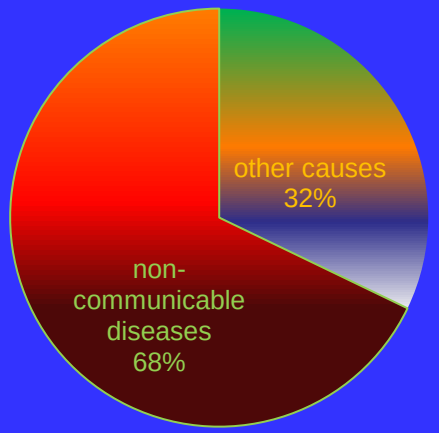
ATHEROSCLEROSIS
pathogenesis
risk factors

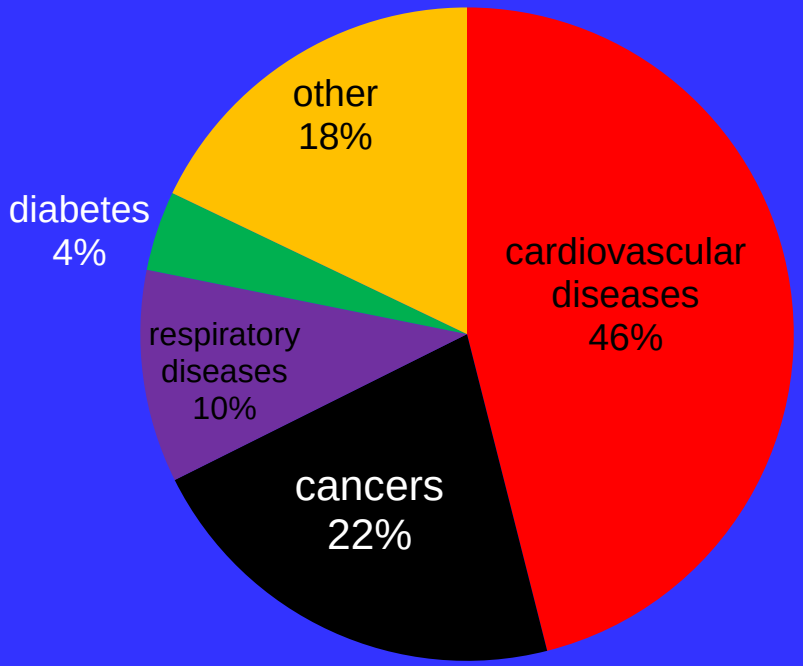
Marek Vecka

Cause of death and burden of disease

worldwide mortality



non-communicable diseases



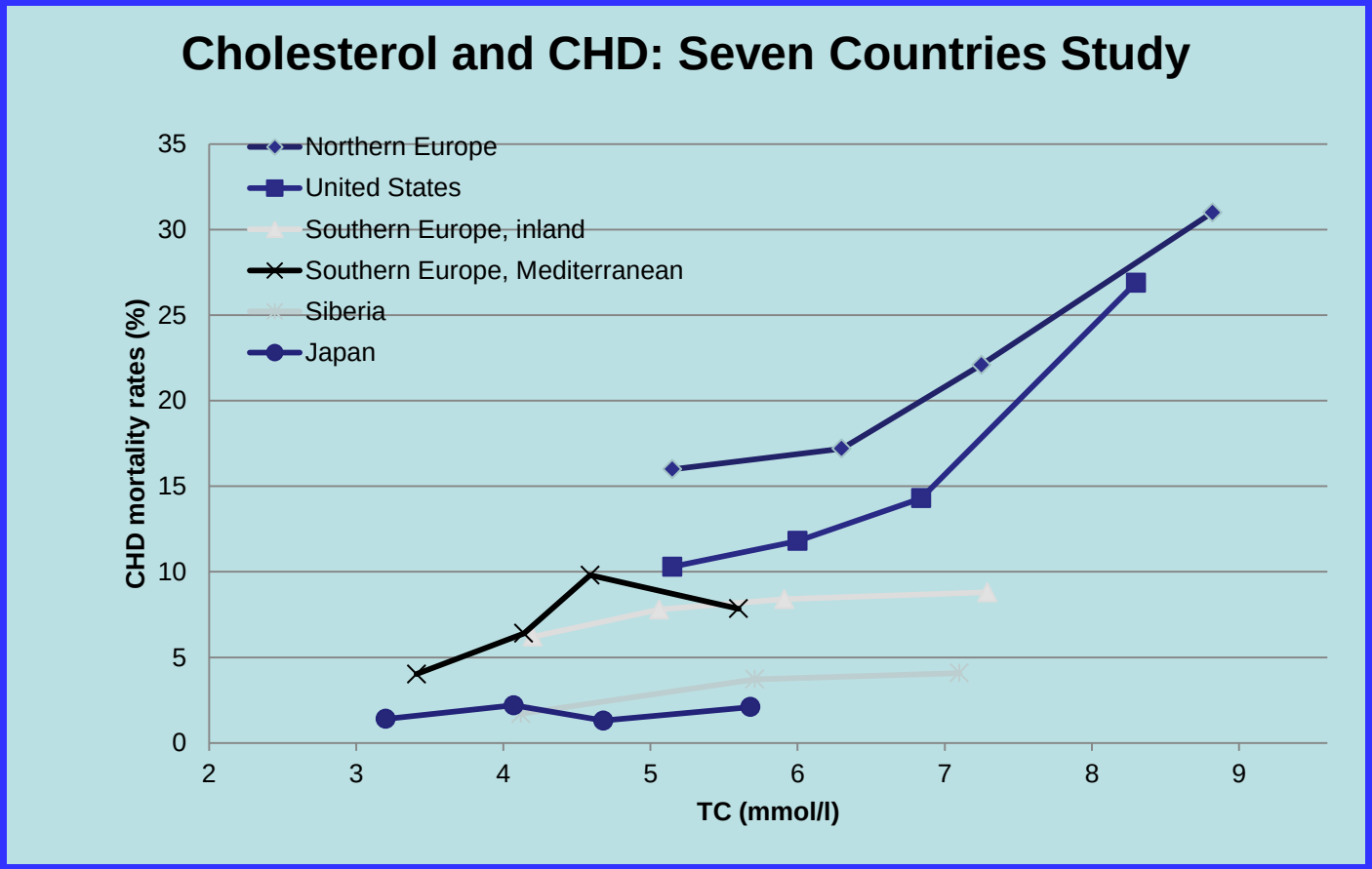
Atherosclerosis

Cardiovascular diseases

atherosclerosis is most important cause

cholesterol plays a crucial role in the pathogenesis of atherosclerosis

Seven countries study: cholesterolemia and mortality



Atherosclerosis

Definition

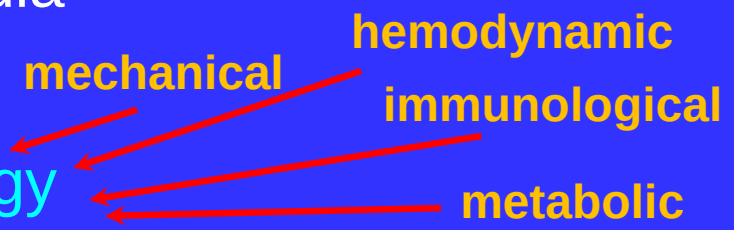
Former approach:

combination of changes in arterial intima

focal accumulation of lipids, complex glycides, blood and blood products, fibrous tissue and calcium, in connection with the changes in media

New definition:

signals of various etiology



proliferative response of endothelium and intima

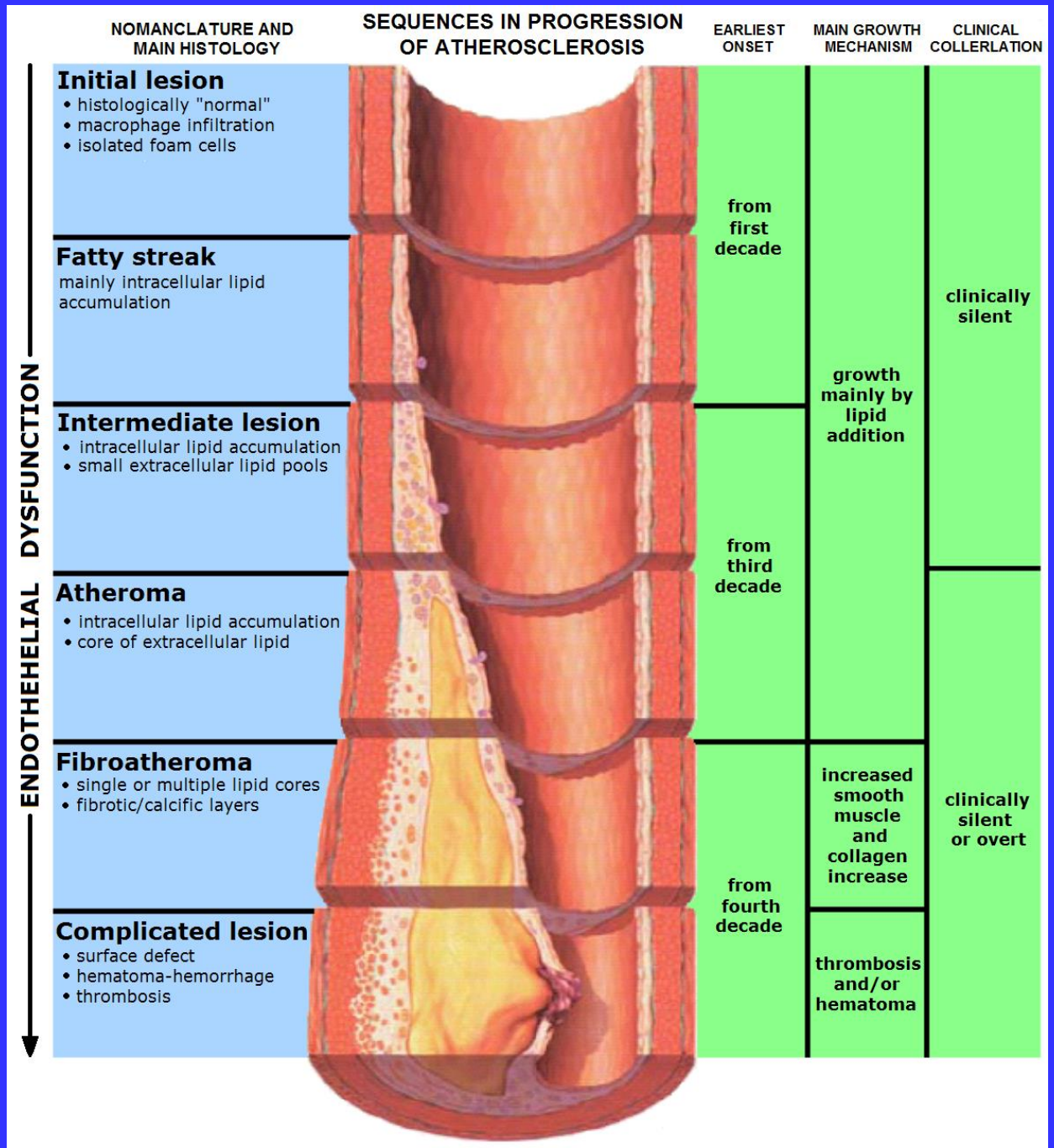
lipid/matrix accumulation

the key role – oxidized lipoproteins

Phases of atherosclerosis

early phase* – *accumulation of lipids

***late phase* – intimal proliferation and adjacent thrombosis**



from Wikipedia/en

Early phase of atherosclerosis

1st type of lesion – isolated foam cells derived from macrophages

2nd type of lesion (*fatty streak*) – accumulation of foam cells

3rd type of lesion (*intermediary lesion)* – small amounts of extracellularly deposited lipids (debris from foam cells)

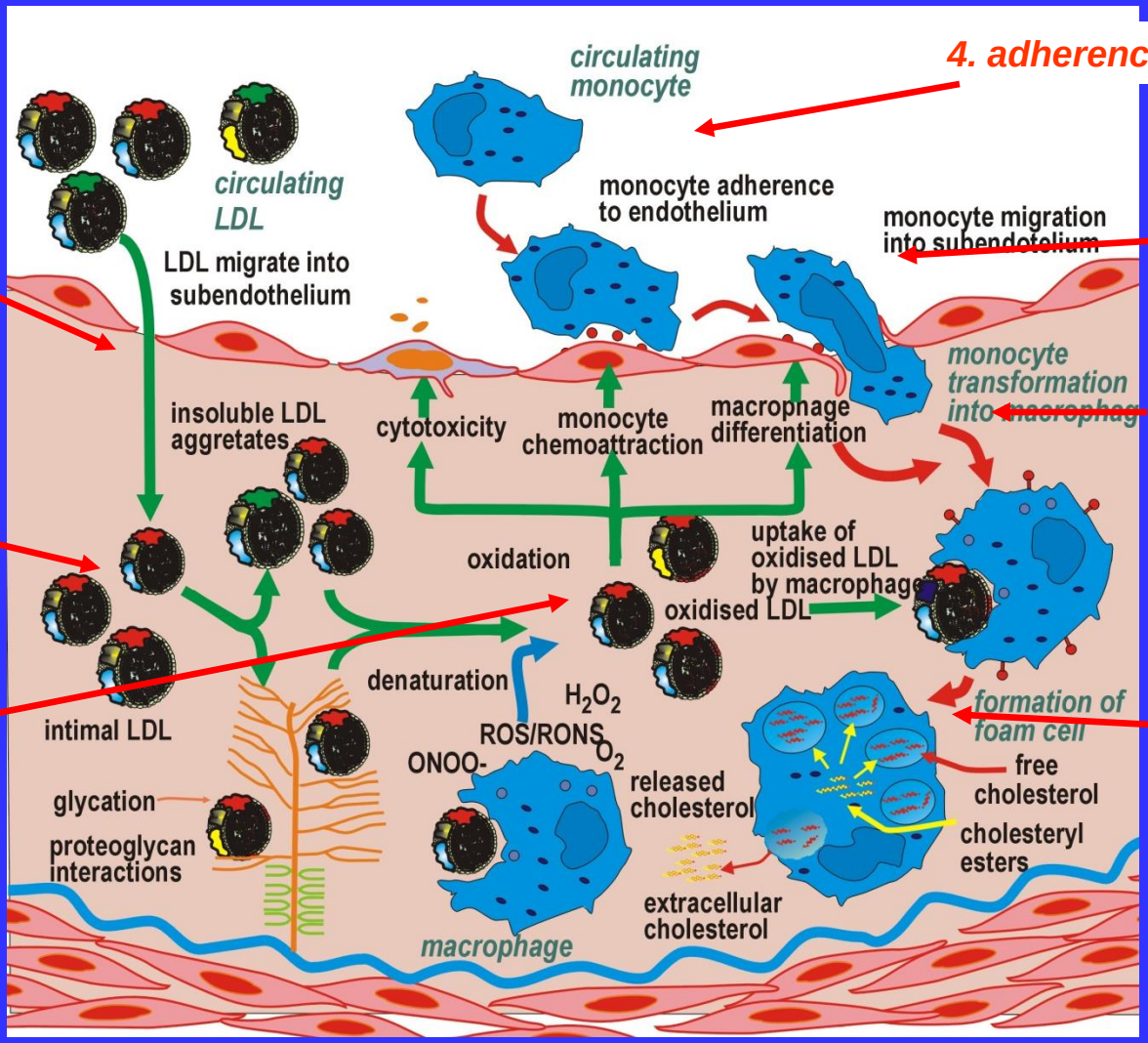
4th type of lesion (*atheroma*) – lipid core localised in the basis of the lesion (almost only extracellularly accumulated lipids)

DEVELOPMENT OF FATTY STREAK

1. transendothelial transport of LP

2. retention of LP

3. oxidative modification of LP



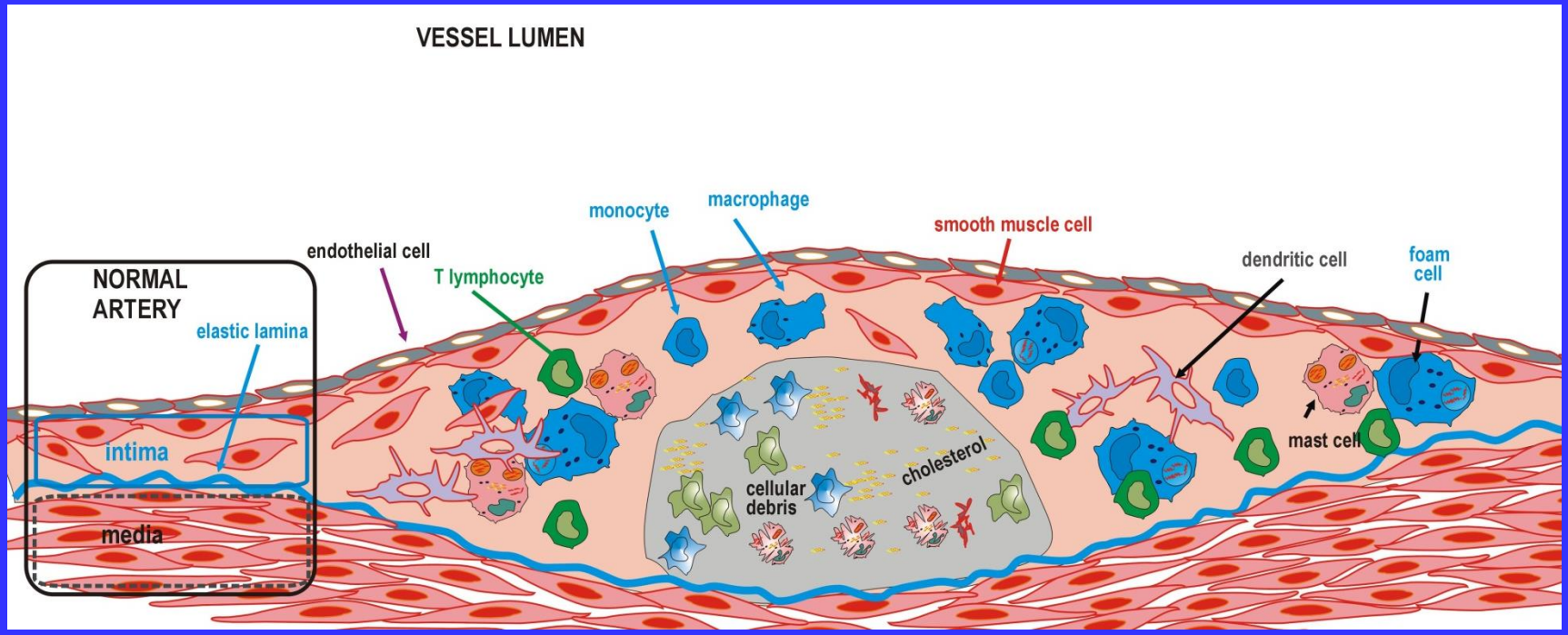
Late phase of atherosclerosis

5th type of lesion (*fibroatheroma*) – proliferation and expression of secretional phenotype of SMC, ↑ synthesis of extracellular matrix (colagen and elastic fibres), the cover = thin layer of smooth muscle cells forming fibrous crust ("cap") over the lipid core

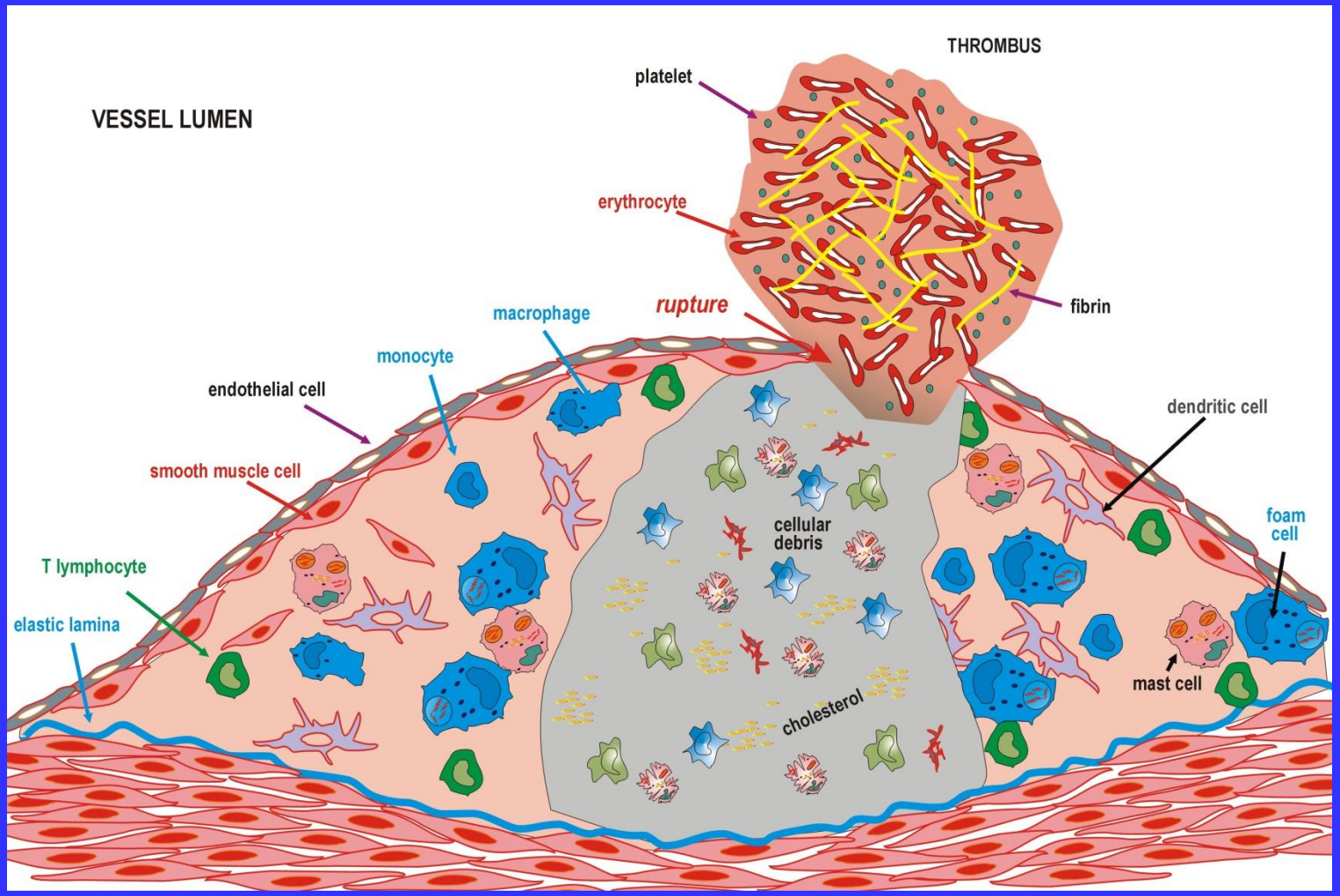
6th type of lesion *(complicated lesion)* - exulceration, hemmorhage into plaque, calcification of necrotic material and artery wall thrombosis

unstable plaque – *see further*

ATHEROSLEROTIC PLAQUE



PLAQUE THROMBOSIS



Atherothrombosis

sudden/impredictable rupture of atherosclerotic plate → platelet activation and thrombus formation

erosion of the plate

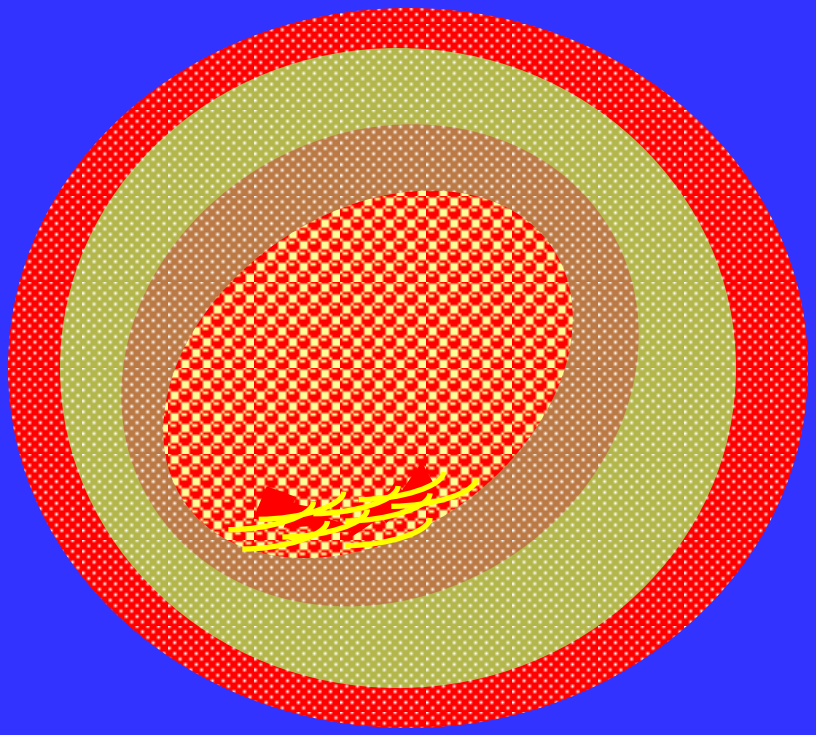
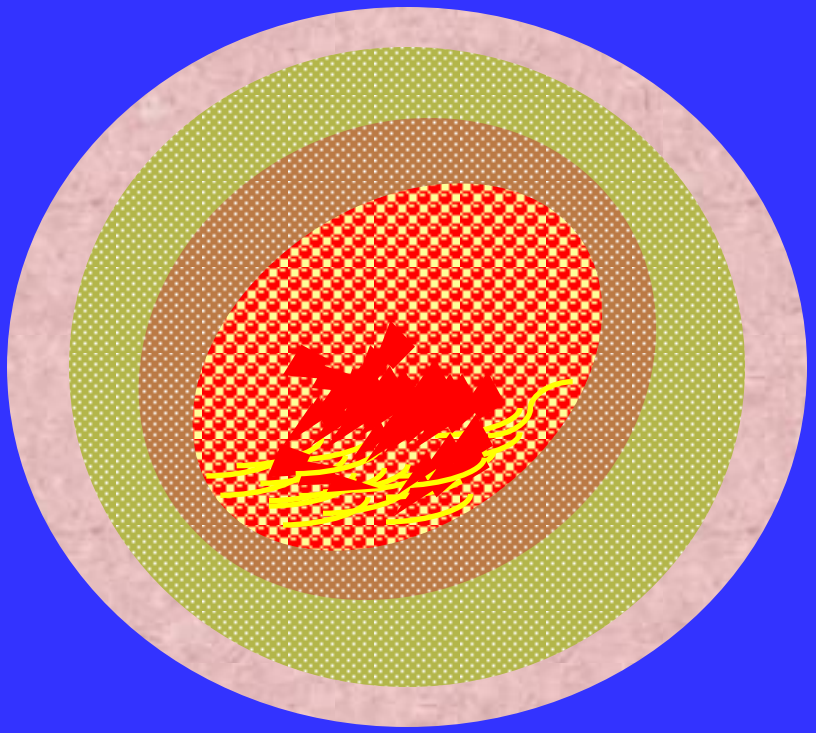


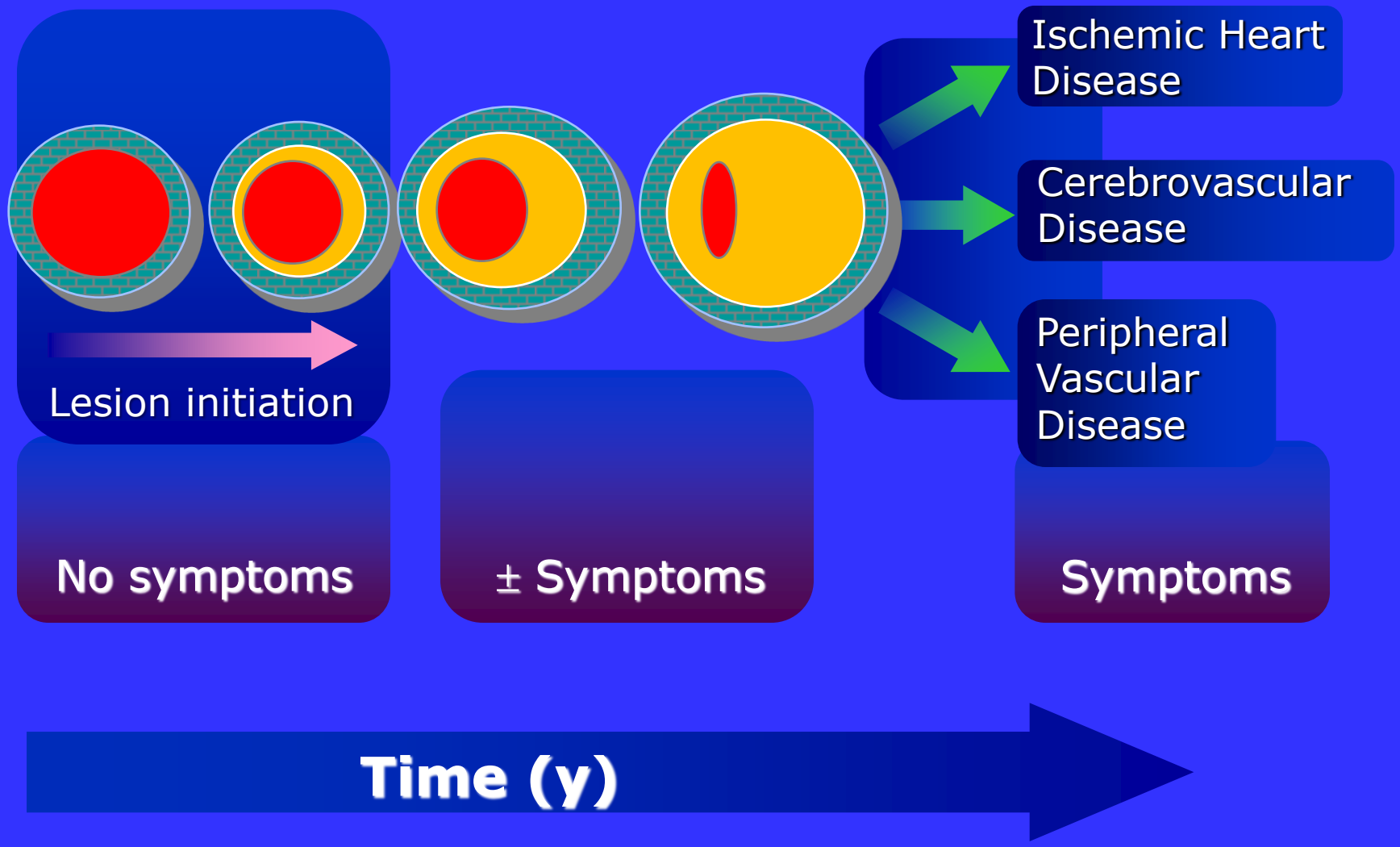
plate rupture



Characteristics of unstable plate in coronary artery

	unstable plate	stable plate
size	30 - 40 % stenosis eccentric	
core lipids	cca 40 % (FC cryst.)	cca 10 %
monocytes/ macrophages/ foam cells	30 % (v/v)	10 % (v/v)
vascular SMC	3 – 5 %	10 – 15 %

Schematic Time Course of Human Atherogenesis



Obviously, we wouldn´t like to end like this....

Risk factors of atherosclerosis and coronary heart disease

Risk factor

= abnormality found in individual without manifestation of ATS during clinical/laboratory examination

present risk factor ⇨ ↑ relative risk of future manifestation of ATS

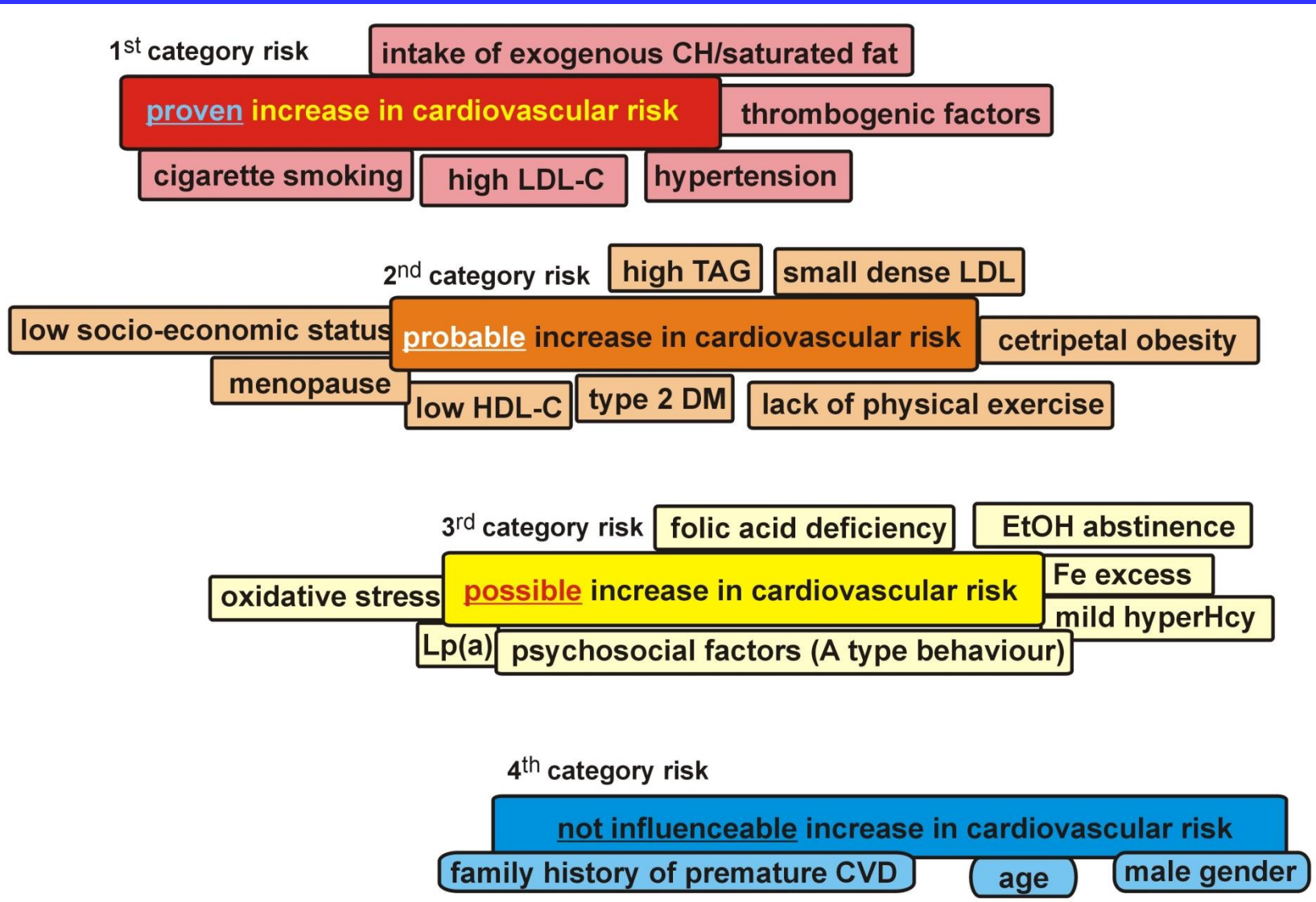
not causally connected
neither denies one another

manifestation of atherosclerosis

this must be supported by intervention studies

↑ incidence raises with ↑ incidence of risk factor
association with risk factor should be *independent, gradual and continual*
risk factors act synergically and/or additively

Categories of cardiovascular risk factors



Risk factors of CAD

- ✓ **Unmodifiable risk factors**
- **gender**
- **positive family history (genetic background)**
- **age**
- **ethnicity**

- ✓ **Modifiable risk factors**
- **smoking**
- **hypertension (LVH, ECG, ECHO)**
- ***hyper LDL-C***
- ***hypo HDL-C***
- ***hyper TG***
- **diabetes mellitus**
- ***sedentary life***
- ***obesity***
- **inflammation**
- **social factors (socio-economic status, type A/B of behaviour)**
- **exogenous estrogens**

A. UNMODIFIABLE RISK FACTORS

Risk factors of CVD for stratification of risk in primary prevention of CHD

A. Unmodifiable risk factors

I. Age and gender

age: > 45 years in men,

> 55 years in women

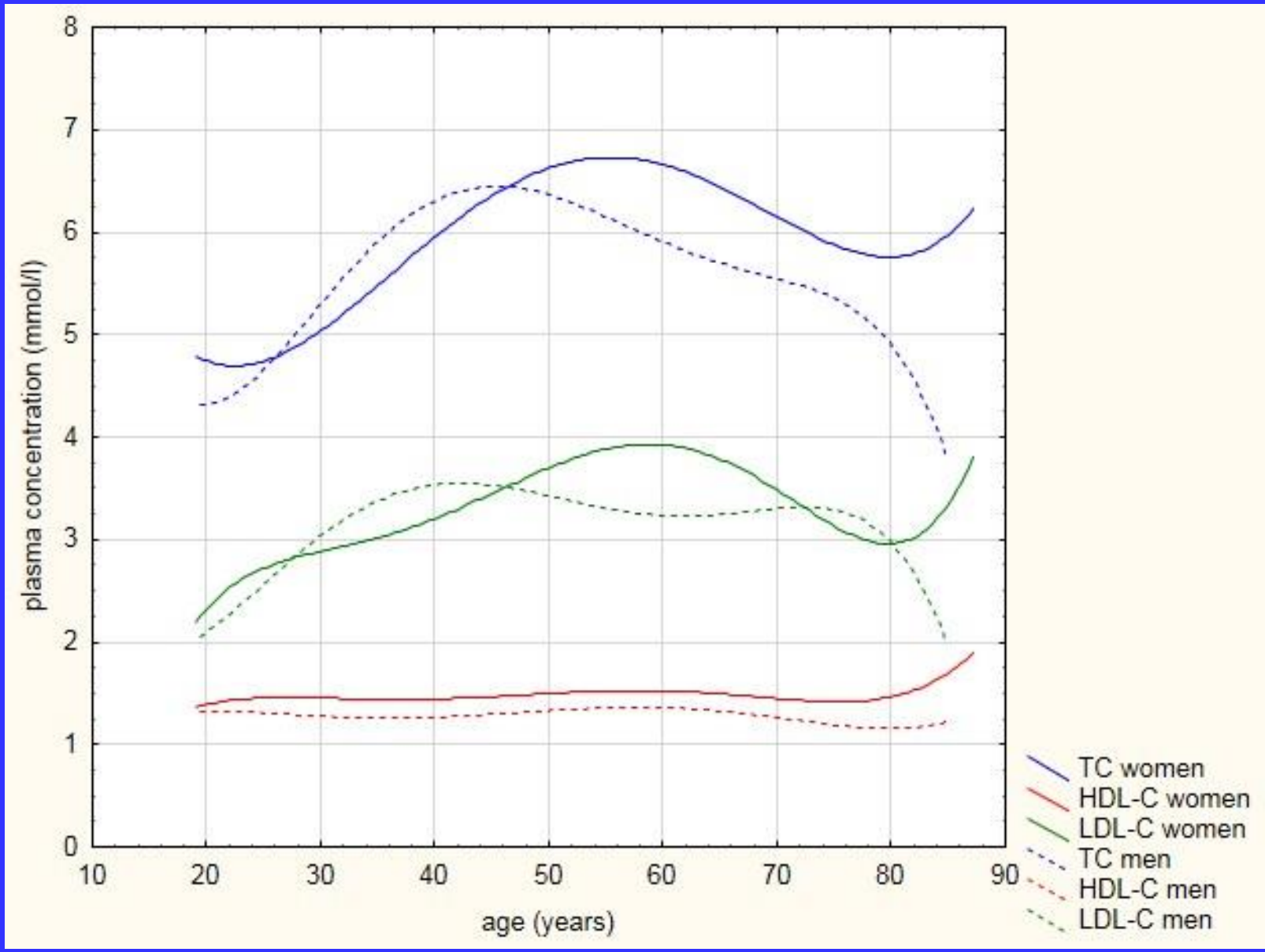
II. Family history of early CHD

< 55 years in male first-stage relatives

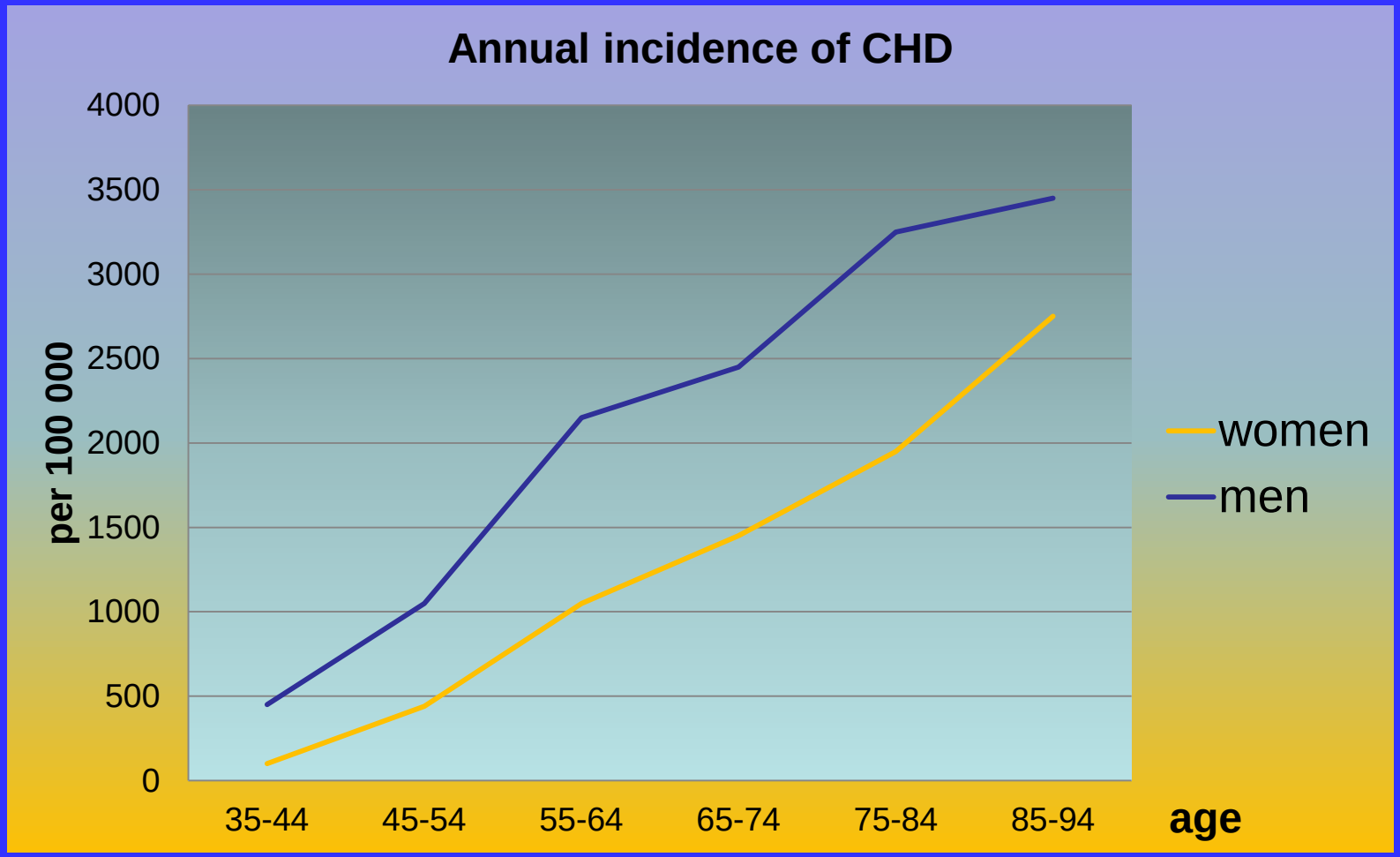
< 65 years in female first-stage relatives

National Cholesterol Education Program (NCEP), ATP III, 2004

Lipid change with age and gender



CHD incidence – effect of age and gender



Risk factors of CVD for stratification of risk in primary prevention of CHD

II. Family history of early CHD

Candidate genes:

Apolipoproteins (A-I+CIII+AIV, AII, B, CI, CII, E, $Lp_{(a)}$)

Receptors (LDL-R, Ins-R, ILGF1-R,SCR-1, SCR-2, AGTR1, PPARG1)

Enzymes (CETP, LCAT, HL, LPL, CBS, renin, ACE, PON1, NOS, MTHFR)

Endothelium function (ELAM, MMP3)

Coagulation factors (thrombine, vWf, f.VII, fibrinogen, PAI-1, t-PA, f.XII)

Growth and inflammatory factors (ILGF-1, IL-6, insulin, PDGF-β, TGFβ-1)

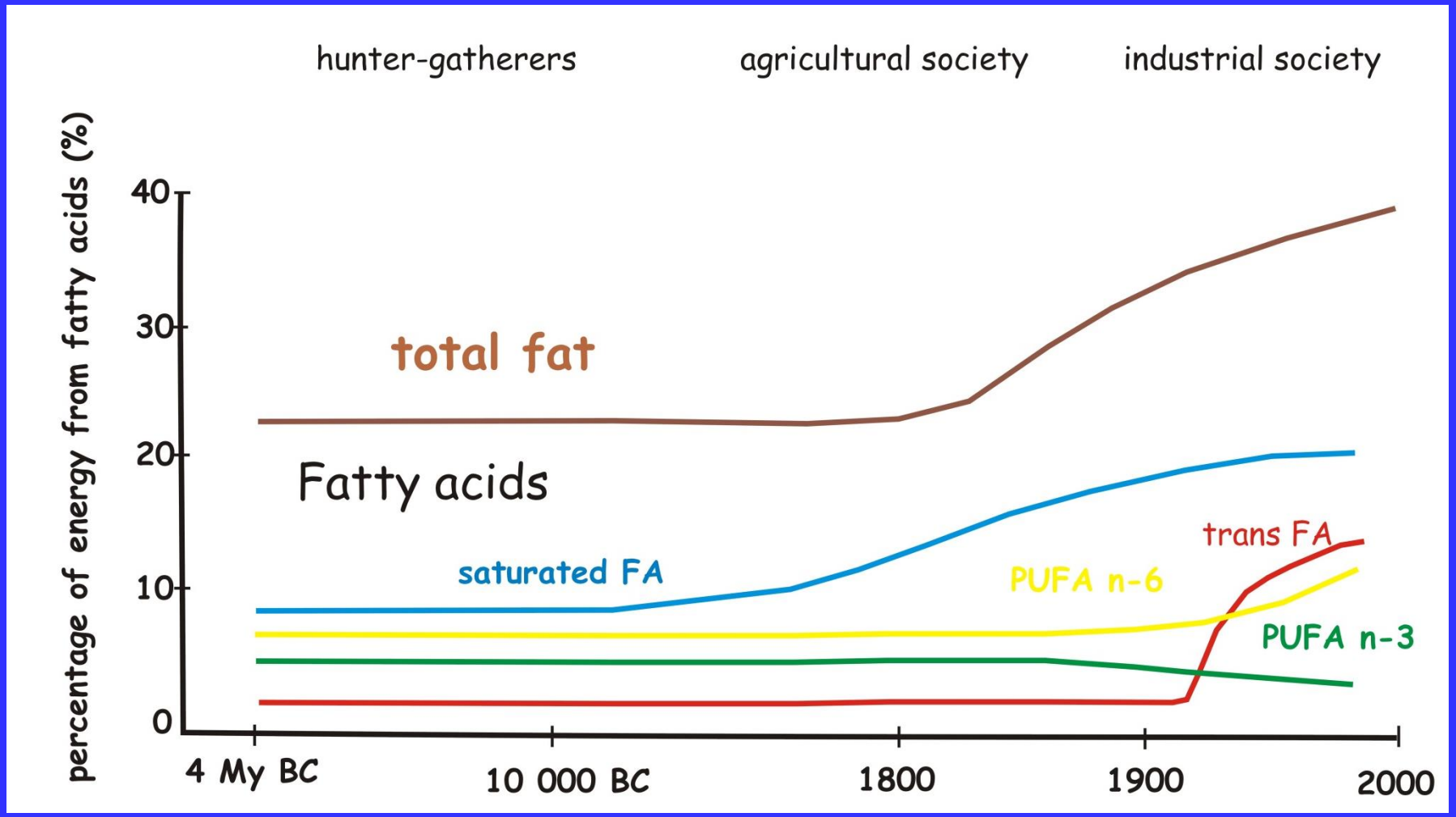
Membrane Transporters (ABCA1)

Gender (ESR1)

Other (CRP, ADIPOQ)

B. MODIFIABLE RISK FACTORS

Intake of fatty acids



Excessive intake of saturated fats

potentiates the rise in plasma TC:

$$\Delta TC = 2.74\,\Delta\,SFA - 1.31\,\Delta\,PUFA + 1.5\,C^{-1/2}$$

but not all SFA are similar:

C12:0 - C14:0 - C16:0 > C18:0

Intake of EtOH

Ethanol abuse = more than 40 g EtOH daily

(high E substrate → ↑ NADH in liver → ↓ FA oxidation → fat=TAG excess)

induction of HTAG → ↑ VLDL (↑ synthesis in hepatocytes)

→ ↑ HDL-C (↑ apo A-I synthesis in enterocytes)

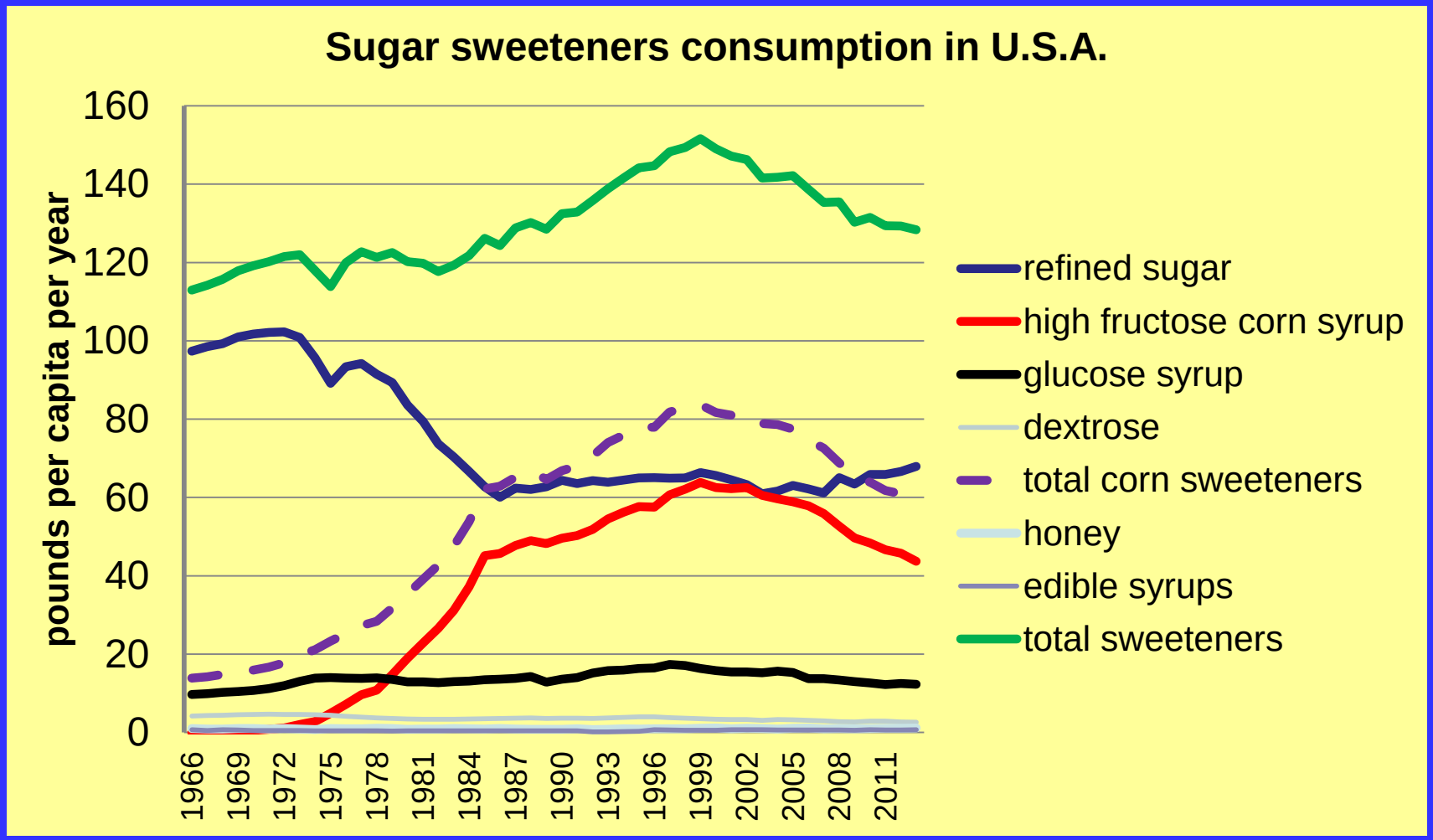
Zieve syndrome

can be a result of chronic EtOH abuse

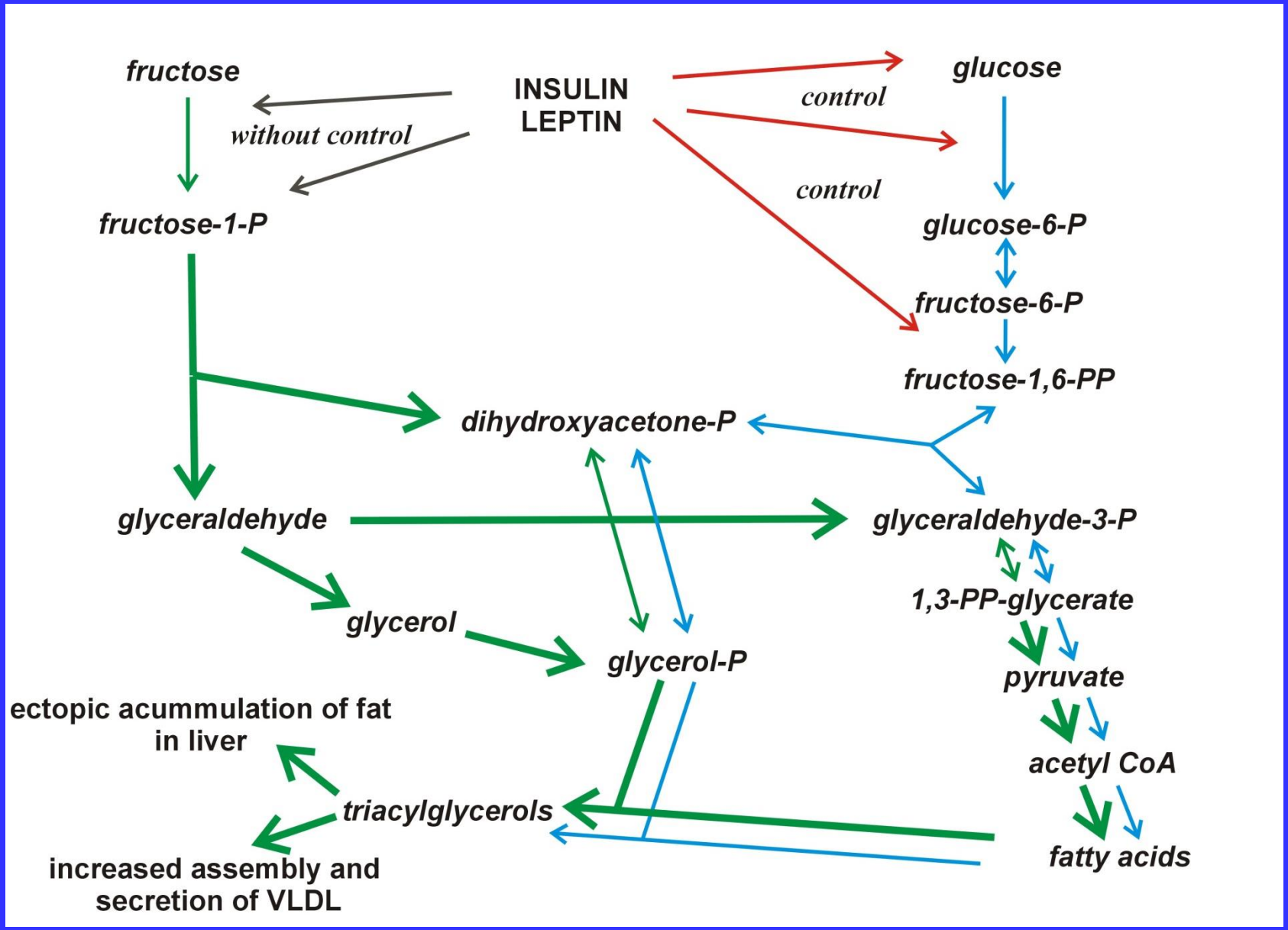
- hyperlipoproteinemia with high CH/VLDL-C and low HDL-C
- secondary deficiency of LCAT
- jaundice and reversible hemolytic anemia

healthy liver → **EtOH** → **steatosis** → **EtOH** → **cirrhosis** → **cancer**

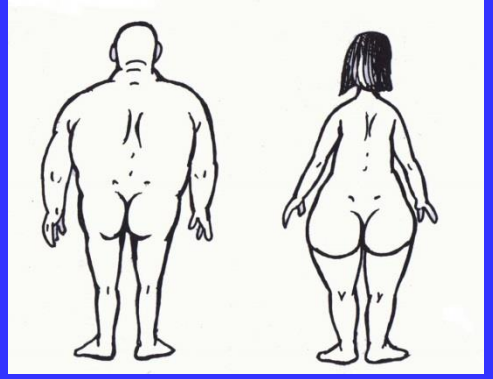
Intake of sugar



Intake of fructose



Overweight and obesity



Gynoid obesity - **only increased TAG and VLDL**

Android obesity - **often with ALP**

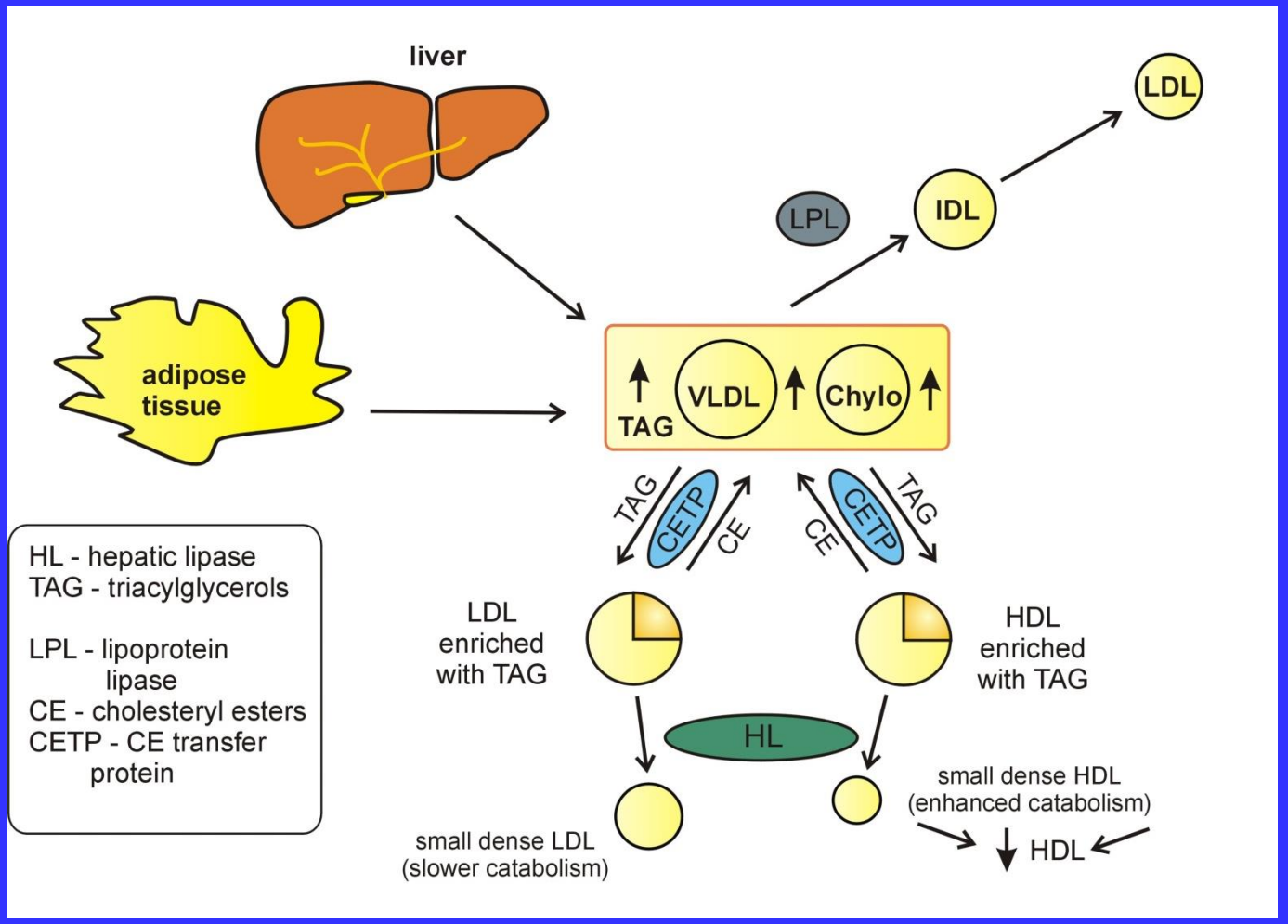
(oxidative stress, ↑ coagulability, chronical inflammation)

atherogenic lipid phenotype (ALP)

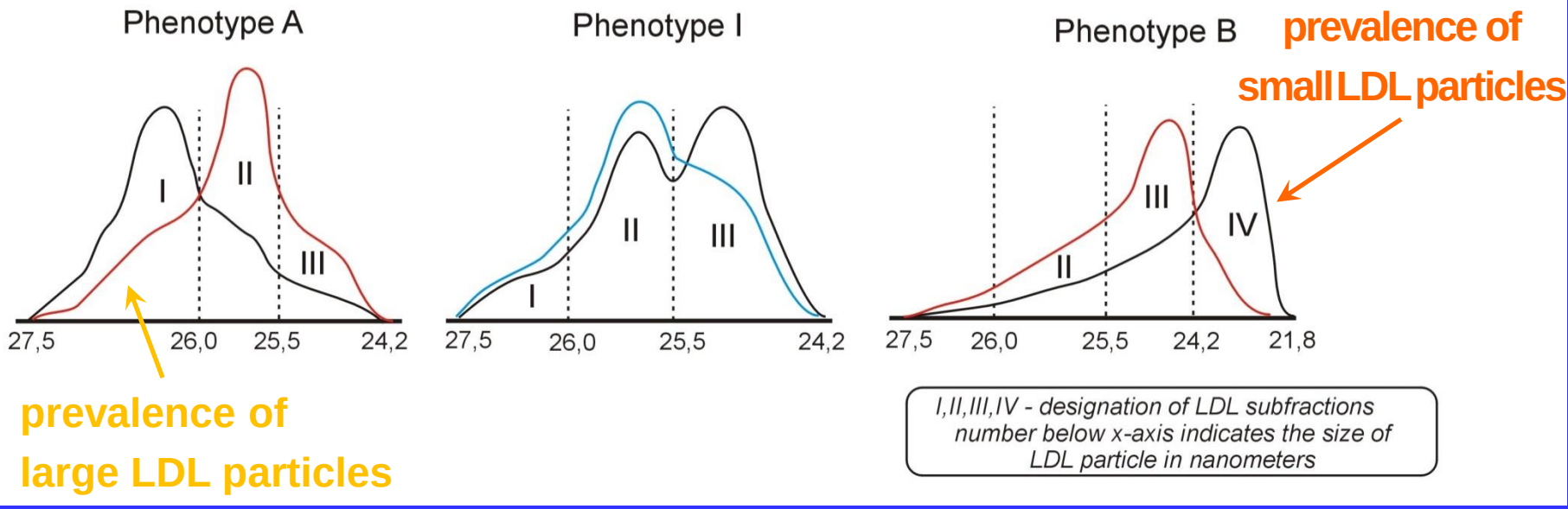
↑ TAG (VLDL) + ↓ HDL-C + ↑ sdLDL

(↑ NEFA, ↑ LDL- apoC-III+)

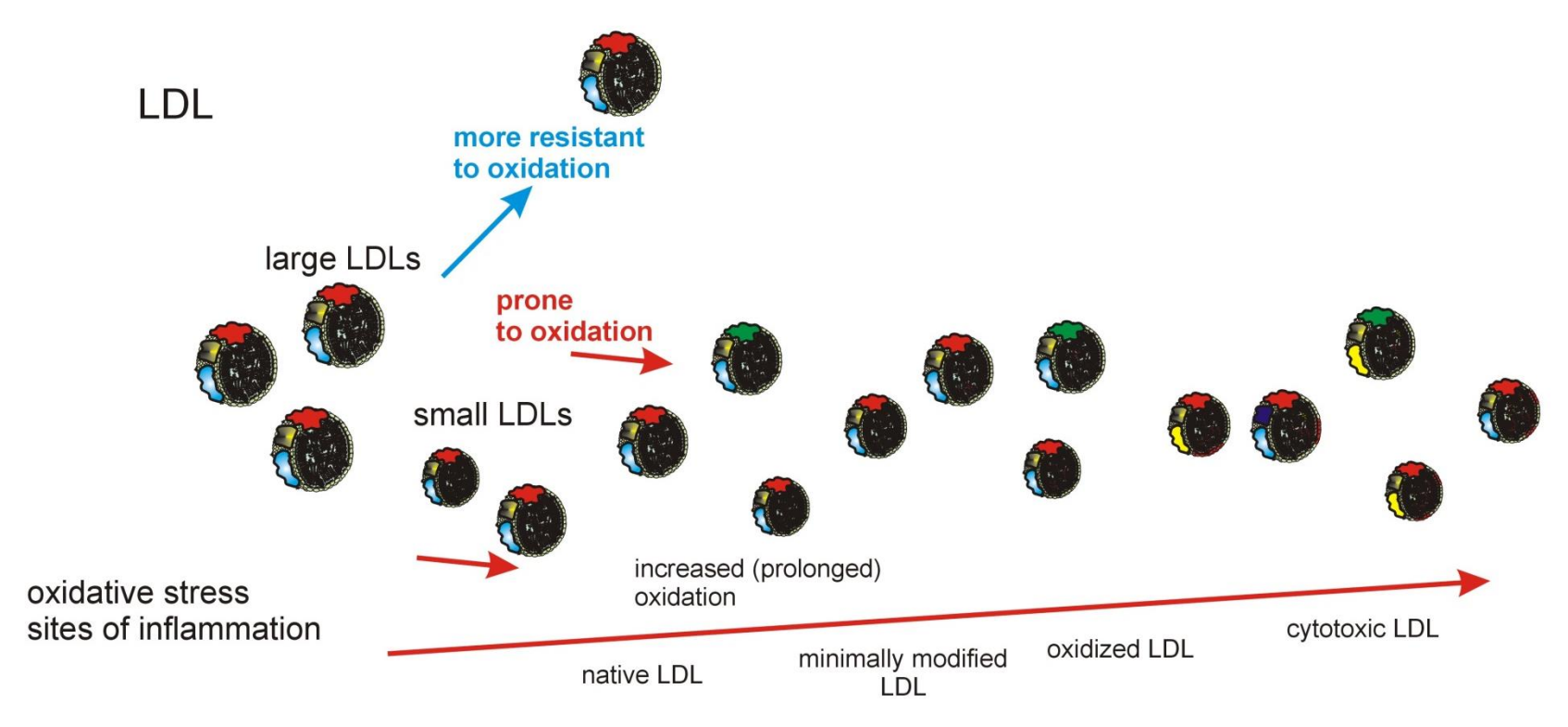
Effect of higher concentrations of particles rich in triacylglycerols on LDL and HDL metabolism



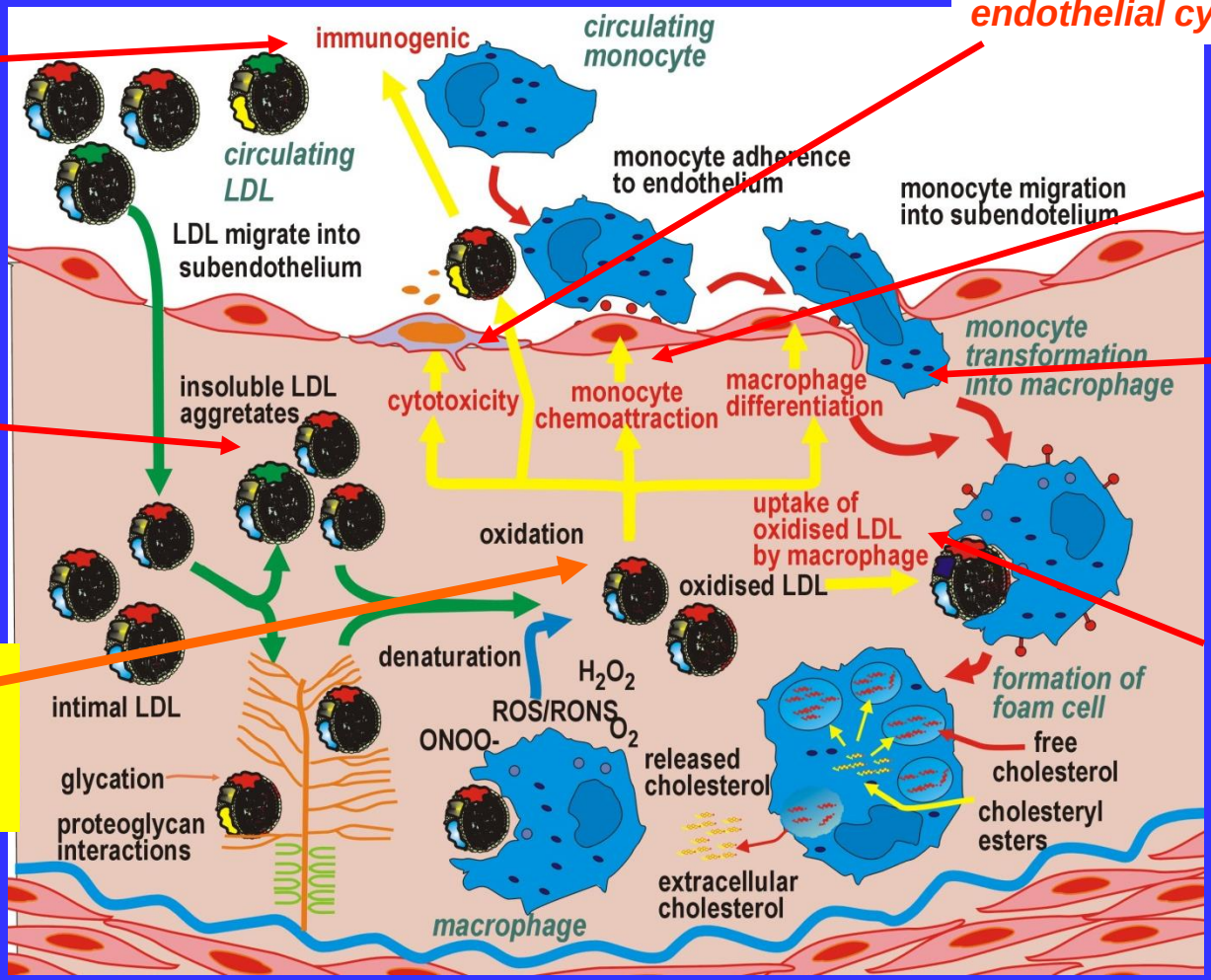
Phenotypes of LDL size



Generation of oxidatively modified LDLs



Properties of oxidatively modified LDL



Mechanisms of antiatherogenic effect of HDLs

I. Direct effects on lipoprotein metabolism

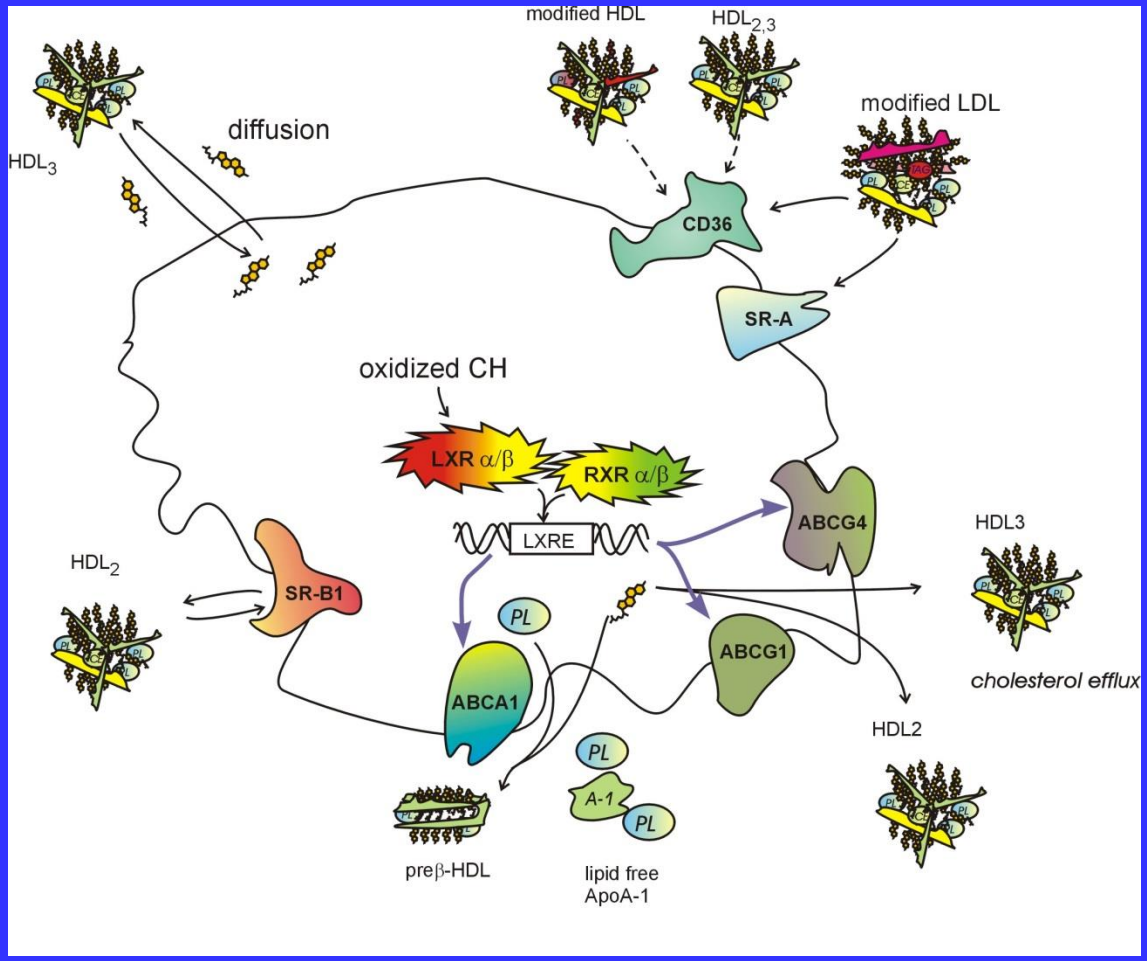
- **reverse transport of CH to liver** *(CH acceptor from cells)*
- **↑ catabolism (VLDL → IDL → LDL)** *(TAG acceptor via CETP)*
- **block transendothelial LDL transport** *(closure of junctions)*
- **VLDL,LDL protection to oxidation** *(PON-1, PAFAH carrier)*
- **oxLDL cytotoxicity inhibitor** *(PON-1, PAFAH carrier)*

II. Other effects

- **anti- and dysaggregative effects on thrombocytes**
- **antiarrhytmic effects**
- **restauration of endothelial dysfunction**
- **inhibition of expression of cytoadhesive molecules**

Reverse cholesterol transport

sterol transport from macrophages



Risk factors of CVD for stratification of risk in primary prevention of CHD

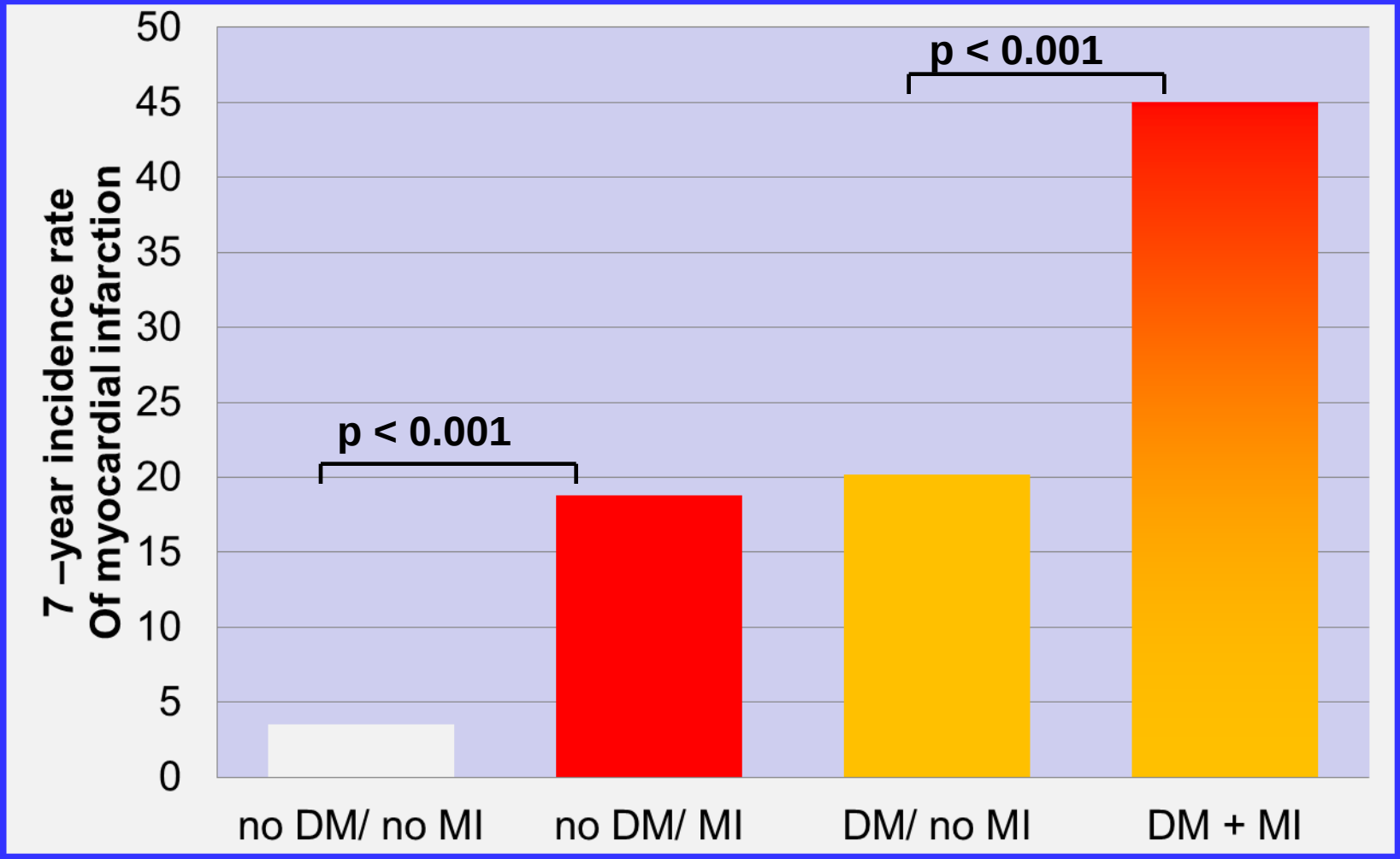
B. Modifiable risk factors

Diabetes mellitus

considered as an equivalent of CHD, the presence of DM classifies the patient to the same risk group as those with already manifested ATS

National Cholesterol Education Program (NCEP), ATP III, 2004

Incidence of myocardial infarction in diabetics



Risk factors of CVD for stratification of risk in primary prevention of CHD

B. Modifiable risk factors

Cigarette smoking

cigarette smoking in the last month

Hypertension

BP > 140/90 mmHg, or antihypertensive medication

Total plasma cholesterol

< 5.2 mmol/l – 5.2-6.1 mmol/l – > 6.2 mmol/l

appropriate borderline high

National Cholesterol Education Program (NCEP), ATP III, 2004

Risk factors of CVD for stratification of risk in primary prevention of CHD

B. Modifiable risk factors

LDL-cholesterol

< 2.6 mM	2.6 – 3.3 mM	3.4 – 4.0 mM	4.1 – 4.8 mM	> 4.9 mM
optimal	slightly above normal	borderline high	elevated	considerably increased

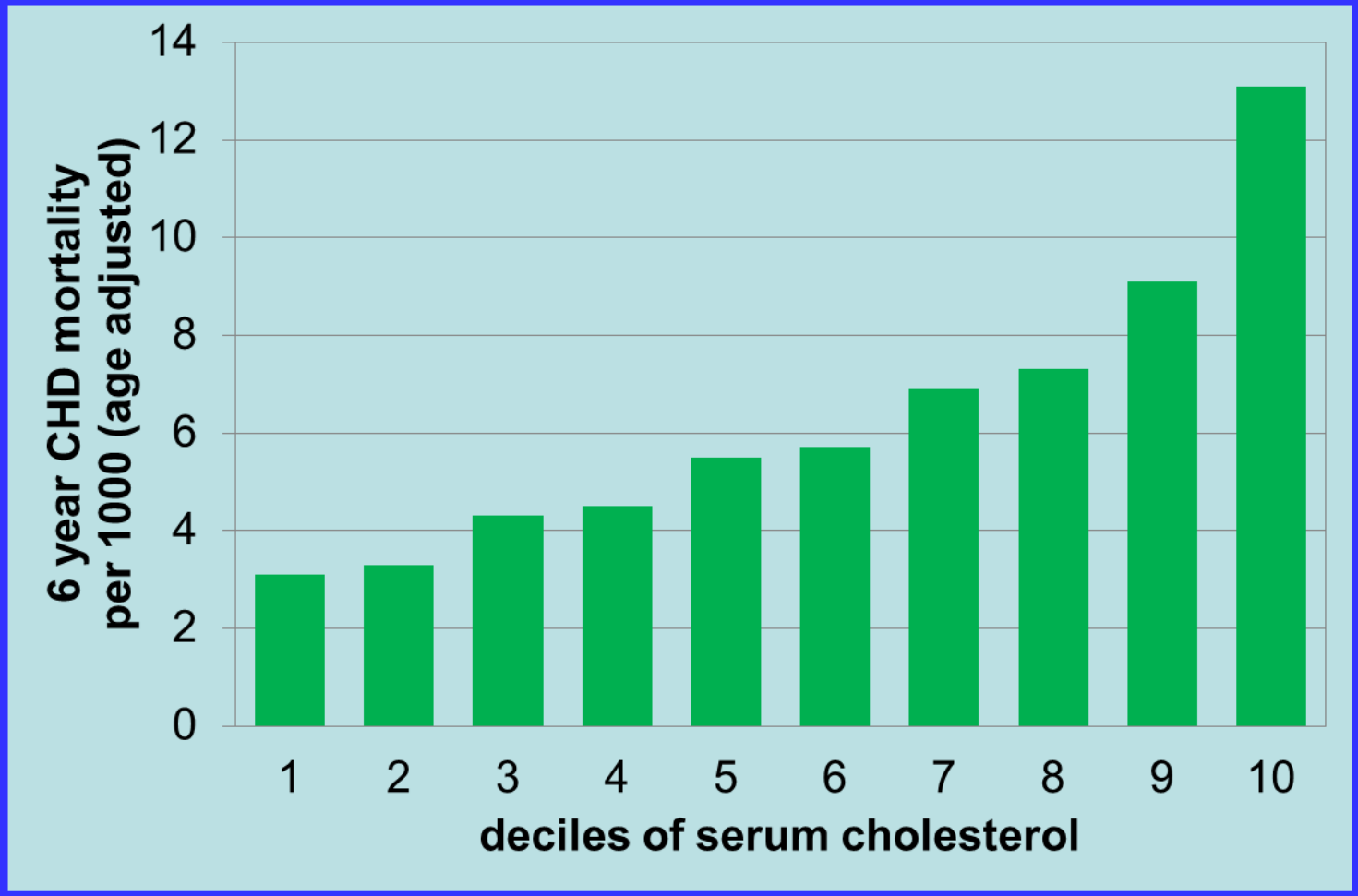
HDL-cholesterol

< 1.0 mmol/l	1.0 – 1.6 mmol/l	> 1.6 mmol/l
low	normal	„negative risk factor“

subtracts 1 RF from risk calculation

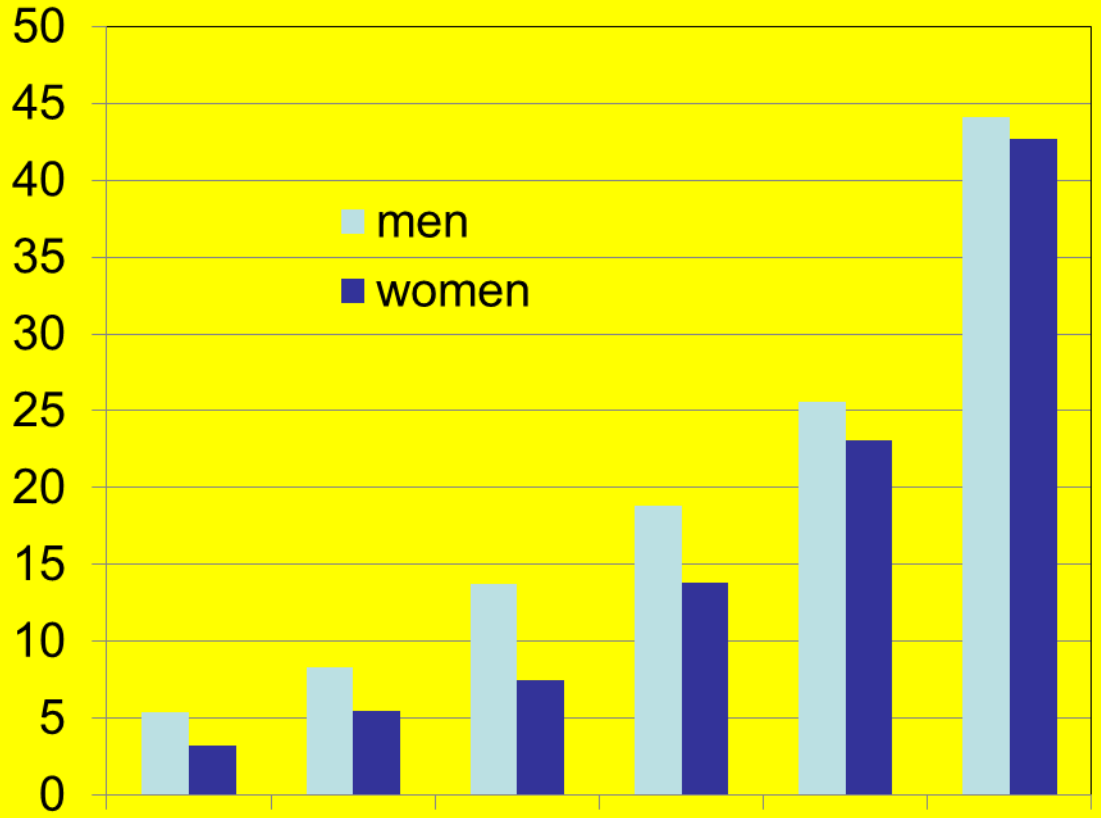
National Cholesterol Education Program (NCEP), ATP III, 2004

Cholesterolemia and mortality



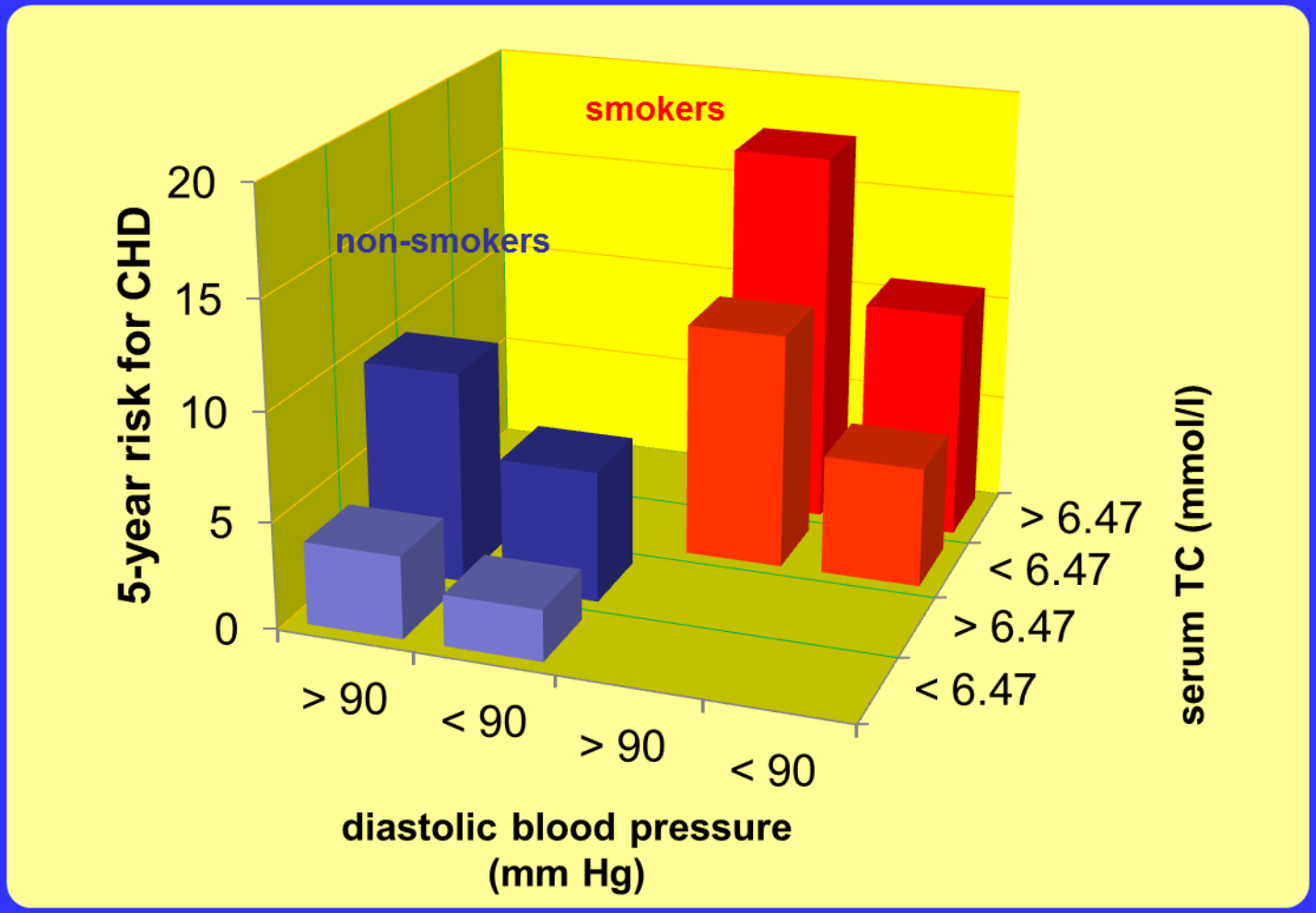
Additive properties of risk factors

10-year probability (%) for probands aged 42-43 yrs



blood pressure 150-160 mmHg	+	+	+	+	+	+
HDL 0.83-0.90 mmol/l	–	+	+	+	+	+
TC 6.20-6.77 mmol/l	–	–	+	+	+	+
cigarette smoking	–	–	–	+	+	+
diabetes mellitus	–	–	–	–	+	+
left ventricular hypertrophy	–	–	–	–	–	+

multiplicative effect of risk factors



Other supposed risk factors for CHD

Lp[a]

chronic inflammation

(CRP, SAA) $\rightarrow$ HDL remodelation

mild hyperhomocysteinemia

states with hypercoagulation

chronic infection

- *Chlamydia pneumoniae*
- CMV
- HSV-1

Lipoprotein(a)

Lipoprotein particle resembling LDL

apo (a) attached to apo B-100 with S-S bond

- similar to plasminogen

function of Lp(a)

not fully resolved

Lp(a) competes with plasminogen for fibrin binding sites

inhibits fibrinolysis *in vitro*

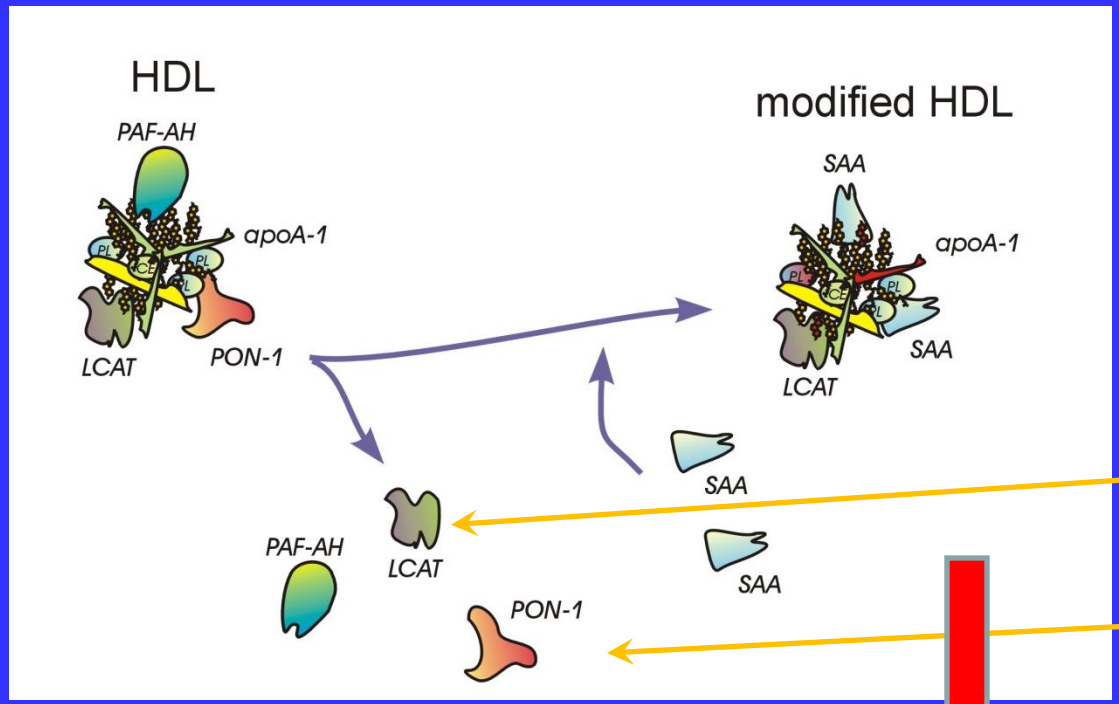
carrier for oxPL in plasma?

high Lp(a) → high risk for cardiovascular disease

SAA and HDL remodelation

functionally defective HDL particles

acute phase response/inflammation



decreased capacity for RCT

decreased antioxidant capacity of HDL

HDL particles lacking antiatherogenic functions

Homocysteine

1. Hcy is noncoding amino acid
 - has SH group ⇨ redox balance

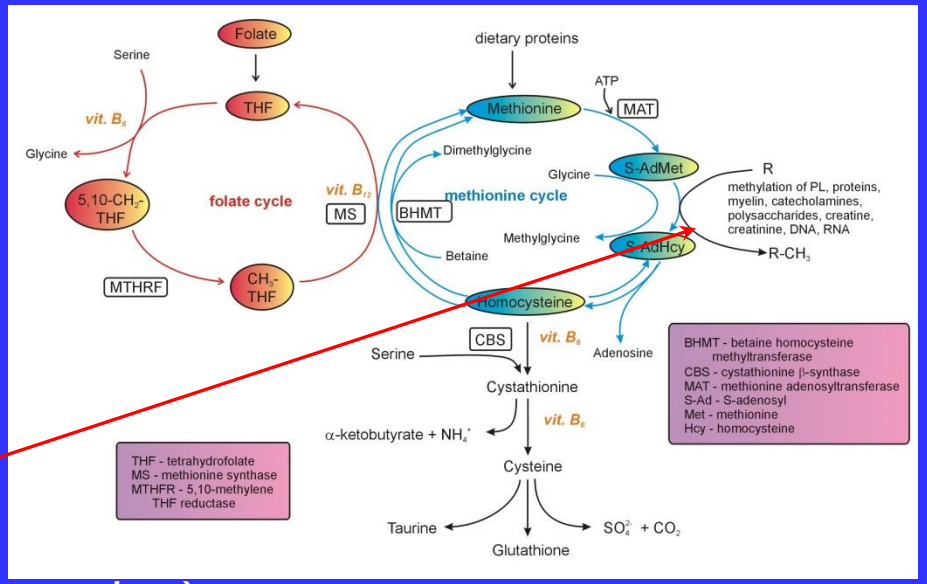
⇩

connection with oxidative stress

2. Hcy is linked to methylation events

⇩

possible DNA methylation (gene expression)



Mild hyperhomocysteinemia suggested as a risk factor for atherosclerosis

- controversial results of interventional studies
- important factor in those with DM + nephropathy, thrombosis

Hypercoagulable states

= states with venous/arterial thrombosis

predisposition for thrombosis ⇒ easy thrombus formation

damaged vessel wall

a) mutations in factor V (Leiden), prothrombin

- linked to higher risk of MI/CAD (in younger?)

b) hyperhomocysteinemia (see previous slide)

c) antiphospholipid syndrome/SLE

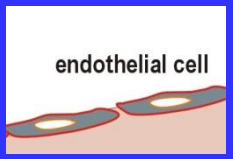
- associated with CAD, stroke

Cell types involved in atherogenesis:

- **endothelial cells (EC)**
- **thrombocytes**
- **blood monocytes, macrophages (mo/ma)**
- **smooth muscle cells (SMC)**
- **T-lymphocytes**

Cell types involved in atherogenesis

Endothelial cells (EC):



transendothelial transport of apoB LP: LDL, IDL, Lp(a)

(inhibited by HDL)

contraction of EC ⟷ ***vascular homeostasis*** ⟷ **relaxation of EC**

catecholamines — **Endothelium Derived Relaxing Factor**

angiotensin, vasopresin — **PGI_2 NO histamin**

dyslipidemia + oxidative stress (ox-LDL, high Hcy, …smoking)

physical factors: shear stress, hypertension

⇓⇓

endothelial dysfunction

impaired vasodilatation (↓NO availability)

activated EC ⇒ ↑ synthesis of local mediators:

- **cell adhesion molecules: CAM by Il-1, TNFα, β (T-cells, Mf)**
- **differentiating factors: MCP-1, MCSF-1 (oxLDL)**
- **adhesion molecules: ELAM (ox-LDL)**

Cell types involved in atherogenesis

Thrombocytes:

- ***hypercholesterolemia*** → **megakaryocyte ABCG4↑** → **platelets ↑**

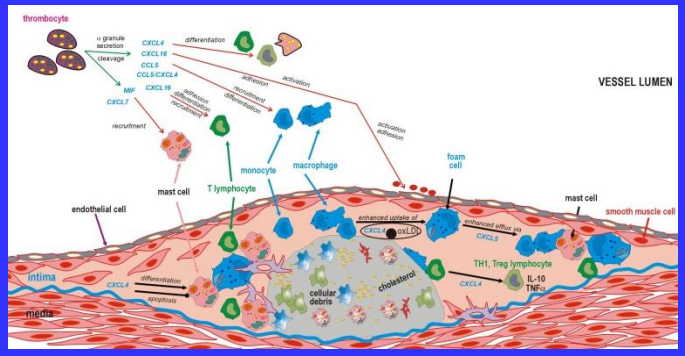
monocyte/macrophage

platelet activation by PAF, 12-HETE → **secretion of TxA_2, 5-HT**

aggregation and degranulation

releasing of growth factors for SMC – PDGF

many chemokines affecting monocytes/macrophages/T cells



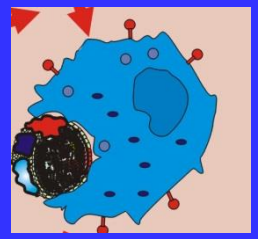
Cell types involved in atherogenesis

Monocytes/macrophages:

I. monocytes

- can differentiate in macrophages (*via* MCP-1 etc.)

II. macrophages

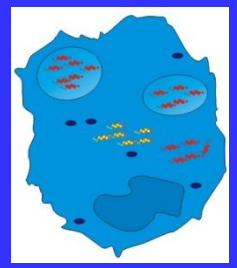


- express receptors for LP: β-VLDL receptor, Ac-LDL-receptor, B/E-receptor Fc-receptor (for complex Ab-LDL)

- synthesize PAF, Il-1, Il-6, TNFγ, MDGF

- ox-LDL causes expression of genes and synthesis of 15-LO, MCSF, MCP-1

III. foam cells



- not able to migrate from the cell wall

- if the capacity for FC is exceeded → dysruption of lysosomes → apoptosis → cellular debris

Cell types involved in atherogenesis

Smooth muscle cells (SMC):

phenotype switch*:** ← ***atherogenic stimuli

contractive → synthetic (active) type of SMC

↓

migration from media → intima

proliferation and production of

glykosaminoglycans, colagen

elastin, growth factors, cytokines

proliferation of SMC

stimulation

PDGF 12-HETE

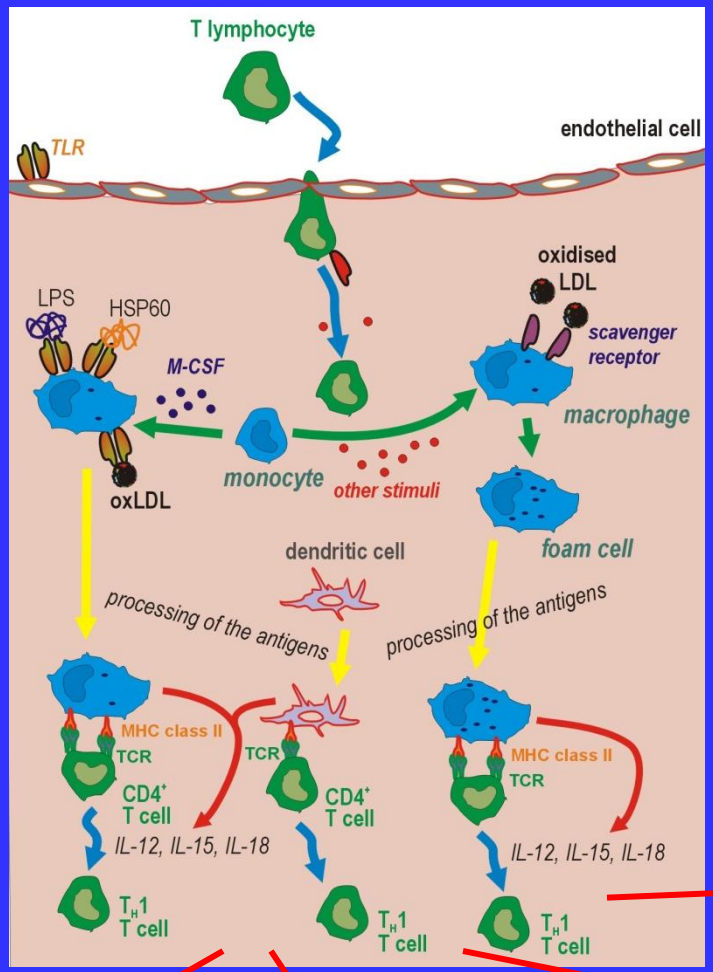
IGF-1

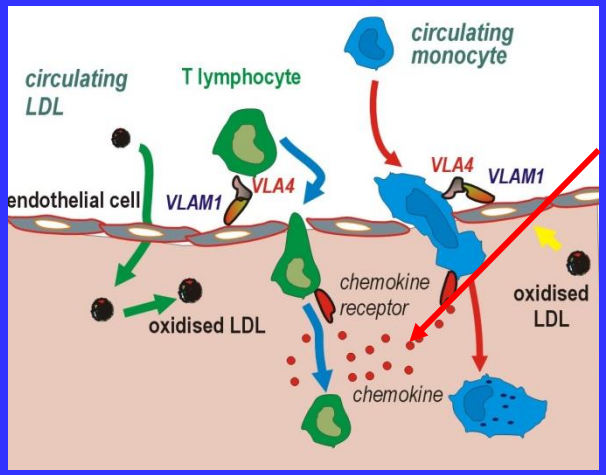
inhibition

heparin NO

PGI_2 INFγ

Mobilisation and activation of immune cells in atherosclerotic plate





migration of monocytes

T cells into arterial tissue is supported by locally produced chemokines

proapoptotic factors

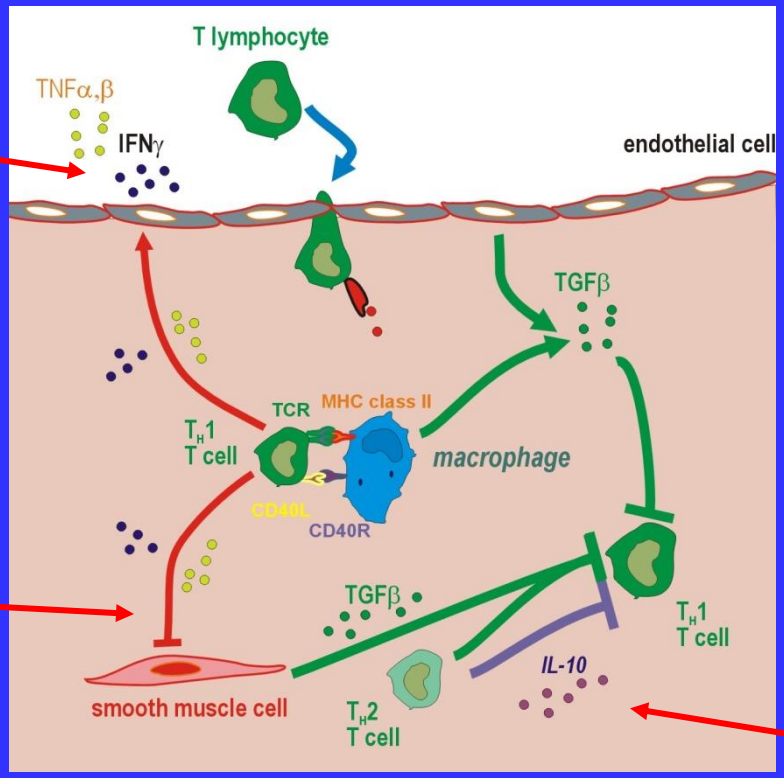
proteases

procoagulants

proinflammatory cytokines

Mobilisation and activation of immune cells in atherosclerotic plate

IFNγ a TNFα,β induce expression of CAM (cell adhesion molecule) in endothelial cells



IFNγ inhibits proliferation of SMC

IL-10 and TGFβ attenuate inflammation

Gender specificity of risk factors

women vs. men:

estrogen rec α/β → vessel vasodilatation

same spectrum of risk factors for CAD, but worse for women in:

smoking: *(↓E dep vasodilatation)*

central obesity: metabolic syndrome is more often in women → diabetes: 50% higher risk in women for CHD

dyslipidemia: hyperTAG/low HDL-C - more detrimental for women

physical inactivity: relative risk for CHD higher 4.7% (vs. 3.4% in M)

Specific risk factors:

1. **menopause → overall worsening of risk profile**
2. **PCOS → obesity/metabolic syndrome**
3. **HRT → ??effect on CHD??**
4. **Preeclampsia → impaired endothelial function/vasodilatation**
5. **Oral contraceptives(low-dose/3rd generation) → ~↓CHD risk**

Further reading

Textbooks, monographs

Lehninger Principles of Biochemistry (6th Ed); Nelson DL, Cox MM (Eds.), Susan Winslow, New York (U.S.A.) 2013

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Stamler J, Wentworth D, Neaton JD, for the MRFIT Research Group: Is relationship Between Serum Cholesterol and risk of Premature Death from Coronary Heart Disease Continuous and Graded? *JAMA* 1986; **256**: 2823-2828.

Web sources

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http://www.bioguo.org/CADgene/index.php
http://www.who.int/healthinfo/en - WHO reports
http://www.trialresultscenter.org - resource for trials (e.g. for cardiology trials)