Why focus on Lipoprotein (a)

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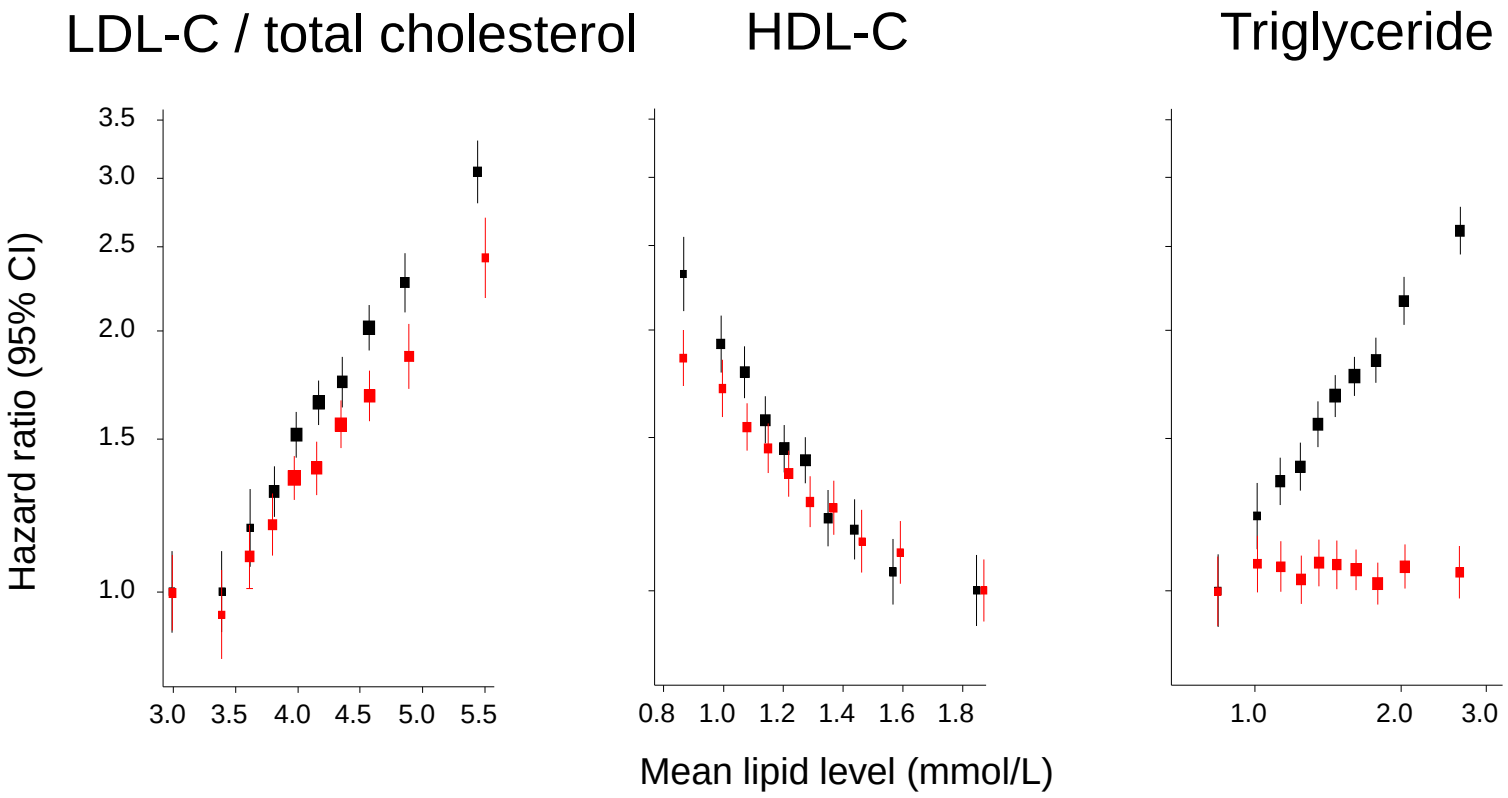
Duality of Interest Declaration

Consultant or speaker for:
Amgen, AstraZeneca, Boehringer Ingelheim, Eli Lilly, Janssen, Novo Nordisk, Pfizer, Sanofi

Grants: Boehringer Ingelheim, Novartis, Roche

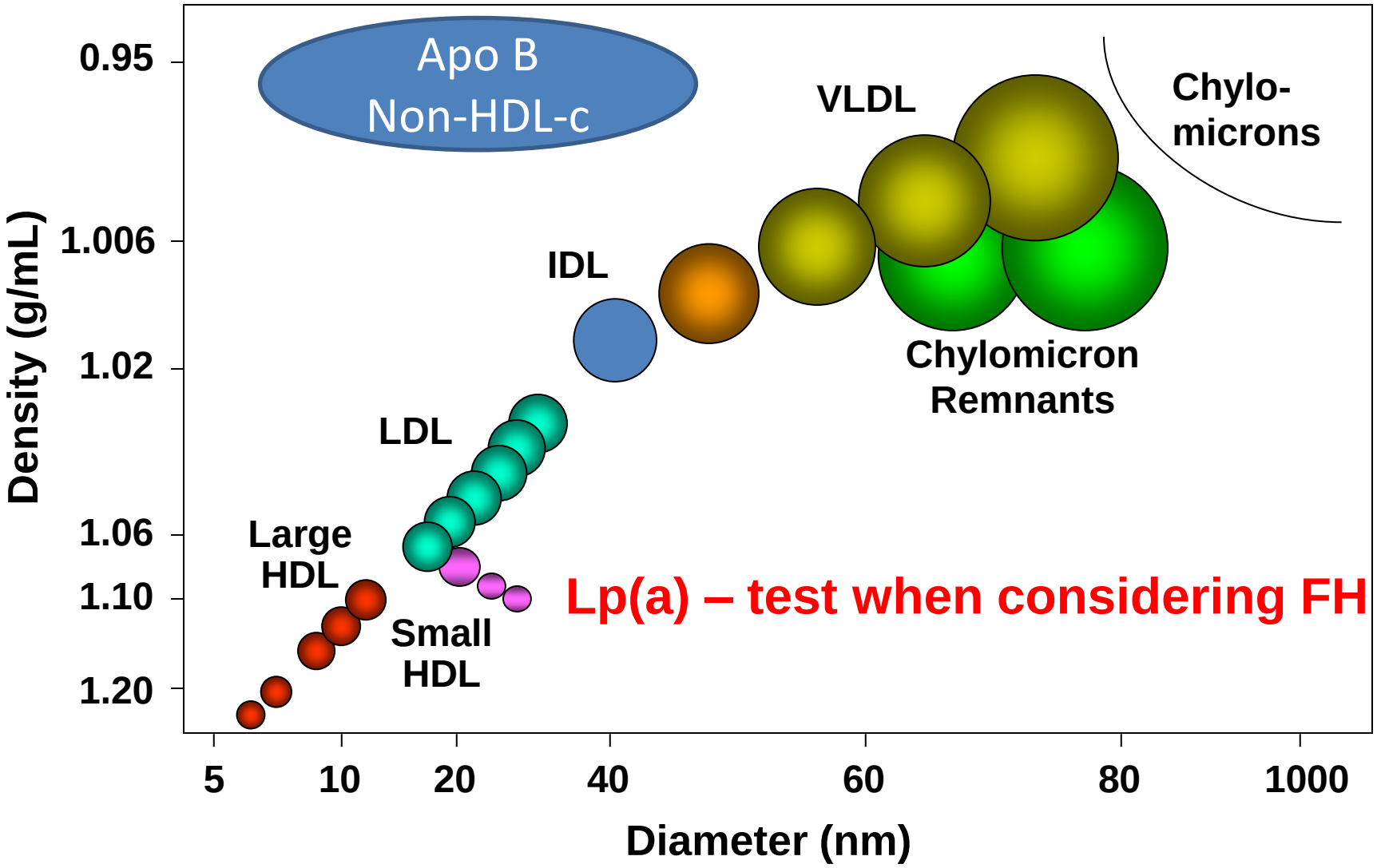
What is the "dependence" of associations with coronary heart disease?

300,000 participants, 13,000 incident CHD outcomes



Sarwar et al. ERFC, *JAMA* 2009

Lipoproteins – increases in one but can be multiple



Adapted from Segrest JP. *Adv Protein Chem*. 1994;45:303-369.

What is Lipoprotein (a) ?

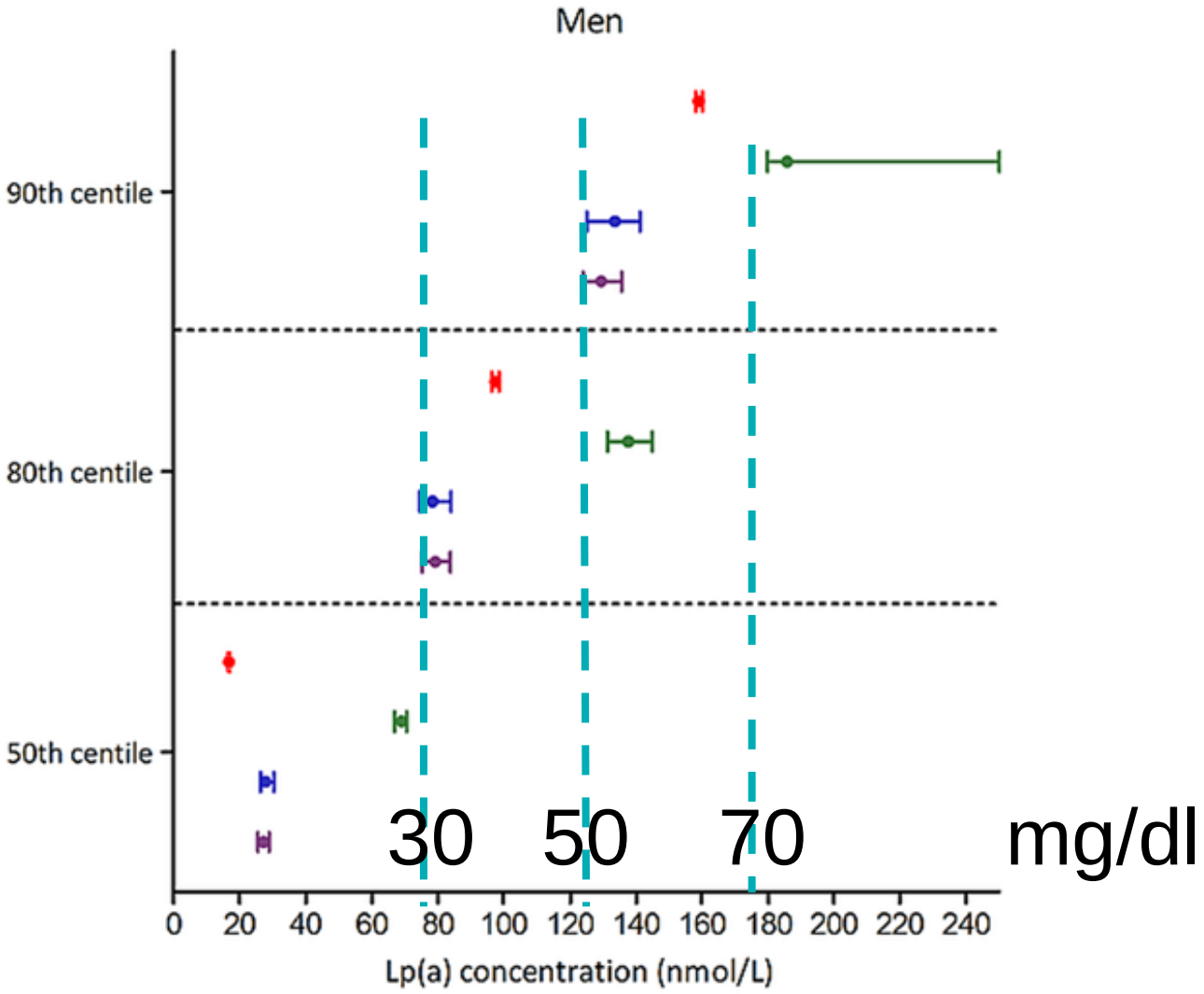
- A LDL particle made by the liver, comprised of both an apolipoprotein(a) and an **apolipoprotein B protein**
- 80–90% **genetic** / Stable across life course
  - Genetic support it to be causal for Cardiovascular disease
  - Not uncommon reason for raised measured LDL-cholesterol
- **Rarely measured** outside specialist lipid clinics in many countries

Results from UK biobank
415K people with Lipoprotein(a) measured

Lp(a)	Lp(a)	Lp(a)	*P*-value for trend
	<20 nmol/L	**20–99.9 nmol/L**	**≥100 nmol/L**
	***n* = 207 908**	***n* = 119 894**	***n* = 85 932**
Age (years)	56.3 ± 8.2	56.7 ± 8.1	56.9 ± 8.0
Male sex (%)	101 214 (48.7%)	52 542 (43.8%)	37 403 (43.5%)
SBP(mmHg)	137.9 ± 18.6	137.7 ± 18.7	138.4 ± 18.7
Total chol (mmol/L)	5.59 (1.12)	5.75 (1.15)	5.86 (1.18)
Baseline CVD (%)	5.4%	5.8%	7.7%
Statin use (%)	15.0%	15.5%	20.2%

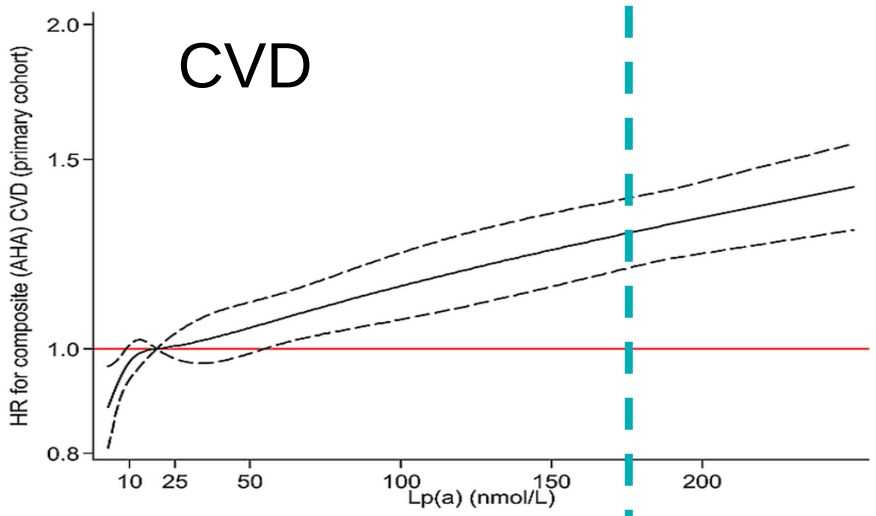
Welsh et a l (2020) EJPC

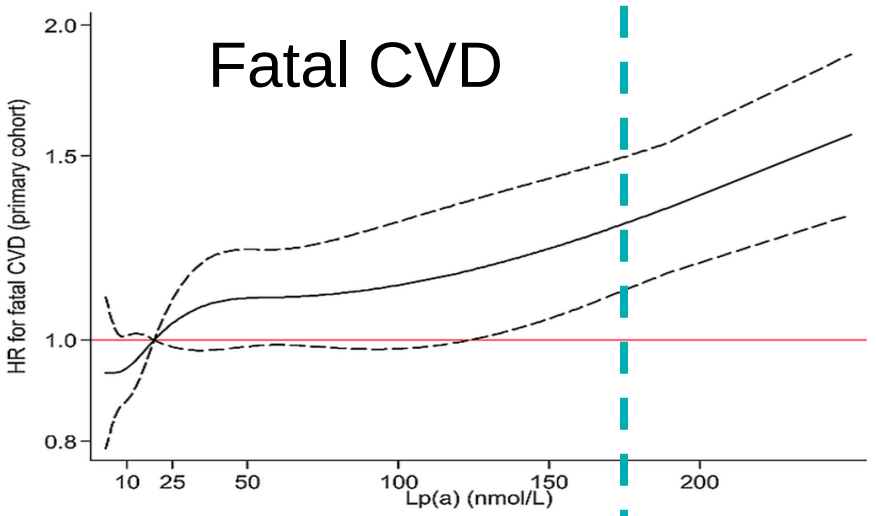
Lipoprotein (a) levels in the UK Biobank population

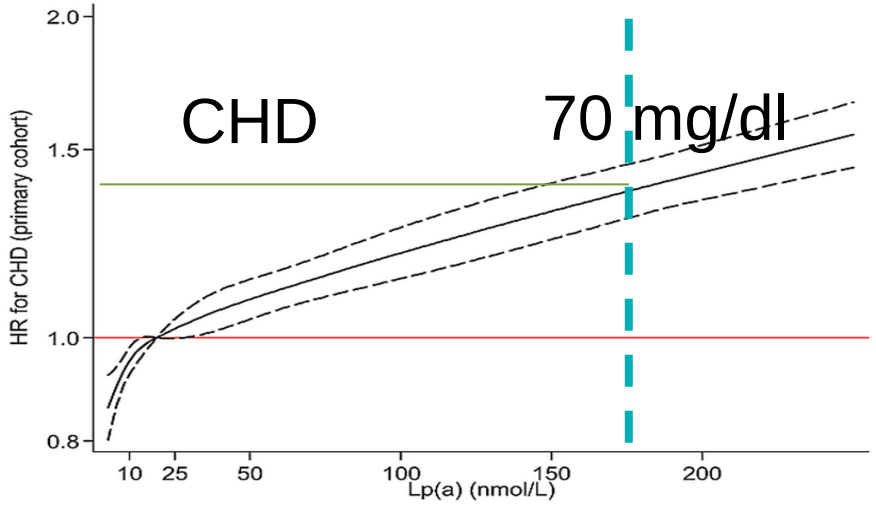


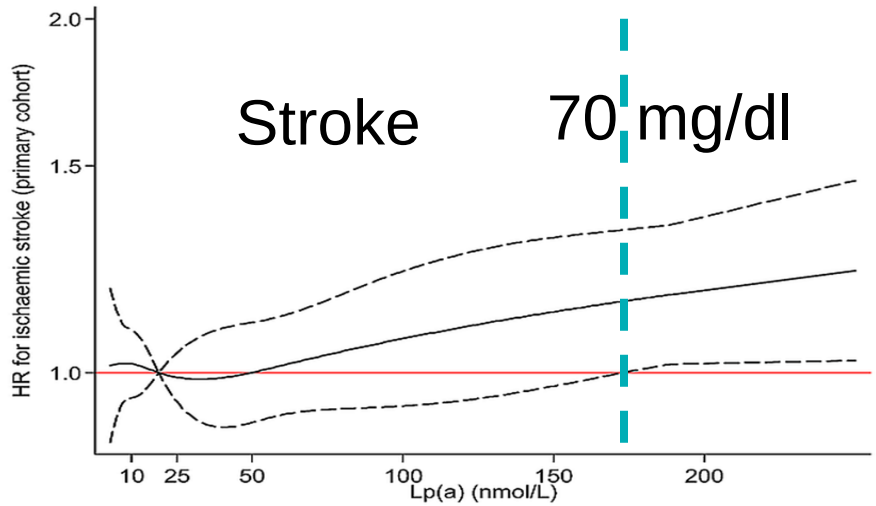
Welsh et a l (2020) EJPC

Lipoprotein (a) associations with cardiovascular outcome in UK Biobank



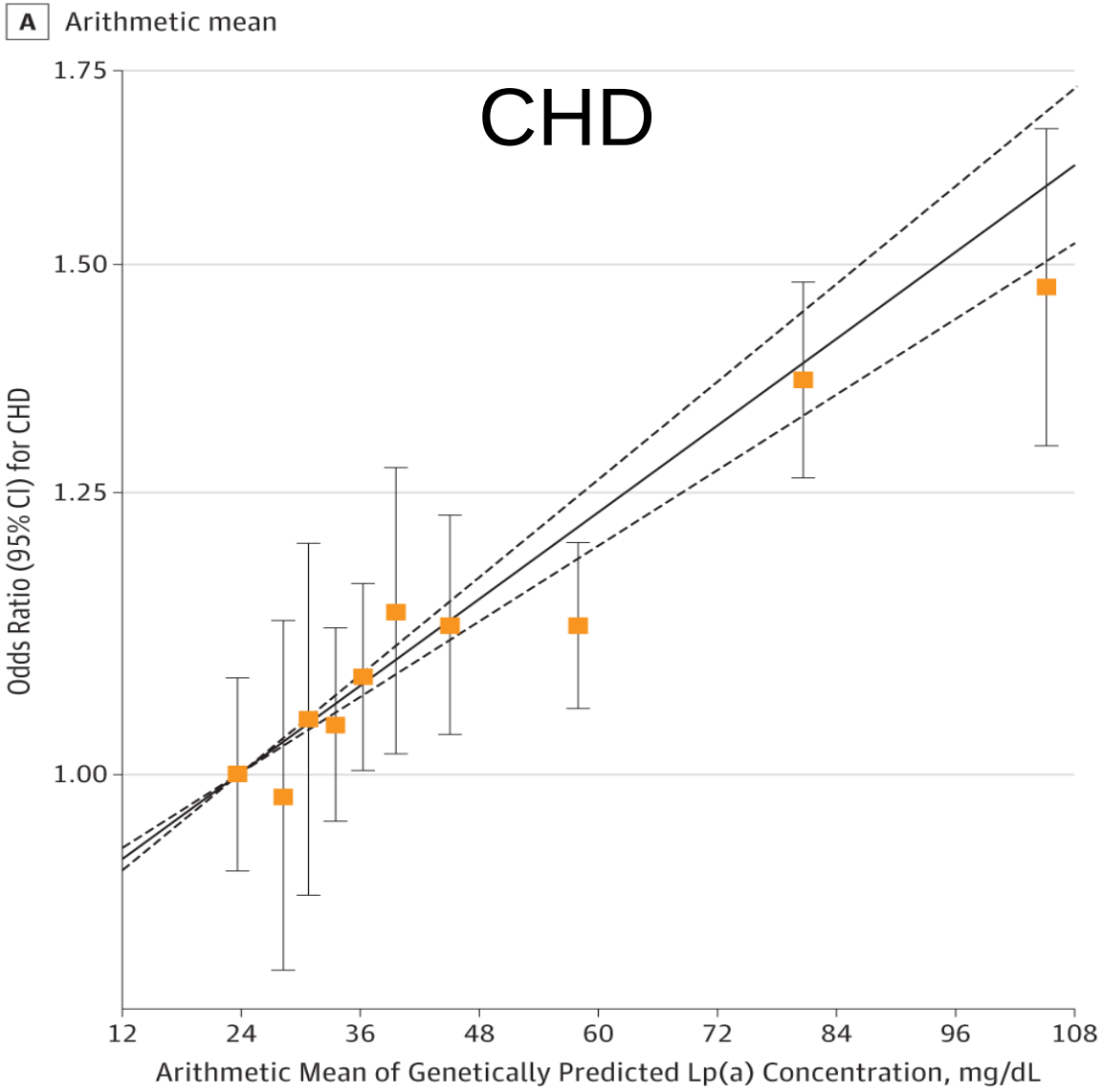






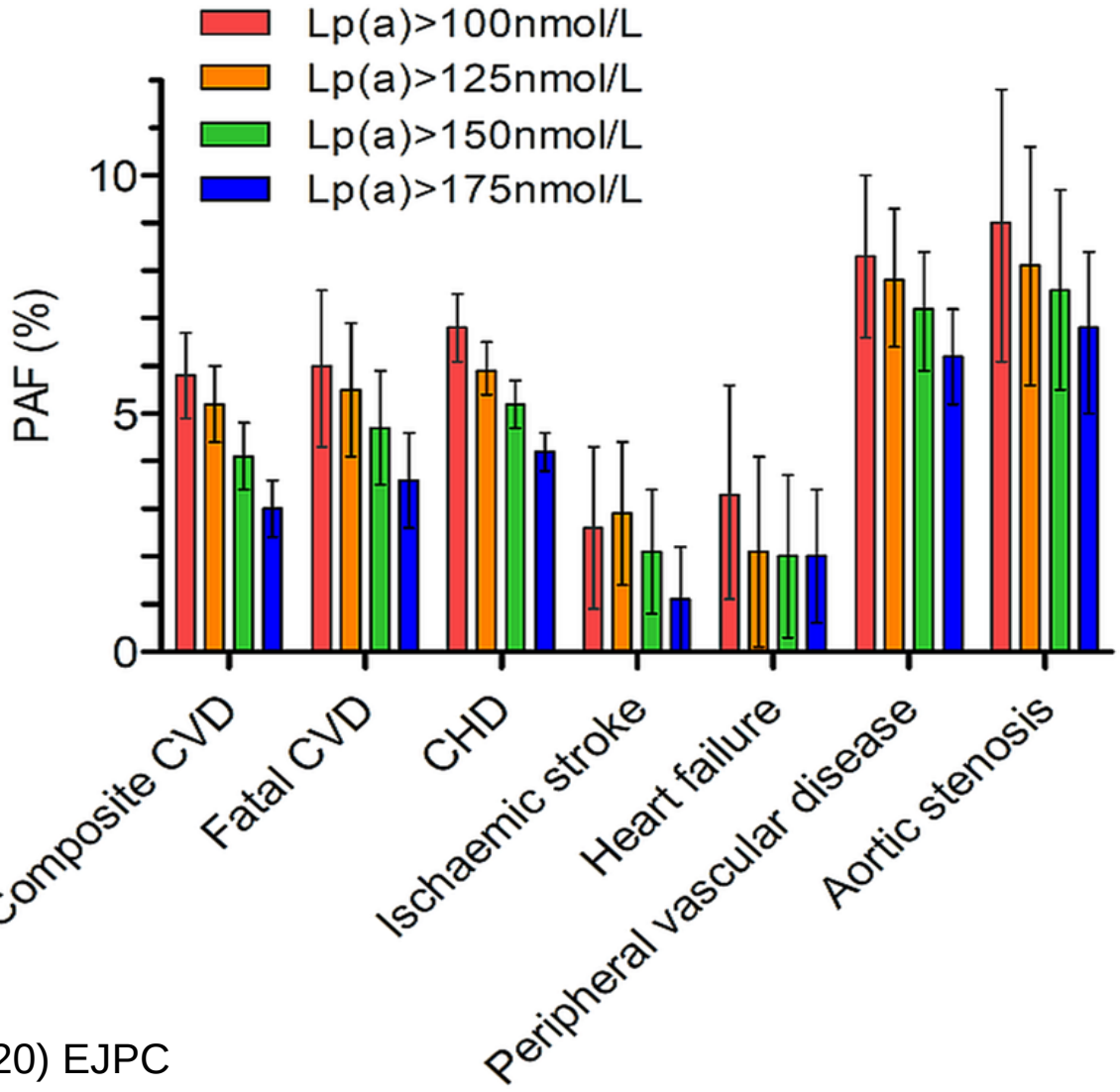
Welsh et al (2020) EJPC

Genetically predicted Lipoprotein and CHD risk



Burgess et al (2018)
JAMA-Cardiology

Population attributable fractions for Lipoprotein (a) for different CV outcomes using UK Biobank



Welsh et a l (2020) EJPC

What could we hope to achieve with Lp(a) reduction ?

- In UKBB
- Baseline CVD ($n = 24\,647$)
  - CVD event rate 11.7 (95% CI 11.3–12.2) per 1000 person years.
  - $n = 3568$ had an Lp(a) above 175 nmol/L (~70mg/dl)
  - Lp(a) reductions ~80% estimated to
  - ↓ CVD risk 20.0% (95% CI 2.1–34.6%)
  - ↓ CHD risk by 24.4% (95% CI 13.5–33.9%)

Welsh et a l (2020) EJPC

Summary

- **High Lipoprotein(a) adds atherogenic risk**
- **Levels >70mg/dl (~175 nmol/l) increase CVD risk ~25-40% relative to ~7-10mg/dl**
  - Such levels may be present in **>14% of people** with CVD
  - Partially picked up due to higher than expected Total and LDL-cholesterol levels, shown not to be FHC
- **Need trial evidence for benefits of its reduction**
- **Time to measure more widely?**
  - Esp. when LDL-c raised, or less clear reasons for an event