# EAS Consensus Paper

## Familial Hypercholesterolaemia in Children and Adolescents: Identifying and Treating Early to Prevent Premature Heart Disease

Slide set adapted from:
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REVIEW

*Prevention*

# Familial hypercholesterolaemia in children and adolescents: gaining decades of life by optimizing detection and treatment

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# Key points about Familial Hypercholesterolaemia (FH)

- One of the most common genetic disorders, affecting 1:200 to 1:250 people
- Inherited in an autosomal dominant manner
- Disabling at a young age and shortens life expectancy.

- Consider Homozygous FH if:

  - LDL-C levels >13 mmol/L (500 mg/dL)
  - Tendon xanthomas in the hands and Achilles tendons
  - Evidence of premature cardiovascular disease, aortic valve disease

- A psychological challenge for families because of the inherited nature of the disorder, the lack of early symptoms in HeFH, and the need for long term lifestyle changes and pharmacologic therapy.

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# What is familial hypercholesterolaemia?

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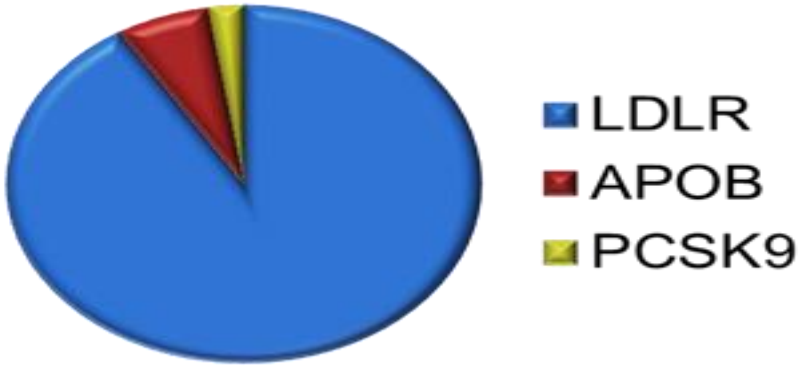
# About FH

FH is an autosomal dominant disorder

- The most common FH-causing mutations are in the gene coding for the LDL receptor (*LDLR*). There are >1500 documented mutations in the *LDLR* gene.
- Less common mutations involve *APOB* and *PCSK9*




- Rarely, mutations in *LDLRAP1* lead to recessive FH

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# FH and atherosclerosis

- FH is an asymptomatic condition . Accumulation of LDL-C in the plasma results in accelerated atherogenesis. If undiagnosed, this leads to premature coronary events, typically in early middle age

- The relative risk for a fatal coronary event in a young adult with FH aged 20-39 years is 80-100 fold greater than age-matched controls

- In general, the severity of atherosclerosis is proportional to the extent and duration of elevated LDL-C – the "Cholesterol -Year- Score"

Schmidt HH et al. Am J Cardiol 1996;77:575-80

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# How common is familial hypercholesterolaemia?

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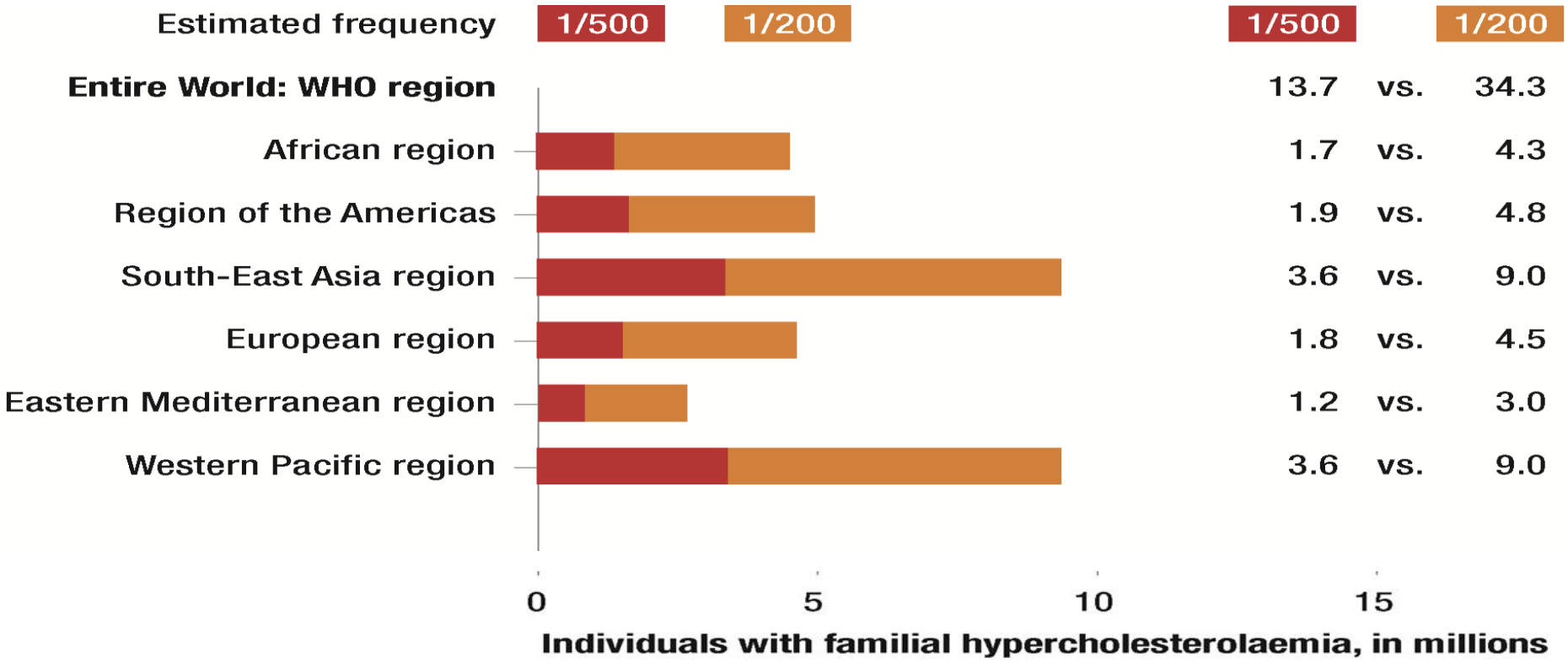
# FH Prevalence

- Heterozygous FH  affects about 1 in 200-250 people
- World-wide nearly 35 million people have  FH




Nordestgaard BG et al. Eur Heart J 2013;34:3478-90a.

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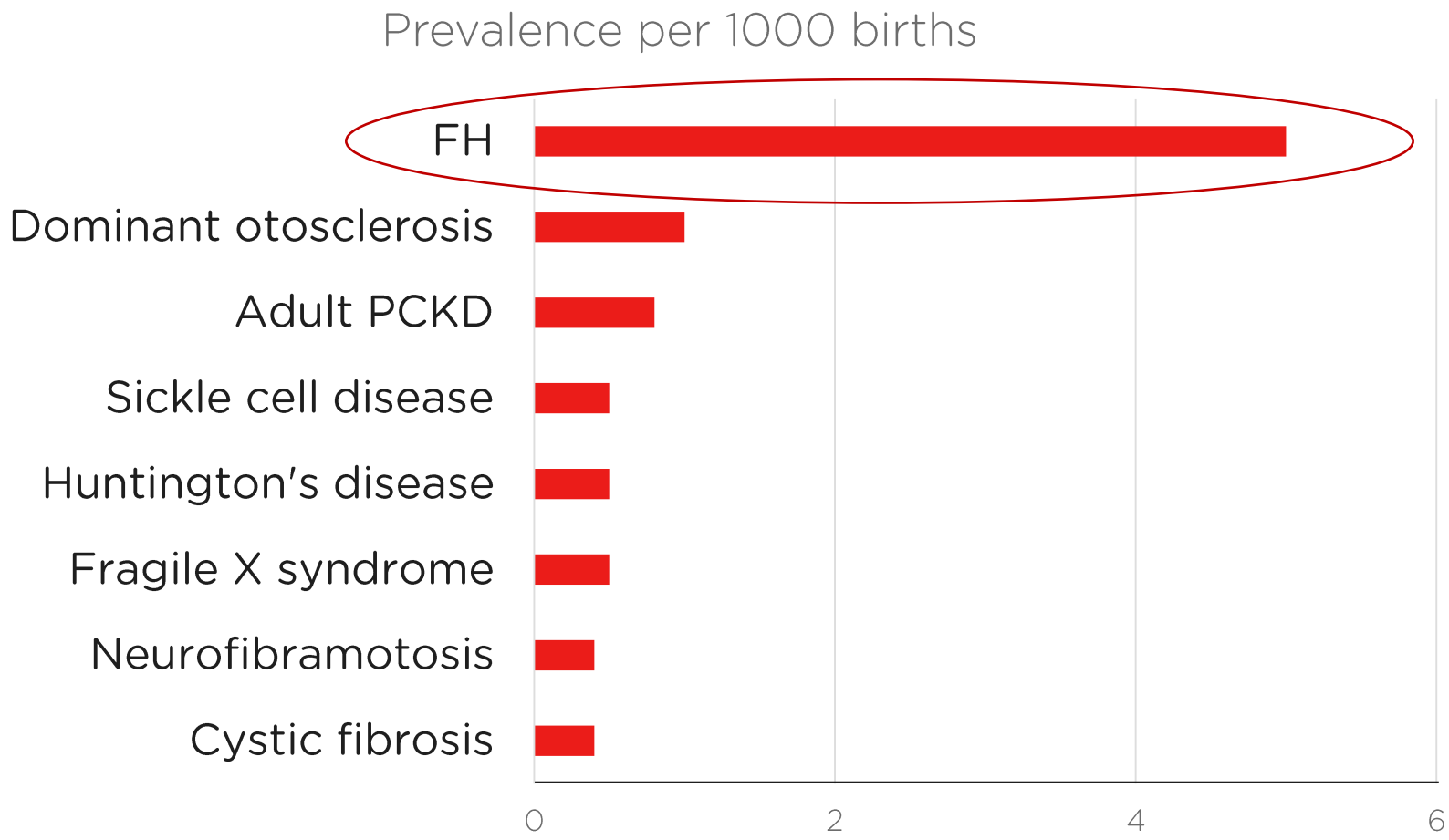
# FH Prevalence

- FH affects about 5 in every 1,000 births
- Worldwide one baby is born with FH each minute




Wiegman A et al. Eur Heart J 2015 Epub ahead of print

# Why we need to identify and treat FH early

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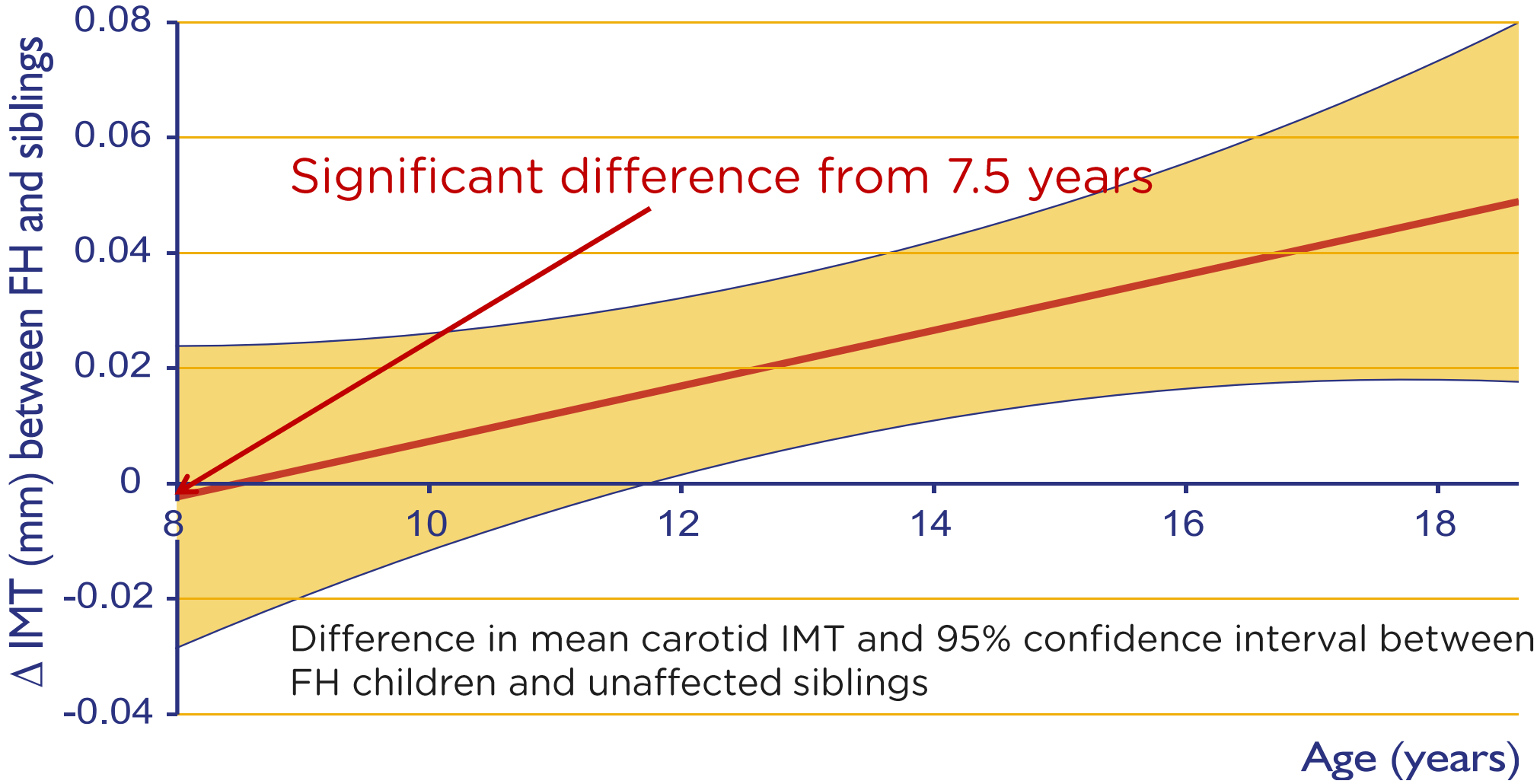
# Carotid IMT: A marker of early atherogenesis in FH children




KustersDM et al. Circ Res 2014;114:307–310

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# Early detection is critical

- Early detection of FH and early initiation of lifestyle and pharmacological treatment is imperative to reduce the life-long burden of elevated LDL-C levels

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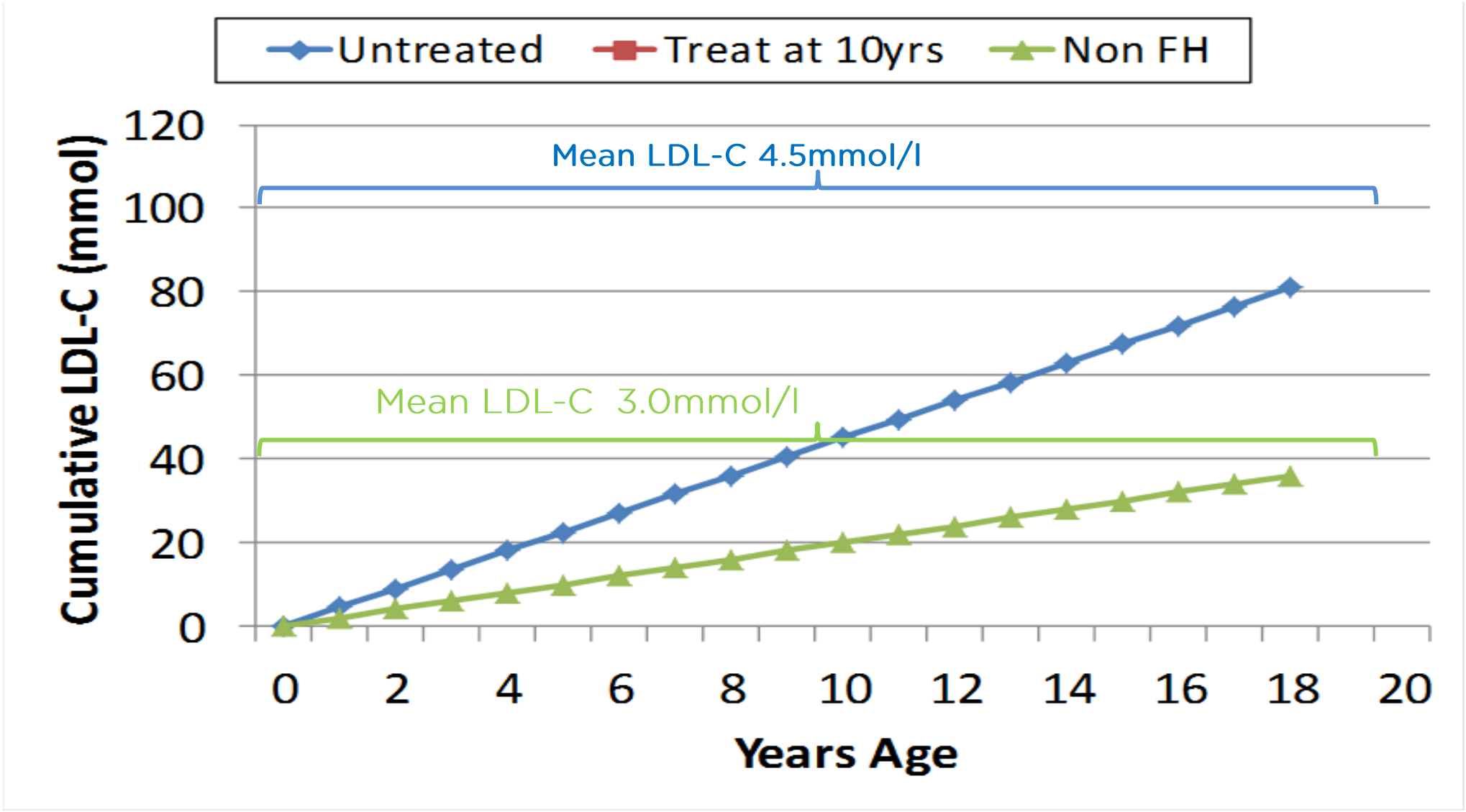
# LDL-C burden in untreated FH children




Adapted from Vuorio A et al. Atherosclerosis 2013;226:315–20.

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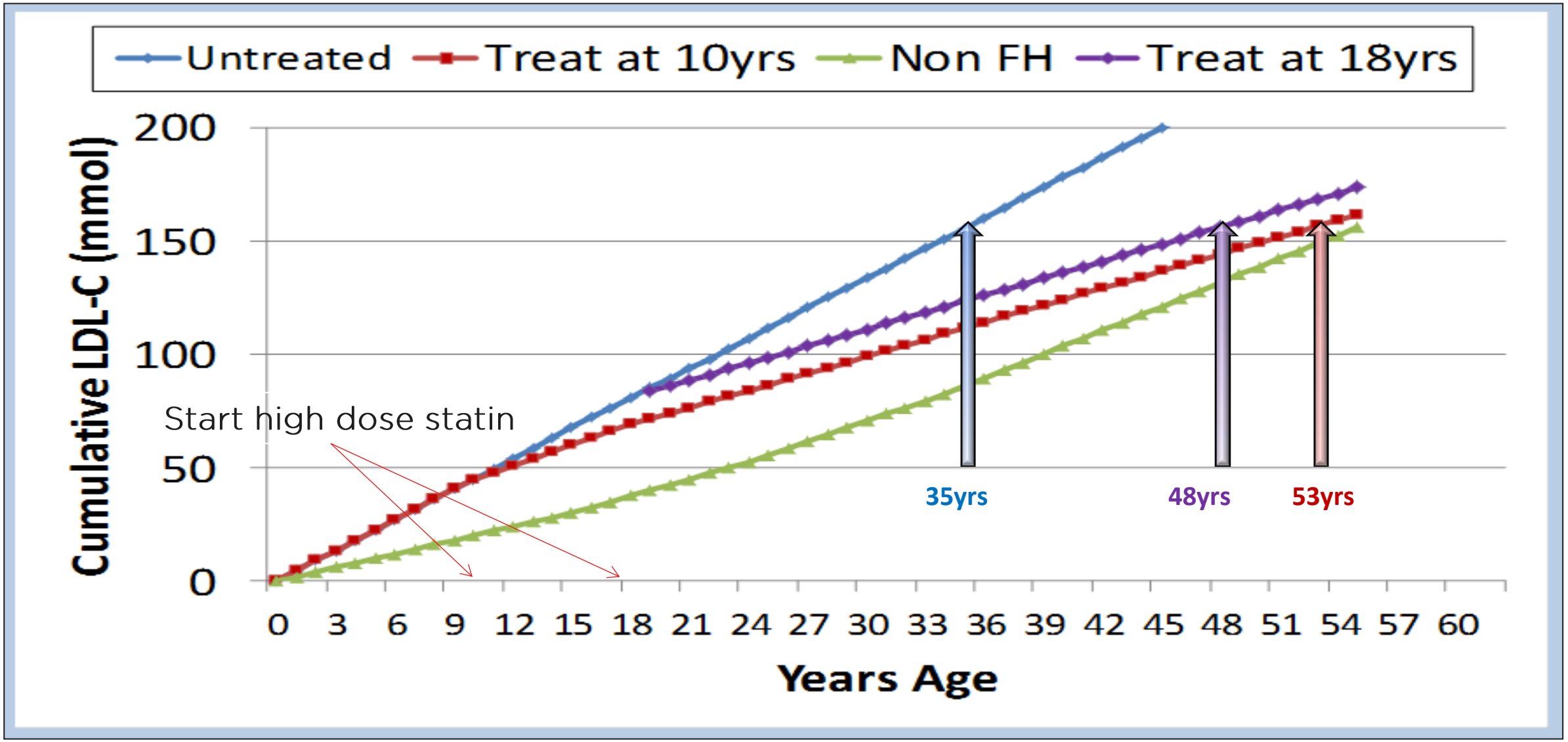
# Early statin treatment delays LDL-C burden




Adapted from Vuorio A et al. Atherosclerosis 2013;226:315–20 based on data from Starr B et al. Clin Chem Lab Med 2008;46:791–803.

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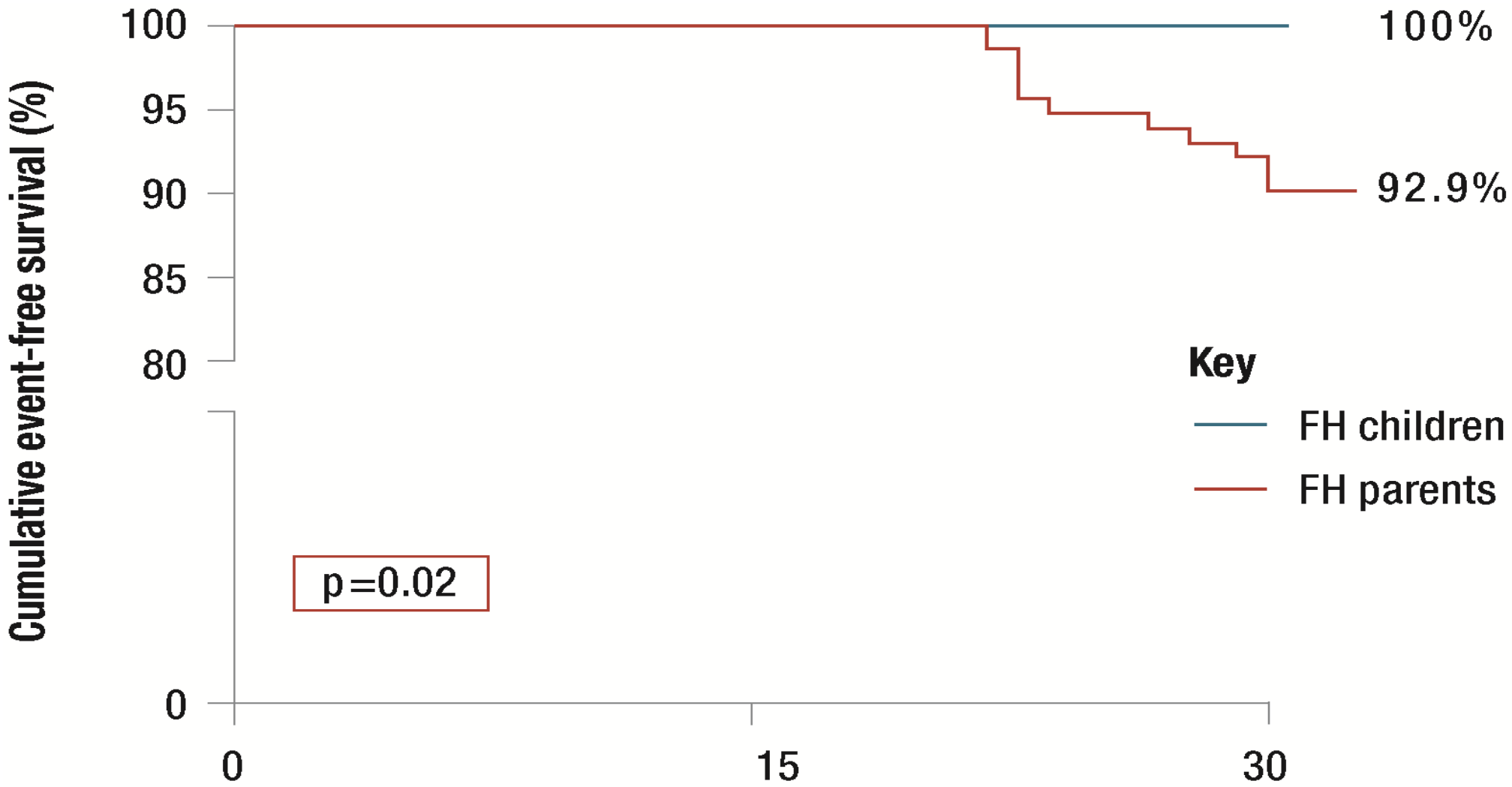
# Impact of early statin treatment on event-free survival




Braamskamp MJ et al. Circulation 2013;128:A17837

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# How to diagnose FH in children

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# Family History + Hypercholesterolemia = FH in Children*

- Cholesterol testing should be used to make a phenotypic diagnosis
  - 5 mmol/L (190 mg/dL), 2 successive occasions over 3 months
  - 4 mmol/L (160 mg/dL) AND family history of premature CVD ± baseline high cholesterol in one parent
  - 3.5 mmol/L (130 mgdL) AND positive genetic diagnosis in the family
- Rule out secondary causes (thyroid, liver or renal dysfunction, concomitant medication, obesity)
- Genetic testing confirms the diagnosis (after parental testing)

*FH Foundation

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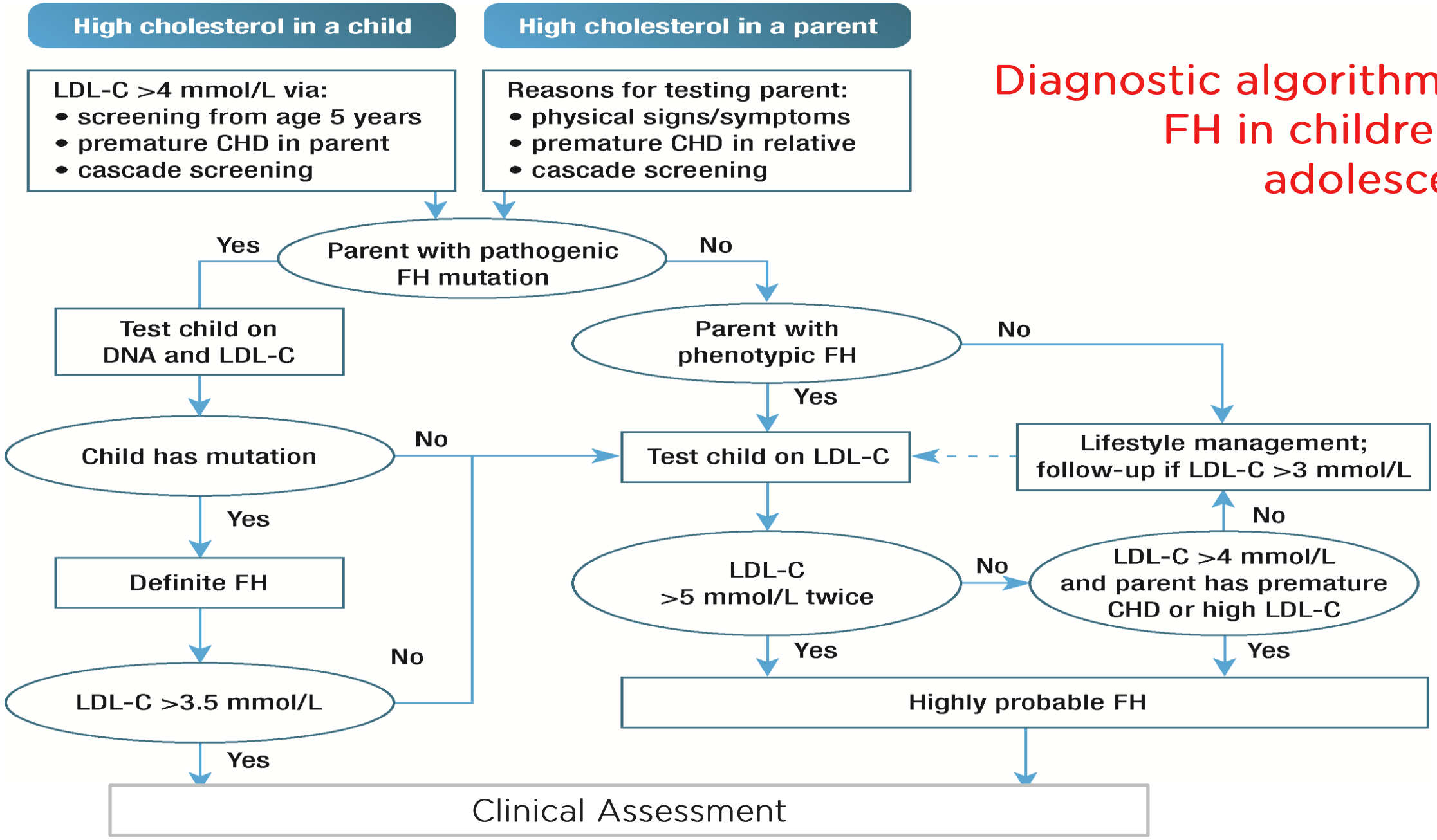
# Diagnostic algorithm for FH in children & adolescents




Wiegman A et al. Eur Heart J 2015 Epub ahead of print

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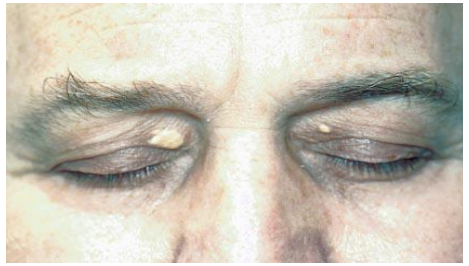
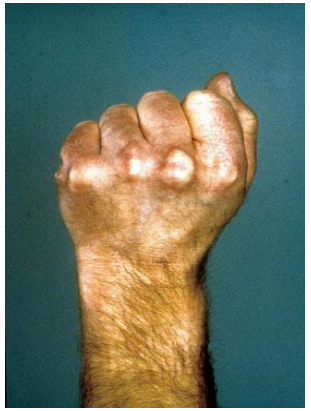
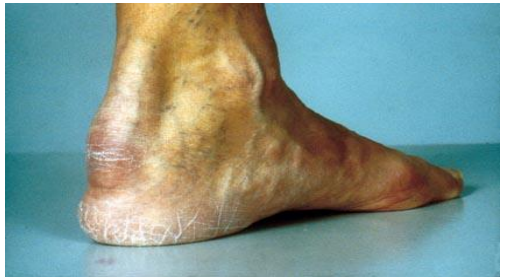
# Consider Homozygous FH

Clinical evidence of:



- Premature  cardiovascular disease
- Corneal Arcus
- Xanthelasma
- Tendon xanthomas in the hands and Achilles tendons





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# The importance of FH screening

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# Screening for FH in children and adolescents

- Despite the importance of early detection, FH remains under-diagnosed
- Cascade screening of families is the most cost-effective strategy to increase FH diagnosis and treatment.
- A genotypic strategy is recommended if DNA testing is available.
- If DNA testing is not available, a phenotypic strategy based on country, age and gender-specific low-density lipoprotein cholesterol (LDL-C) levels should be used

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# Screening for FH in children & adolescents

- Suspected heterozygous FH: Screen from age 5 years
- **Suspected homozygous FH: Screen if clinically suspected (both parents affected or xanthoma present) as early as possible**
- Age at screening should be similar for boys and girls

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# Treating FH children

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# Diet and risk factor control

- Assess cardiovascular  risk factors including lipoprotein (a)
- No smoking
- Encourage exercise
- Diet
  <30% of calories from fat
  <7% of calories from saturated fat
  <200mg cholesterol/day
  appropriate energy for normal growth and sufficient in micronutrients

Early initiation of lifestyle is essential for ensuring long-term adherence.

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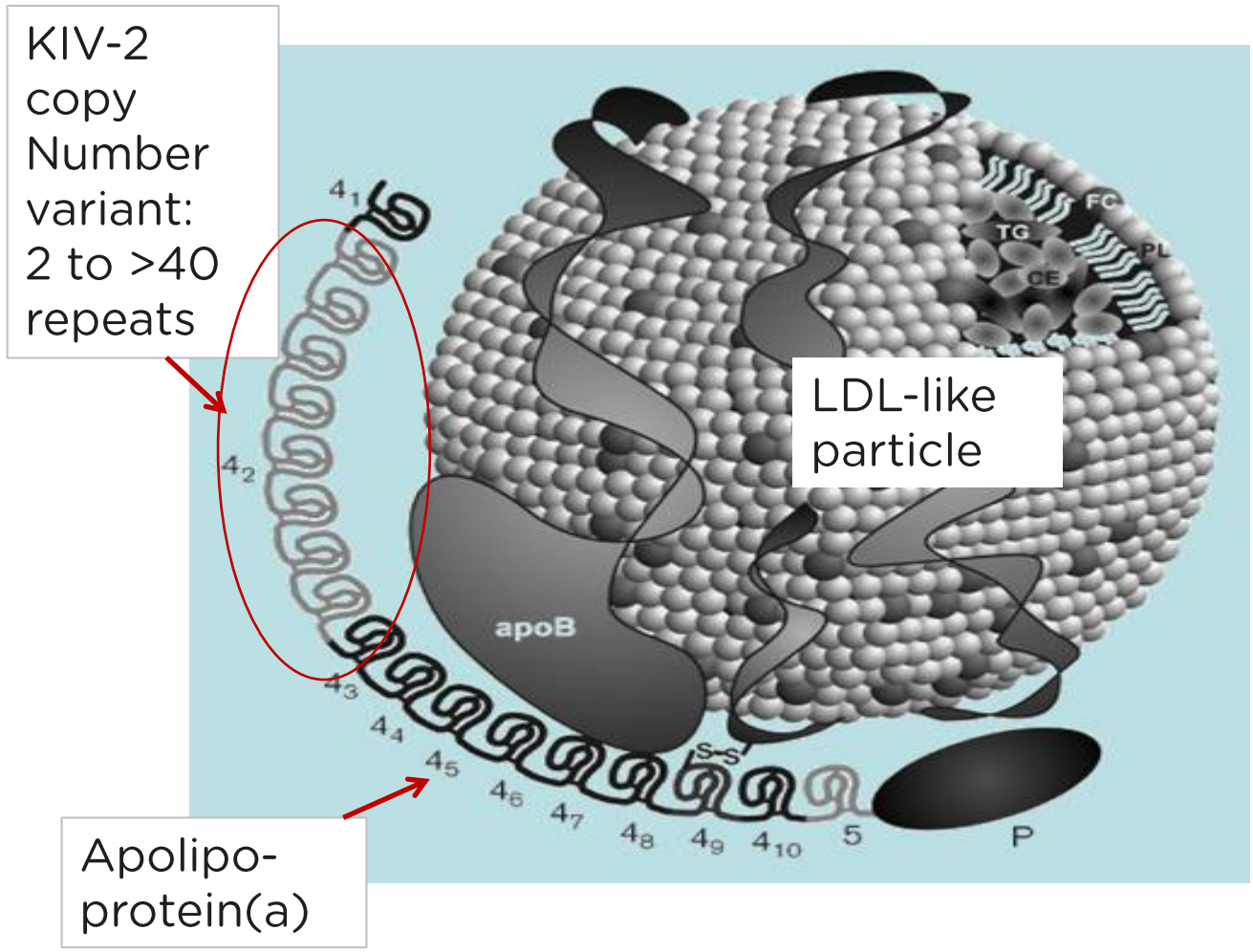
# Risk factors: What is lipoprotein(a)?




- An LDL-like plasma lipoprotein BUT with an additional protein, apolipoprotein(a)
- Apo(a) comprises a series of loop structures called kringles. Kringle IV type 2 has from 2 to >40 copies

- Elevated Lp(a) ->50 mg/dL (80th percentile) is a cardiovascular risk factor
- FH is associated with elevated Lp(a)

Koschinsky et al. Cur Opin Lipidol 2004;15:167-174; Nordestgaard BG et al. Eur Heart J 2010;31;2844-53

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# When to start a statin?

Heterozygous FH:

- Generally, at age 8-10 years (depending on local prescribing information)
- Earlier if considered at very high risk
  - family history of very premature coronary artery disease (30s-40s)
  - diabetes
  - organ transplantation
  - multiple coronary risk factors
- Stronger statins may need to be introduced after puberty in the case of severe mutations

**Homozygous FH: At diagnosis**

Wiegman A et al. Eur Heart J 2015 Epub ahead of print

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# LDL-C Targets in children with FH

8–10 years:
Aim for 50% reduction in LDL-C from pre-treatment level

≥10 years:
<3.5 mmol/L (130 mg/dL) especially if there are additional cardiovascular risk factors, including elevated lipoprotein(a)

Adding ezetimibe or a bile-acid sequestrant may be needed to attain LDL-C goal

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# Homozygous FH

- Children with homozygous FH should be referred to and cared for at a specialised centre

Wiegman A et al. Eur Heart J 2015 Epub ahead of print

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# Monitoring FH children

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# Monitoring treatment in FH children & adolescents

- Monitor weight, growth, physical and sexual development, and well-being
- Measure hepatic aminotransferases at least every 3 months if there is a history of liver disease. Monitor more frequently if levels increase >3-fold x ULN.
- Measure plasma CK levels if musculoskeletal symptoms are reported.
- Measure fasting plasma glucose and/or random HbA1c every 6 months in children on higher doses of statins who are obese or have impaired glucose tolerance.

Wiegman A et al. Eur Heart J 2015 Epub ahead of print

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# Safety: liver & muscle

| | FH n=194 | Sibling n=83 | *P* Value |
|---|---|---|---|
| **Aspartate aminotransferase – IU/l** | | | |
| Median (IQR) | 25.0 (22.0-30.0) | 26.0 (22.0-30.0) | 0.44 |
| > 3x ULN – no. (%) | 1 (0.5%) | 1 (1.1%) | 0.55 |
| **Alanine aminotransferase – IU/l** | | | |
| Median (IQR) | 18.0 (13.0-25.0) | 17.0 (13.0-24.0) | 0.63 |
| > 3x ULN – no. (%) | 1 (0.5%) | 0 (0.0%) | 0.51 |
| **Creatine kinase – IU/l** | | | |
| Median (IQR) | 101.0 (72-150) | 101.0 (82.0-161.0) | 0.28 |
| > 10x ULN – no. (%) | 0 (0.0%) | 2 (2.1%) | 0.03 |

Kusters DM et al. JAMA 2014;312:1055–1057

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# Safety: growth/development

- Growth

| | FH n=194 | Sibling n=83 | *P* Value |
|---|---|---|---|
| Height – m | 1.74 ± 0.1 | 1.76 ± 0.09 | 0.27 |
| Weight – kg | 74.2 ± 14.8 | 73.8 ± 12.9 | 0.82 |
| Body-mass index | 24.4 ± 4.8 | 23.9 ± 3.9 | 0.36 |

- Menarche: 13.1 vs 13.2 years, *P*=0.72

Kusters DM et al. JAMA 2014;312:1055–1057

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# Special issues: adherence

- Check adherence if heterozygous FH children fail to achieve LDL-C targets with combination lipid-lowering treatment.

- Consider referral of non-adherent patients to a dedicated, multidisciplinary clinic

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# Special issues in adolescent girls with FH

Contraception

- Preferred contraceptive measures: low oestrogen oral agents, intra-uterine devices and barrier methods
- Monitor lipids after starting oral contraceptives

Pregnancy

- Counselling is recommended for all women considering pregnancy due to the risk for FH
- Statins should be discontinued: Bile-acid resins are the only safe agents for use in pregnancy and breast-feeding

Wiegman A et al. Eur Heart J 2015 Epub ahead of print

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# Better education about FH a priority

Norwegian  Registry data

- 118 FH patients, treated with statin from age 8-10 years in trials
- 72% (48 of 67 consented) continued on statin
- Only 9% participants had LDL-C ≤ 2.5 mmol/L

Implications

- Statins are severely underused in young adult FH patients.
- Better education of patients and frequent (yearly) consultations therefore seem warranted.

Langlet G et al. EAS Congress Glasgow 2015 [poster]

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# Conclusions

- World-wide, one baby is born with FH every minute
- Identifying and treating children with FH is the key to gaining decades of healthy normal life and making premature coronary heart disease history
- Better awareness and education  are essential to achieving this

Wiegman A et al. Eur Heart J 2015 Epub ahead of print

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# About lipoprotein(a)


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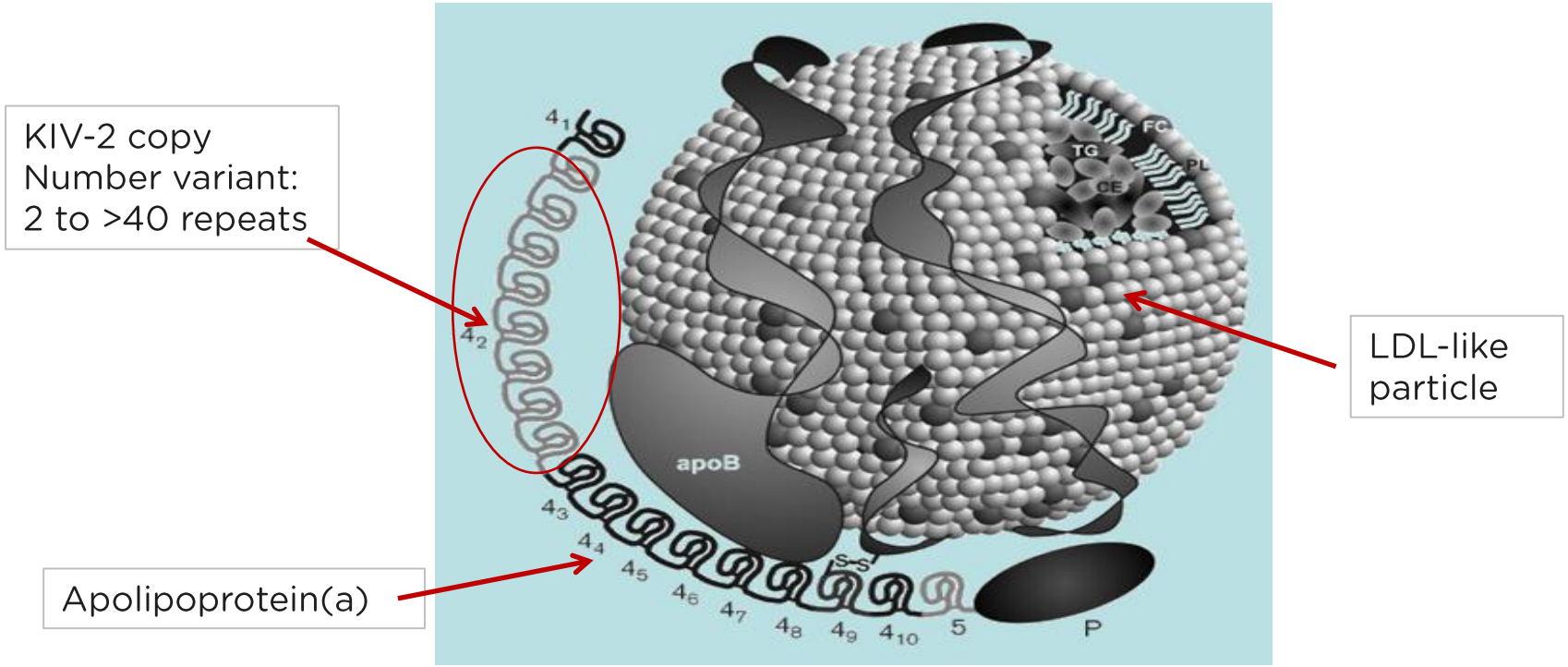
# What is lipoprotein(a)?

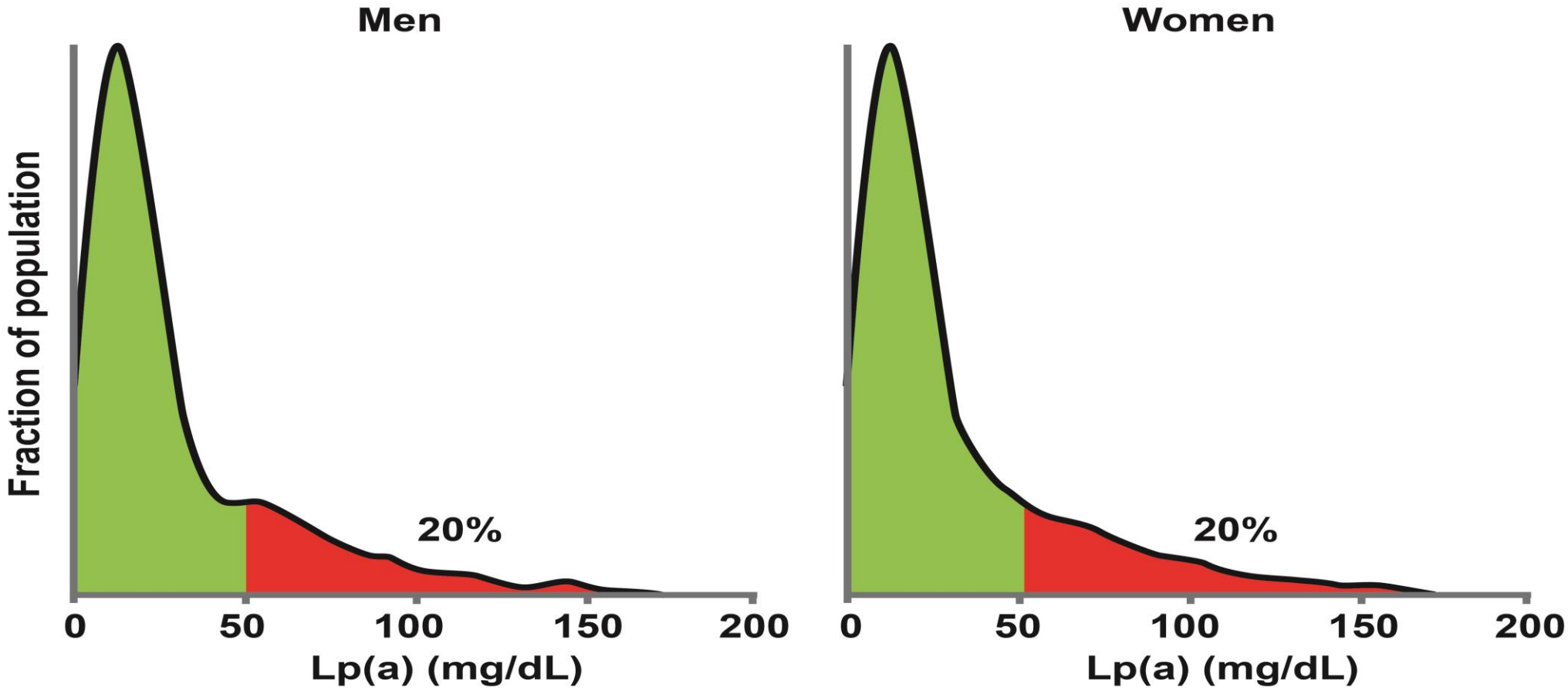
- An LDL-like cholesterol-rich particle  which differs from LDL as it contains an additional protein, apolipoprotein(a).
- Apo(a) comprises a series of loop structures called kringles. Kringle IV type 2 has from 2 to >40 copies




Koschinsky et al. Cur Opin Lipidol 2004;15:167-174

# Plasma Lp(a) levels in general population

20% have plasma Lp(a) levels >50 mg/dL




Nordestgaard BG et al. Eur Heart J 2010;31:2844-53

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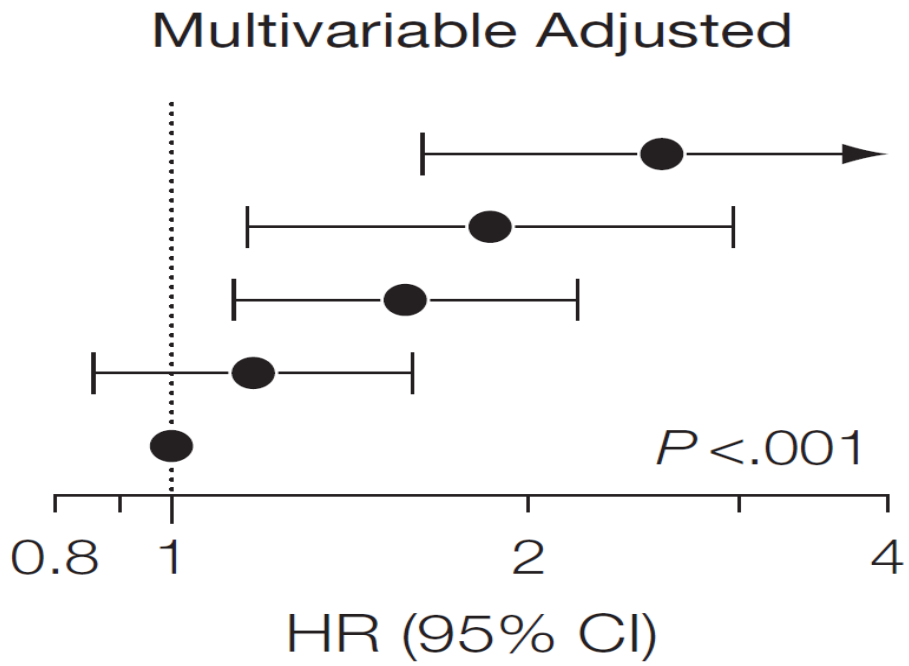
# Lp(a) and cardiovascular risk: Epidemiological evidence

- Copenhagen General Population Study:
- people with Lp(a) > 50 mg/dL had 2-3-fold increased risk for MI

| Lipoprotein(a) | |
|---|---|
| Percentile | mg/dL |
| >95th | >117 |
| 90th-95th | 77-117 |
| 67th-89th | 30-76 |
| 22nd-66th | 5-29 |
| <22nd [Reference] | <5 |




Kamstrup et al. JAMA 2009; 301: 2331-9, Nordestgaard BG et al. Eur Heart J 2010;31:2844-53

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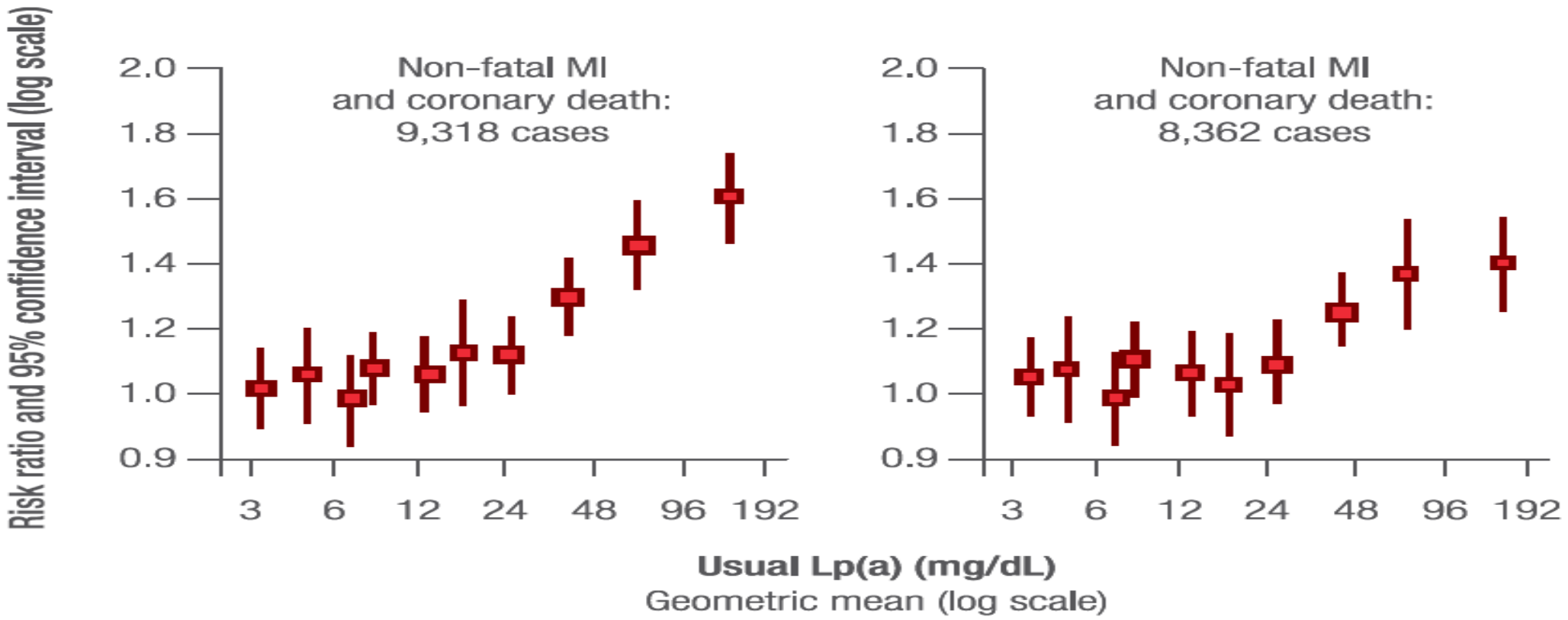
# Lp(a) and cardiovascular risk: Epidemiological evidence

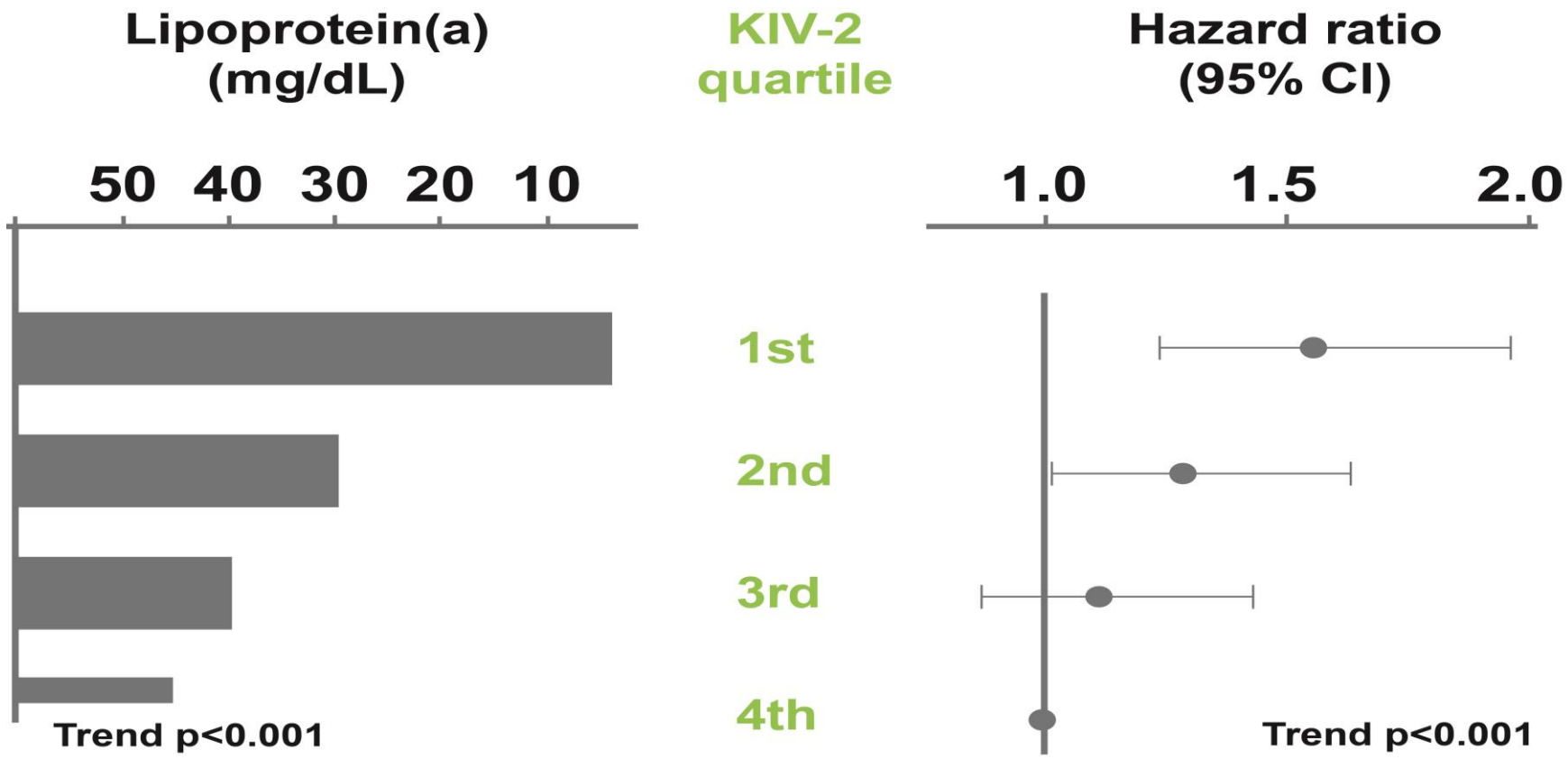
- Emerging Risk Factors Collaboration:
  Each 1 standard  deviation increase in Lp(a) increased CHD risk by 13%




Erqou S et al.  JAMA 2009;302:412-23

# Lp(a) and cardiovascular risk: Genetic evidence

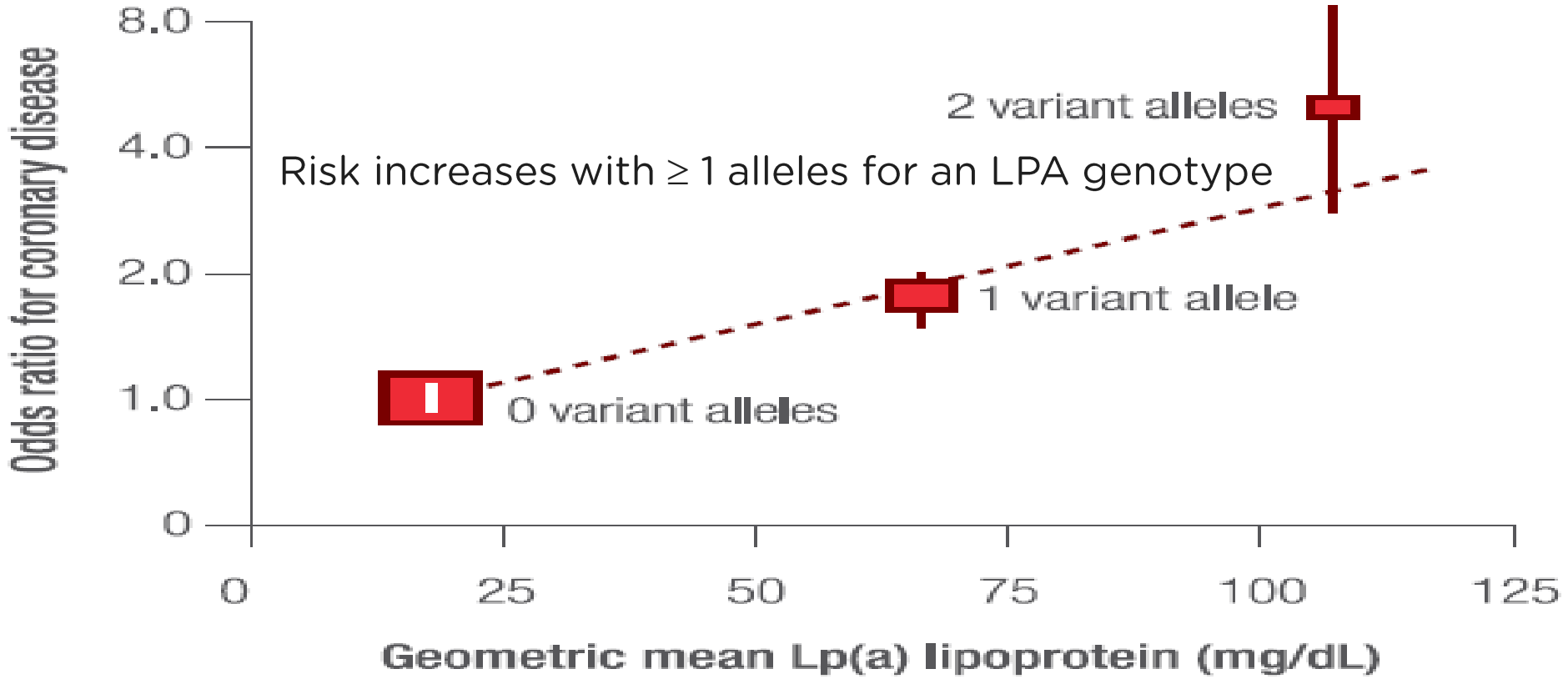
- Decreasing quartiles of kringle IV type 2 repeats were associated with increasing plasma Lp(a) levels and increased MI risk




Kamstrup PR et al. JAMA 2009;301:2331-9

# Lp(a) and cardiovascular risk: Genetic evidence

- Plasma Lp(a) levels and CHD risk increases with ≥1 variant alleles of the *LPA* gene




Clarke R et al. NEJM 2009; 361:2518-28

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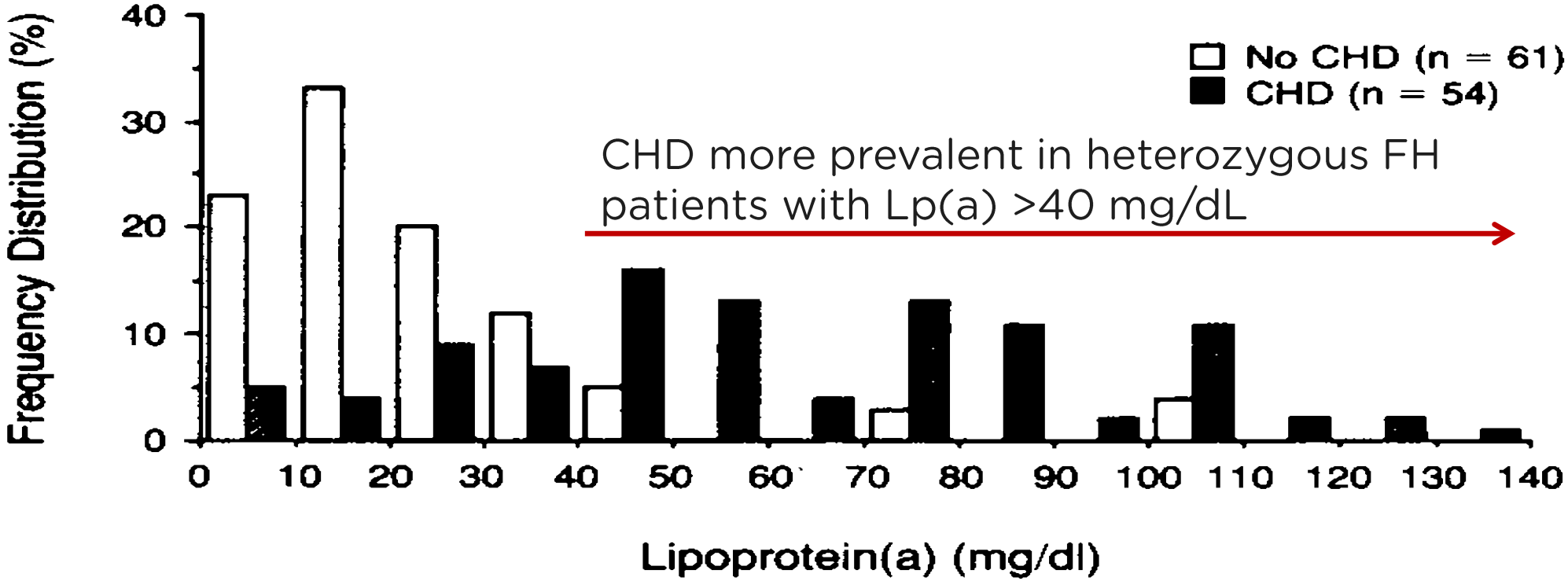
# Lp(a) and FH

- CHD more prevalent in heterozygous FH patients with Lp(a) >40 mg/dL
- Frequency of variant *LPA* allele ~2.5-fold higher in FH patients with CHD than in those without




Seed M et al NEJM 1990;322:1494-9

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# Lp(a) and FH

- Retrospective cohort study of 2400 patients with heterozygous FH
- Lp(a) >30 mg/dL was associated with 1.5-fold increase in CVD risk

| | Univariate | | | Multivariate ($n = 1956$) | | |
|---|---|---|---|---|---|---|
| | RR | 95% CI | *P* value | RR | 95% CI | *P* value |
| Male gender | 2.95 | 2.54–3.43 | <0.0001 | 2.82 | 2.37–3.36 | <0.0001 |
| Smoking (time dependent + lag effect) | 1.79 | 1.55–2.08 | <0.0001 | 1.67 | 1.40–1.99 | <0.0001 |
| Hypertension (time dependent) | 1.42 | 1.15–1.75 | 0.001 | 1.36 | 1.06–1.75 | 0.02 |
| Diabetes (time dependent) | 1.96 | 1.28–3.01 | 0.002 | 2.19 | 1.36–3.54 | 0.001 |
| BMI (kg $m^{-2}$) | 1.03 | 1.01–1.05 | 0.01 | – | – | – |
| HDL risk (males <0.9 mmol $L^{-1}$; females <1.1 mmol $L^{-1}$) | 1.36 | 1.15–1.62 | 0.0004 | 1.37 | 1.15–1.63 | 0.0004 |
| Triglycerides (mmol $L^{-1}$) | 1.12 | 1.05–1.20 | 0.001 | – | – | – |
| Lp(a) risk (>300 mg $L^{-1}$) | 1.46 | 1.23–1.73 | <0.0001 | 1.50 | 1.20–1.79 | 0.0001[a] |
| Homocysteine risk (>15 μmol $L^{-1}$) | 1.57 | 1.24–1.99 | 0.0002 | – | – | – |

[a] $n = 1698$.

Jansen AC et al. J Intern Med 2004;256:482-90

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More information:

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European Heart Journal
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CURRENT OPINION

# Lipoprotein(a) as a cardiovascular risk factor: current status

Børge G. Nordestgaard[1*], M. John Chapman[2], Kausik Ray[3], Jan Borén[4], Felicita Andreotti[5], Gerald F. Watts[6], Henry Ginsberg[7], Pierre Amarenco[8], Alberico Catapano[9], Olivier S. Descamps[10], Edward Fisher[11], Petri T. Kovanen[12], Jan Albert Kuivenhoven[13], Philippe Lesnik[2], Luis Masana[14], Zeljko Reiner[15], Marja-Riitta Taskinen[16], Lale Tokgözoglu[17], and Anne Tybjærg-Hansen[18], for the European Atherosclerosis Society Consensus Panel[†]

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