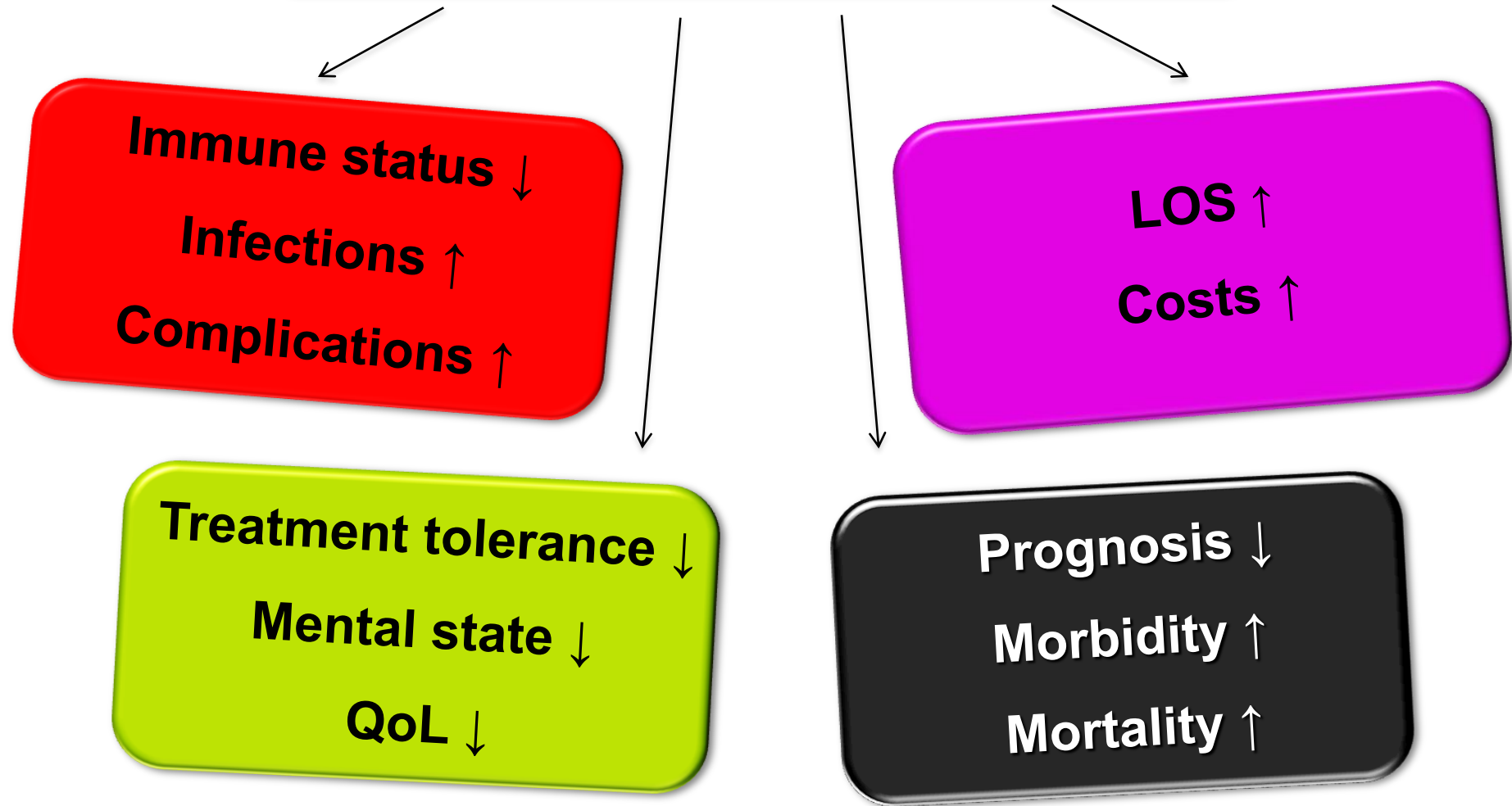
Ausmass des Problems



Ausmass des Problems



Malnutrition

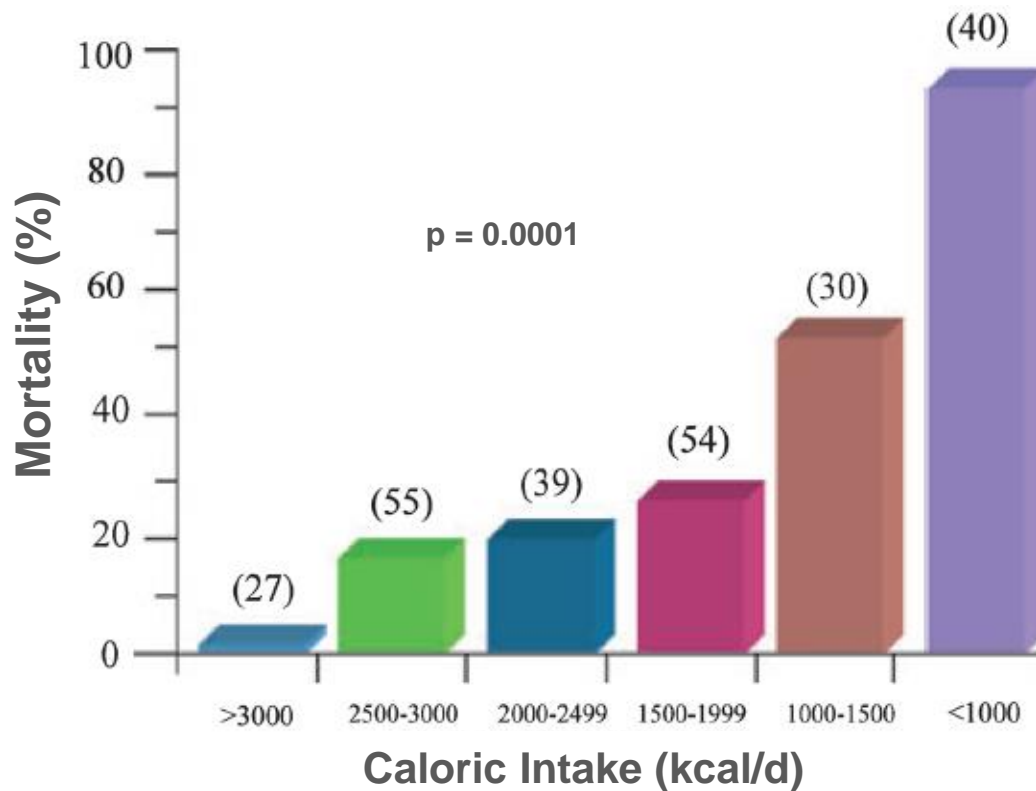


Malnutrition in ALD

- **Malnutrition = most frequent complication of ALD**
- **Severity of malnutrition depends on:**

Prognostic relevance

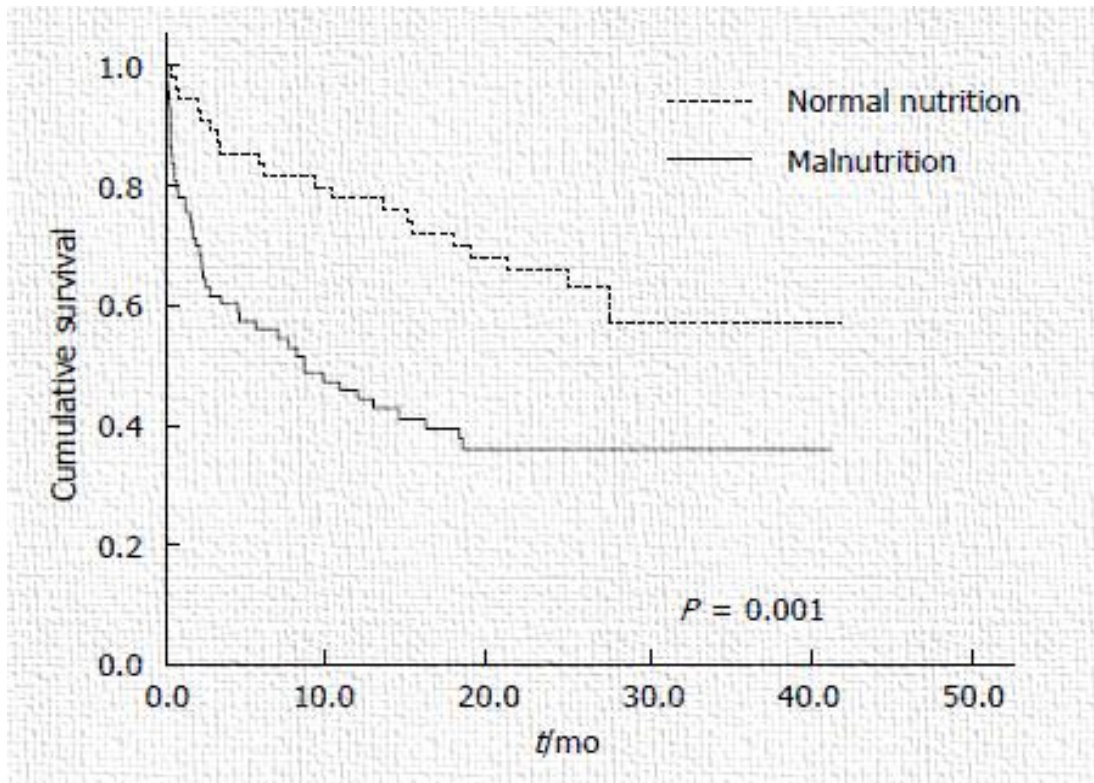
Dietary intake



- Data from two Veterans Administration Cooperative Studies
- n = 245
- Patients with alcoholic hepatitis
- 6- month mortality associated with 1-month daily dietary intake

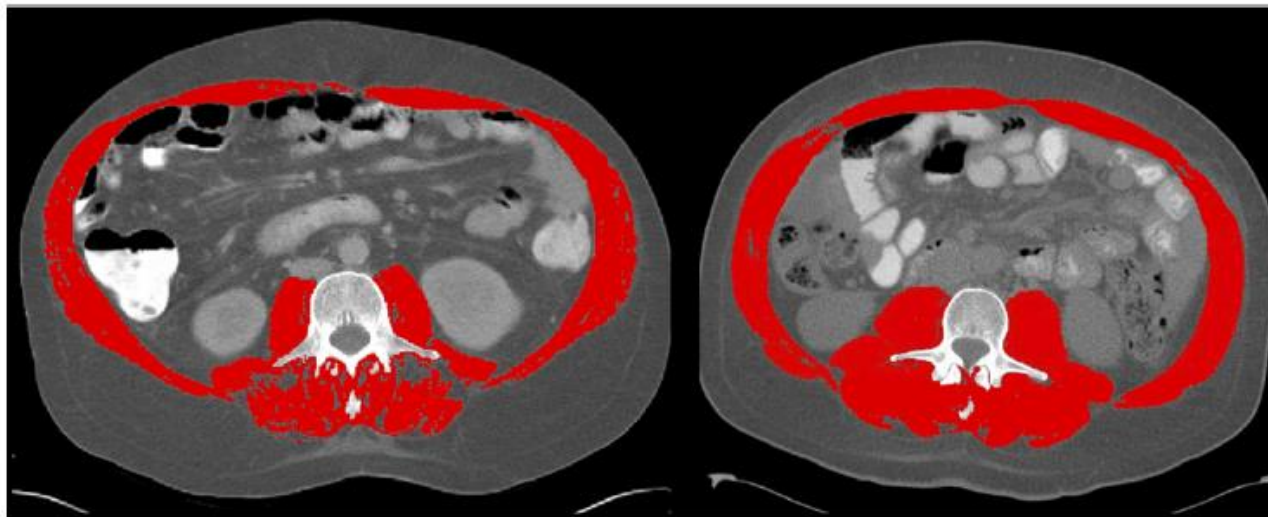
Prognostic relevance

Subjective global assessment (SGA)



Prognostic relevance

Body mass index (BMI) vs. Sarcopenia



Sarcopenic
L3 SMI 50 cm²/m²
(SMI=Skeletal Muscle Index)

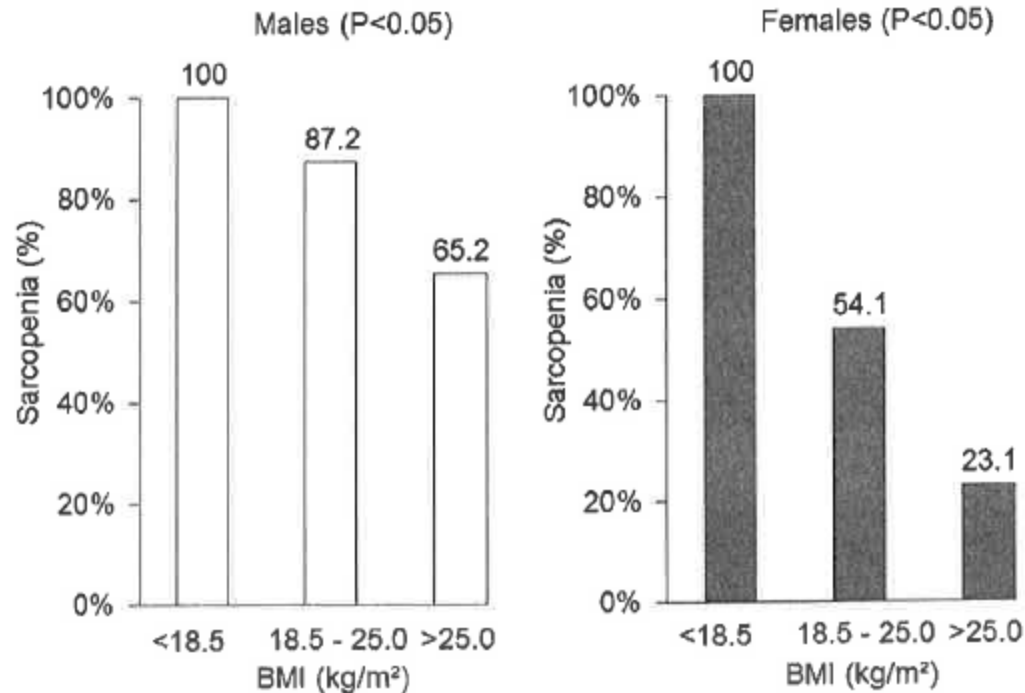
Not sarcopenic
L3 SMI 71 cm²/m²

- Two cirrhotic patients
- Identical BMI (32 kg/m²)
- Abdominal CT images L3

 **Skeletal muscles**

Prognostic relevance

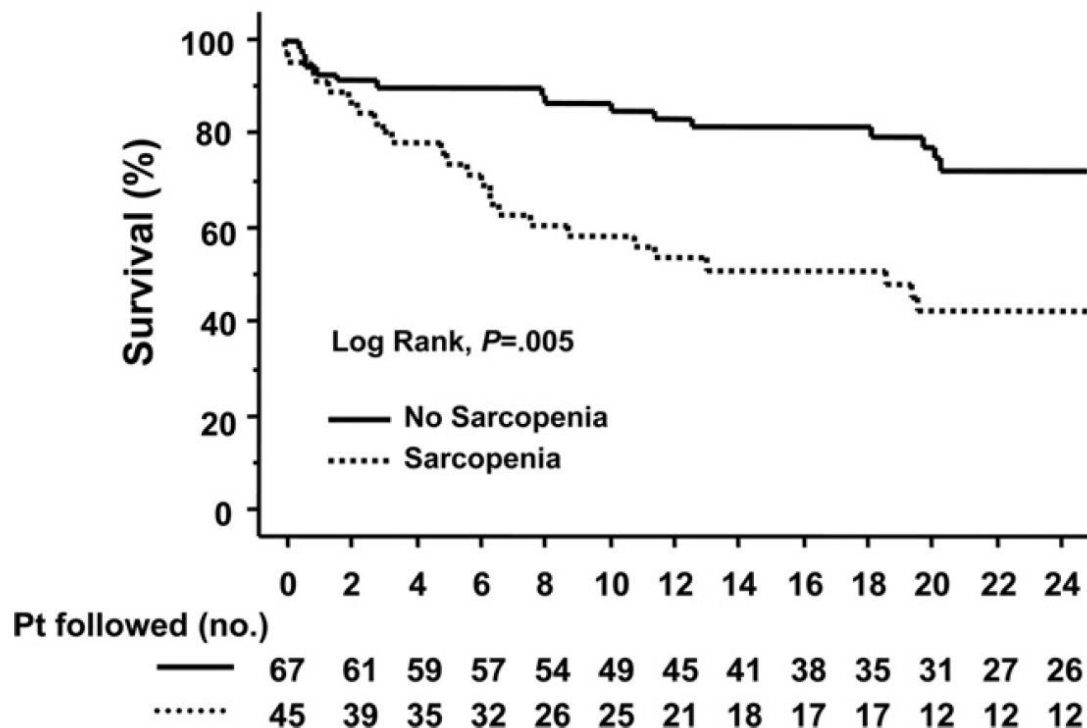
Body mass index (BMI) vs. Sarcopenia



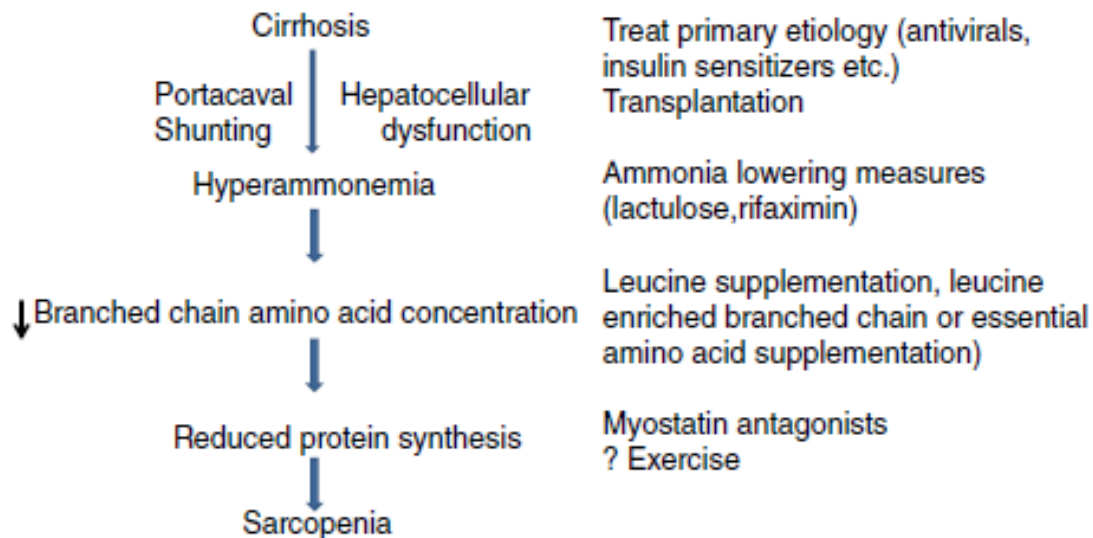
- Retrospective study
- n = 120
- Patients with liver cirrhosis
- Abdominal CT scan

Prognostic relevance

- Sarcopenia is independently associated with mortality



Potential mechanisms of sarcopenia



Malnutrition in ALD

Signs and Symptoms:

- Decreased lean body mass
- Various vitamin deficiencies
- Decrease serum proteins

Basis:

- Decreased food intake
- High caloric content of alcohol (7.1 kcal/g = empty calories)
- Decreased processing and storage of nutrients
- Poor absorption and digestion

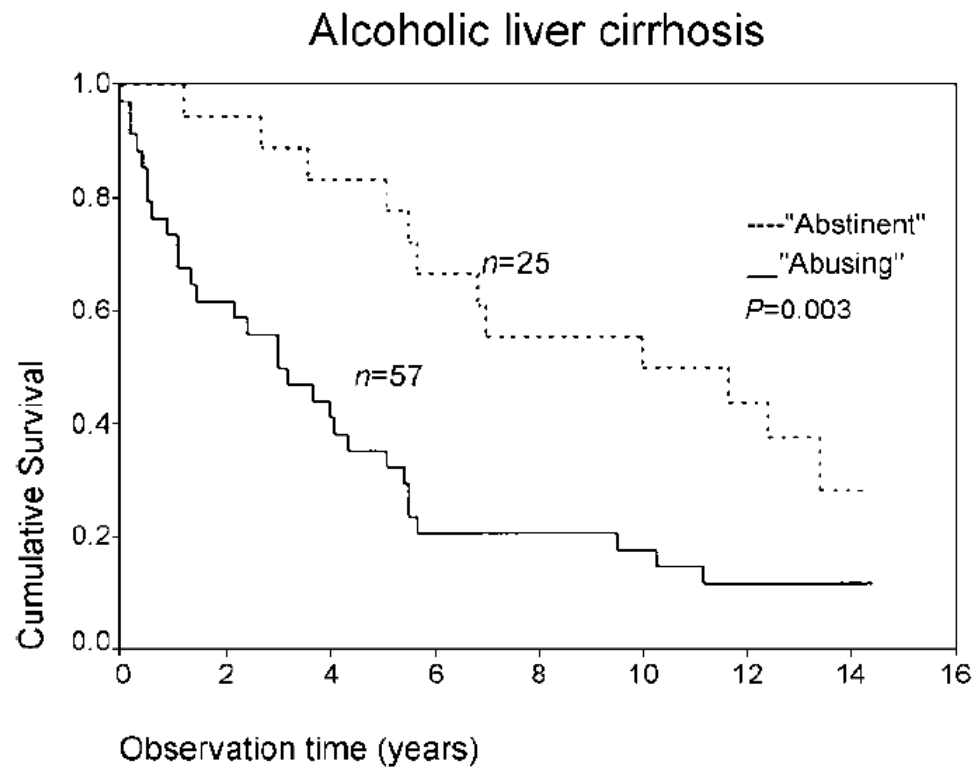


Role of nutrition as therapeutic option

- **Abstinence**
- **Agents to suppress inflammation**
- **Nutritional improvement**
- **Promoters of hepatic regeneration**
- **Modifiers of metabolism**
- **Fibrosis inhibitors**
- **Anabolic steroids**
- **Hypertension**

Treatment of ALD

Abstinence!



- 15-year follow-up study
- n = 100
- „abstinent“ (no or < 10 g ethanol/day)
- 18 patients were not included in the analyses because of death within a month

Treatment of ALD

Nutritional support

- Caloric intake ➡ 2000 kcal (35-40 kcal per kg BW per day)
- Protein intake ➡ 1.2 – 1.5 g per kg BW per/ day
- Encourage late evening snacks and short intervals between meals
➡ decreases post-absorptive state
- 6 to 7 meals/snacks per day, late evening snacks (50 g CHO)
➡ CHO oxidation increase, lipid & protein oxidation decrease

Treatment of ALD ff.

- Late evening snacks high in protein ➡ anabolism at night, preventing muscle loss
- Enteral tube feeding ➡ well-tolerated, may improve hepatic function but no conclusive effect on skeletal muscle
- Parenteral nutrition ➡ long-term effects unknown
- AA, BCAA, leucine supplementation: *see later*

Nutritional therapy in cirrhosis/alcoholic hepatitis – Meta-analysis

- 13 controlled trials (1980 bis 2012)
- n = 329
- 9 enteral, 4 intravenous trials
- at least 75 % of nutritional demands



Reduced mortality (RR 0.80, 95% CI 0.64-0.99)



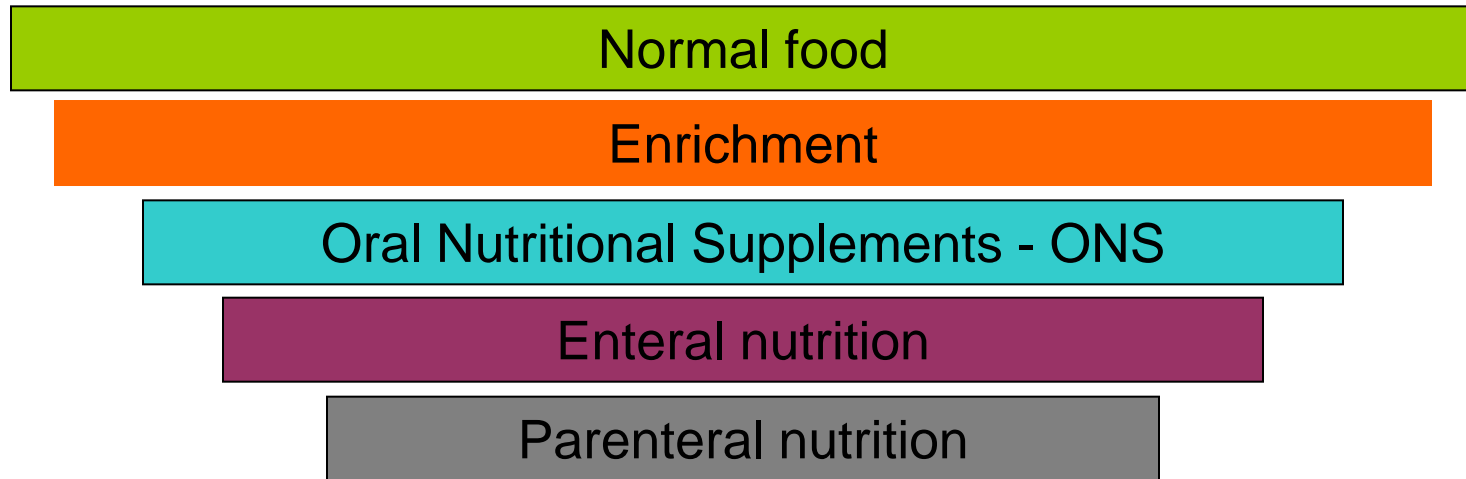
Prevented hepatic encephalopathy (RR 0.73, 95% CI 0.55-0.96)



Prevented infection (RR 0.66, 95% CI 0.45-0.98)

Route of nutritional support

Route of nutritional support:



- Parenteral nutrition is rarely indicated
- ONS may be not effective because of poor intake and compliance
- However ONS are effective when consumed!

Route of nutritional support ff.







Oral Nutritional Supplements

(Synonyme in Deutsch)

- **Trinknahrung**
- **Zusatztrinknahrung (sondenfreie enterale Ernährung)**
- **Orale Supplemente**
- **Trinknahrungssupplemente**

Effect of increase in nutrition

Oral Nutritional Supplements

	ONS Dietary counseling & ONS	DC <small>(Dietary Counseling)</small> Dietary counseling alone
Hand grip		
Peak flow		
QoL	8 x 	3 x 
Re-admissions	26 %	48 %

Today...

Oral Nutritional Supplements

- > 4'000 randomised clinical studies
- > 360'000 participants



Improvement of nutritional status

Oral Nutritional Supplements

- **81-90% Studies: improvement**
- **46-60% Studies: significant improvement**
 - **Highly effective wenn BMI < 20 kg/m²**
 - **Irrespective of place** (hospital, nursing home, community)



Decrease in LOS

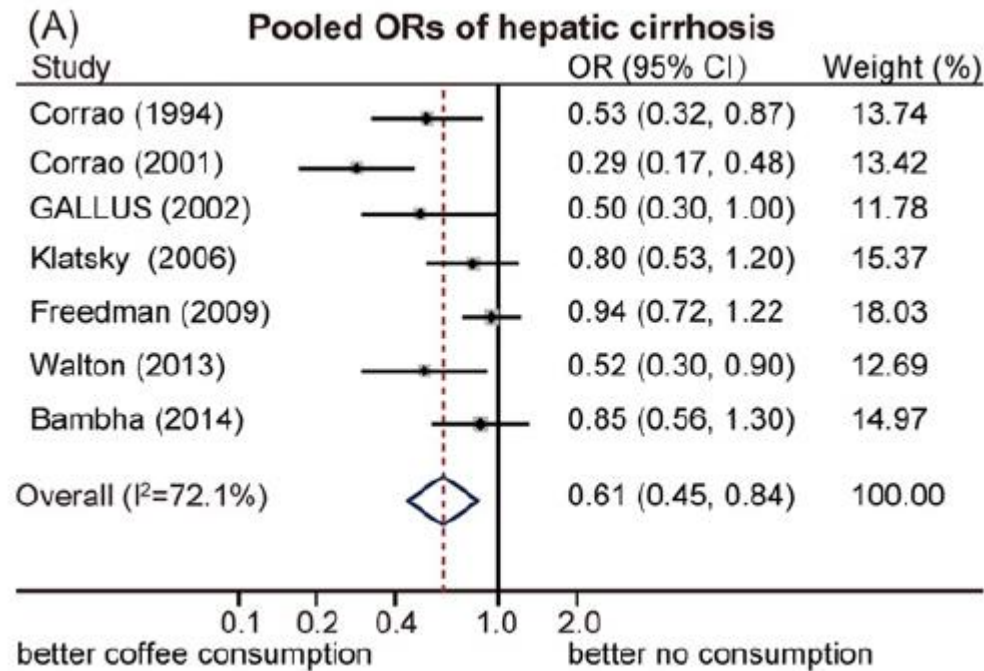
Average decrease:



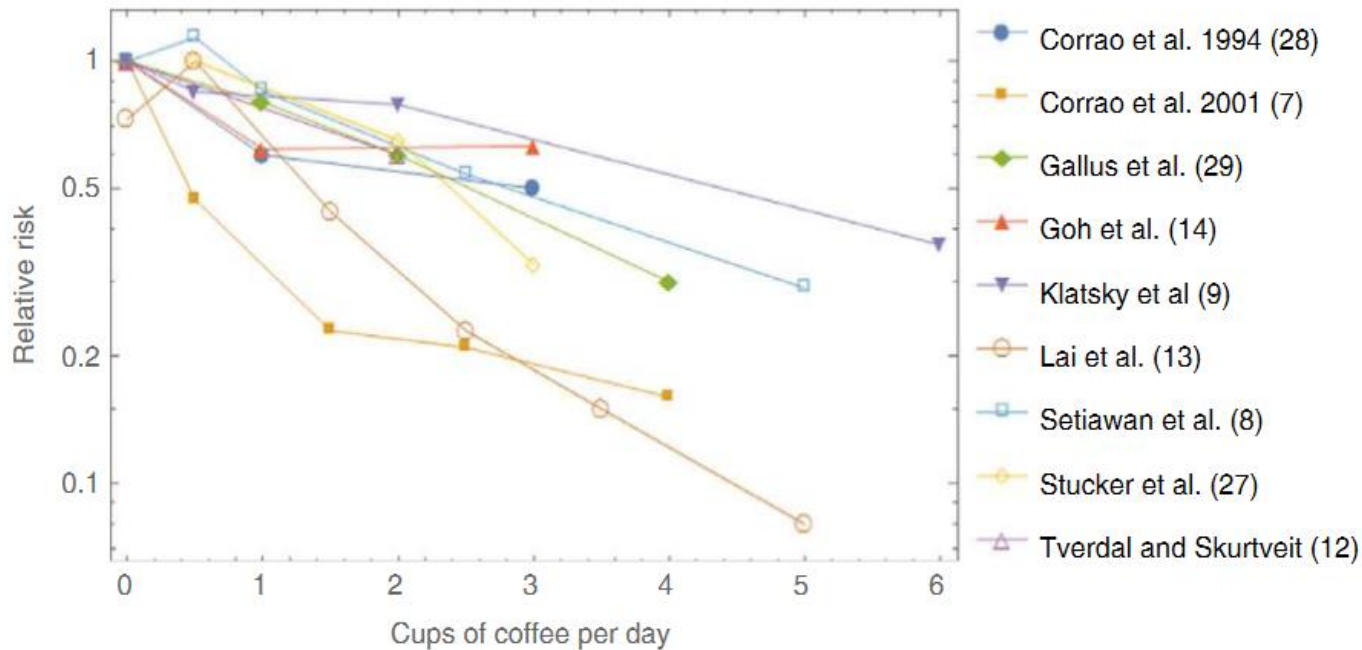
Schützt Kaffee die Leber – oder doch viel mehr?

Vom Gift zum rezeptfreien Allheilmittel: Kaffee macht Karriere

Decrease in liver cirrhosis by coffee consumption (Meta-Analysis)



Relation between cups of coffee & liver cirrhosis

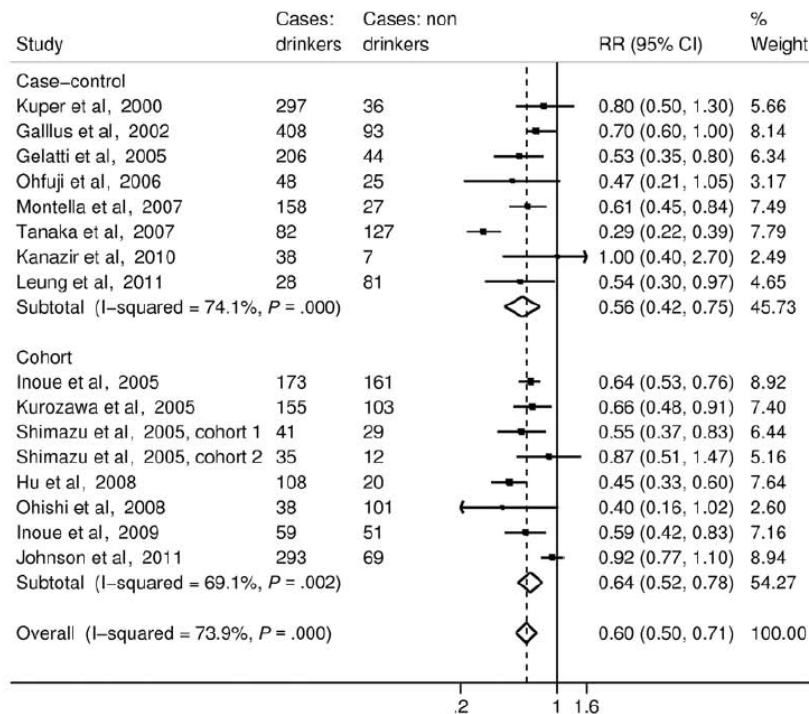


Kennedy OJ ET al. Systematic review with meta-analysis: coffee consumption and the risk of cirrhosis. *Aliment Pharmacol Ther* 2016;43:562-74

Liver-associated mortality & coffee consumption

**Decrease in mortality by 46 %
if daily consumption is
2-3 Tassen coffee
(RR 0.54, 95% CI 0.17-0.50)**

HCC risk & coffee consumption



- ✓ RR 0.60 any coffee consumption
- ✓ RR 0.72 low consumption Konsum (~ 1-3 Tassen?)
- ✓ RR 0.44 high consumption (~ 3- >8 Tassen?) (versus no consumption)

Coffee consumption 1/cancer development

- **Liver cancer** (RR 0.50)
- **Colorectal cancer** (RR 0.83)
- **Postmenopausal breast cancer**
- **Advanced prostate cancer**
- **Survivors with breast or prostate cancer**

Coffee consumption 1/cancer development

Potential mechanisms of plant chemicals

(Phytochemicals, e.g. Polyphenole)

- Decrease in oxidative damage
- Regulation of DNA-repair
- Antiproliferativ
- Antiangiogenetic
- Antimetastatic
- Etc.

Treatment of ALD



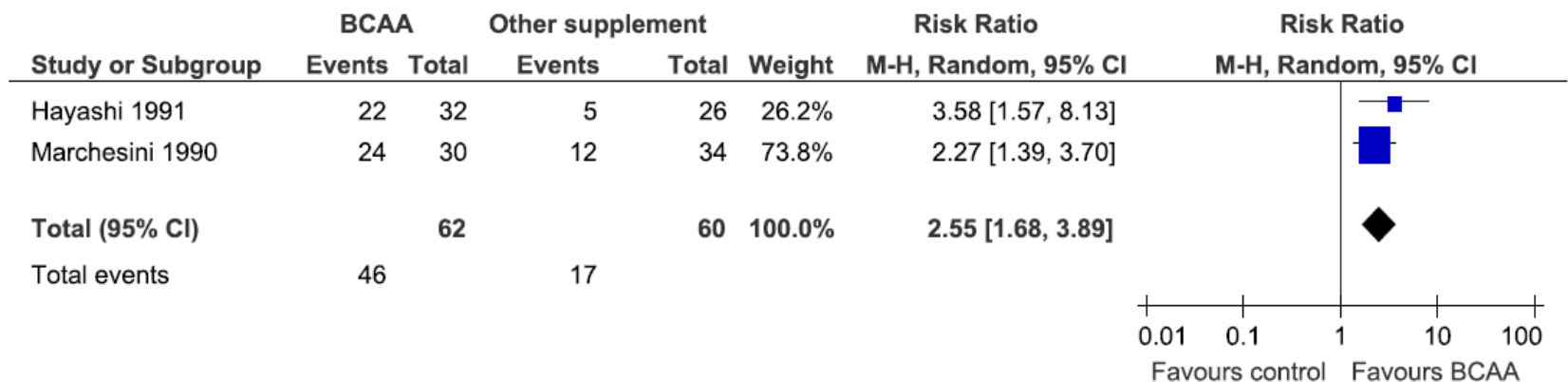
NAS (No Added Salt) Diet

- No salt cooking
- Up to 100 g hard cheese per wk
- Up to 4 slices bread per d
- Limit processed foods/salty foods (sauces, soups, crisps, cured meats etc.)

Type of formula - BCAA

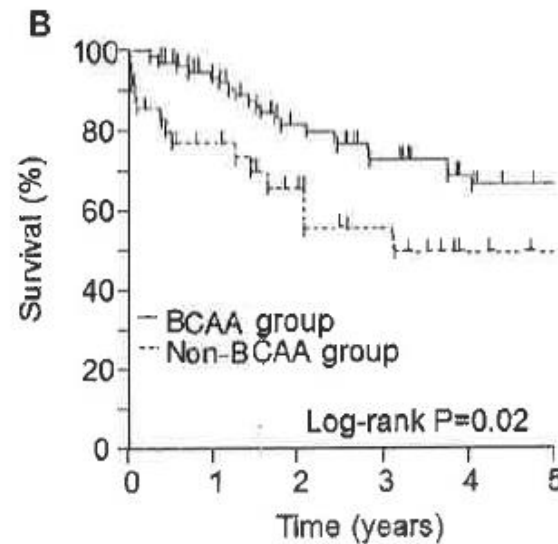
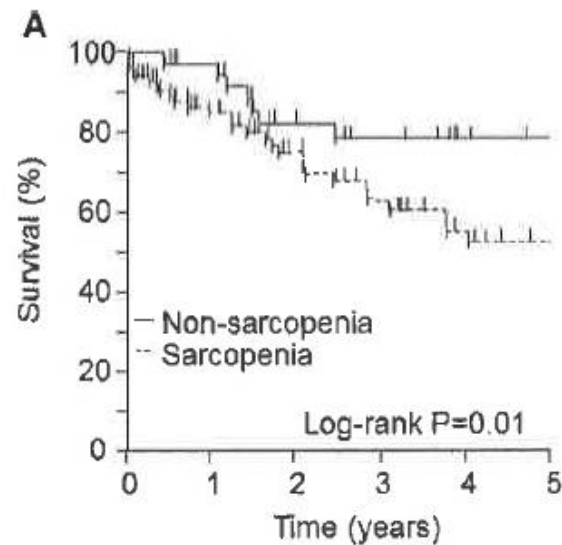
Branched-chain amino acids:

- „Use BCAA-enriched formulae in patients with hepatic encephalopathy arising during enteral nutrition.“ [ESPEN guidelines]
- Improvement in hepatic encephalopathy:



Therapeutic relevance

Effect of BCAA supplementation – Nutritional intervention!



- BCAA > 1 yr
- BCAA granules 3x daily after meals
- BCAA = 4 g
 - 952 mg isoleucine
 - 1904 mg leucine
 - 1144 mg valine

- Retrospective study (n = 120), abdominal computed tomography scan

BCAA – The Evidence

Hepatic Encephalopathy (HE)

- No convincing evidence for BCAA
- Meta-Analysis: Improvement of mental state, no benefit for survival
- Postoperative (liver resection) no increase HE with conventional AA solution
- Liver adapted AA solution (increased BCAA) in more severe HE (III-IV)

Type of formula – Fatty acids

Dietary fatty acids – investigated in animal models:

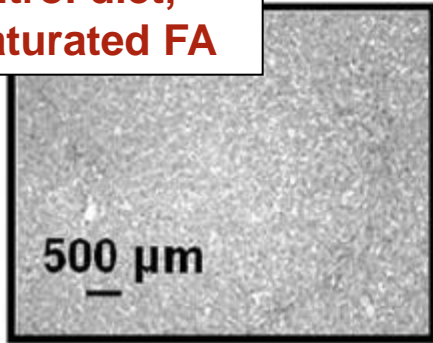
Saturated fat, % energy	Treatment	Protein	Carbohydrate	Corn oil	Saturated fat ¹	Ethanol
				<i>g/L</i>		
0	Control	133	115	52	0	0
	Ethanol	133	5	52	0	90
10	Control	133	115	40	12	0
	Ethanol	133	5	40	12	90
20	Control	133	115	28	24	0
	Ethanol	133	5	28	24	90
30	Control	133	115	16	36	0
	Ethanol	133	5	16	36	90

¹ Saturated fat = beef tallow:MCT oil (18:82, v:v).

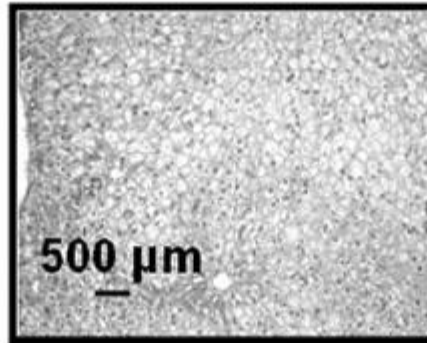
- Rats fed intragastrically by total enteral nutrition
- Diets with or without alcohol
- Difference in saturated fatty acid

Type of formula – Fatty acids

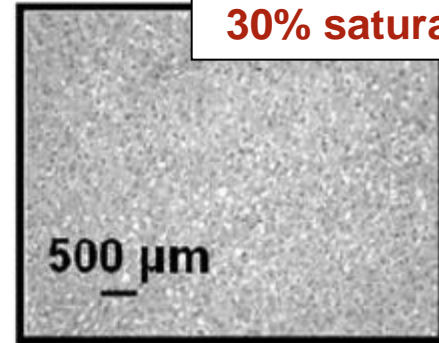
**Control diet,
0% saturated FA**



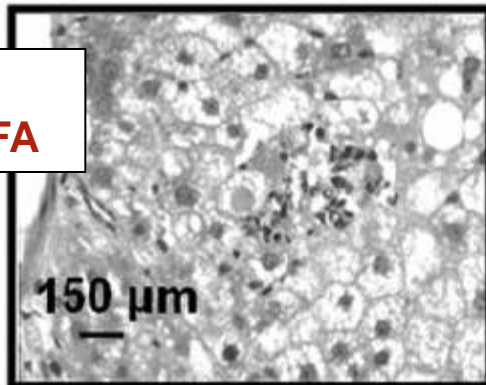
**Ethanol diet,
0% saturated FA**



**Ethanol diet,
30% saturated FA**

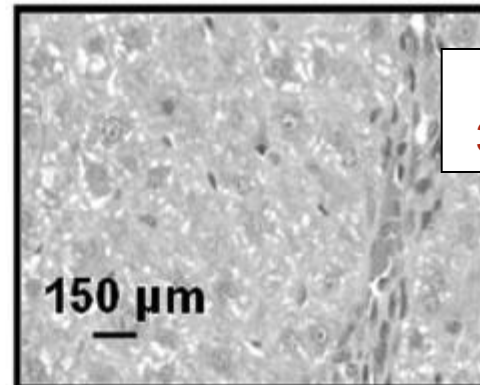


**Ethanol diet,
0% saturated FA**

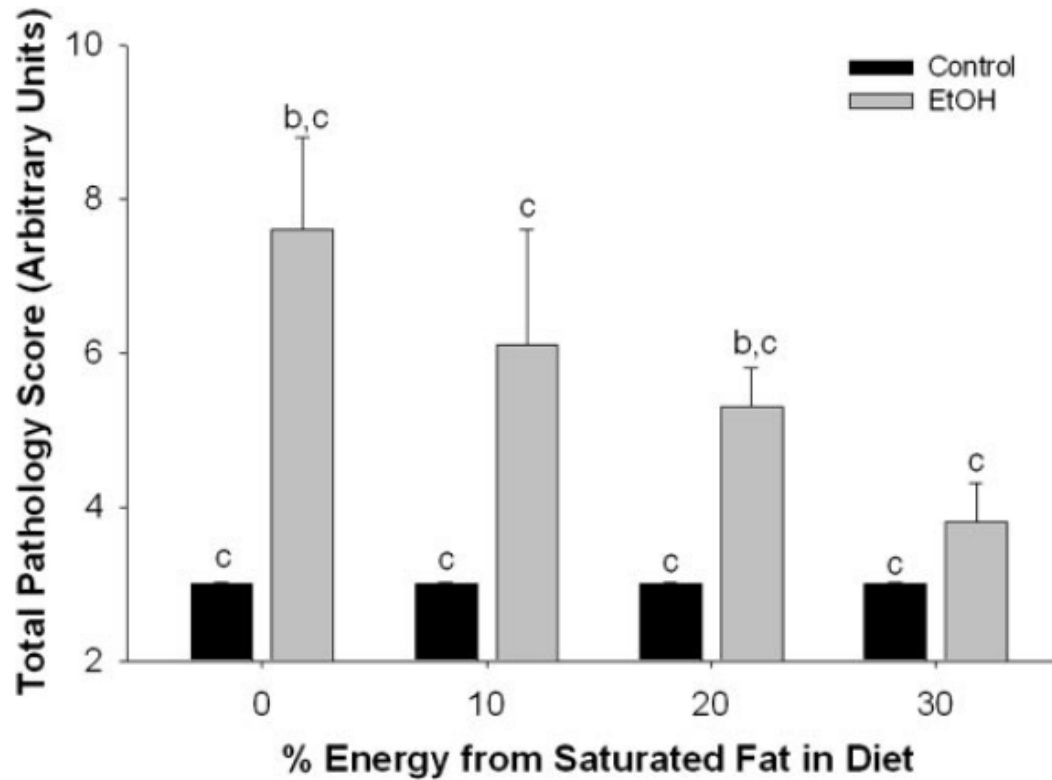


Vesicular steatosis / macrophage infiltration

**Ethanol diet,
30% saturated FA**



Type of formula – Fatty acids



Unsaturated fatty acids:
➤ increase oxidative stress

Saturated fatty acids
➤ are protective

In ALD – things may be different



GOOD
Saturated Fats

VS



BAD
Unsaturated Fats



Nutritional therapy– health effects

Very likely:

- Nutritional status ↑

Probable:

- Mortality ↓
- Cell mediated immunity ↑
- Liver injury ↓ (glycoproteins, caseine, various polyphenols)
- Infectious complications ↓ (serotonin, the calming transmitter ↑)
- Hospitalizations ↓

Conclusion

Nutrition is a risk factor for and in ALD:

- Nutritional status, especially overweight, increases the risk for developing ALD.
- Malnutrition is the most frequent complication and adversely affects mortality (and morbidity).
- Data investigating the effect of nutritional therapy on clinical parameters are sparse. **Giving ONS have to be considered!**
- There is a need for standardized assessments of nutritional parameters in ALD.

Conclusion

Considering the risk versus benefit:



- **Nutritional therapy is an essential therapeutic intervention in ALD!**



Besten Dank für Ihre Aufmerksamkeit