Konzumace alkoholu a metabolické změny

Tomáš Zima
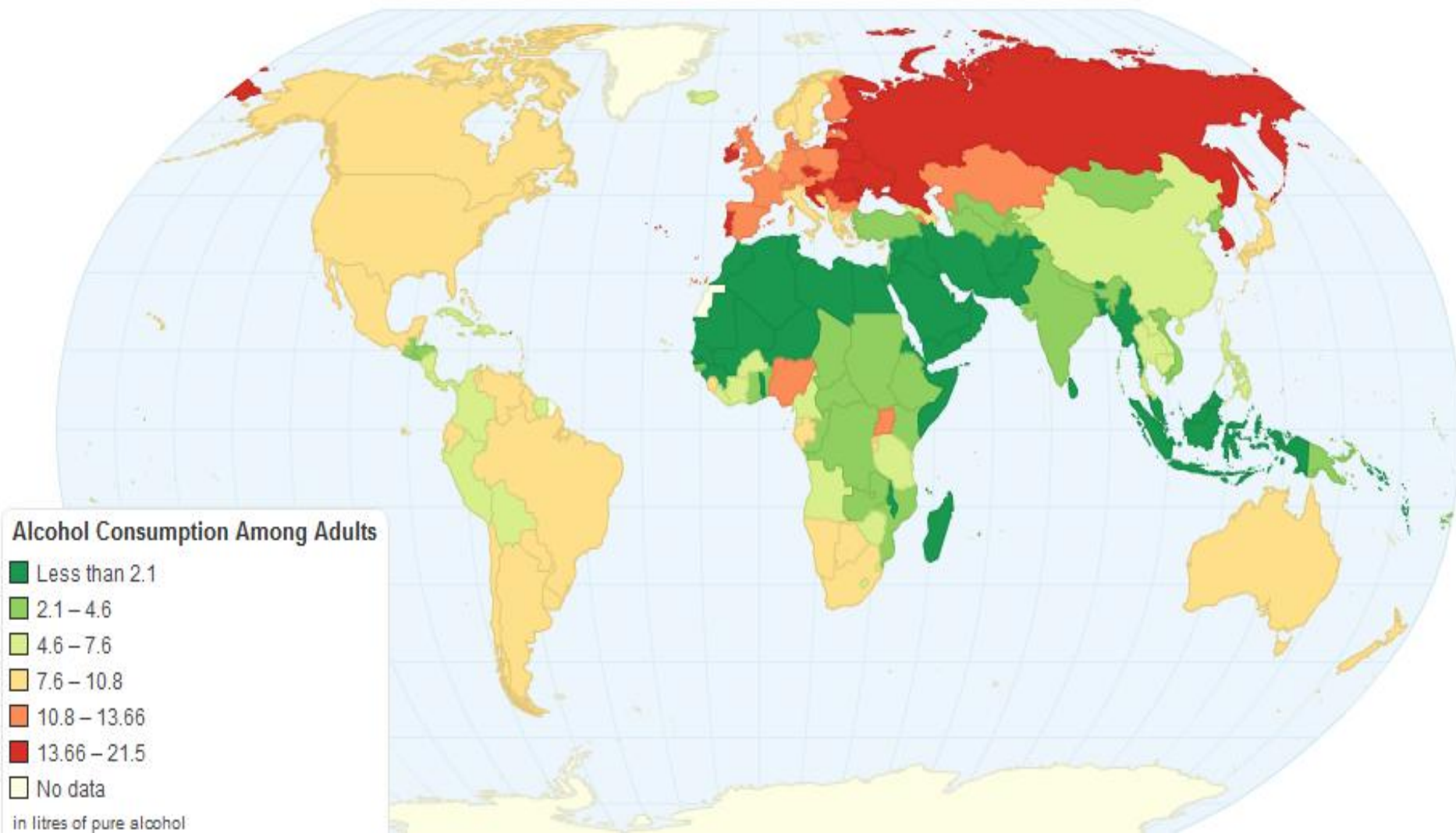
Brno 9. května 2018
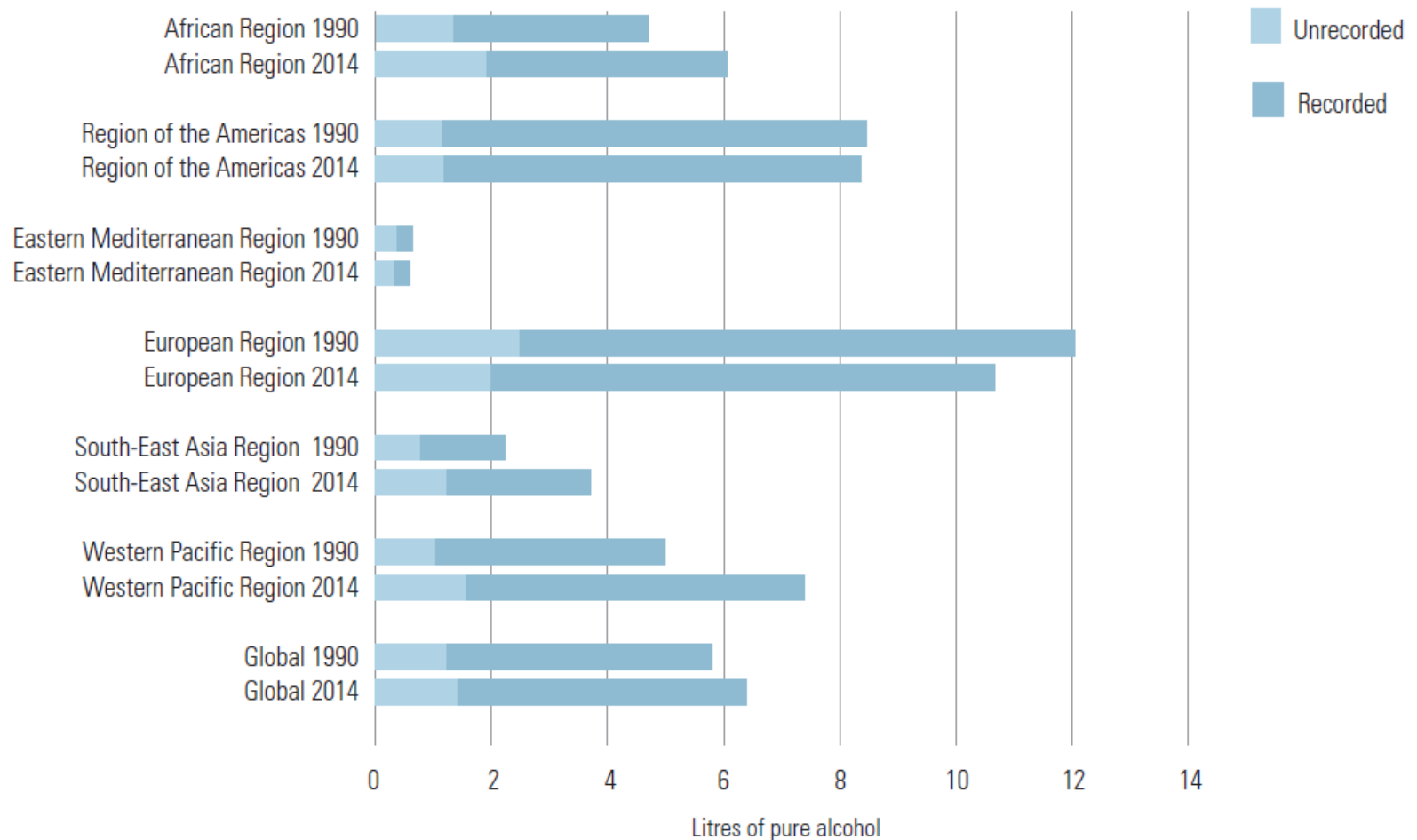
Alcohol Consumption Worldwide

Current Worldwide Alcohol Consumption Among Adults

Alcohol Consumption Among Adults
- Less than 2.1
- 2.1 – 4.6
- 4.6 – 7.6
- 7.6 – 10.8
- 10.8 – 13.66
- 13.66 – 21.5
- No data

in litres of pure alcohol

Alcohol consumption per capita 1990-2014

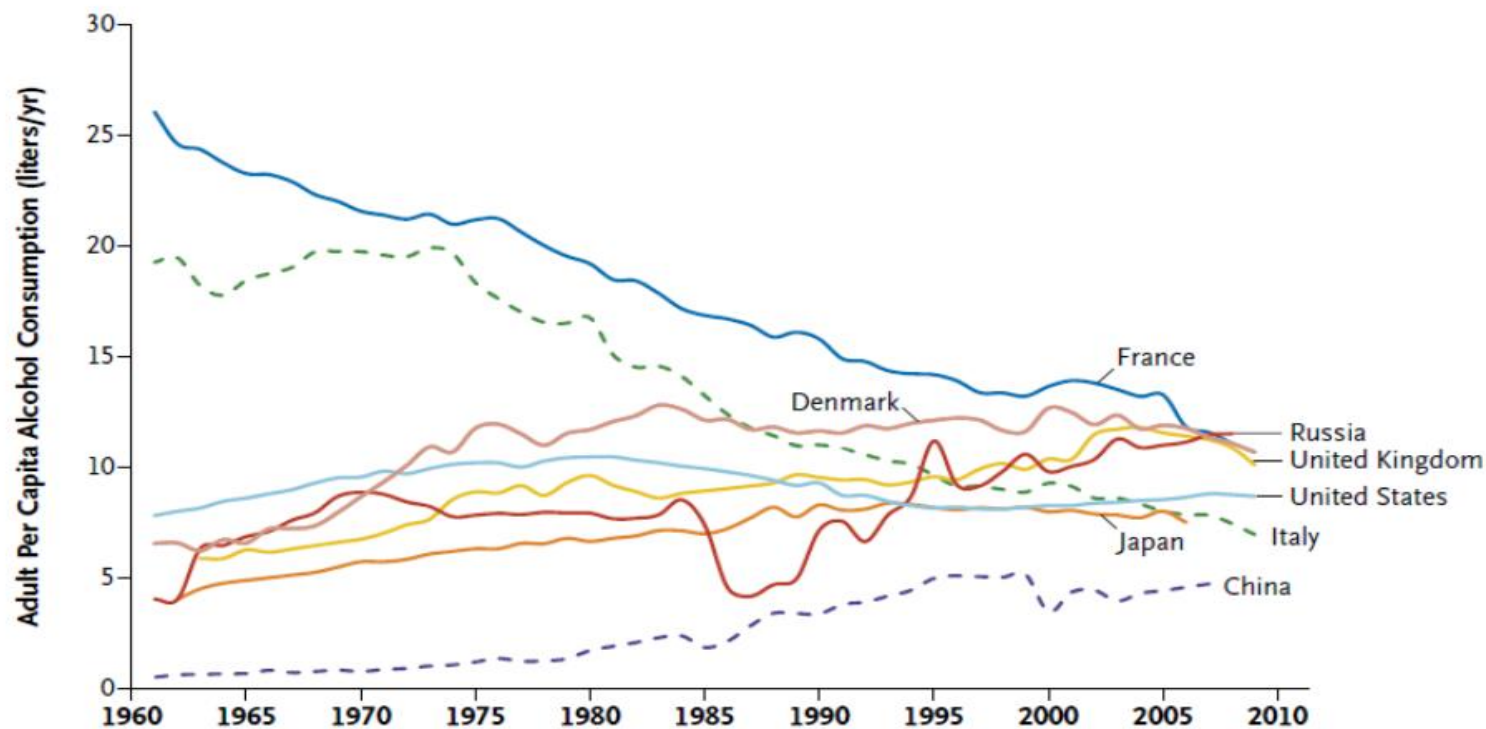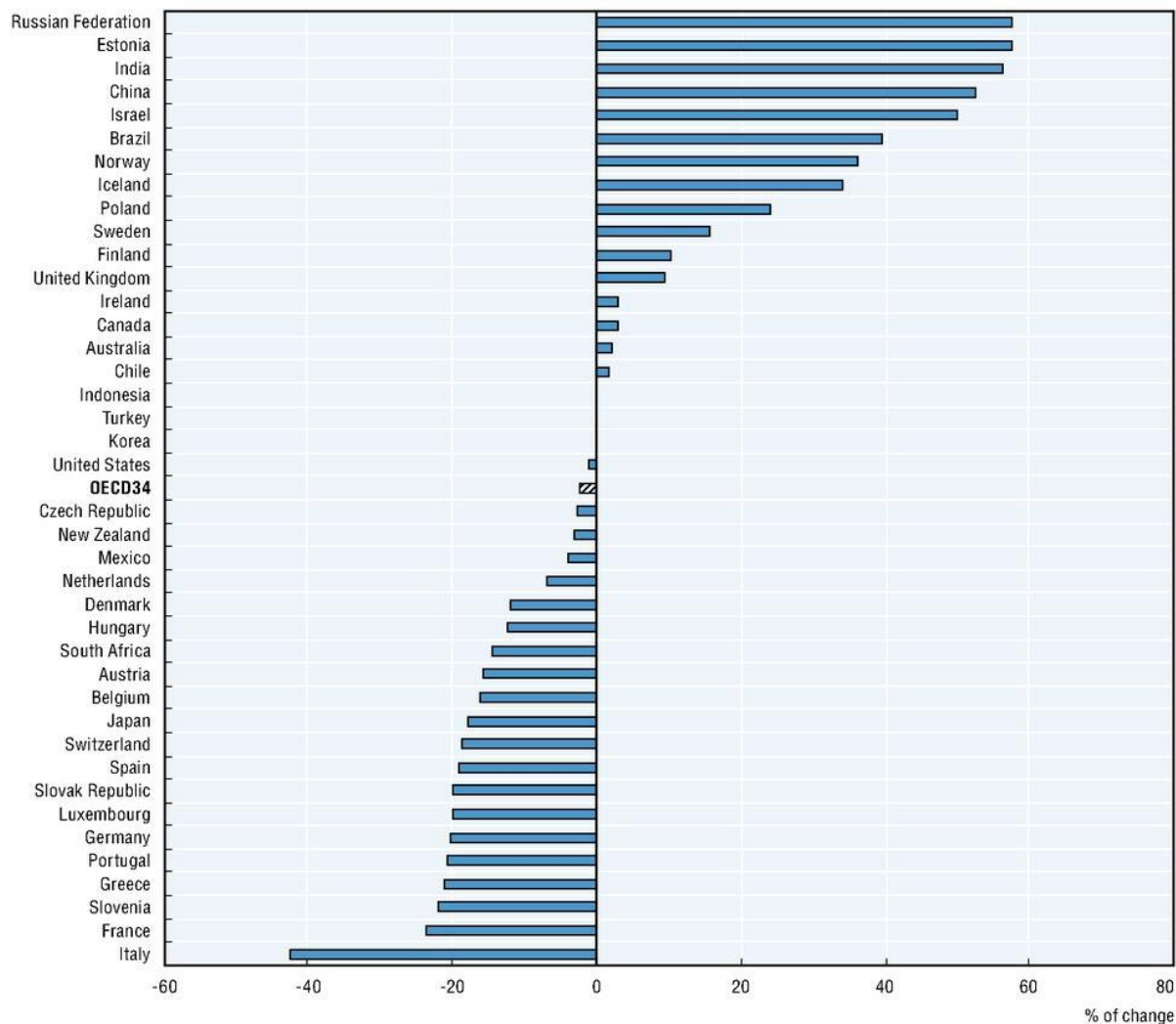# Trends in adults per capita alcohol consumption in different countries

Figure 3. Trends in Recorded Per Capita Alcohol Consumption by Adults in Selected Countries.

In addition to recorded consumption, there is unrecorded consumption in some countries. For example, in 2005, adult per capita unrecorded consumption was estimated to be less than 0.5 liters per year in Japan and France; 1 to 2 liters per year in China, the United Kingdom, and the United States; and close to 5 liters per year in Russia. Data are from the WHO Global Information System on Alcohol and Health (http://apps.who.int/gho/data/node.main.GISAH).

Increase of alcohol consumption

- **Germany, Holand**

    1950-1990   4X

- **Czechoslovakia, Czech Republic**

    1953 - 3.1 l per capita

    1982 - 8.9 l per capita

    1999 - 9.9 l per capita

    2002 - 10.2 l per capita

    2005 - 9.8 l per capita

    2017 - 9.9 l per capita

Change in alcohol consumption among adults, 1992-2012 (or nearest year)

Source: OECD Health Statistics 2014.

StatLink http://dx.doi.org/10.1787/888933180261

Trends in alcohol per capita in different region in Europe
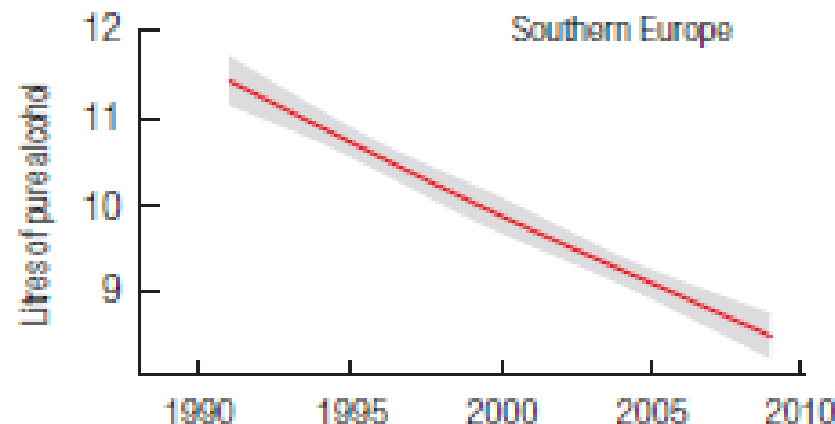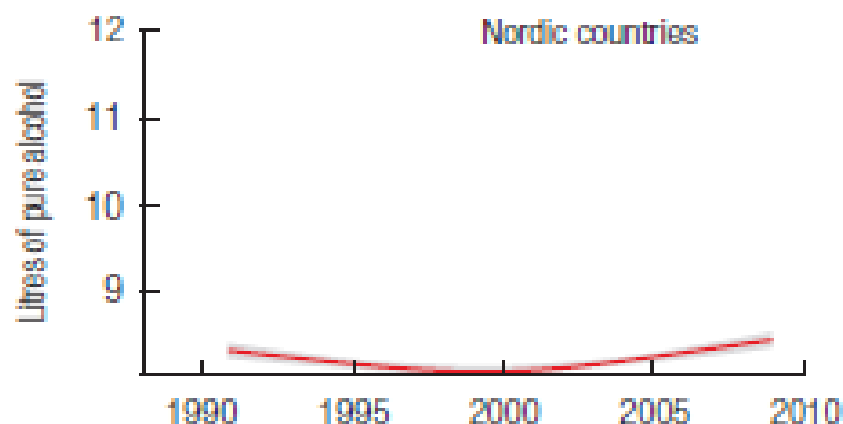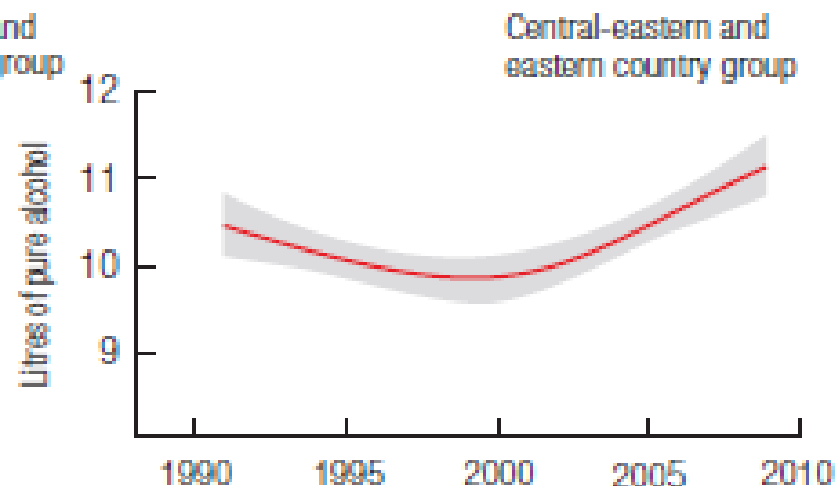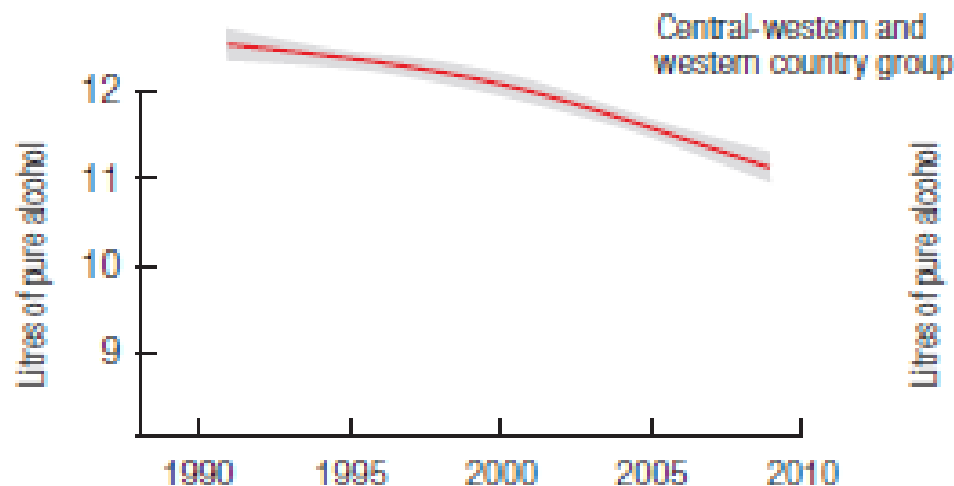
* The 95% confidence intervals are represented as shading.

Consumption levels by type of alcohol, and country drinking score
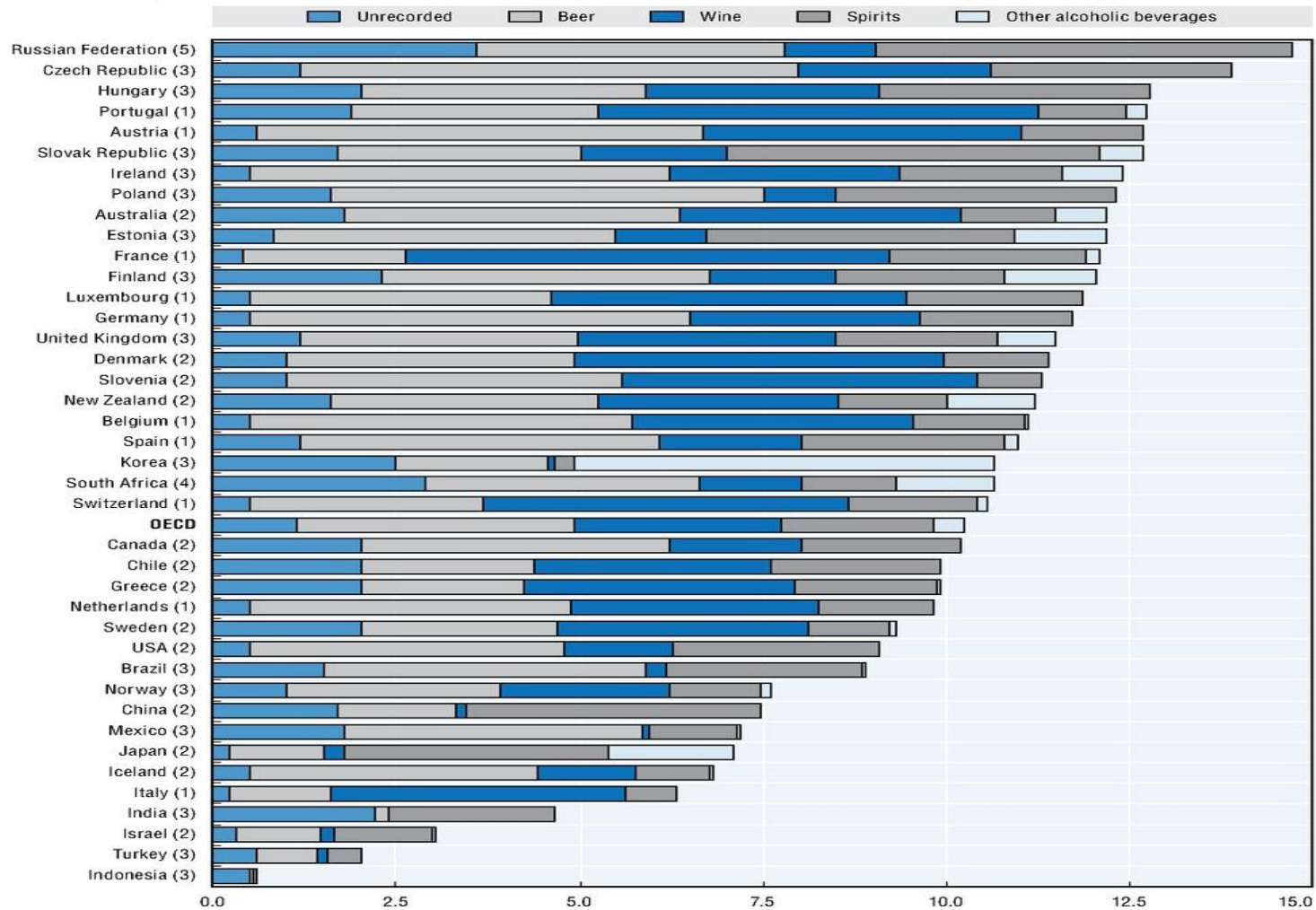
Note: The drinking score is defined as 1 least risky, 2 somewhat risky, 3 medium risky, 4 very risky, 5 most risky.
Source: WHO GISAH database, 2014.

StatLink http://dx.doi.org/10.1787/888933180287

Metabolisms of etanol in hepatocyte

ETOH

NADPH

$O_2^{\cdot -}$

MEOS

NADP$^+$

NAD$^+$

ADH

NADH

ACETALDEHYDE

Aldehyde-oxidase
Xanthine-oxidase

$O_2^{\cdot -}$

ALDH

NAD$^+$

NADH

ACETATE
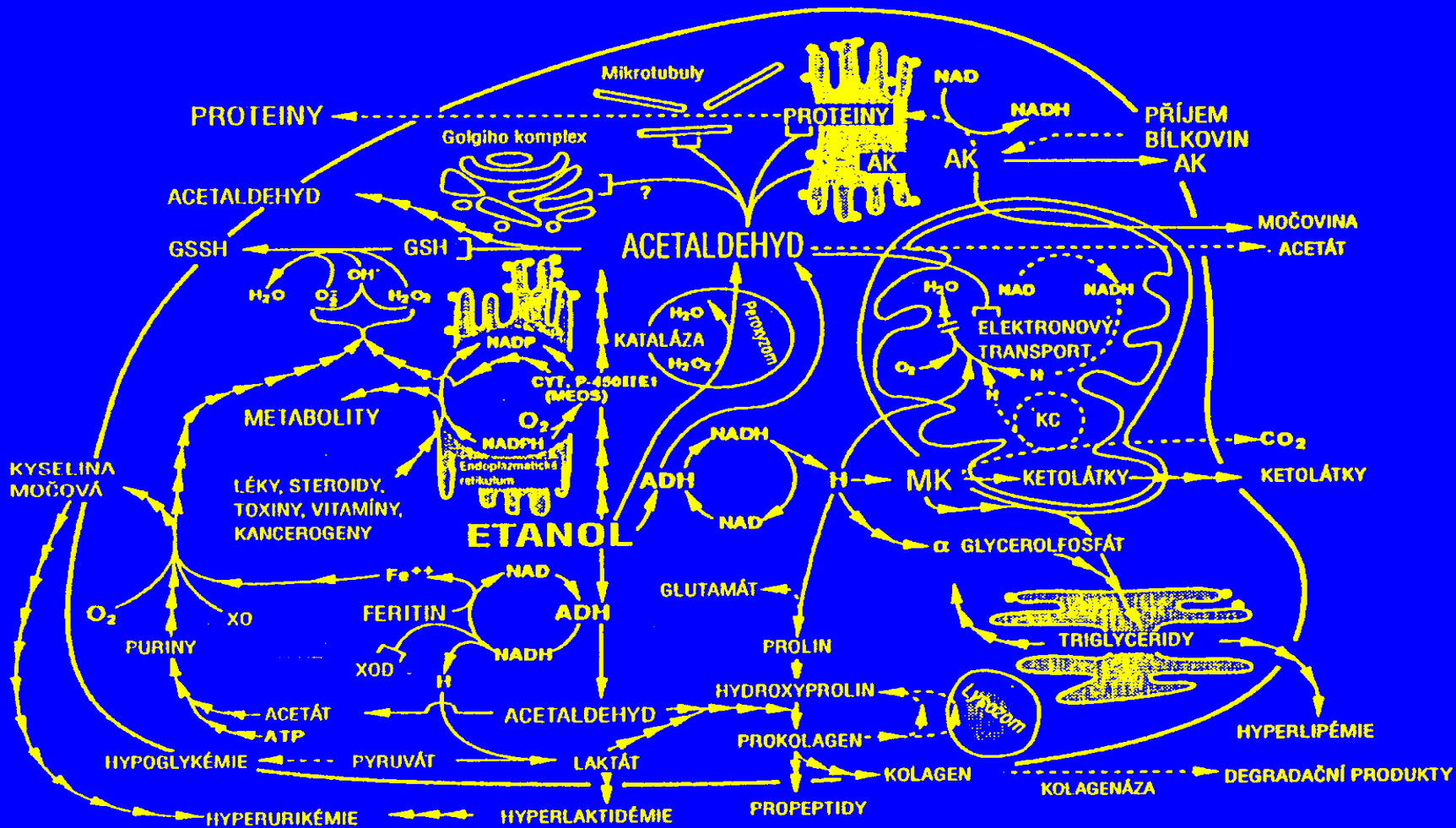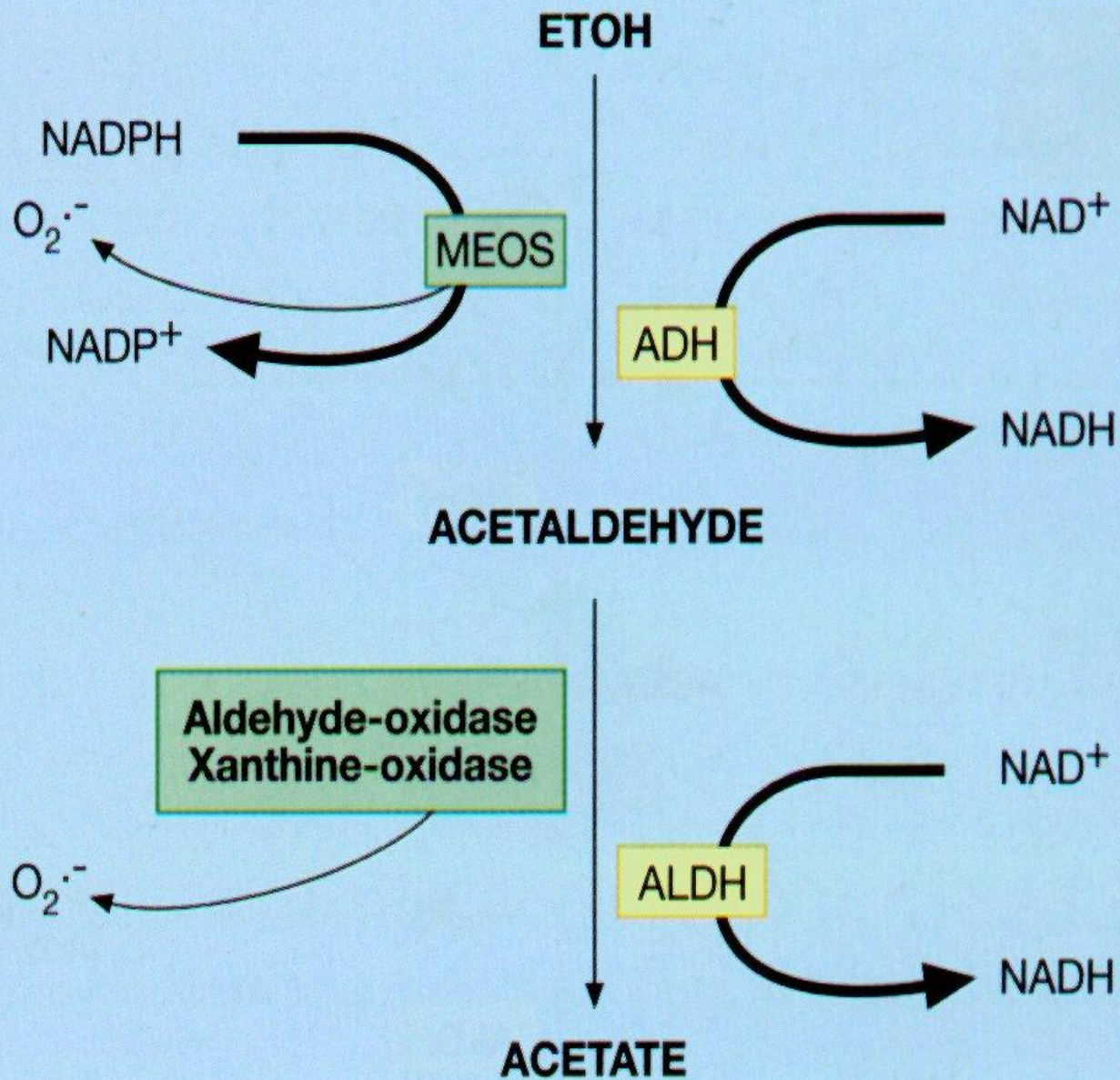
Metabolisms of ethanol

All systems should lead to toxic damage

- Alcohol dehydrogenase
  - Dimeric proteins, two active site
  - Classes I-V
  - Genes ADH 1-7
  - Proteins – α β γ μ σ χ
  - Chromosome 4

- MEOS – CYP2E1
- Catalase
- Non-oxidative metabolism

Metabolic effect I

Via direct effect

- Membrane alterations
- Malnutrition

Via ADH and AlDH oxidation

- Increasing NADH
- Changing of redox potential

Oxidation of ADH and AlDH

- *Increasing*
  - Lactate
  - Uric acid
  - Ketone bodies

- *Decreasing*
  - Gluconeogenesis
  - Krebs cycle
  - Glucuronidations

- *Acidosis*

- *Oxidative stress*

Metabolic effects II

Via acetaldehyde

- Toxic and reactive substances
- Impairment of mitochondrial transport
- Oxidative stress
- Modification of proteins and DNA
- Interferention with DNA repair
- Binds to proteins and forms neoantigens
- Delays cell cyle progression

Metabolic effects III

Via MEOS

- Activation of hepatotoxins and cancerogens

- Changes of oxidation of alcohols – e.g. retinol

- Increasing of beta-oxidation of fatty acids and esterification of fatty acids

OXIDATIVE STRESS AND ETHANOL METABOLISM
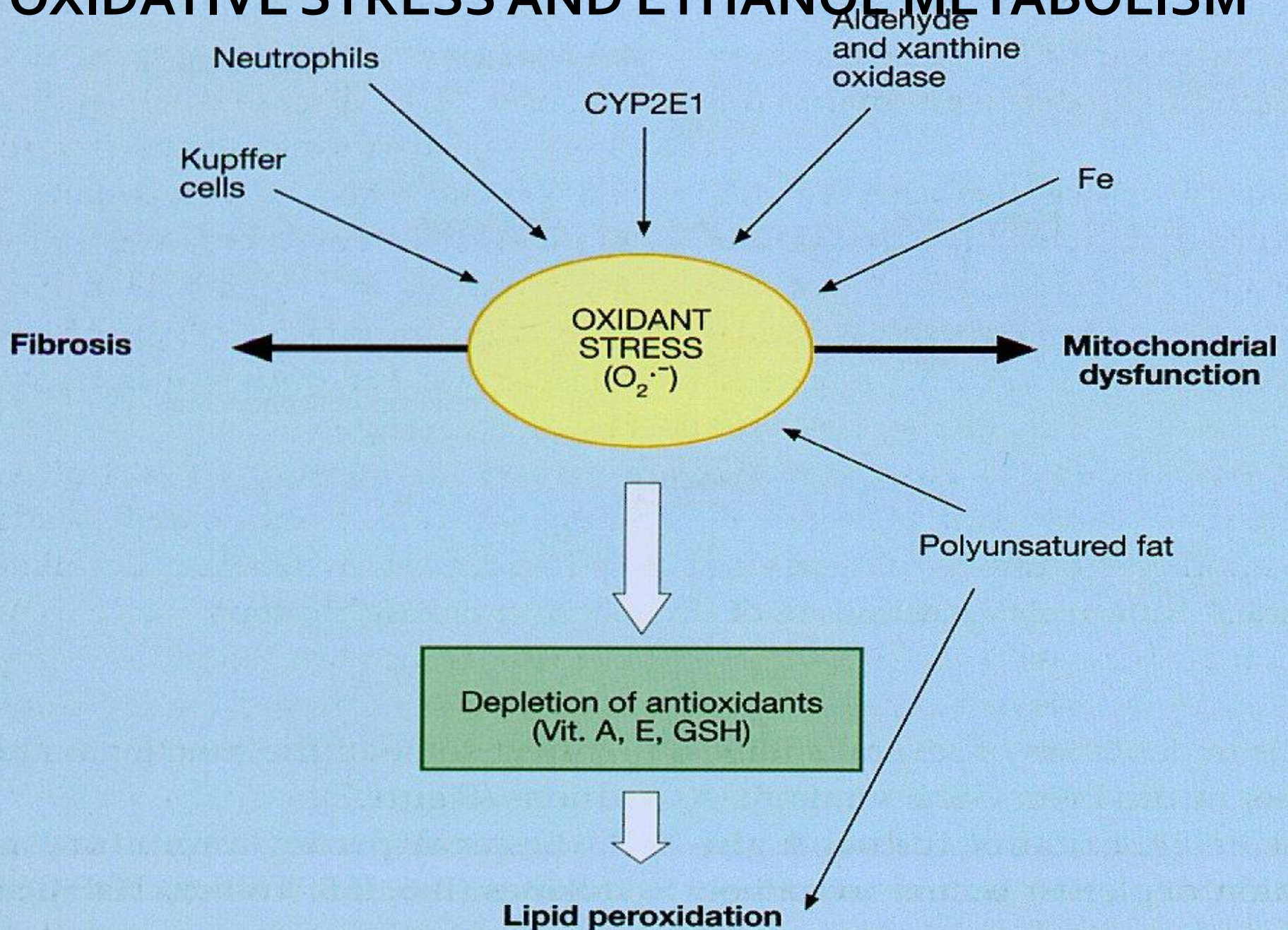
Ethanol-induced oxidative stress mechanisms
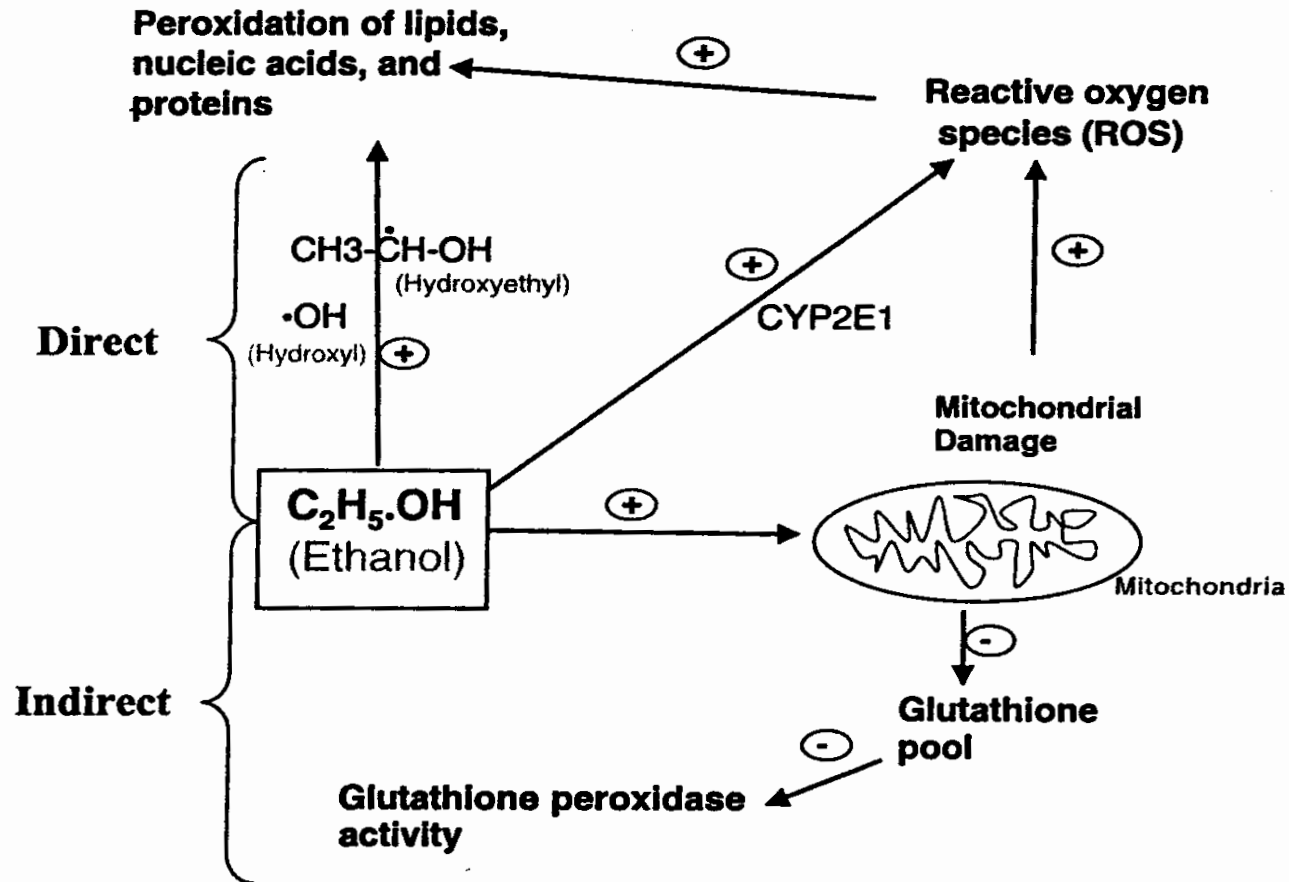
Alcohol related diseases I

- **Liver diseases**
  - Alcohol is the most frequent cause of liver cirrhosis in Europe and US
  - Alcoholic liver disease constitutes 1/3 – 1/2 of patients indicated for liver transplantation.
- **Injuries**
- **Nutritional deficiencies**
- **Cardiovascular diseases**
- **Cancer**

Major theories of alcohol liver damage

Steatosis – fibrosis – cirhossis - carcinoma

- Neutrophil infiltration
- Centrilobular hypoxia
- Genetic factors
- Antigenic adduct formation - derived from lipid peroxidation products 4HNE and MDA
- Action of injurious cytokines, endotoxin,

Acetaldehyde and CYP2E1 as Pathogenetical Factors in ALD
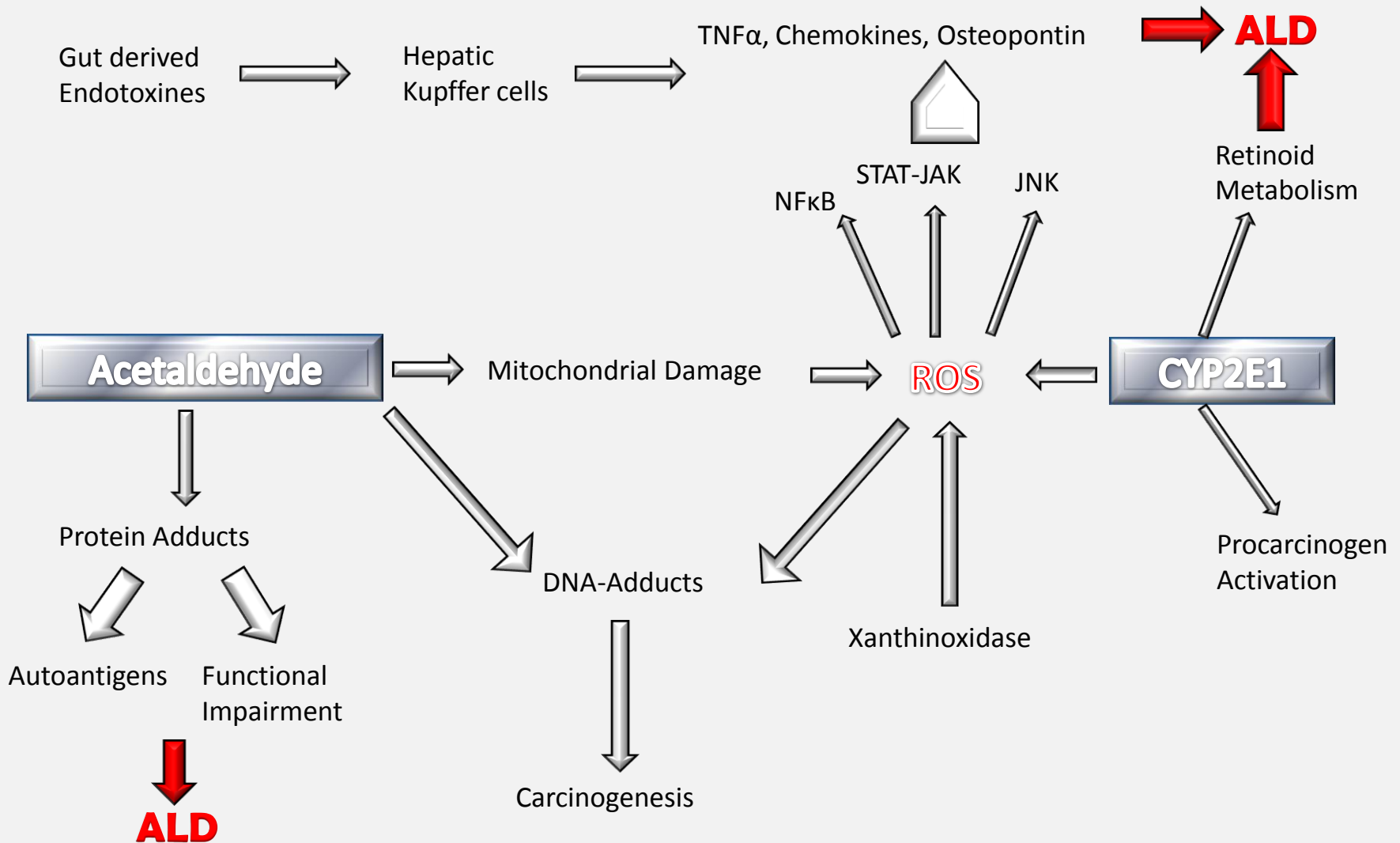
Alcohol related diseases II

- Damage of nervous system
- Development of osteoporosis
- Pancreas damage
  - Chronic pancreatitis 50%
- Fetal alcohol syndrome
  - 1.3 new born child /1000 child
    - Hypotrofy of fetus
    - Changes of intelect
- Myopathy and cardiomyopathy
  Acute and chronic myopathy,

NADPH-diaphorase positive neurons – stratum griseum superficiale
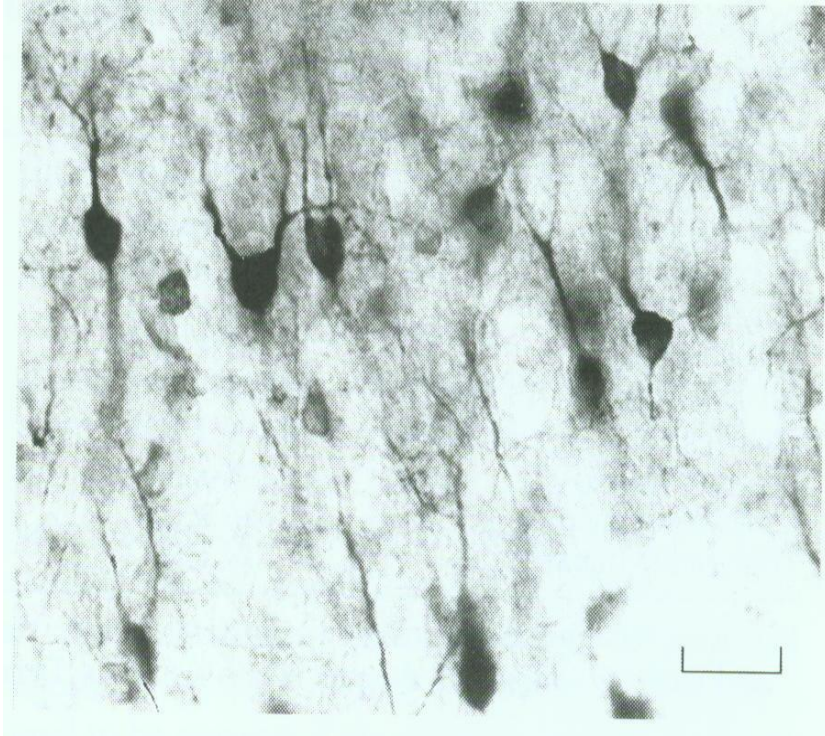
Controls

Ethanol-fed rats

Zima et al
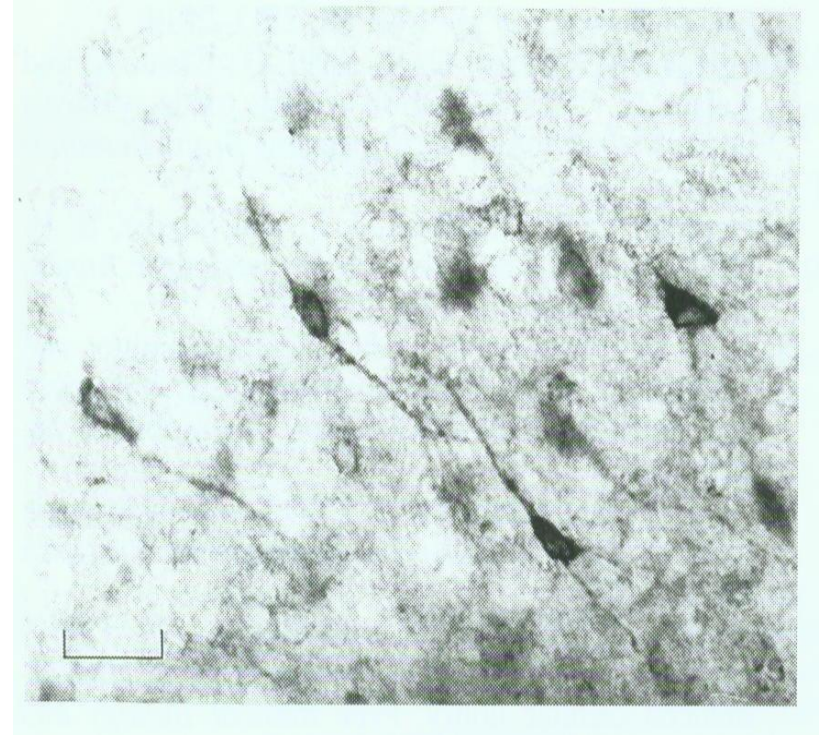
Alcohol and cancers

- ## Upper digestive tract
  - 25-68 % risk factor – alcohol
  - very common, especially in Europe
  - 5.2% of all cancer cases worldwide
  - 6.4% of all cancer cases in Europe
- ## Liver – hepatocelullar carcinoma
  - 5. most frequent cancer
  - 3. most frequent cause of cancer mortality
  - Main risk factors for HCC in Europa and USA - Alcohol abuse, HC, NASH
- ## Breast cancer – controversial data
- ## Colon cancer –
  - WHO concensus conference - higher 20 g/ 12,5 g – metanalysis EtOH/daily increasing the risk

Alcohol and cancer

ORGAN	DAILY ETHANOL (g)		LITERATURE
	MEN	WOMEN	
UADT	25-49 (2.3-3-6)	10-20 (4.6)	Bofetta + Garfinkel 1990 Maier + Sennwald 1994 Harty et al. 1997
LIVER	>24 (Cirrhosis)	>12 (Cirrhosis)	Burger et al. 2000 (MA)
BREAST	-	>20 >12 (1.4)	Burger et al. 2000 & Smith-Warner et al.1998 (MA) Fuchs et al. 1995 Thun et al. 1997
COLORECTUM (POLYPS)	>30-50(2.5) >30 (1.8)	>30-50(2.5) >30 (2.5)	Scheppach et al. 1999 (MA) Cho et al. 2004 (MA) Keanny et al. 1995

Chronic alcohol consumption is a risk factor for upper alimentary tract cancer, liver cancer

Table Association Between Level of Alcohol Consumption and the Development of Certain Types of Cancer

Type of Cancer	Pooled RR (95% Confidence Interval) Associated With Alcohol Consumption*		
	25 g/day	50 g/day	100 g/day
Oral and Pharyngeal Cancer	1.75 (1.70–1.82)	2.85 (2.70–3.04)	6.01 (5.46–6.62)
Laryngeal Cancer	1.38 (1.32–1.45)	1.94 (1.78–2.11)	3.95 (3.43–4.75)
Esophageal Cancer	1.51 (1.48–1.55)	2.21 (2.11–2.31)	4.23 (3.91–4.59)
Liver Cancer	1.17 (1.11–1.23)	1.36 (1.23–1.51)	1.86 (1.53–2.27)

*The consumption levels analyzed correspond to approximately two, four, and eight standard drinks per day, respectively. A standard drink is frequently defined as 12 fl oz of beer, 5 fl oz of wine, or 1.5 fl oz of 80-proof distilled spirits, all of which contain approximately 0.5 oz (14 g) of pure alcohol.

SOURCE: Bagnardi et al. 2001

Ethanol metabolism and ADH, AlDH Polymorphisms

ADH1B*2/ADH1C*1

ETHANOL → ACETALDEHYDE → ACETATE
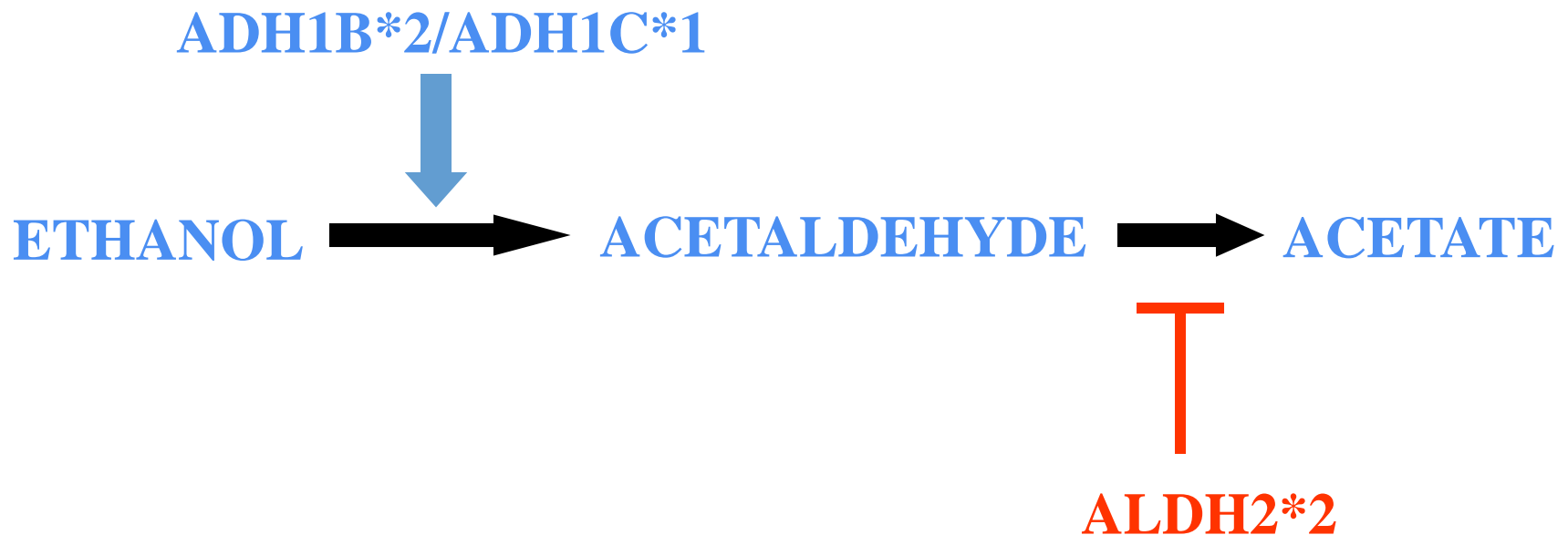
ALDH2*2

e.g - ADH1B, ADH1C, ALDH2 increase in UADT Cancers in central Europen population   Hashibe 2006
 - ALDH2*2 gene polymorphism is predictor of development cancer in Japanese alcoholics – Yokoyama 1998

Mechanisms of alcohol-mediated carcinogenesis
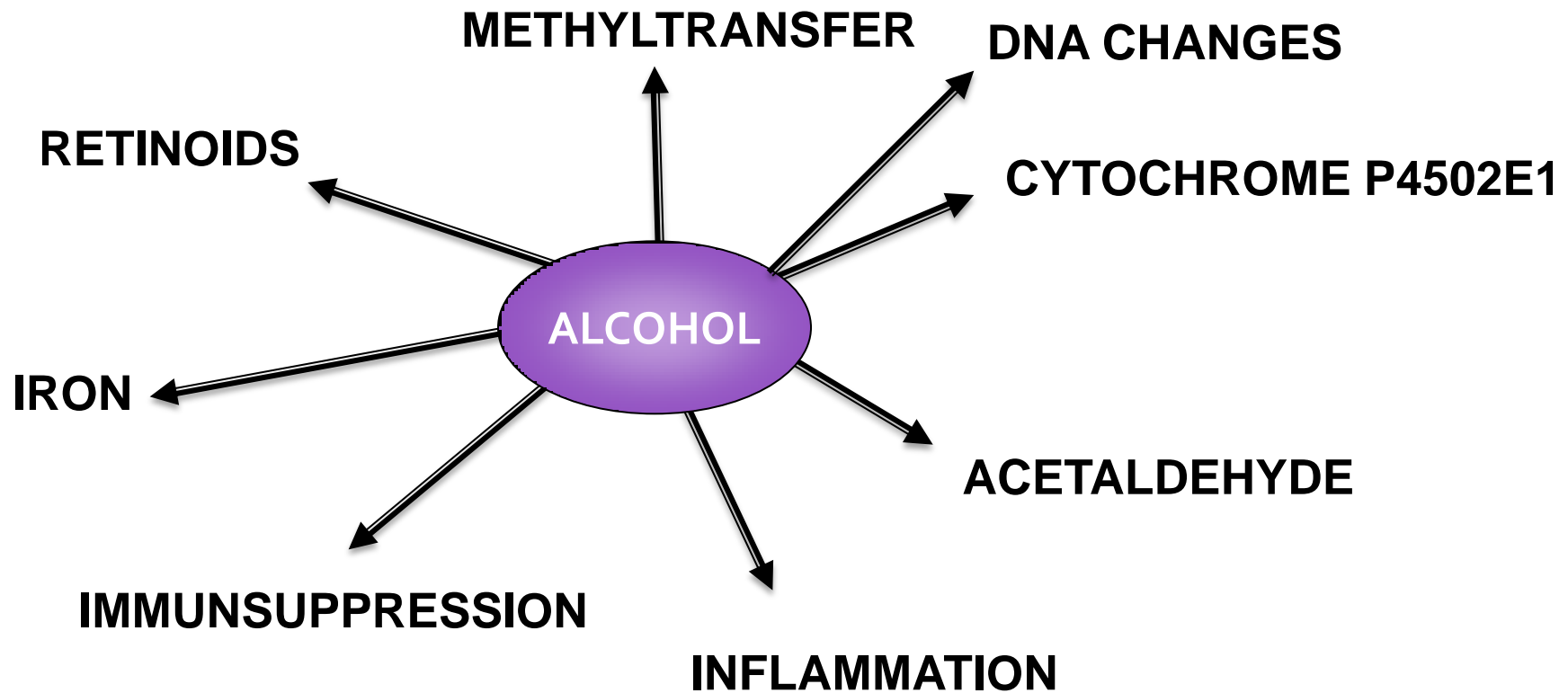
Estimated increase in the relative risk of incident cancer per 10-g/d increase in alcohol intake (drinkers only) Million Women Study

Allen 2009

Cancer site or type (ICD-10)	Number of cases in drinkers	% increase in relative risk (95% CI) per 10-g/day increase in alcohol	
Larynx (C32)	99	44 (10 to 88)	
Oral cavity and pharynx (C00-C14)	557	29 (14 to 45)	
Liver (C22)	223	24 (2 to 51)	
Esophagus (C15)	534	22 (8 to 38)	
Breast (C50)	21971	12 (9 to 14)	
Rectum (C19-C20)	1633	10 (2 to 18)	
Malignant melanoma (C43)	1999	4 (-3 to 12)	
Pancreas (C25)	947	4 (-6 to 15)	
Lung (C34)	3468	3 (-2 to 9)	
Leukemia (C91-C93, C95)	742	3 (-8 to 16)	
Brain (C71)	684	1 (-11 to 14)	
Colon (C18)	3122	1 (-5 to 6)	
Cervix (C53)	325	0 (-16 to 19)	
Ovary (C56)	2713	-1 (-7 to 5)	
Endometrium (C54)	2948	-3 (-8 to 3)	
Multiple myeloma (C90)	573	-4 (-16 to 10)	
Bladder (C67)	657	-7 (-18 to 5)	
Stomach (C16)	545	-7 (-19 to 7)	
Renal cell carcinoma (C64)	803	-12 (-22 to -1)	
Non-Hodgkin lymphoma (C82-C85)	1704	-13 (-19 to -5)	
Thyroid (C73)	305	-25 (-39 to -8)	

Alcohol and cancer - conclusion

- Alcoholic beverages are carcinogenic to humans.

- 10% of all cancers in men and 3% in women could be attributed to alcohol consumption.

- The occurence of malignant tumours of the oral cavity, pharynx, larynx, oesophagus, liver, colorectal cancer and female breast is causally related to alcohol consumption.

- Association is suspected for pancreas and lung cancer.

Mechanisms of Alcohol Induced Tisssue Injuries

Mechanisms of Alcohol Induced Tissue Injuries

Direct and Indirect Effects of Alcohol

Liver damage
Pancreatic damage
Gastrointestinal damage

Cardiovascular damage — Heart

CNS damage — Brain

Indirect effects of alcohol → ↑ Acetaldehyde metabolite formation
↑ Metabolic disregualtion; e.g. increase catabolism
Malnutrition
Altered circulating cytokine expression
Neurohormonal activation

Direct effects of alcohol:
↑ Inflammatory markers; e.g. TNF, SDF-1, IL -6, IL-1 INF-g
↑ Oxidative stress "ROS"
Mitochondrial dysfunction
↑ Endoplasmic Reticulum (ER) stress
Disruption of Protein biosynthesis
Dysregulation of protein metabolism

Heart damage: ↑ Inflammatory markers
Contractile dysfunction
Cardiac arrhythmia
Cardiomyopathy
Heart failure

Brain damage: ↑ Neuroinflammation
Altered hippocampus structure and function
Neuronal damage

Fron in Pharmacol 2018, vol 9, art 81

FIGURE 1 | Mechanisms of alcohol-induced tissue injuries.

Estimated future years of life lost by extent of alcohol consumption (compare - 0-100g/week)

Lancet 2018, 391, 1513-23
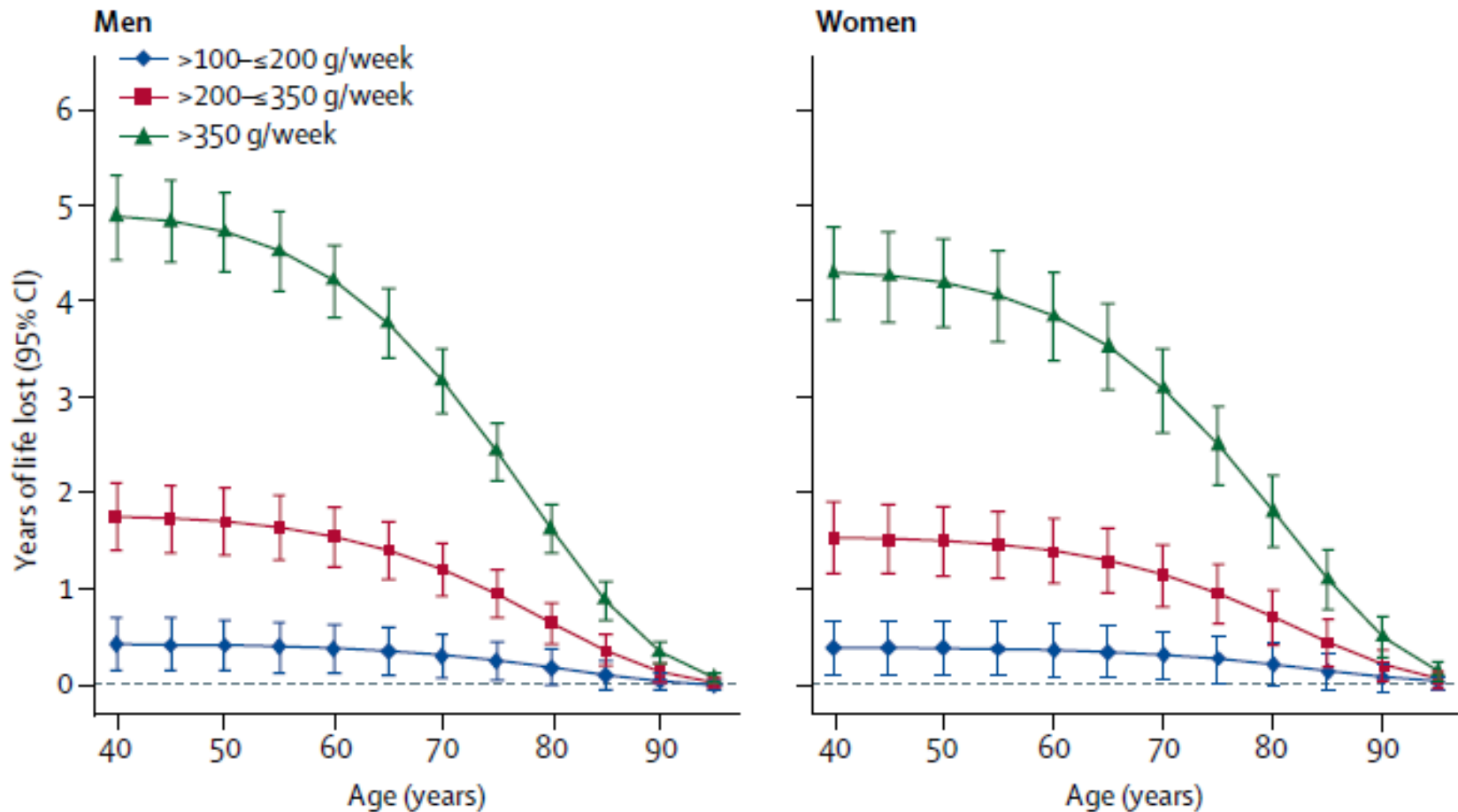
Different risk of alcohol- related diseases in Europe – 7 x

1424*

527*

197*

Eastern part of the European Region

Entire European Region

Mediterranean part of the European Region

Legend:
- Liver cirrhosis
- Cancer
- Cardiovascular diseases
- Injuries

*Annual deaths per million people
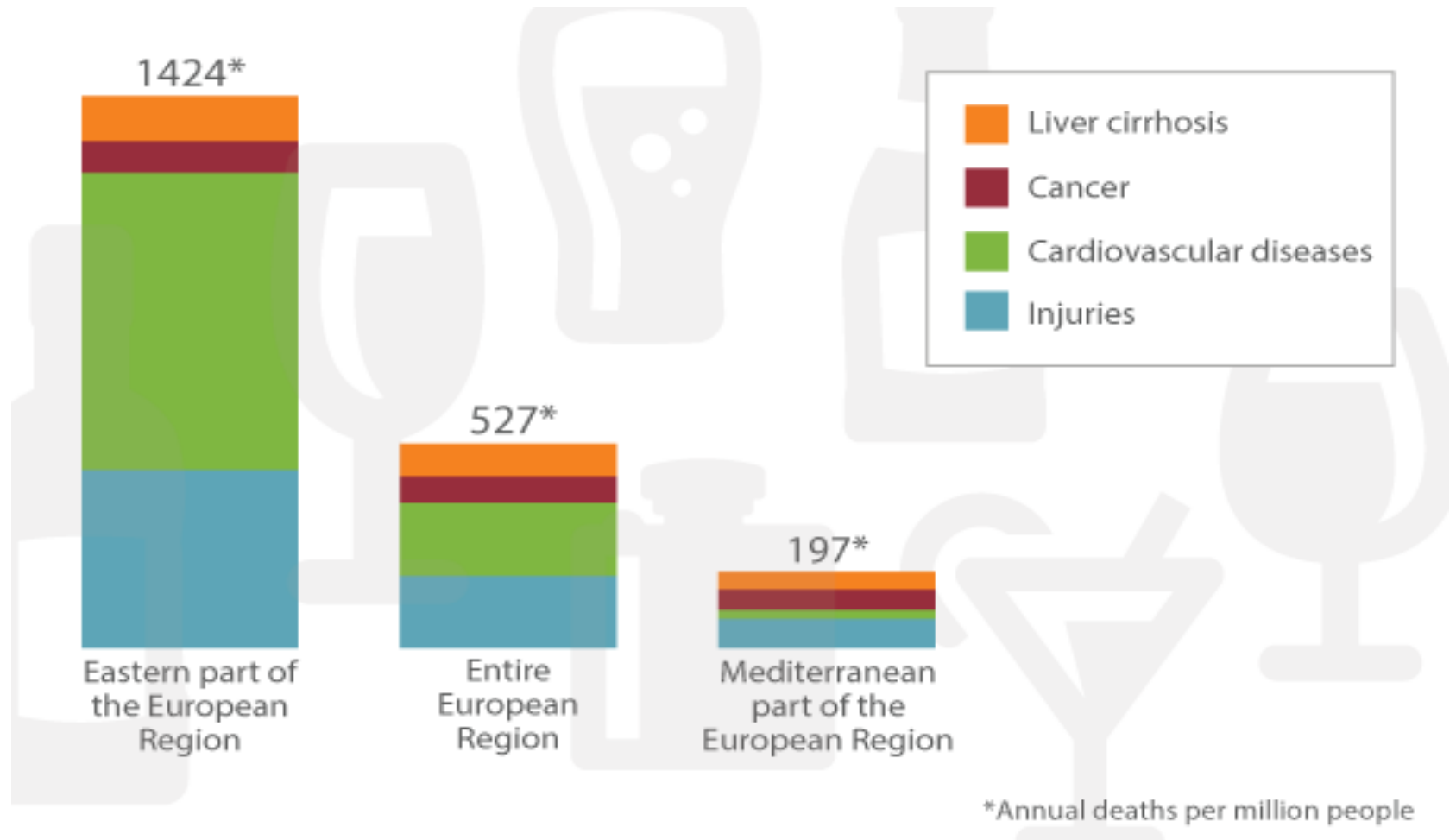
Alcohol and Europe

- EU –losses 125 mld EUR/year
- 55 million adults are estimated to drink at harmful levels in the EU (more than 40g of alcohol)
- Harmful alcohol consumption is estimated to be responsible for approximately 195 000 deaths a year in the EU due to e.g. accidents, liver disease, cancers, suicides etc.
- Harmful alcohol use is the 3rd biggest cause of early death and illness in the EU, behind tobacco and high blood pressure.
- 1 in every 7 deaths in men and 1 in every 13 deaths in women in the group aged 15–64 years was due to alcohol consumption
- **Alcohol influencing to deaths in young generation (15-29 years) World 5%, Europe 25% , Eastern Europe 33%**

Co-operations and support

- *Colleagues and friends*
  - *Helmut Seitz*
  - *Marta Kalousová*
  - *Otto Lesch*
  - *Petr Popov*
  - *Michal Miovský*
  - *.....*
- *Colleagues and laboratory staff from my department*
- *Studies were supported by grants given by the Czech Ministery of Health and the Czech Ministery of Education and Charles University*

Si nimium bibis, non diu eris in vivis.
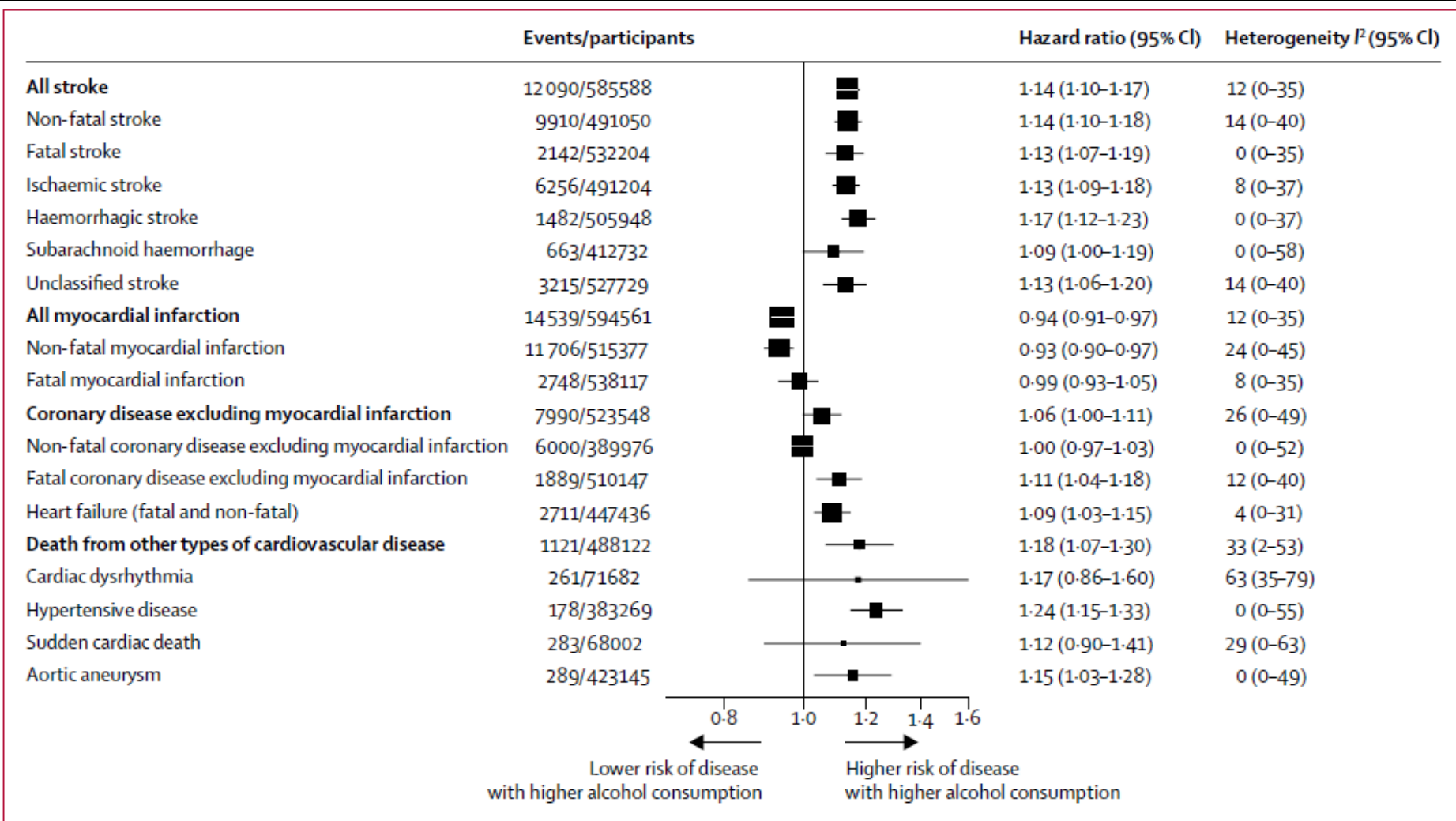
Hazard ratios for subtypes of cardiovascular outcomes in curent drinkers (>100 g /week)

	Events/participants		Hazard ratio (95% CI)	Heterogeneity I^2 (95% CI)
All stroke	12090/585588		1·14 (1·10–1·17)	12 (0–35)
Non-fatal stroke	9910/491050		1·14 (1·10–1·18)	14 (0–40)
Fatal stroke	2142/532204		1·13 (1·07–1·19)	0 (0–35)
Ischaemic stroke	6256/491204		1·13 (1·09–1·18)	8 (0–37)
Haemorrhagic stroke	1482/505948		1·17 (1·12–1·23)	0 (0–37)
Subarachnoid haemorrhage	663/412732		1·09 (1·00–1·19)	0 (0–58)
Unclassified stroke	3215/527729		1·13 (1·06–1·20)	14 (0–40)
All myocardial infarction	14539/594561		0·94 (0·91–0·97)	12 (0–35)
Non-fatal myocardial infarction	11706/515377		0·93 (0·90–0·97)	24 (0–45)
Fatal myocardial infarction	2748/538117		0·99 (0·93–1·05)	8 (0–35)
Coronary disease excluding myocardial infarction	7990/523548		1·06 (1·00–1·11)	26 (0–49)
Non-fatal coronary disease excluding myocardial infarction	6000/389976		1·00 (0·97–1·03)	0 (0–52)
Fatal coronary disease excluding myocardial infarction	1889/510147		1·11 (1·04–1·18)	12 (0–40)
Heart failure (fatal and non-fatal)	2711/447436		1·09 (1·03–1·15)	4 (0–31)
Death from other types of cardiovascular disease	1121/488122		1·18 (1·07–1·30)	33 (2–53)
Cardiac dysrhythmia	261/71682		1·17 (0·86–1·60)	63 (35–79)
Hypertensive disease	178/383269		1·24 (1·15–1·33)	0 (0–55)
Sudden cardiac death	283/68002		1·12 (0·90–1·41)	29 (0–63)
Aortic aneurysm	289/423145		1·15 (1·03–1·28)	0 (0–49)

Scale: 0·8 1·0 1·2 1·4 1·6

← Lower risk of disease with higher alcohol consumption

Higher risk of disease with higher alcohol consumption →

Lancet 2018, 391, 1513-23

Calculation for protective effective of alcohol

- 100g/week = 15 g/day
- 200g/week = 30 g/day
- 15-30 g/day

- 0,3-0,6 L beer (50g/L)
- 1-2 dl wine (150g/L)
- 0,3-0,9 dl Spirit (400g/L)