Understanding the increased cardiovascular risk of high Lp(a) levels

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PHYSICIANS' ACADEMY FOR CARDIOVASCULAR EDUCATION
PACE-CME

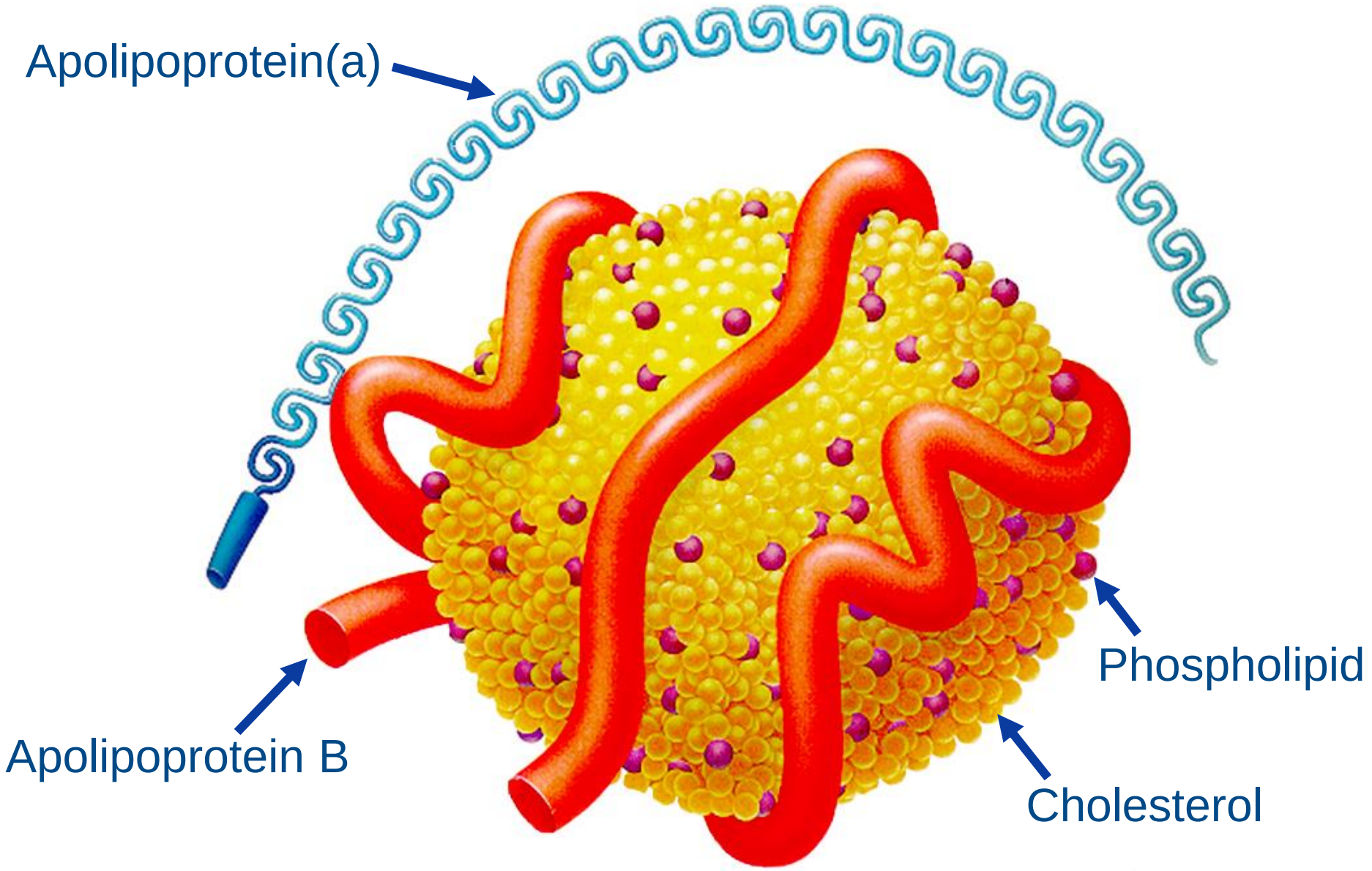
Disclosures

Advisory board and/or lecture fees: Amgen, Kaneka and Novartis

Objectives

1. Epidemiology of Lp(a)
2. Genetic basis of Lp(a)
3. Mendelian randomization studies
4. When should Lp(a) be tested

Lp(a) - the mysterious brother of LDL



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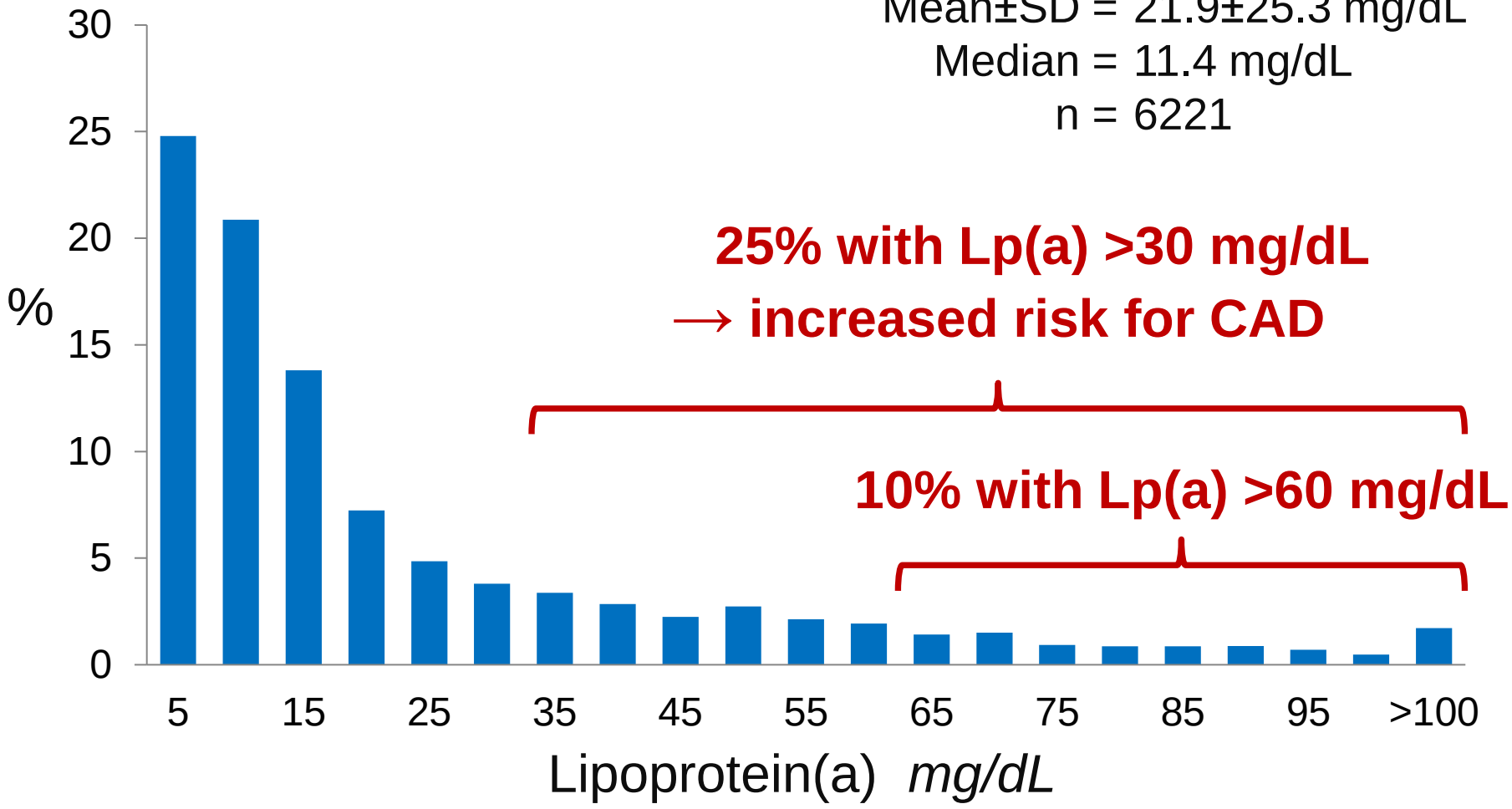
Lawn; Sci.Am. 266:54-60, 1992

Distribution of Lp(a) concentrations

General population
KORA F3 & F4 Cohorts
Mean±SD = 21.9±25.3 mg/dL
Median = 11.4 mg/dL
n = 6221



25% with Lp(a) >30 mg/dL
→ increased risk for CAD

10% with Lp(a) >60 mg/dL

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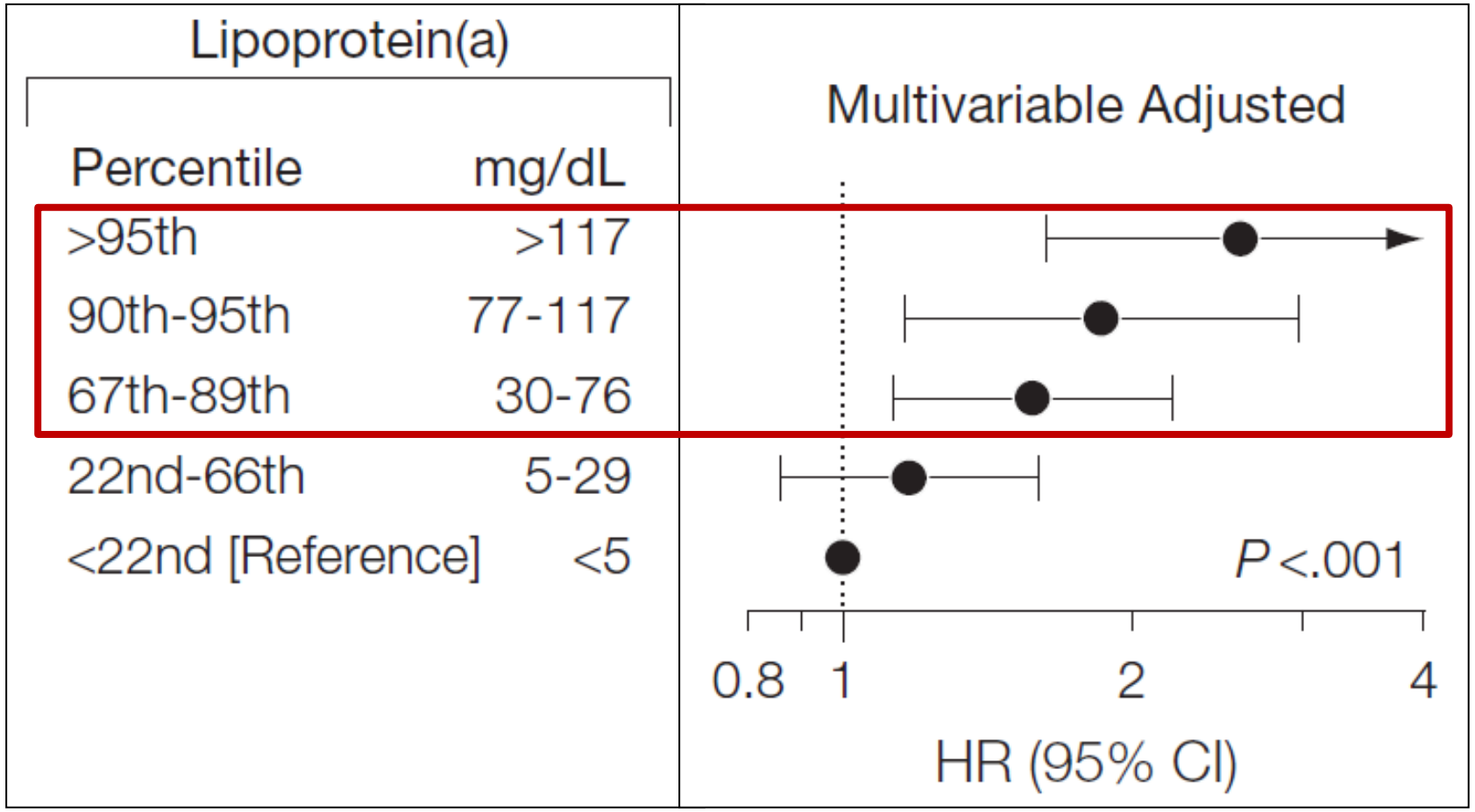
J. Int. Med. 273: 6-30, 2013 (updated)

Lp(a) and risk for myocardial infarction

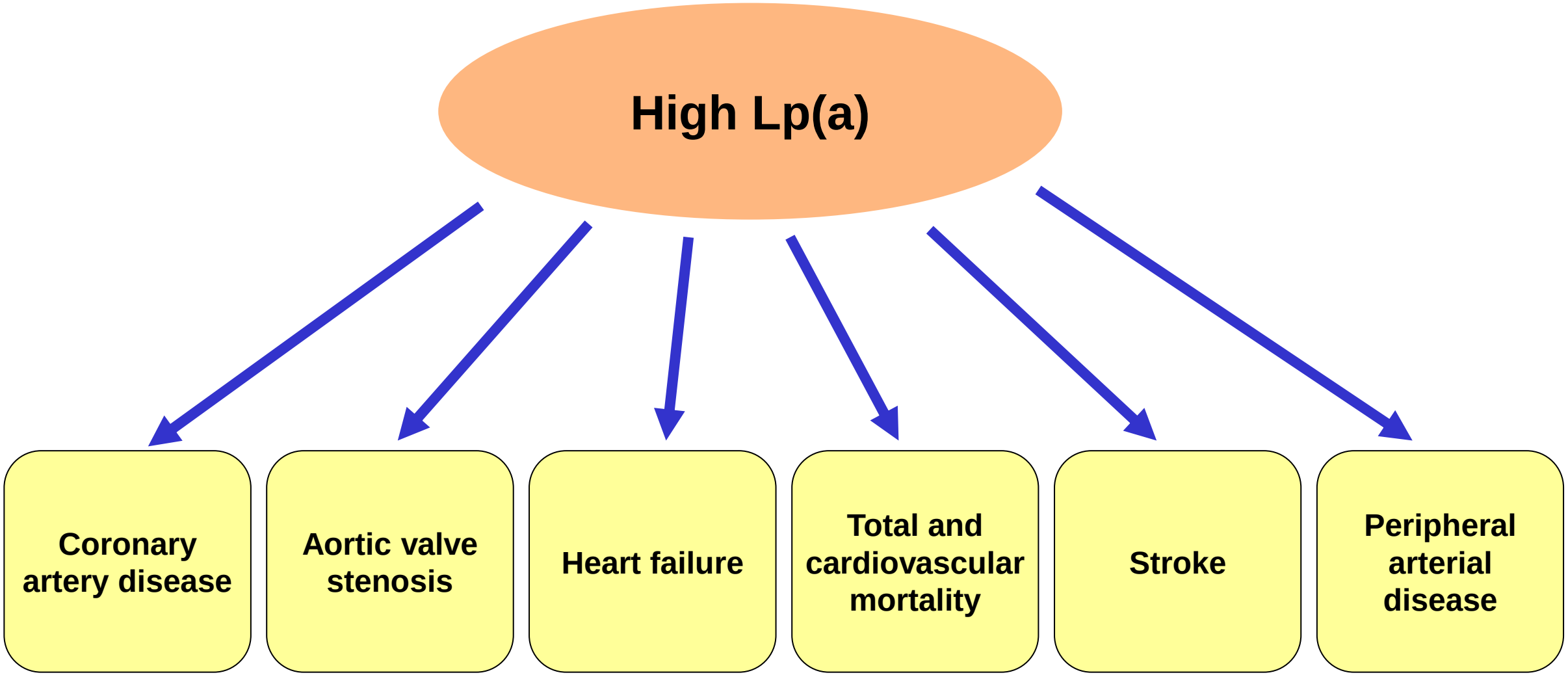
Results from the Copenhagen City Heart Study



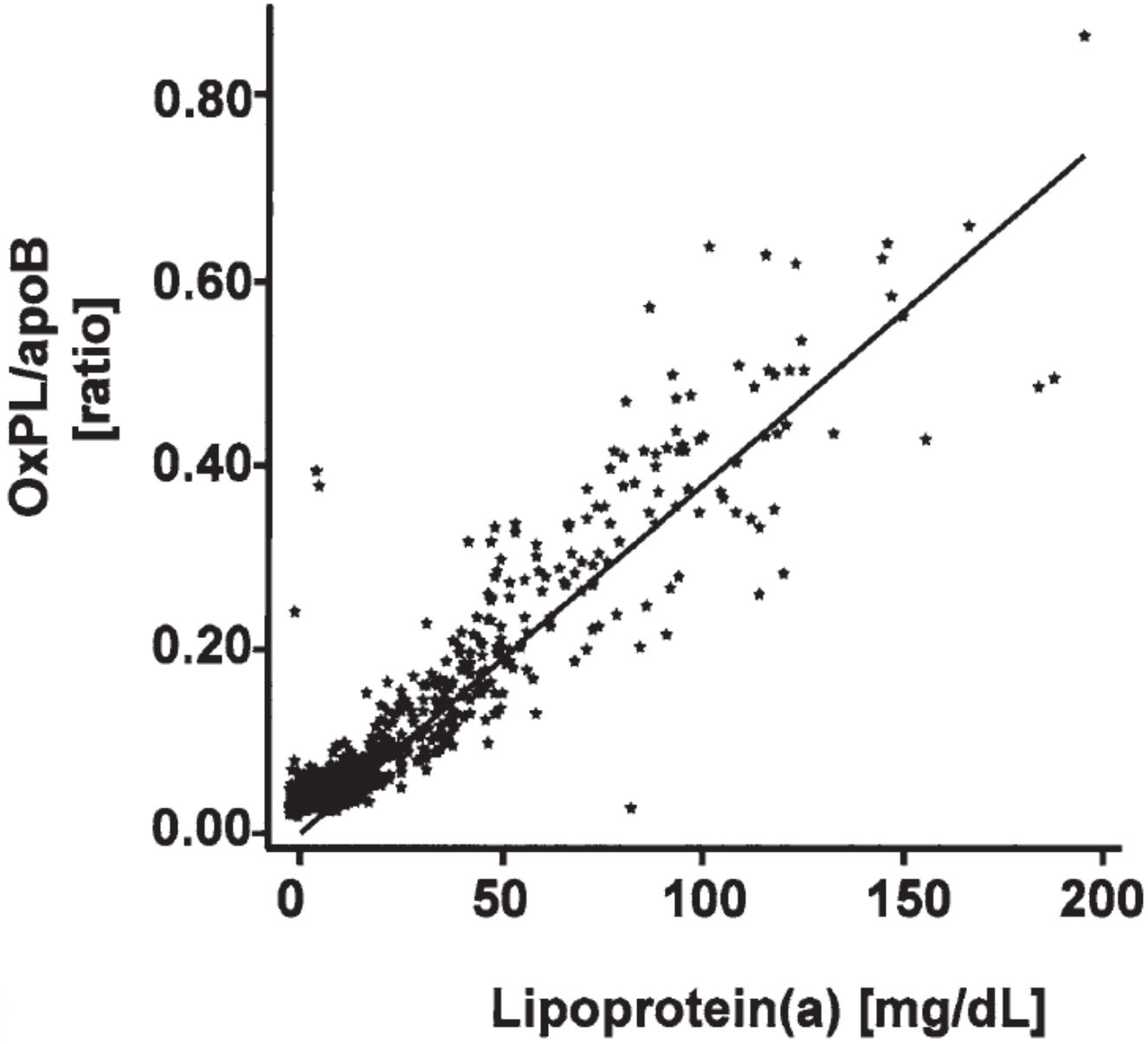
A third of the population!

Kamstrup et al.: JAMA 301:2331-9, 2009

Extension to other clinical outcomes



Oxidized phospolipids: Bruneck Study



→ Role of Lp(a) and OxPL in the inflammation of the arterial wall

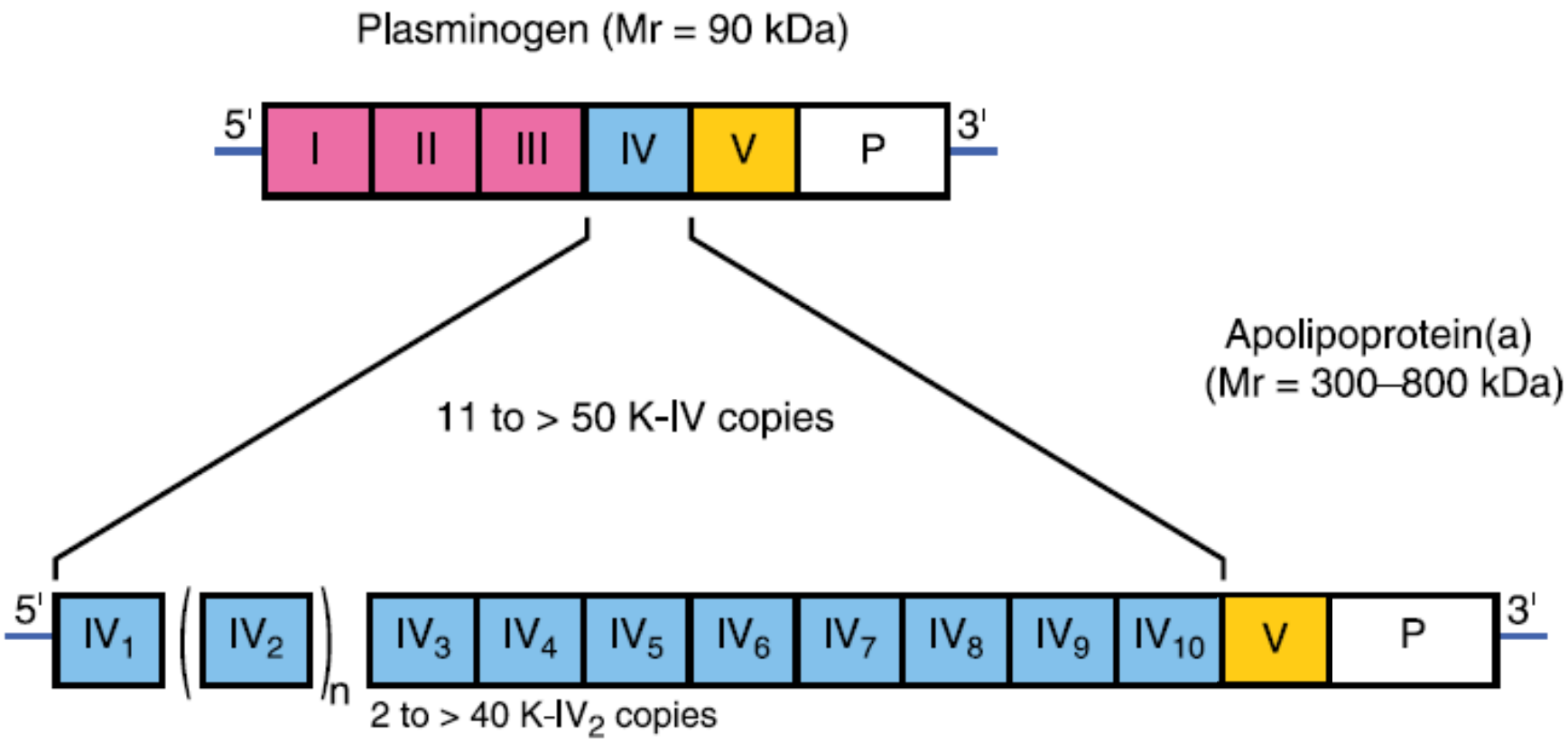
Tsimikas et al.:
J.Am.Coll.Cardiol. 47:2219-28, 2006

Genetic basis of Lp(a)

Lp(a): the lipoprotein with the strongest genetic regulation

- >90% of the Lp(a) concentrations are genetically determined
- Main determinant is the apo(a) size polymorphism
- But additional single nucleotide polymorphisms (SNPs) contribute to the genetic regulation

Molecular basis of apolipoprotein(a)



5.6 kB per K-IV repeat

→ copy number variation (CNV)

→ **hard to resolve with modern sequencing methods (NGS)**

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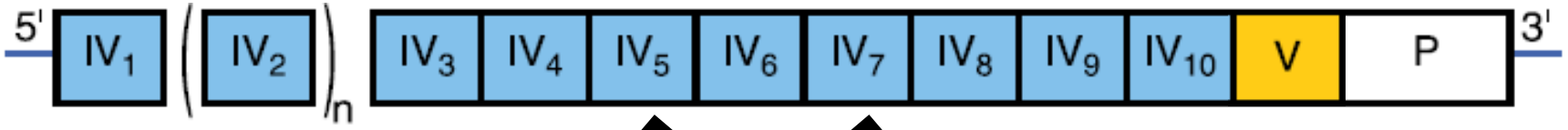
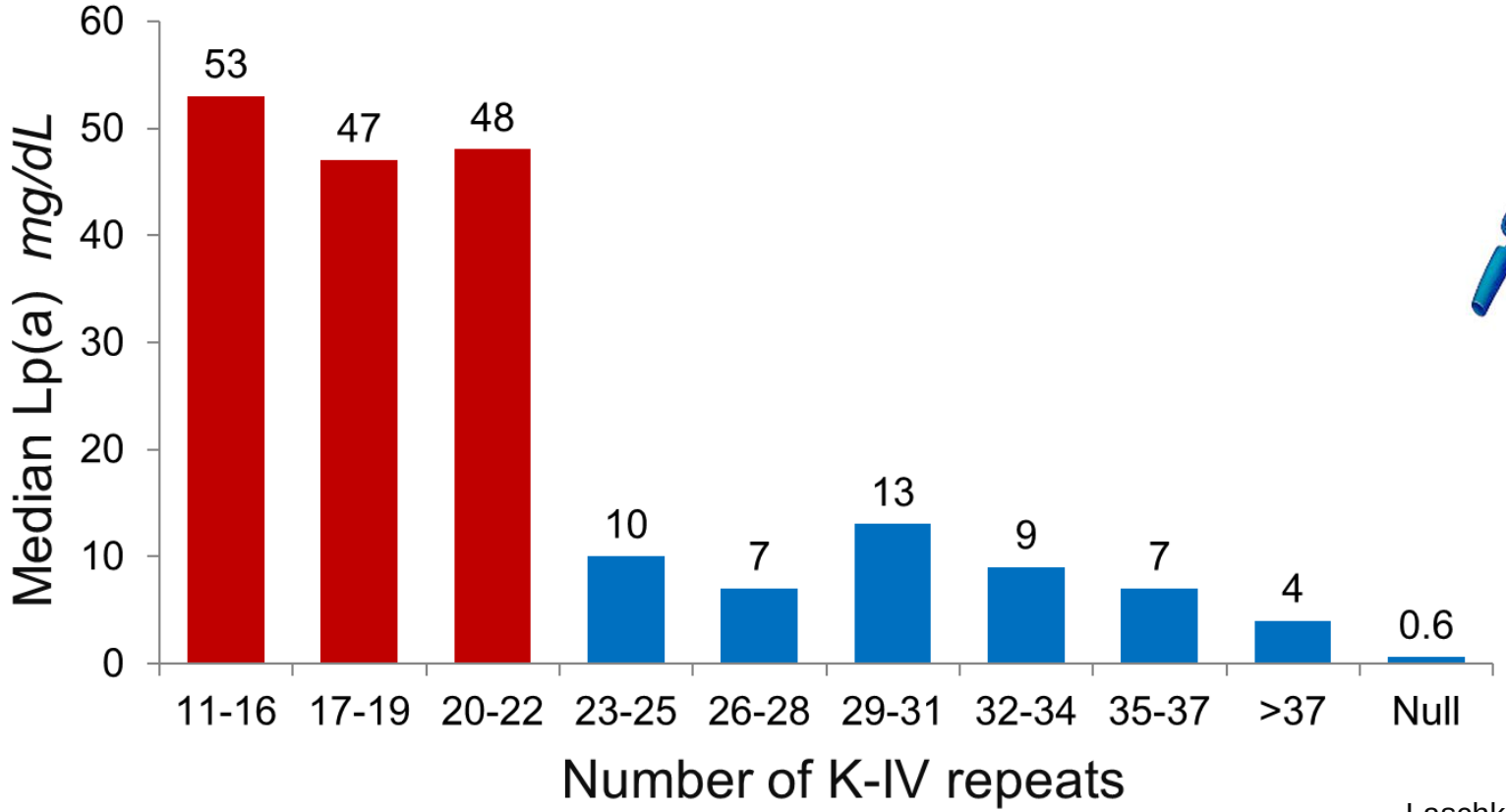
Curr Cardiovasc Risk Reports 6: 12-20, 2012

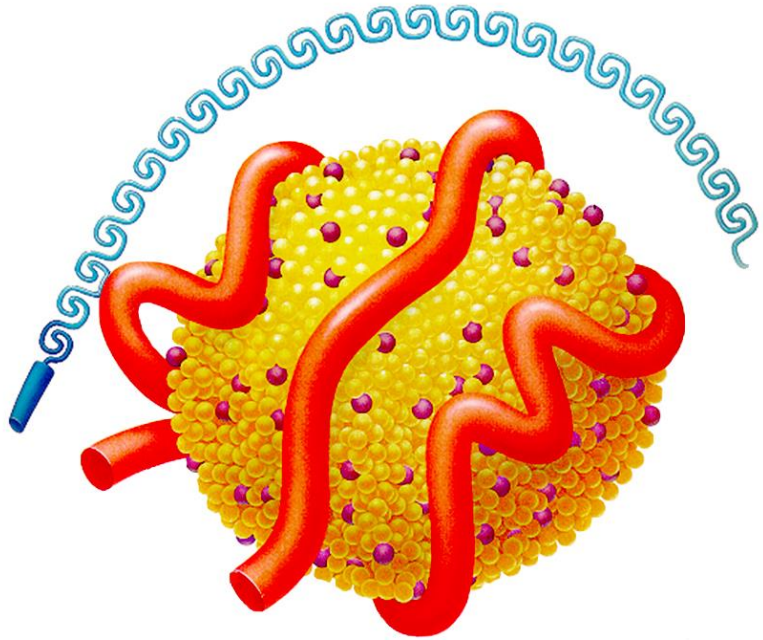
Relation between K-IV repeats and Lp(a) concentrations



11-22 copies = small isoforms

>22 copies = large isoforms





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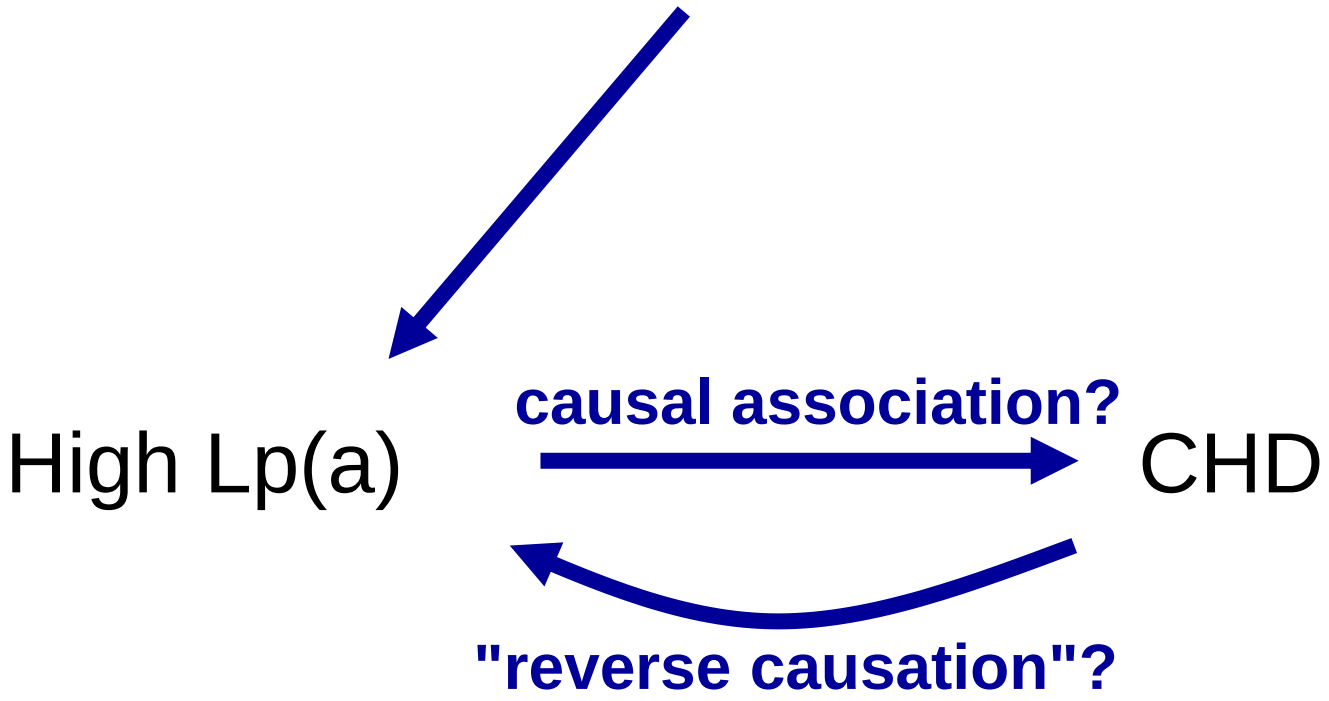
Laschkolnig et al.: Cardiovasc Research 103: 28-36, 2014

Why do we believe that high Lp(a) is a causal risk factor for CHD?

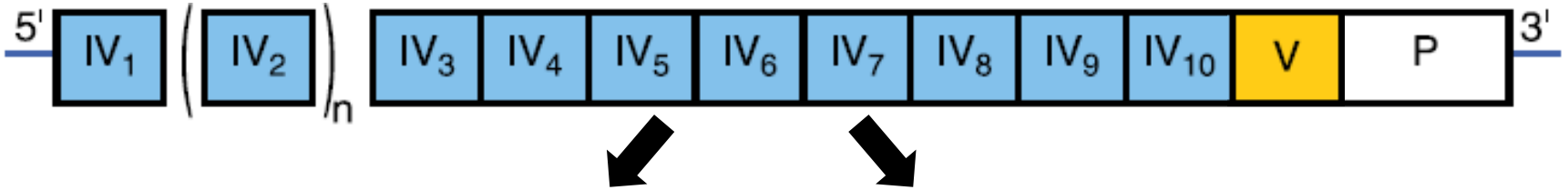
Mendelian randomization studies

Lp(a) and CHD: cause or consequence?

Strong genetic instrument
(=genetic variants)?



K-IV repeat polymorphism: the best example of a genetic instrument



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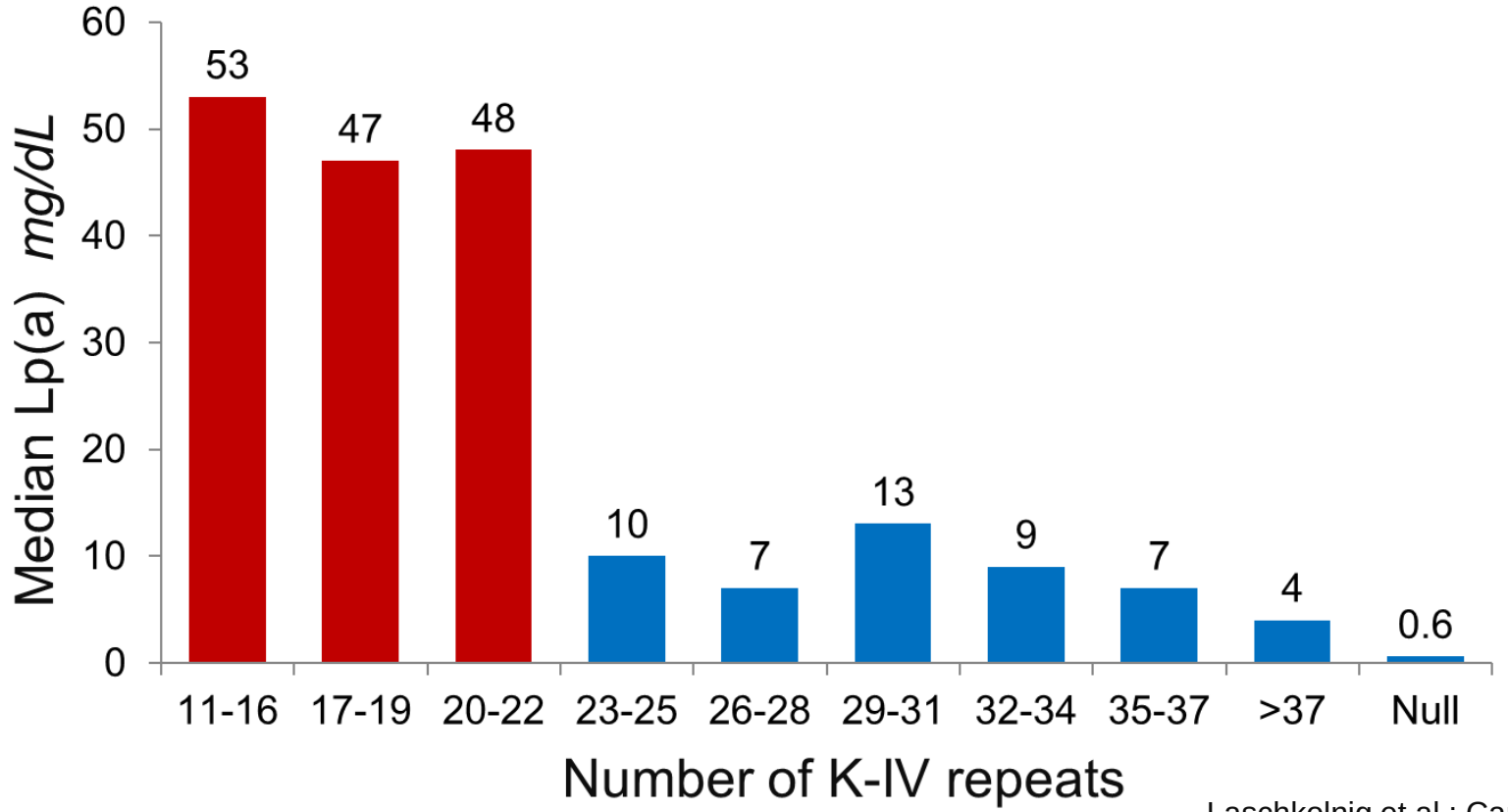

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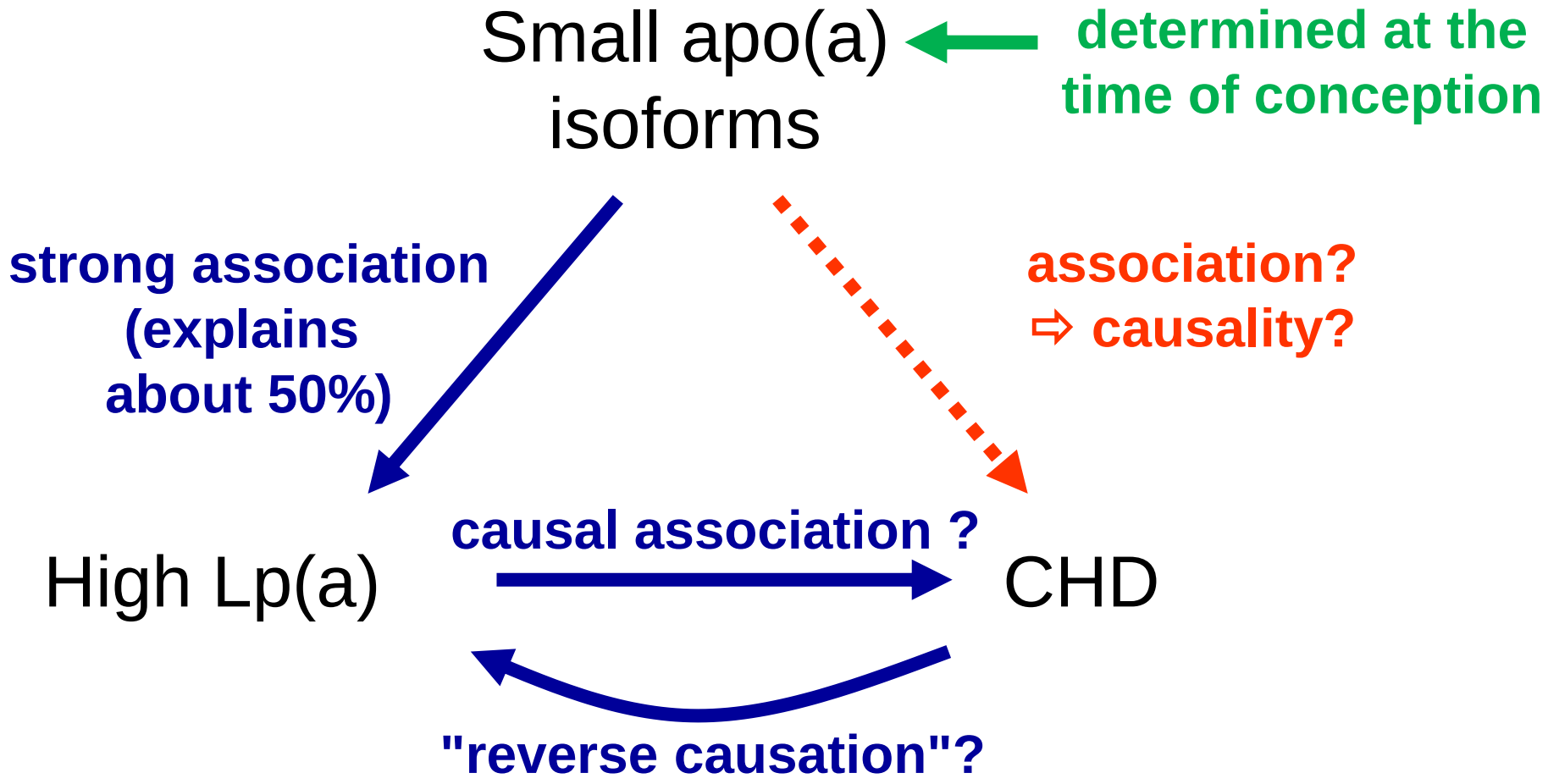
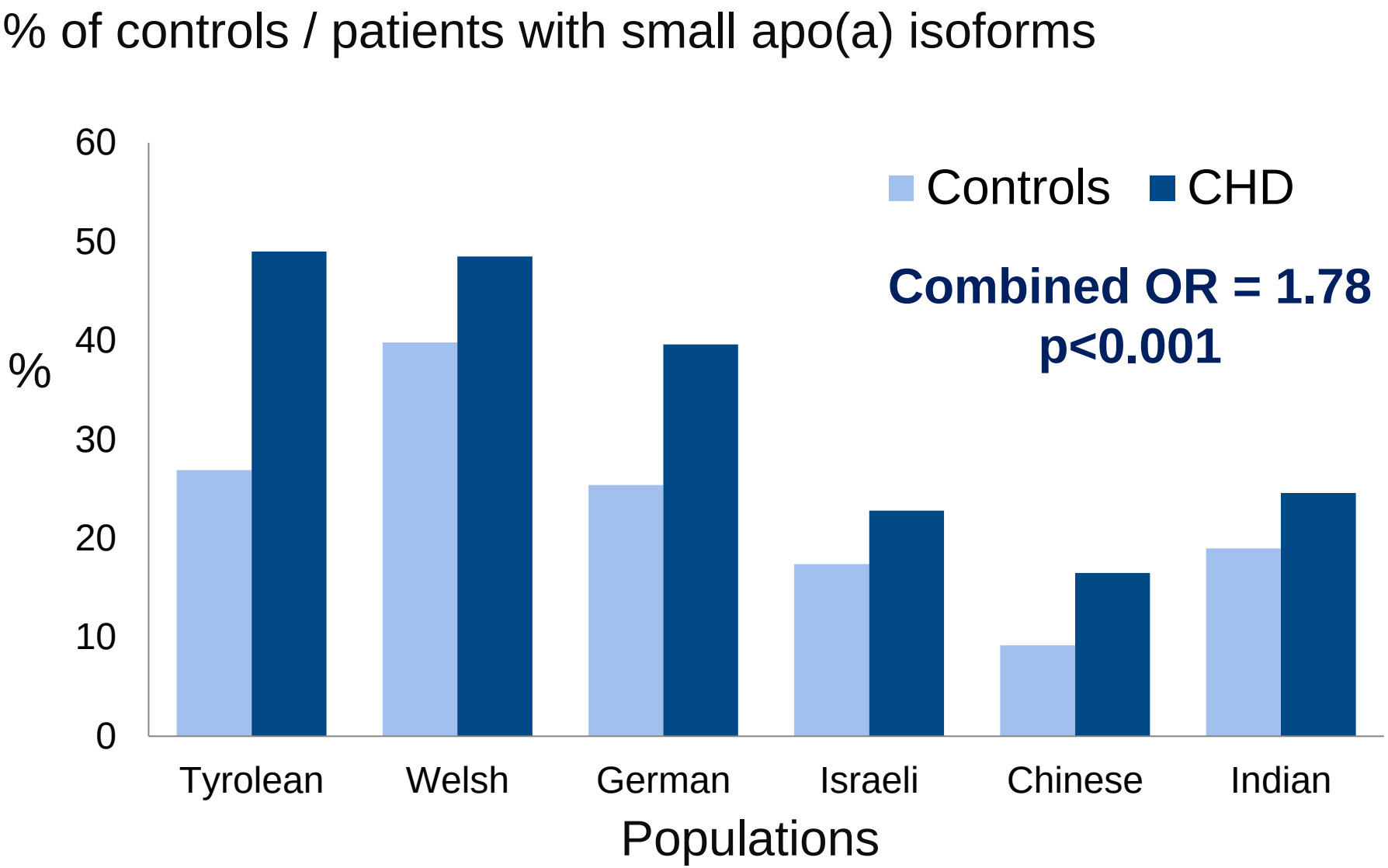
Laschkolnig et al.: Cardiovasc Research 103: 28-36, 2014

Lp(a) and CHD: Mendelian randomization



Do carriers of small apo(a) isoforms more often have CHD?

Apo(a) isoforms and risk for CHD



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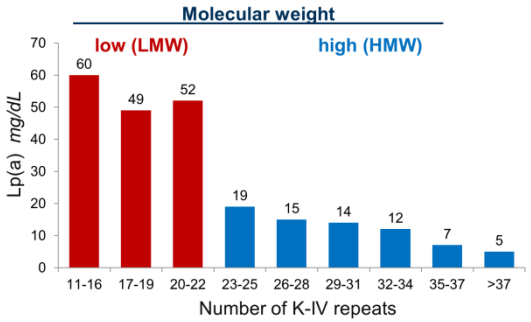
Sandholzer et al.: Arterioscler Thromb 12: 1214-26, 1992

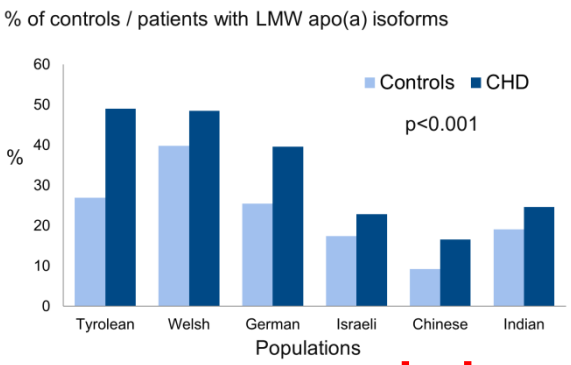
Lp(a) concentrations, apo(a) isoforms and CVD



strong association (explains about 50%)

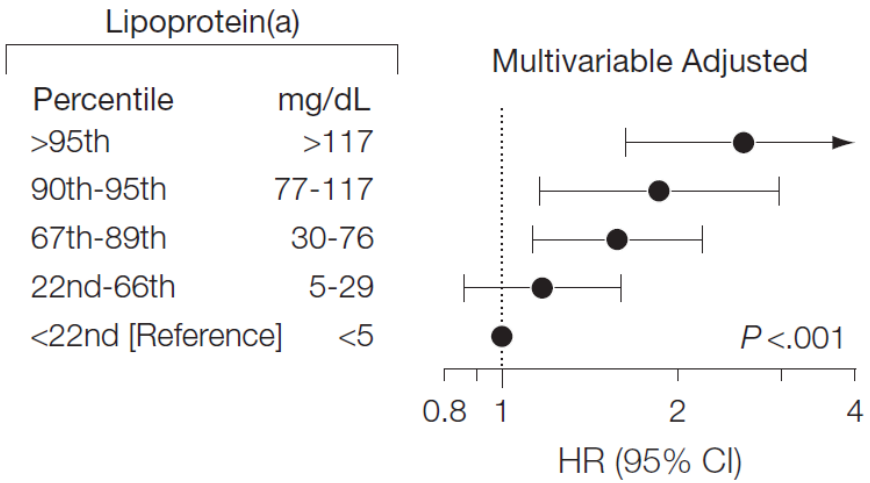
Small apo(a) isoforms

25-35% of the population



strong association

High Lp(a) → **causal association** → **CHD**



Kronenberg: Cardiovasc.Drugs Ther.: 30:87-100, 2016

When should Lp(a) be tested?

Synopsis of recent various guidelines …

- **<u>Lp(a) should be measured in subjects with intermediate or high risk for CVD or CHD</u>**
  - Personal history of premature CVD (especially when no other risk factors are present)
  - In persons with moderate to high risk of CVD using various scoring systems
  - Recurrent CVD despite statin therapy
  - Familial hypercholesterolemia or other genetic genetic dyslipidemias
  - Family history of premature CVD
  - Family history of high Lp(a)

But there are changes going on …

New dyslipidemia guidelines

ESC/EAS GUIDELINES

2019

Lp(a) measurement should be considered at least once in each adult person's lifetime

Eur.Heart J. 41:111-188, 2020

Canadian Cardiovascular Society
Leadership. Knowledge. Community.

2021

We recommend measuring Lp(a) level once in a person's lifetime as a part of the initial lipid screening.

Can.J.Cardiol (in press)

doi: 10.1016/j.cjca.2021.03.016

Idea behind: don't wait until the first event occurs

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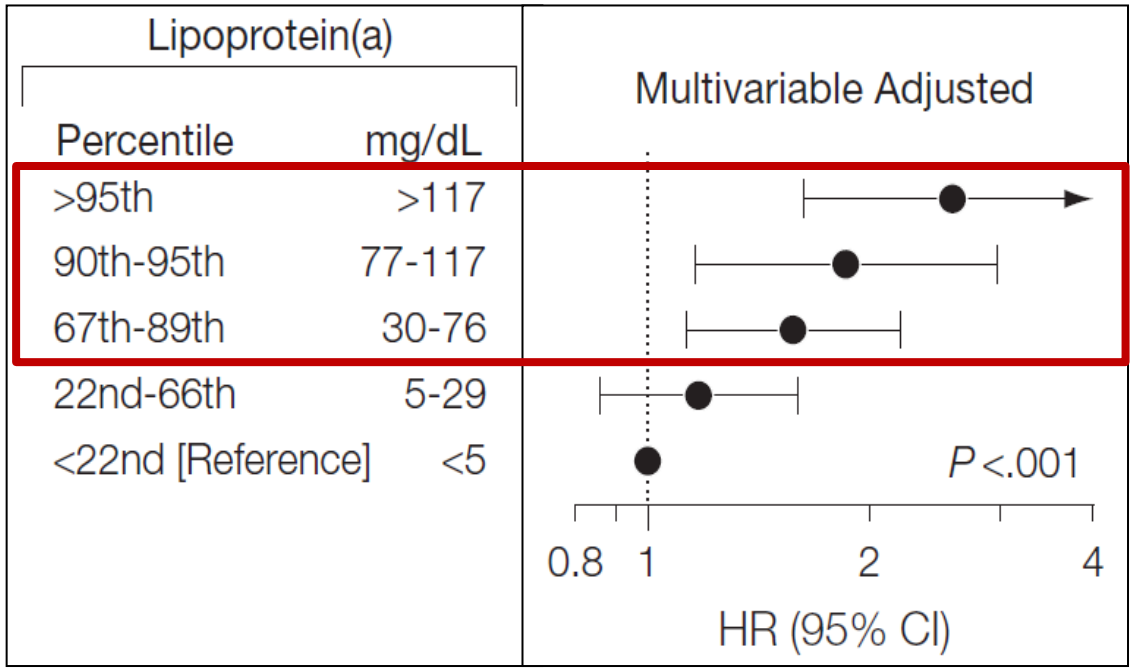
Concluding remarks



Kamstrup et al.: JAMA 301:2331-9, 2009

Strong support by genetic data

Need to test for Lp(a)

Recent Guidelines:

Measure Lp(a) level at least once in a person's lifetime

See the results always in context with other risk factors

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