Epidemiology of alcoholic liver disease: Gender differences

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Symposium on:
New models and mechanisms for alcohol-mediated liver toxicity

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Introduction

- Women have increased susceptibility to the detrimental effects of alcohol
- Women develop alcoholic liver disease at a lower intake of alcohol than males
- What are the mechanisms behind this gender difference?

Gender differences - Topics of Discussion

- Alcohol consumption
- Alcoholic liver disease
- Physiology
- Metabolism of alcohol
- Hormonal effects
- Role of Endotoxin

Alcohol consumption – Gender differences

- 9:1 m/f – Italy (Bellentani. Gut 1997;41:845-50.)
- In America 13-33% of alcoholics are women
- Alcohol consumptions by women is increasing
- Women consume less alcohol than men (W: 15.7 g/d; M: 43.8 g/d)
- Women are less likely to be heavy users
- Duration of drinking is similar in males and females

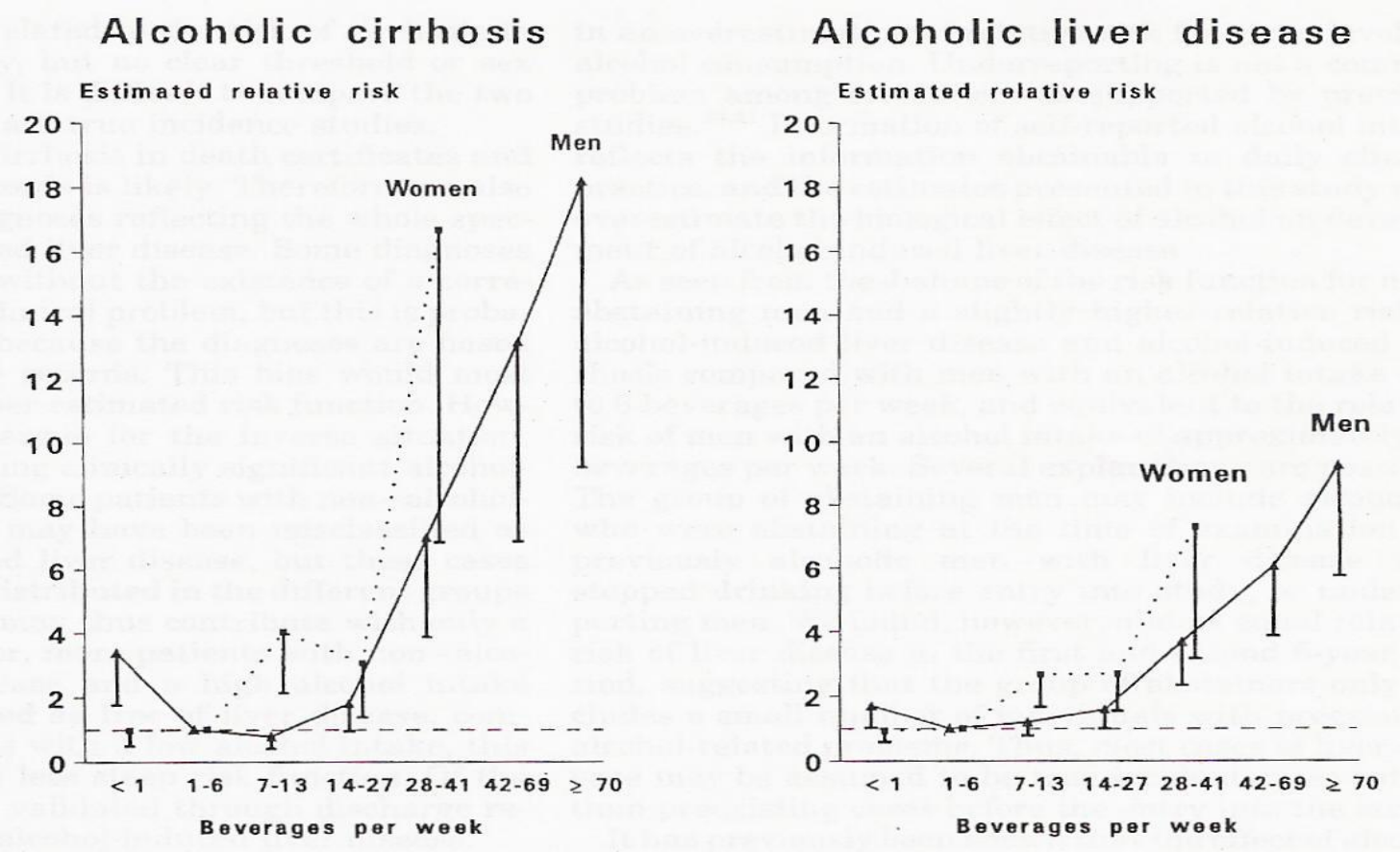
Mandayam S, et al. Semin Liver Dis 2004; 24: 217-32

Alcoholic liver disease – Gender differences

- Women have a **higher risk of developing cirrhosis** than men for any given level of alcohol intake
- In **men** the risk of cirrhosis increases with alcohol intake greater than about **60 g/d** (40-80)
- In **women** the risk of cirrhosis increases with alcohol intake greater than about **40 g/d** (20-60)
- For an intake of 4-6 drinks per day women have a risk of developing cirrhosis 3 times that of men
- In women with an intake of 4-6 drinks per day the risk of developing cirrhosis is 16 times that of abstinent women
- In women alcoholic liver disease **develops more rapidly** and **progression** of alcoholic hepatitis **is greater** than in men

Becker U, et al. Hepatology 1996;23:1025-9. Mandayam S, et al. Semin Liver Dis 2004; 24: 217-32

Alcoholic liver disease – Higher risk in females



From: Becker U, et al.

Ascites in cirrhosis – Higher risk in females

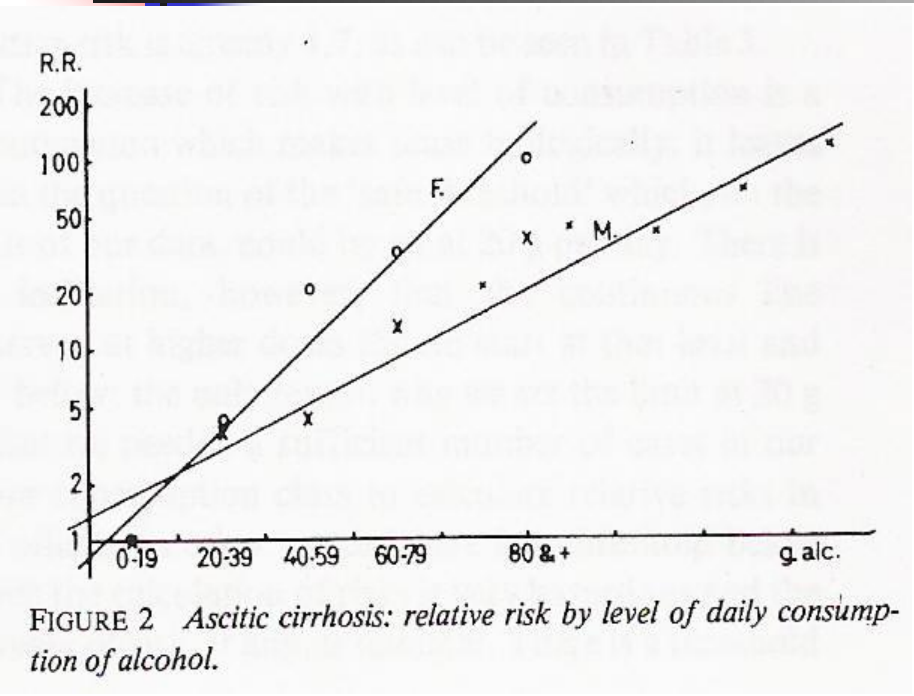


FIGURE 2 *Ascitic cirrhosis: relative risk by level of daily consumption of alcohol.*

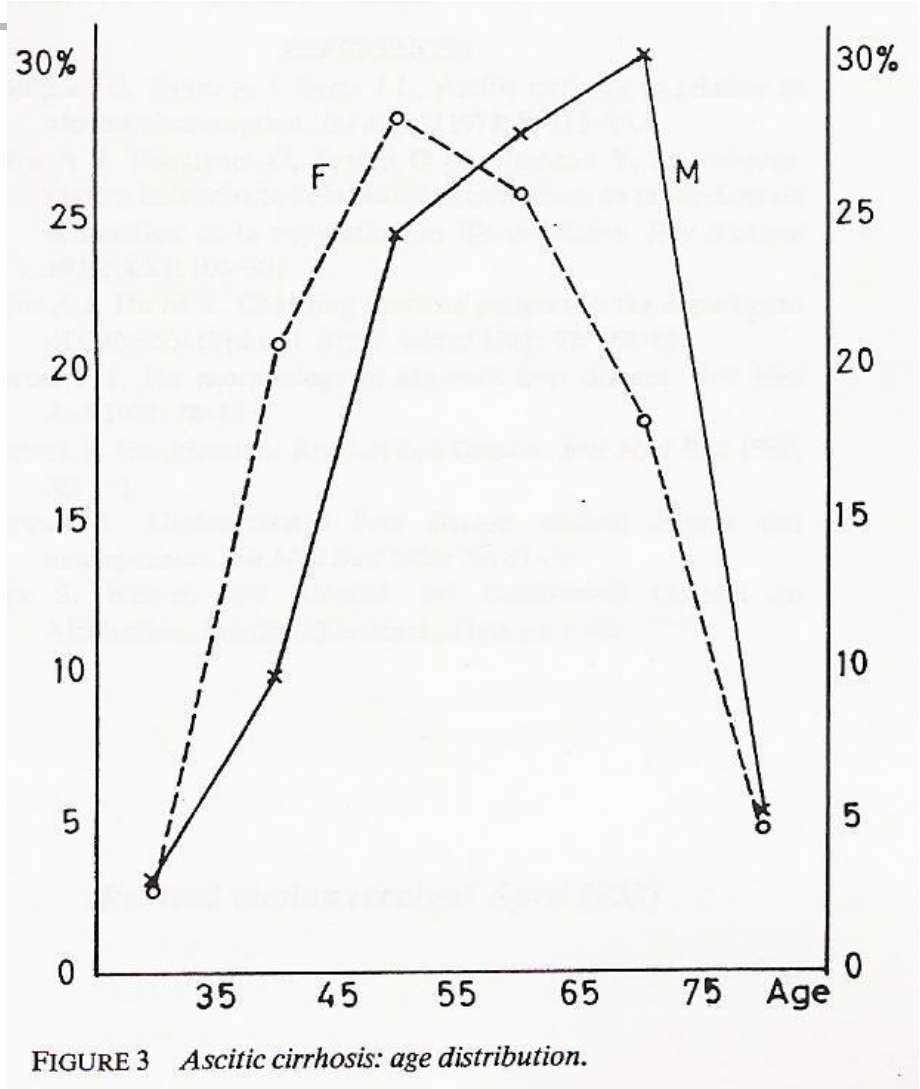


FIGURE 3 *Ascitic cirrhosis: age distribution.*

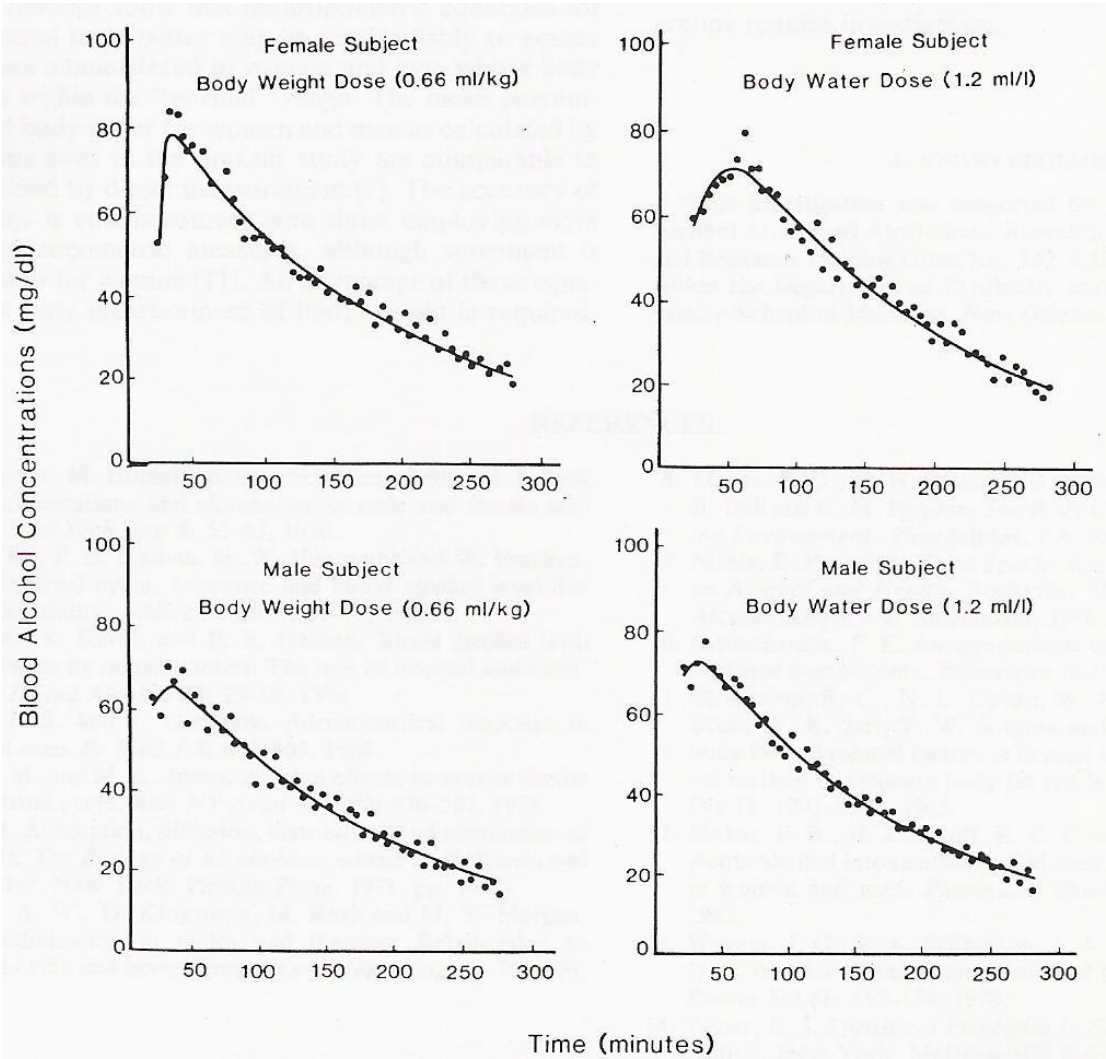
In females the risk of ascites is greater and it occurs earlier

From: Tuyns AJ et al

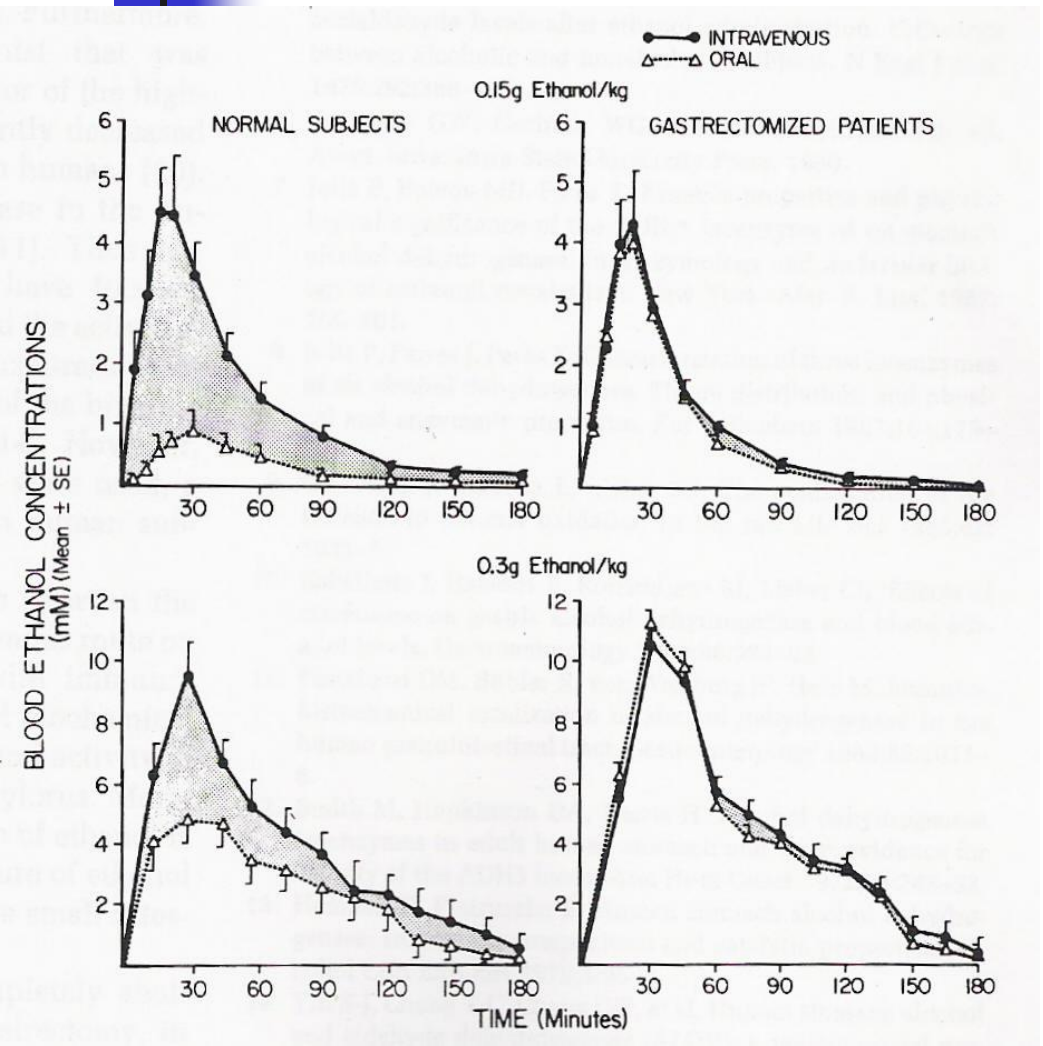
Alcohol Intoxication – Influence of total body water

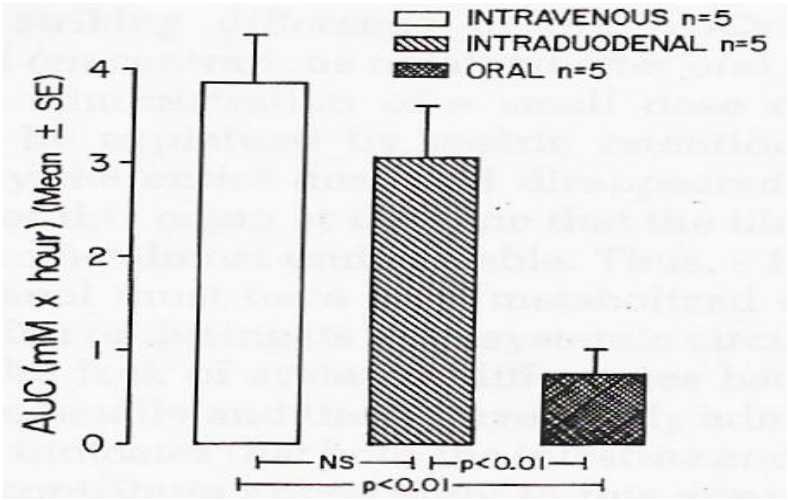
- Equivalent alcohol doses based on body weight leads to higher blood alcohol concentrations (BAC) in women
- Women have less body water per kilogram body weight than men
- Equivalent alcohol doses based on total body water give similar blood alcohol concentrations (BAC) in men and women

From: Goist KC et al.



Alcohol – Gastric first-pass metabolism



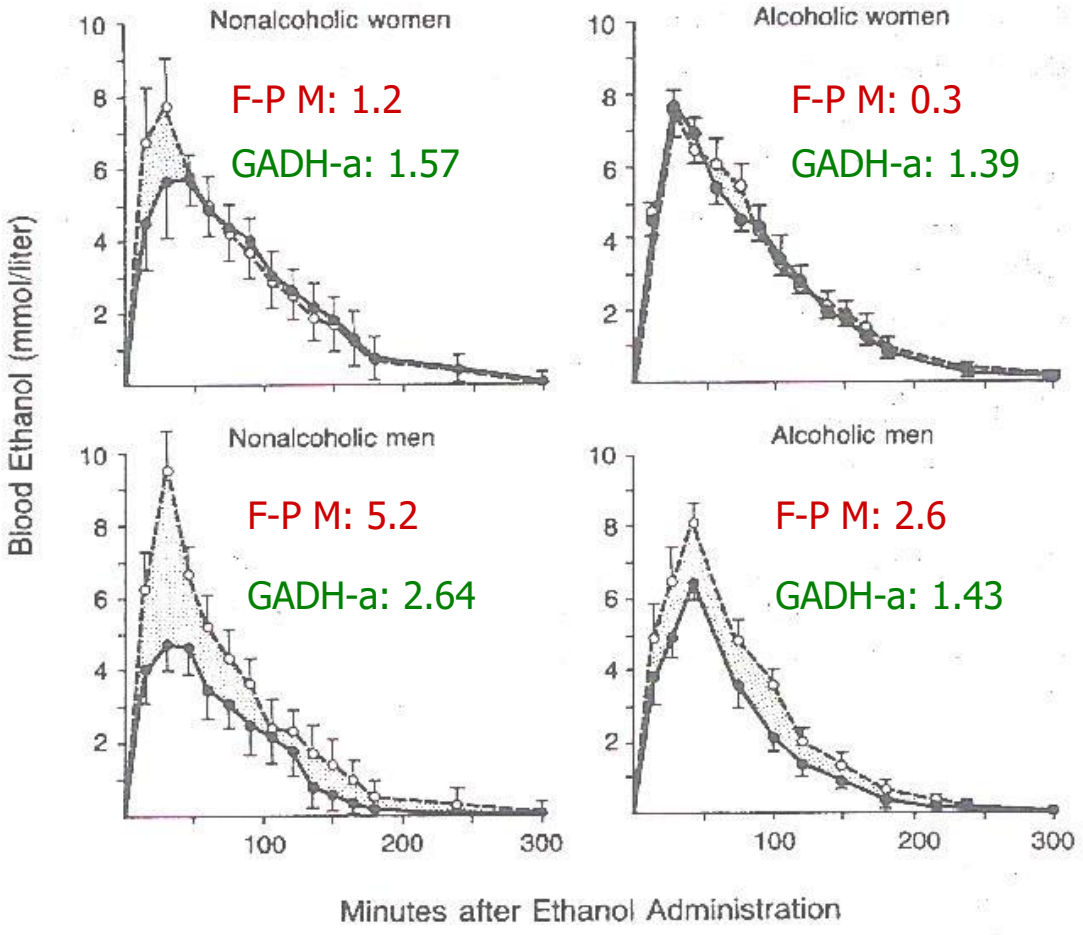


- Gastric first-pass metabolism of alcohol is significant
- The gastric mucosa is a protective barrier against alcohol

From: Caballeria et al.

Alcohol – Gastric first-pass metabolism and ADH-activity

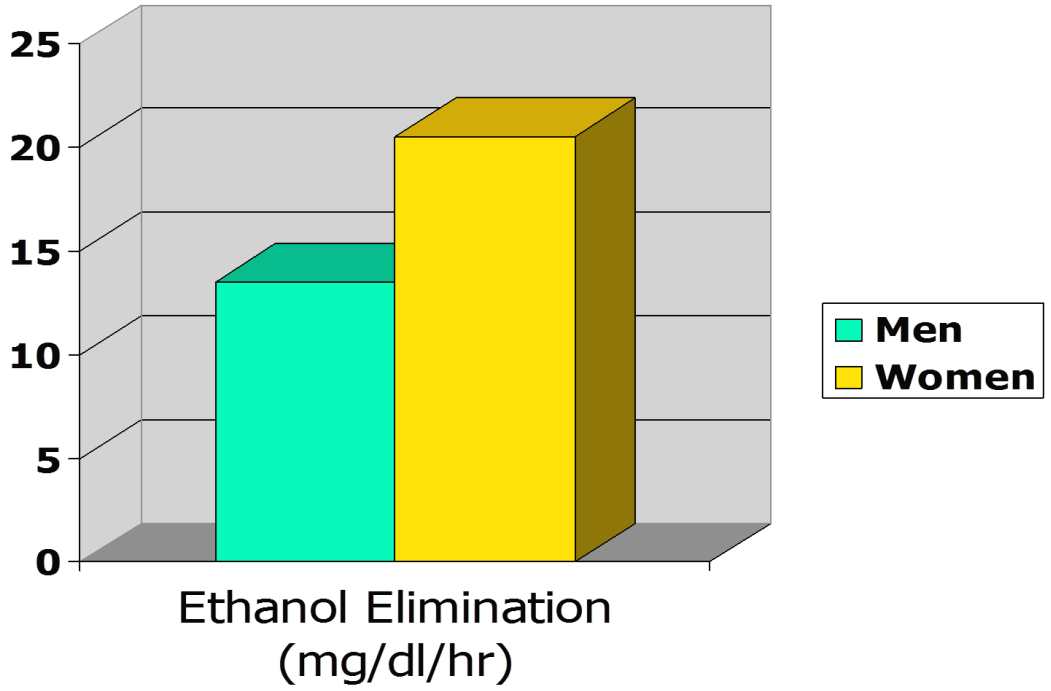
- Gastric First-Pass Metabolism (F-P M) of alcohol and Gastric Alcohol Dehydrogenase (GADH) Activity is significantly less in women
- Both are decreased in alcoholism
- The bioavalability of alcohol is increased in women



From: Frezza et al.

F-P M in mmol/liter x hour; GADH-a in nanomoles/min

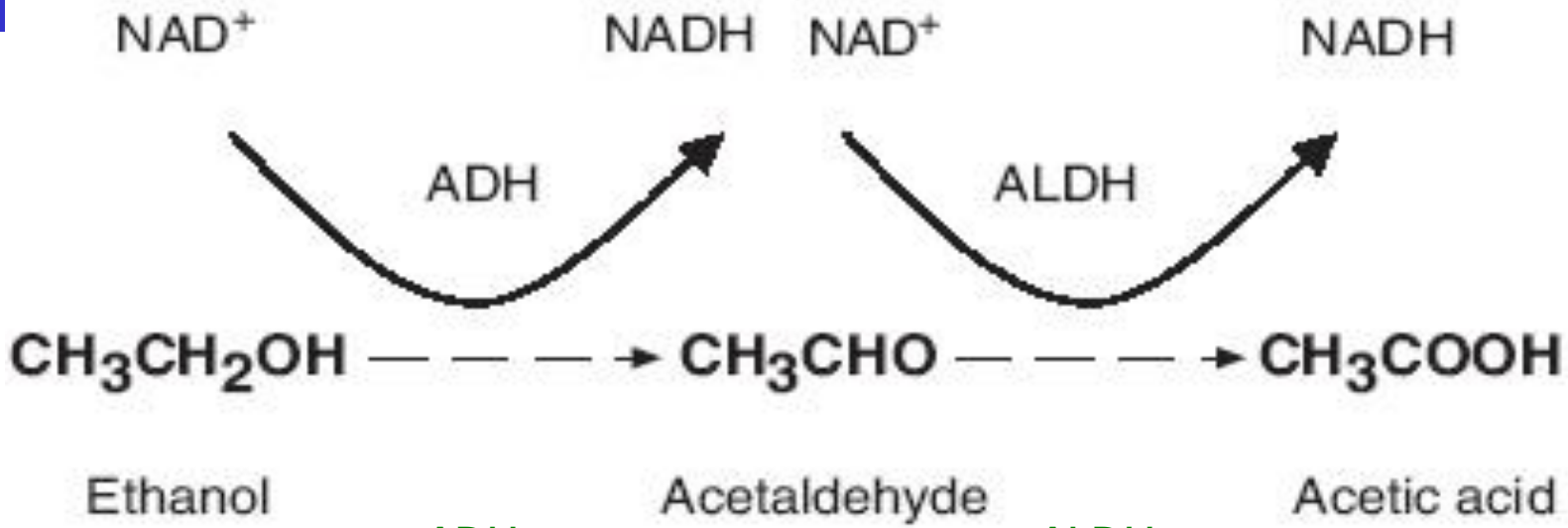
Alcohol Elimination Rate (AER) – Gender difference



- 0.6 g ethanol/kg BW given to nine pairs of siblings
- Women had higher ethanol elimination rates than men – the liver is relatively larger

From Mishra L, et al.

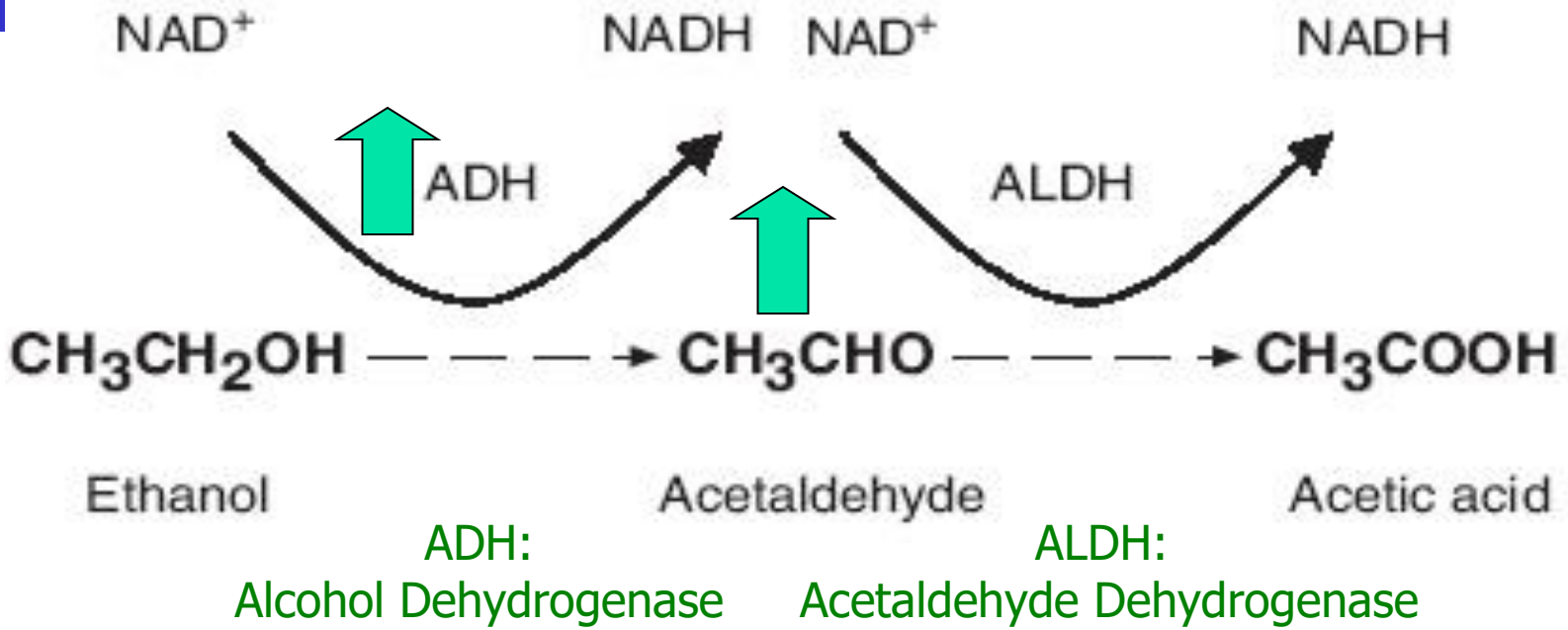
Alcohol metabolism – Main pathway



ADH:
Alcohol Dehydrogenase

ALDH:
Acetaldehyde Dehydrogenase

Alcohol metabolism – Main pathway



In women:

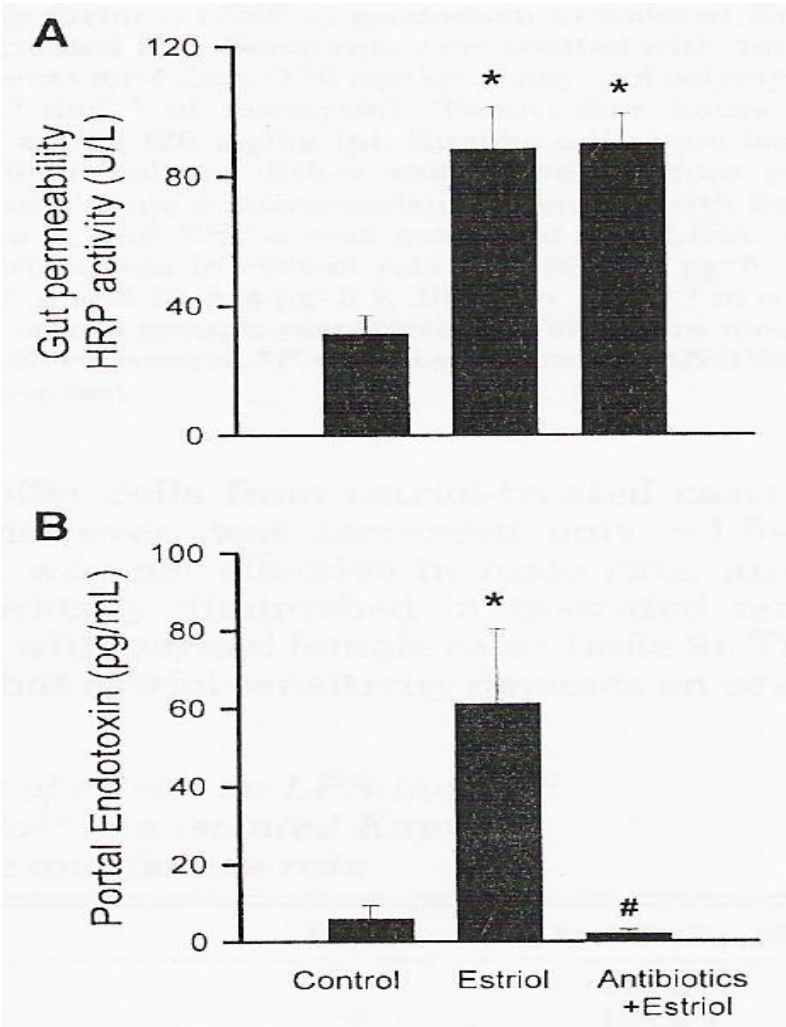
- ↑ liver ADH activity
- ↑ acetaldehyde concentration → aldehyde adducts
- ↑ hepatocyte injury

Molecular mechanisms – Role of endotoxin

- Endotoxin (lipopolysaccharide (LPS)) is a component of the cell wall of Gram-negative bacteria
- Alcohol increases gut permeability to endotoxin
- Endotoxin can bind to CD14-receptors of Kupffer cells
- This can stimulate their production of cytochines, reactive oxygen species (ROS) and tumor necrosing factor α (TNFα)
- This will activate the stellate cells to produce more extracellular matrix components
- This is an important step towards fibrosis and cirrhosis

Molecular mechanisms - Influence of estrogen

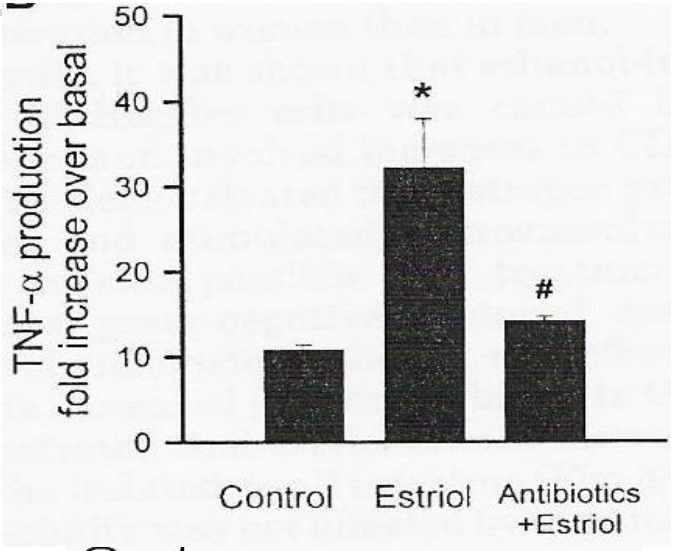
- Estriol increases gut permeability to endotoxin
- Estriol increases portal endotoxin level → increased endotoxin load to the liver
- Antibiotics neutralizes the formation of endotoxin

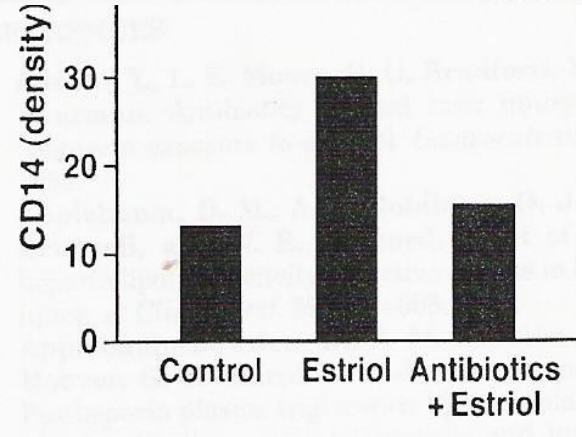


From: Enomoto N, et al.

Molecular mechanisms - Influence of estrogen

- Estriol increases expression of the CD14 receptor in Kupffer cells.
- Estriol thereby increases their production of tumor necrosing factor α (TNFα) and cytochines
- Estriol increases the liver damage – parallel increases in AST and ALT





From: Enomoto N, et al.

Factors of increased risk in women - Summary

- Volume of distribution of alcohol is less → higher blood alcohol concentration
- Gastric first-pass metabolism is less → higher blood alcohol concentration
- Hepatic alcohol elimination rate (AER) is greater → higher concentration of acetaldehyde → hepatocyte injury
- Gut permeability to endotoxin is greater → increased Kupffer cell production of tumor necrosing factor α (TNFα) → increased injury of hepatocytes

Conclusion

- For solidarity and other reasons:

Drink Less!!!