Disorders of lipids and lipoprotein metabolism

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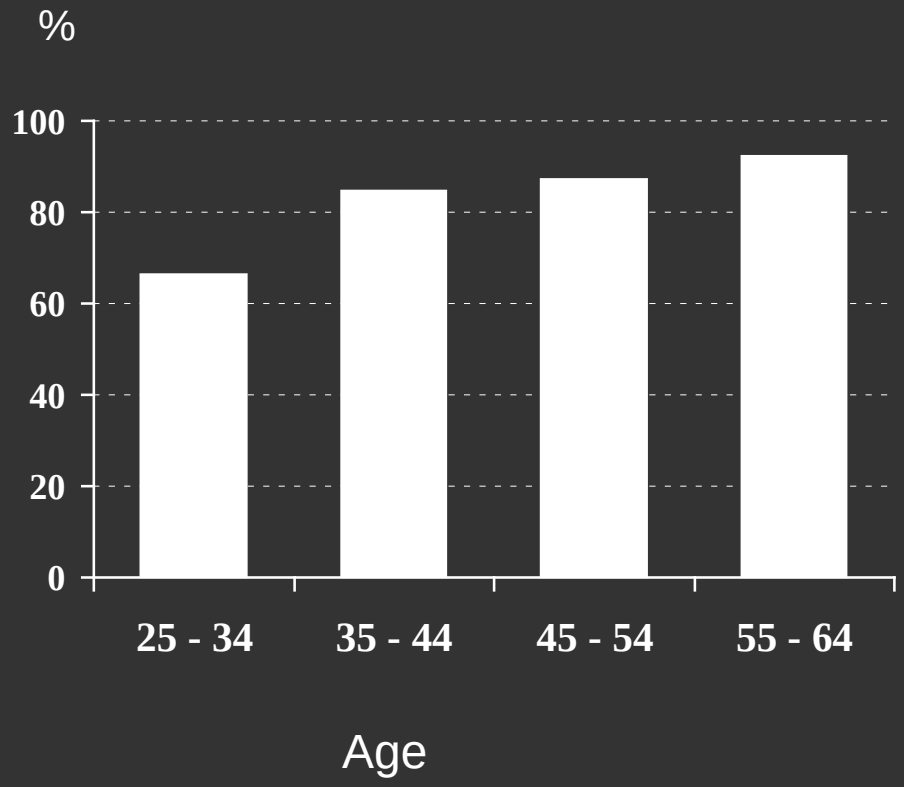
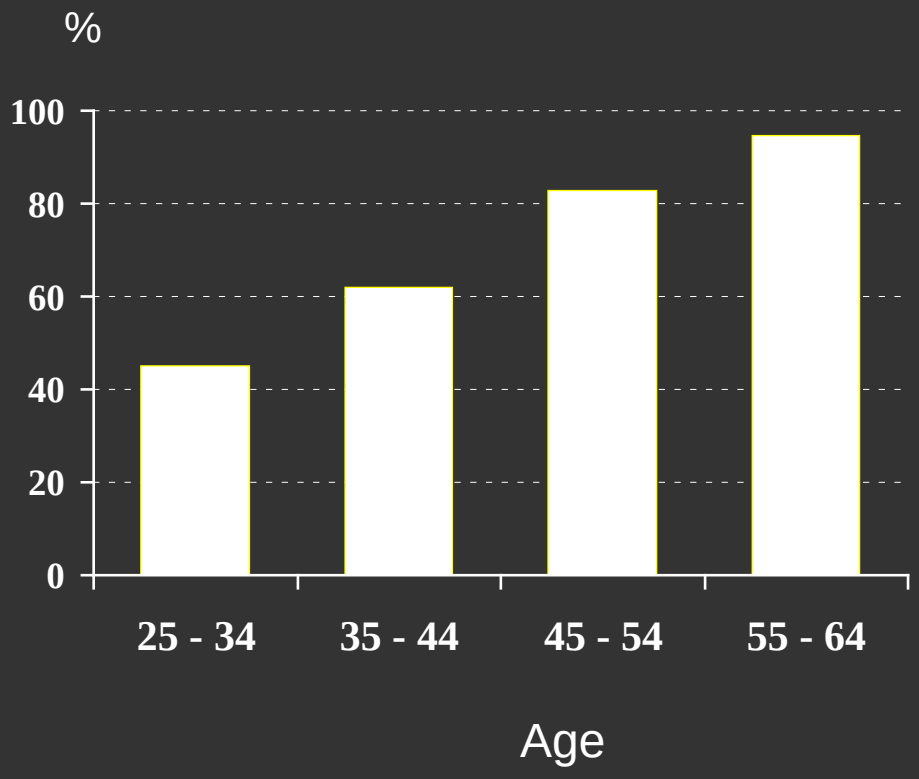
Dyslipidemia in the population

Men

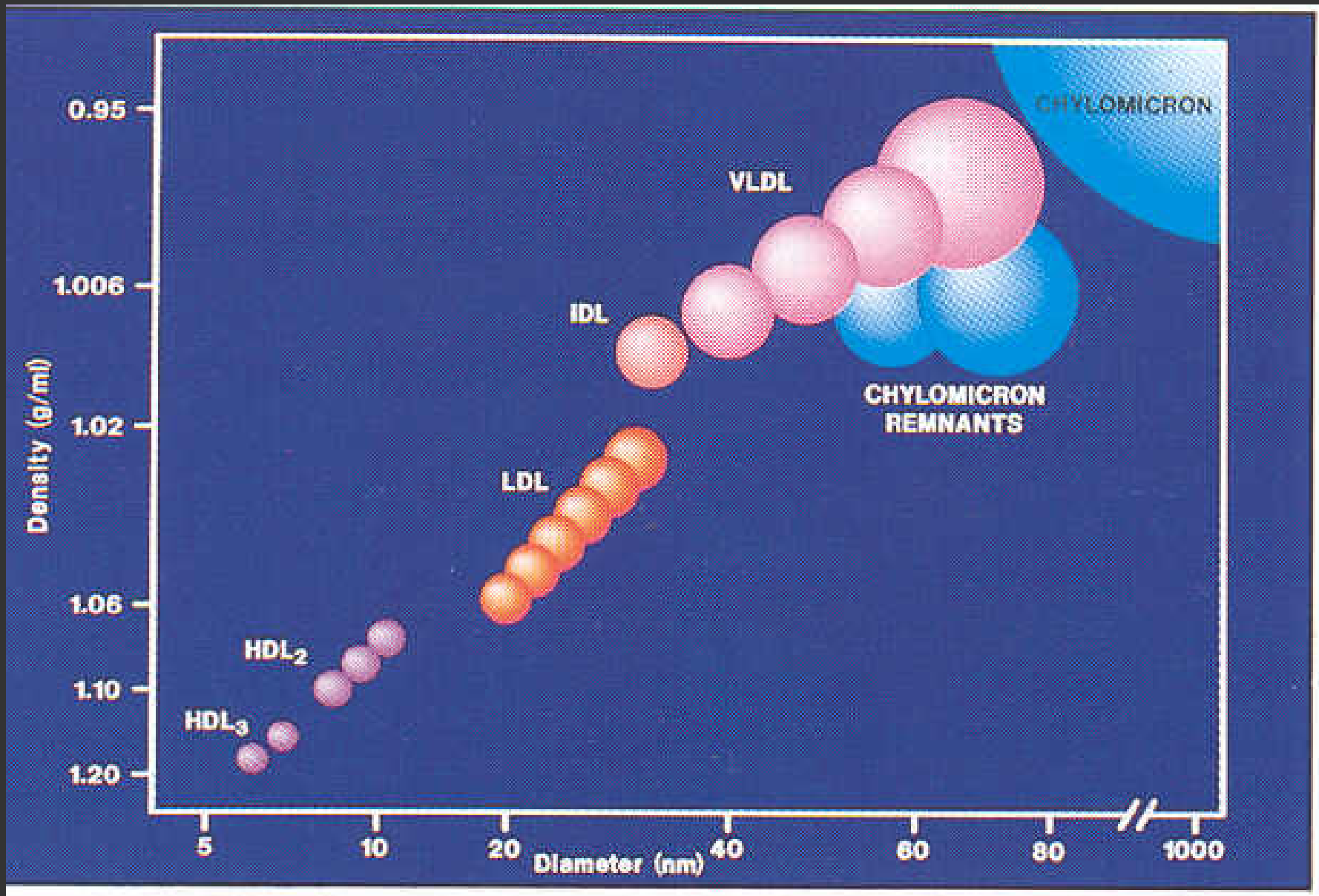


Women



TC $\geq$ 5.0 or HDL-ch. < 1.0 or LDL-ch. $\geq$ 3.0 or TG $\geq$ 2 mmol/l or treatment with hypolidemic drugs

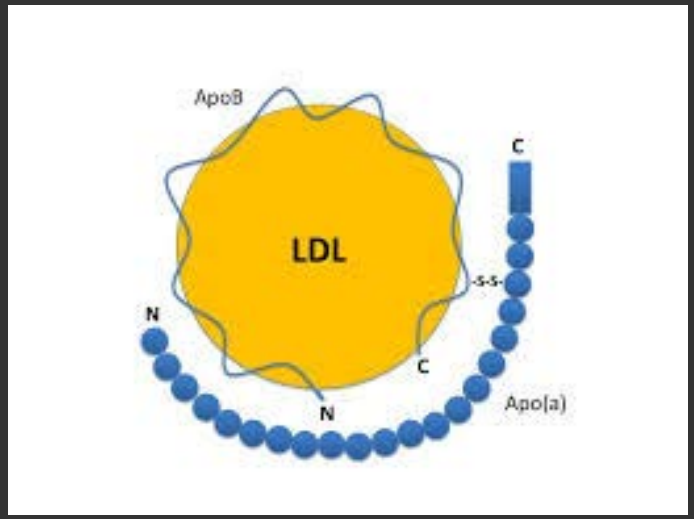
LP particles



Lipoprotein(a)

- LDL particle + apolipoprotein(a)

- Apolipoprotein(a)
  - Structure similar to plasminogen
  - Inhibition of fibrinolysis
    - ↑ risk of artery occlusion (thrombosis)



Lipoprotein(a)

- Physiological concentration:
  - < 75 nmol/l (0,3 g/l)

Apolipoprotein B

- Surfice of the VLDL, LDL particles
  - 1 particle = 1 molecule of apo B
- Number of apo B = number of LDL + VLDL particles
- Function: binding of the LDL-particles to the LDL-receptorvs

Target levels of LDL-cholesterol (mmol/l)

	Low risk people	Moderate risk people	High risk people	Very high risk people
LDL-Ch	< 3,0	< 2,6	< 1,8	< 1,4

Guidelines exist to help CV risk estimation

- ESC/EAS guidelines stratify risk using various criteria, including SCORE
  - Relative risk calculated using tables that take into account sex, smoking status, SBP and cholesterol

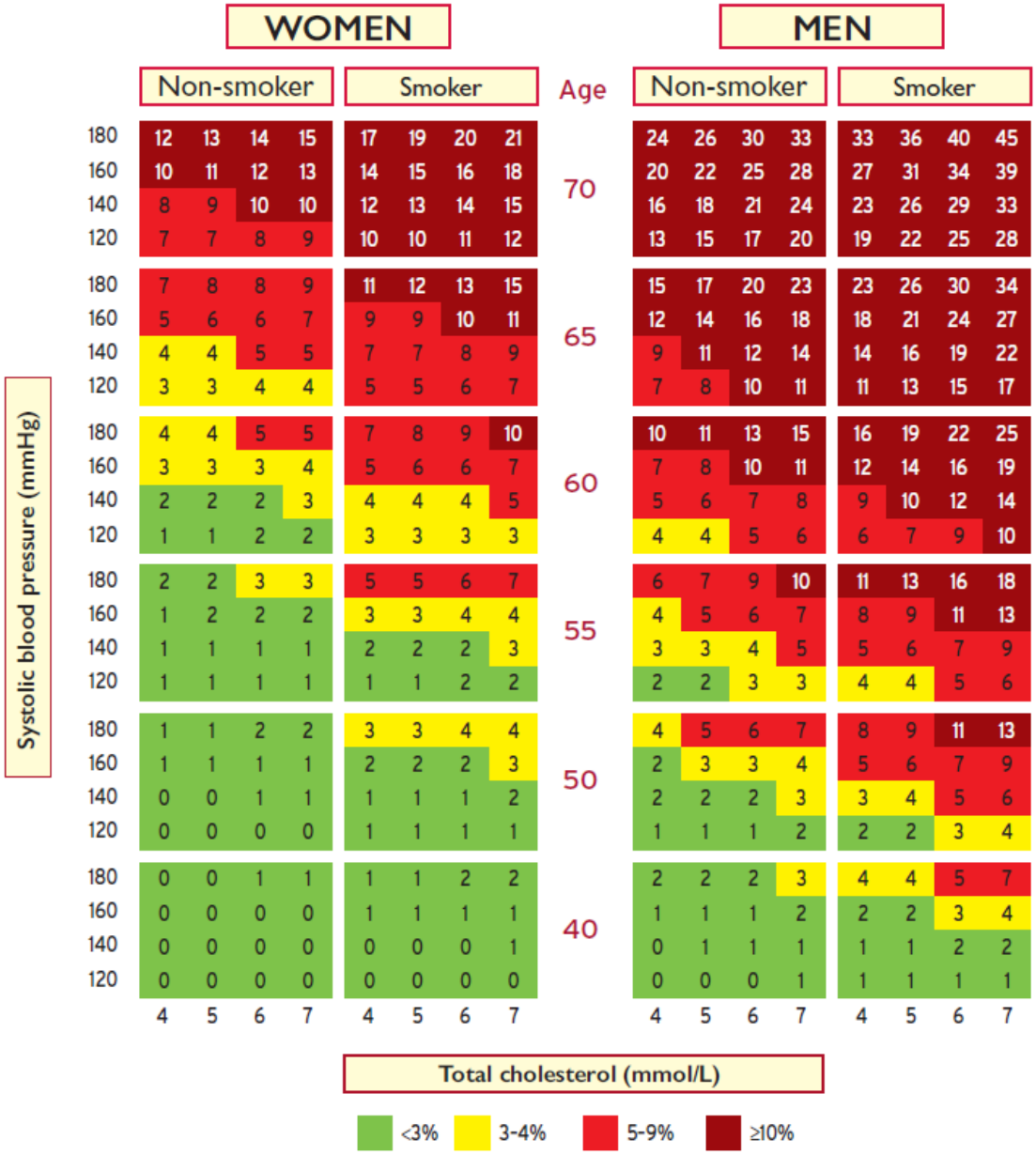
Very high risk	**High risk**	**Moderate risk**	**Low risk**
Subjects with any 1 of: • CVD • T2DM, or T1DM + target organ damage • Severe CKD (GFR <30mL/min/1.73m^2) • SCORE relative risk estimate ≥10%	Subjects with: • Markedly elevated single risk factors, such as cholesterol >8 mmol/L or BP >180/110mmHg • Most other people with DM • Moderate CKD (GFR 30–59mL/min/1.73m$^{2)}$ • SCORE ≥5% and <10%	SCORE ≥1 and <5% at 10 years • Many middle-aged subjects belong to this category	SCORE <1% and no qualifiers

Piepoli MF et al. Eur Heart J 2016;37:2315–2381.

SCORE Cardiovascular Risk Chart

10-year risk of fatal CVD

High-risk regions of Europe



Optimal levels of blood lipids

HDL-Ch	M > 1,0 mmol/l	F > 1,2 mmol/l
Tg	M < 1,7 mmol/l	F < 1,7 mmol/l

How to decrease LDL-cholesterol? Lifestyle management

	Magnitude of the effect
Lifestyle interventions to reduce TC and LDL-C levels	
Avoid dietary trans fats	++
Reduce dietary saturated fats	++
Increase dietary fibre	++
Use functional foods enriched with phytosterols	++
Use red yeast rice nutraceuticals	++
Reduce excessive body weight	++
Reduce dietary cholesterol	+
Increase habitual physical activity	+

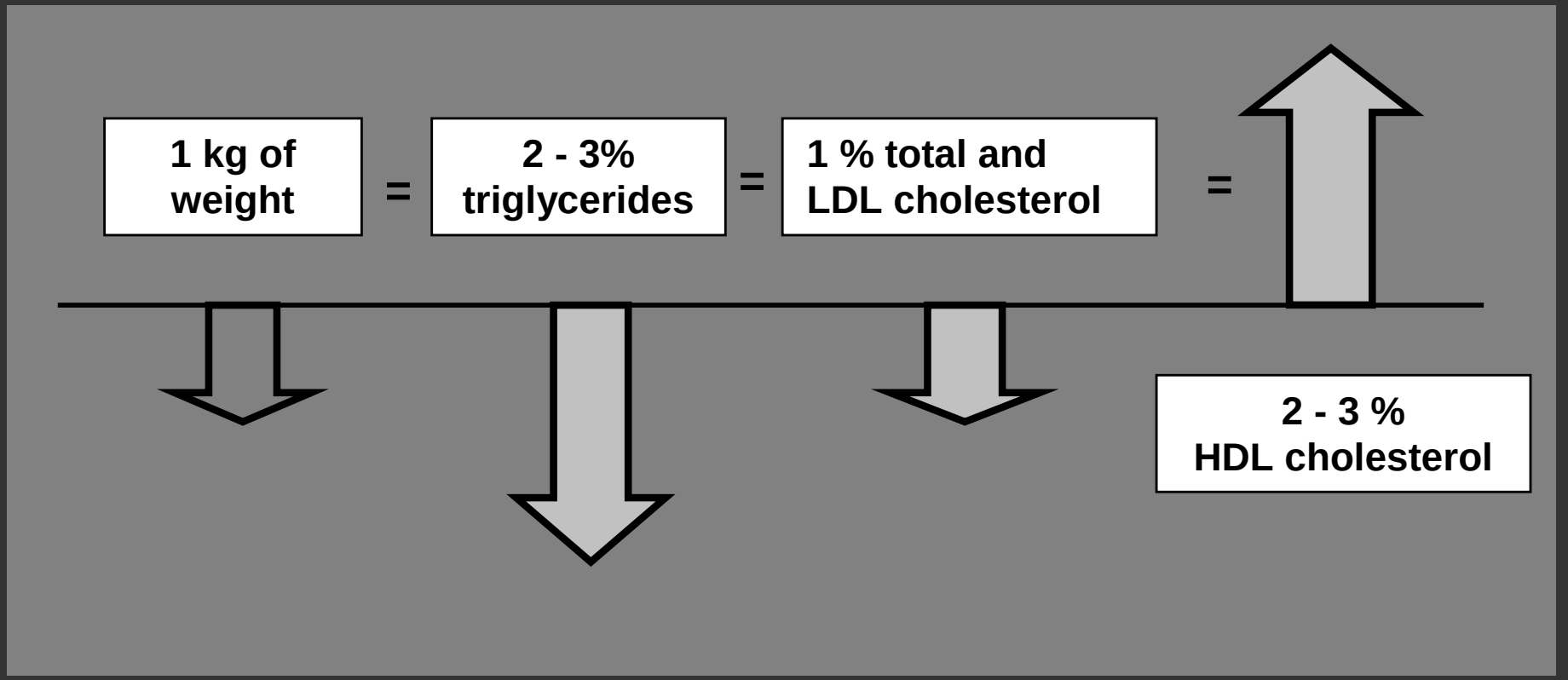
How to decrease triglycerides?

	Magnitude of the effect
Lifestyle interventions to reduce TG-rich lipoprotein levels	
Reduce excessive body weight	+
Reduce alcohol intake	+++
Increase habitual physical activity	++
Reduce total amount of dietary carbohydrates	++
Use supplements of n-3 polyunsaturated fats	++
Reduce intake of mono- and disaccharides	++
Replace saturated fats with mono- or polyunsaturated fats	+

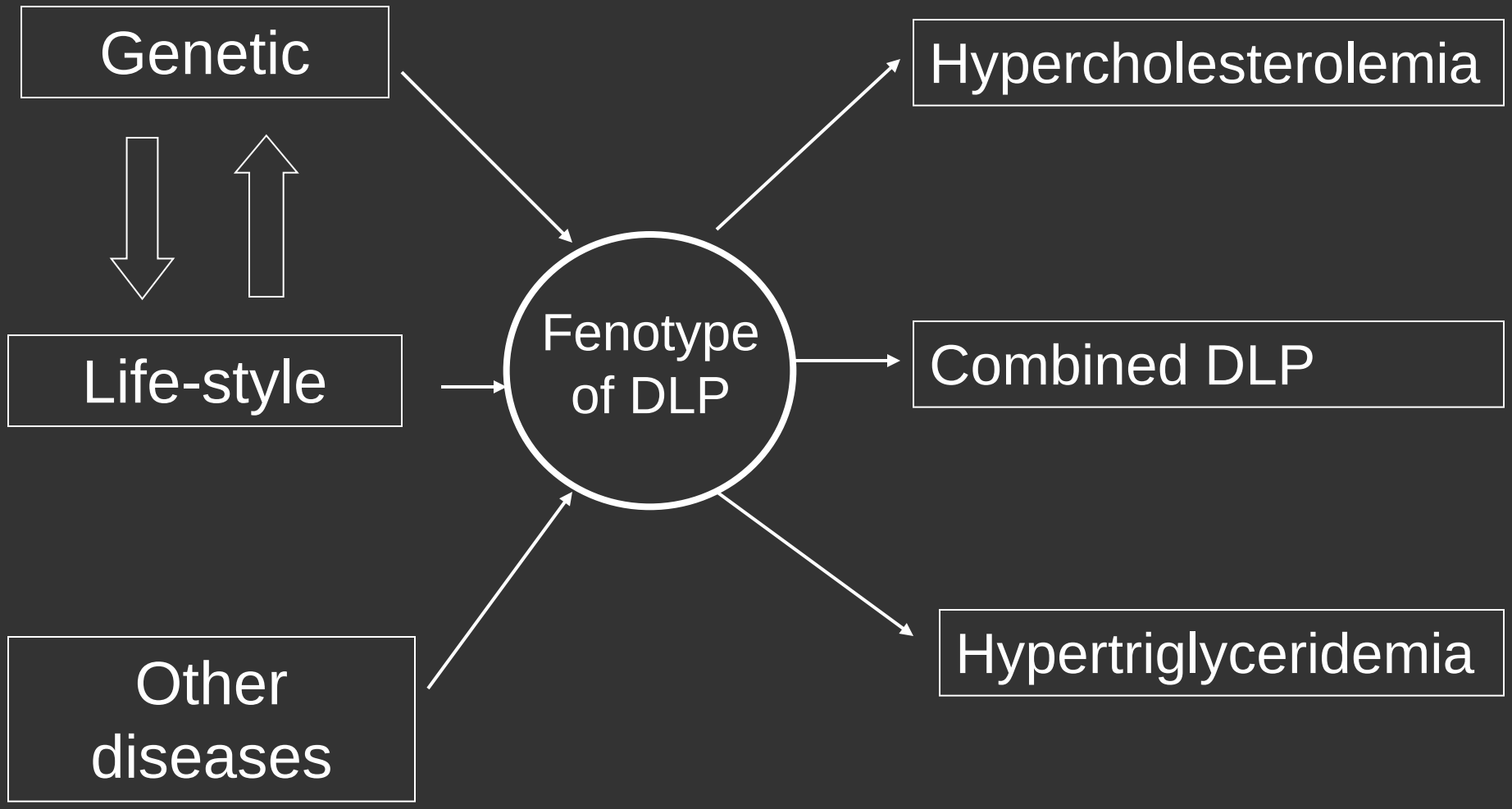
How to elevate HDL-cholesterol?

	Magnitude of the effect
Lifestyle interventions to increase HDL-C levels	
Avoid dietary trans fats	++
Increase habitual physical activity	+++
Reduce excessive body weight	++
Reduce dietary carbohydrates and replace them with unsaturated fats	++
Modest consumption in those who take alcohol may be continued	++
Quit smoking	+

Weight reduction and blood lipids



Etiology of dyslipidemia



Therapeutic classification of DLP

- Hypercholesterolemia
- Hypertriglyceridemia
- Mixed hyperlipidemia

- Primary (inherent) DLP
- Secondary DLP

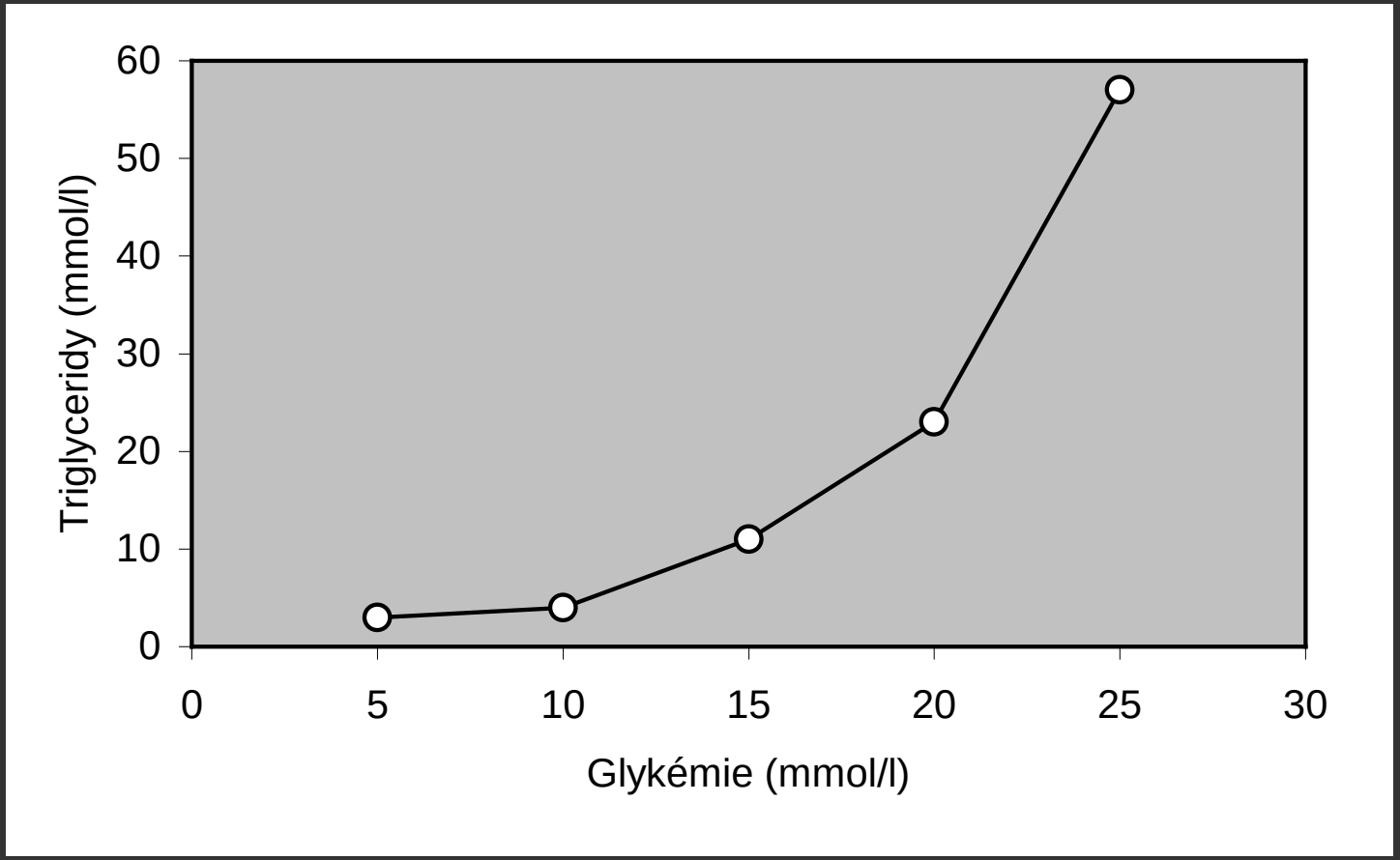
Secondary DLP

- Endocrine diseases
- Liver diseases
- Kidney diseases
- Drugs-induced DLP
- Toxonutritive DLP
- DLP induced by environmental influences

DLP due to endocrine diseases

- Diabetes mellitus
  - Undercontrolled
- Hypothyreoidism
- Hyperfunction of suprarenal glands
  - Cushing disease
- Pregnancy (physiological DLP)

DM a DLP


60
50
40
30
20
10
0
Triglyceridy (mmol/l)
0
5
10
15
20
25
30
Glykémie (mmol/l)

DLP due to hepatic diseases

- Cholestasis
  - Primary biliary cirrhosis
- Parenchyma liver disease
  - Hepatitis (no steatosis)

DLP due to renal diseases

- Nephrotic syndrome
- Chronic renal failure
  - Haemodialysis, peritoneal dialysis
- Renal transplantation

Drugs-induced DLP

- Immunosuppressive
  - Cyclosporine A
  - Corticosteroides
- Retinoids
- Antihypertenzive drugs
  - High doses of
    - Thiazid diuretics, non-selective β-blockers

Toxonutritive DLPs: alcohol

- Alcohol increases blood lipids !!!
- This effect is dose-dependent
  - Individual sensitivity to the alcohol
- This type of DLP is not atherogenic
- Leading cause of secondary DLP resistant to the therapy

Alcohol and lipids

Ethanol → acetaldehyde → AcetylCoA → FA→ Tg → VLDL

- The higher alcohol intake, the higher blood lipid level
  - Tg, TC

DLP induced by the life style

- Food
  - High intake of saturated fats, sugar
    - Fructose
- Alcohol

- Smoking
  - ↓ HDL-Ch, ↑ LDL-cholesterol

- Physical inactivity
  - ↓ HDL-Ch, ↑ Tg

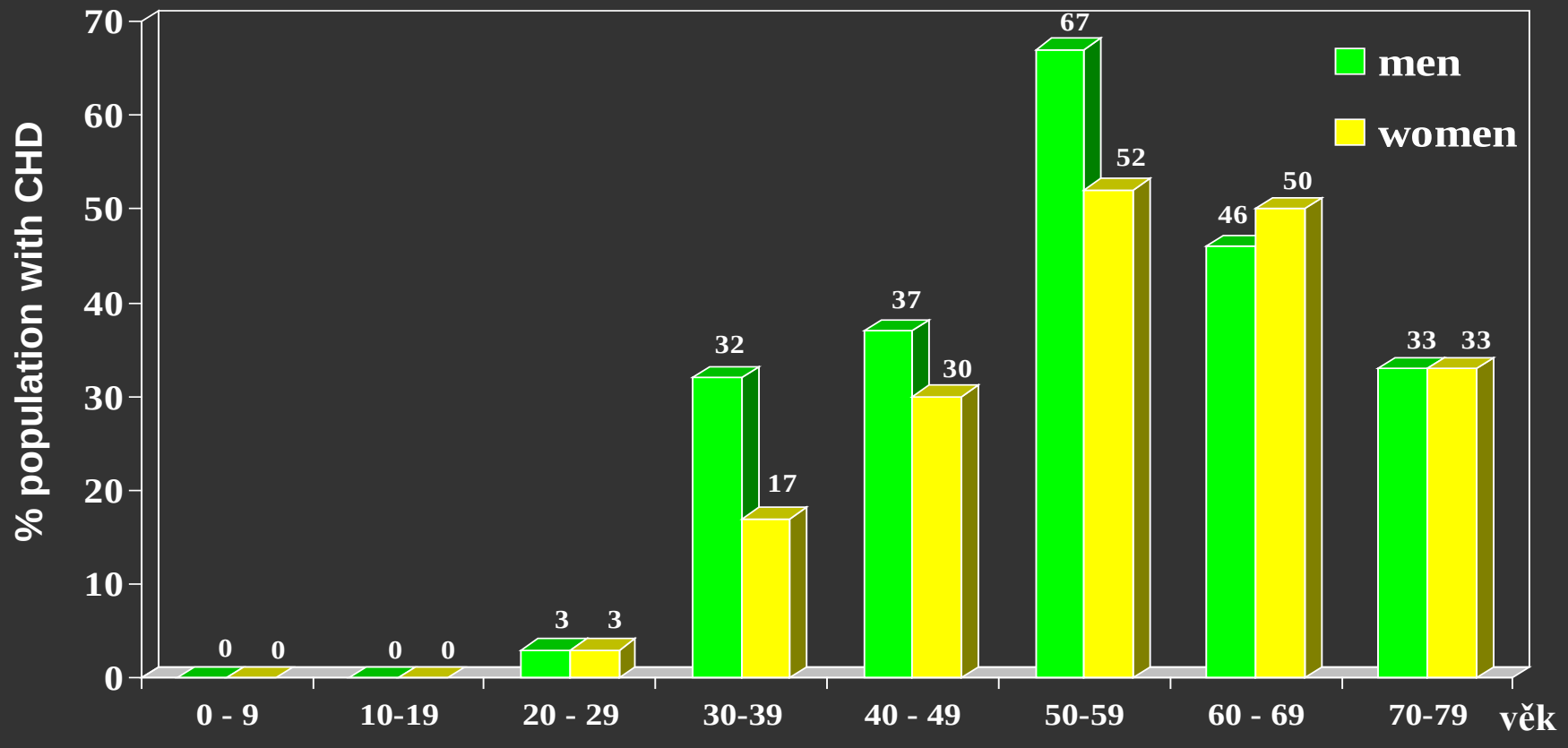
Primary DLP (genetic DLP)

- Hypercholesterolemia
  - Familial hypercholesterolemia
  - *Polygenic HCH*
- *Hypertriglyceridemia*
  - *Familial HTg*
- *Mixed DLP*
  - *Familial combined DLP*

Familial hypercholesterolemia

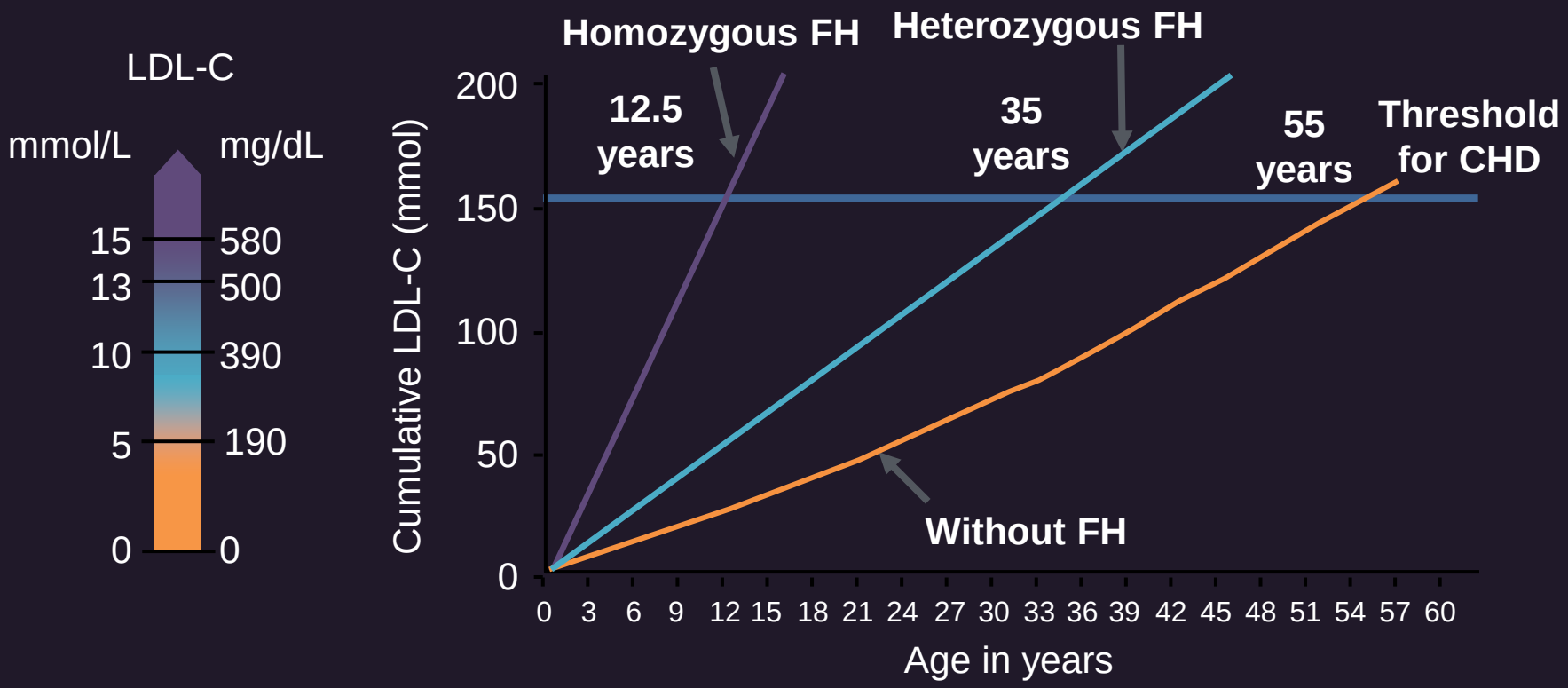
- Cause
  - Defective LDL-receptor gene
  - Defective apo B gene
- Frequency: 1: 500 (heterozygote form)
- Heredity: autosomal dominant
- Pathophysiology: ↓ catabolism of LDL
- Lab: chol. 9-15 mmol/l
  - Physiological level of Tg, HDL-ch)
- Premature CHD
- Xantomatosis - relative rare

CHD in heterozygotes FH



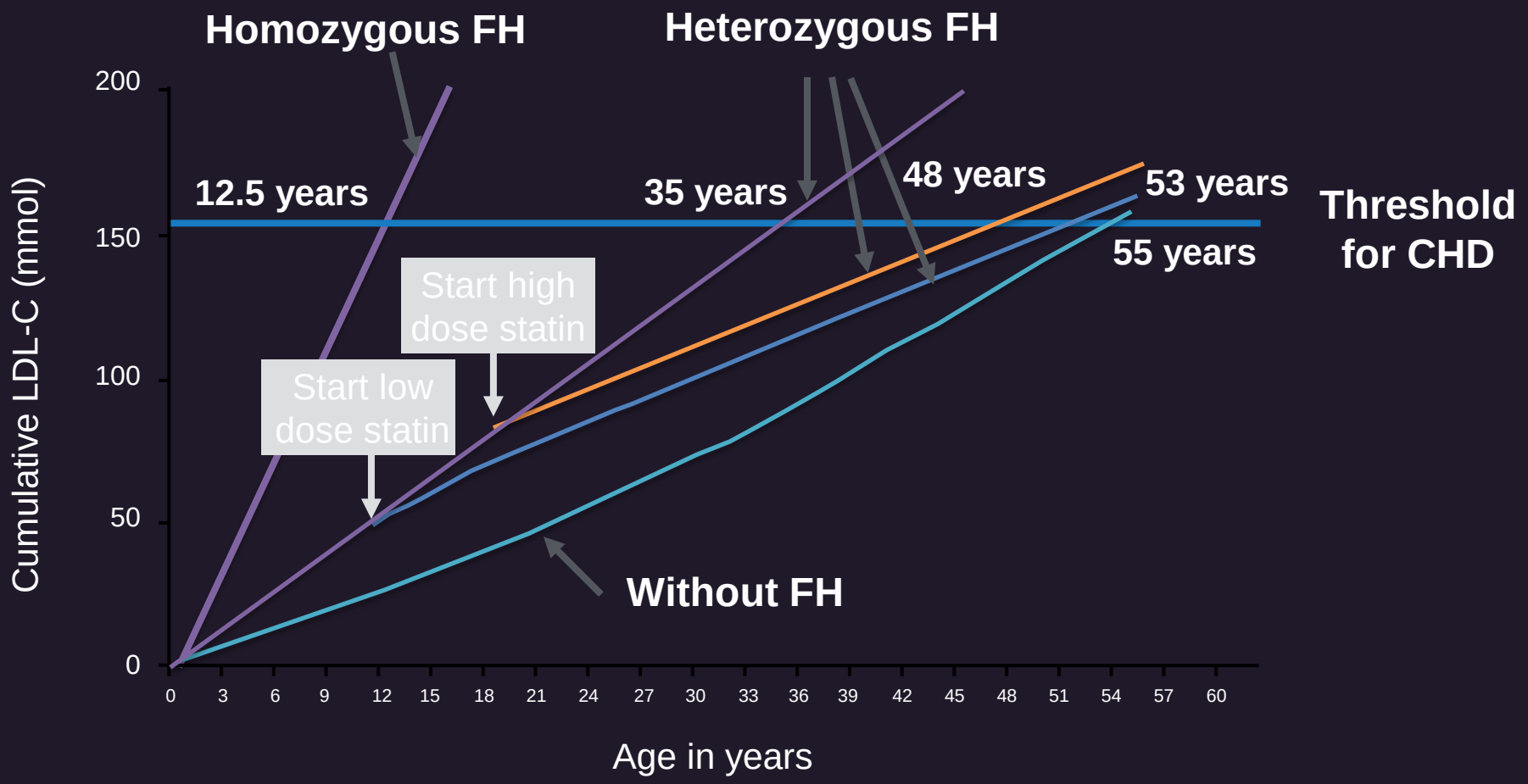
Thompson et al., 1989

Familial hypercholesterolaemia patients reach LDL-C threshold levels for CHD at an early age



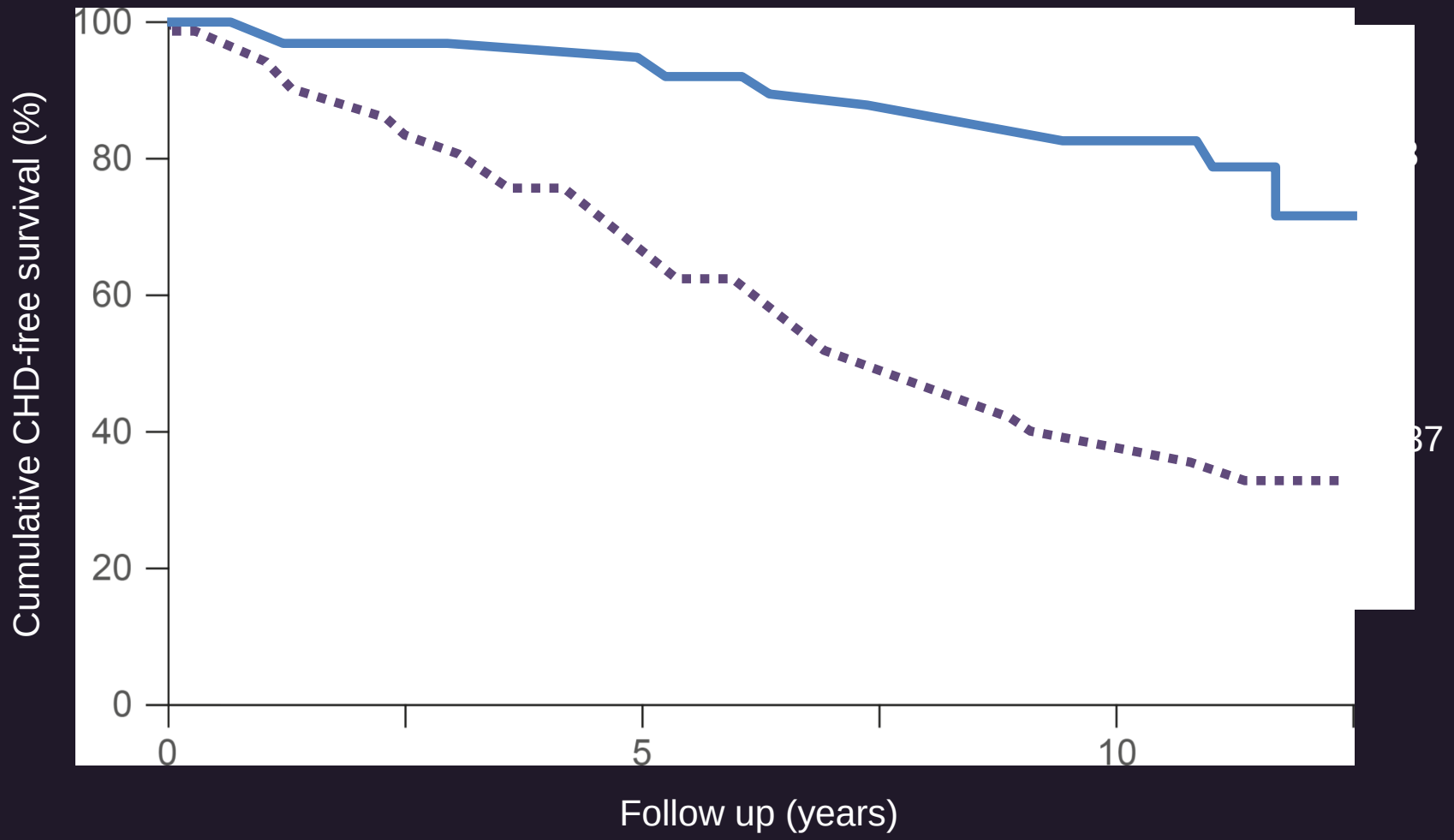
Cuchel et al. Eur Heart J 2014;35:2146–2157.
Nordestgaard et al. Eur Heart J 2013;34:3478–3490.

Early or high-intensity lipid lowering in FH patients delays onset of CHD



Nordestgaard et al. Eur Heart J 2013;34:3478–3490.

Untreated FH is associated with poor prognosis



Versmissen et al. BMJ 2008;337:a2423.

Non-pharmacology treatment of DLP

- Stop smoking !!!

- Regular physical activity
- Weight loss
  - If overweight or obesity
- Diet
  - ↓ saturated FA, sugar (fructose), trans-FA
  - ↑ vegetable, fruits, unsaturated FA, fiber

Pharmacotherapy of DLP

Decrease of LDL cholesterol	Statins Ezetimibe Resins PCSK9-inhibitors
Decrease of triglycerides Elevation fo HDL cholesterol	Fibrates

Table 5 Intervention strategies as a function of total cardiovascular risk and untreated low-density lipoprotein cholesterol levels

	Total CV risk (SCORE) %	Untreated LDL-C levels					
		<1.4 mmol/L (55 mg/dL)	1.4 to <1.8 mmol/L (55 to <70 mg/dL)	1.8 to <2.6 mmol/L (70 to <100 mg/dL)	2.6 to <3.0 mmol/L (100 to <116 mg/dL)	3.0 to <4.9 mmol/L (116 to <190 mg/dL)	≥4.9 mmol/L (≥190 mg/dL)
Primary prevention	<1, low-risk	Lifestyle advice	Lifestyle advice	Lifestyle advice	Lifestyle advice	Lifestyle intervention, consider adding drug if uncontrolled	Lifestyle intervention and concomitant drug intervention
	Class[a]/Level[b]	I/C	I/C	I/C	I/C	IIa/A	IIa/A
	≥1 to <5, or moderate risk (see *Table 4*)	Lifestyle advice	Lifestyle advice	Lifestyle advice	Lifestyle intervention, consider adding drug if uncontrolled	Lifestyle intervention, consider adding drug if uncontrolled	Lifestyle intervention and concomitant drug intervention
	Class[a]/Level[b]	I/C	I/C	IIa/A	IIa/A	IIa/A	IIa/A
	≥5 to <10, or high-risk (see *Table 4*)	Lifestyle advice	Lifestyle advice	Lifestyle intervention, consider adding drug if uncontrolled	Lifestyle intervention and concomitant drug intervention	Lifestyle intervention and concomitant drug intervention	Lifestyle intervention and concomitant drug intervention
	Class[a]/Level[b]	IIa/A	IIa/A	IIa/A	I/A	I/A	I/A
	≥10, or at very-high risk due to a risk condition (see *Table 4*)	Lifestyle advice	Lifestyle intervention, consider adding drug if uncontrolled	Lifestyle intervention and concomitant drug intervention	Lifestyle intervention and concomitant drug intervention	Lifestyle intervention and concomitant drug intervention	Lifestyle intervention and concomitant drug intervention

Target levels of non HDL-chol. (mmol/l)

	Low risk people	Moderate risk people	High risk people	Very high risk people
LDL-Ch	< 3,0	< 2,6	< 1,8	< 1,4
Apo B g/l		< 1,0	< 0,8	< 0,65
Non HDL-ch.	< 3,8	< 3,4	< 2,6	< 2,2