Sademi
Sociedad Andaluza de Medicina Interna

Fademi
Fundación Andaluza de Medicina Interna

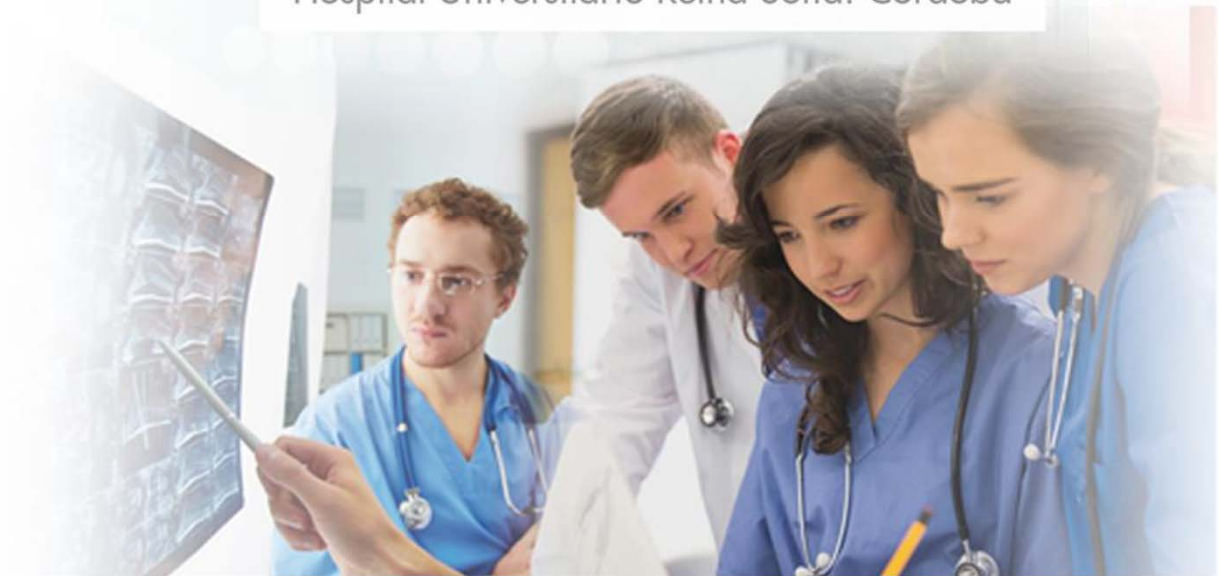
XXXIII

Congreso Sociedad Andaluza de Medicina Interna (SADEMI)

IV Encuentro de Enfermería de Medicina Interna de Andalucía

8, 9 y 10 de Junio de 2017

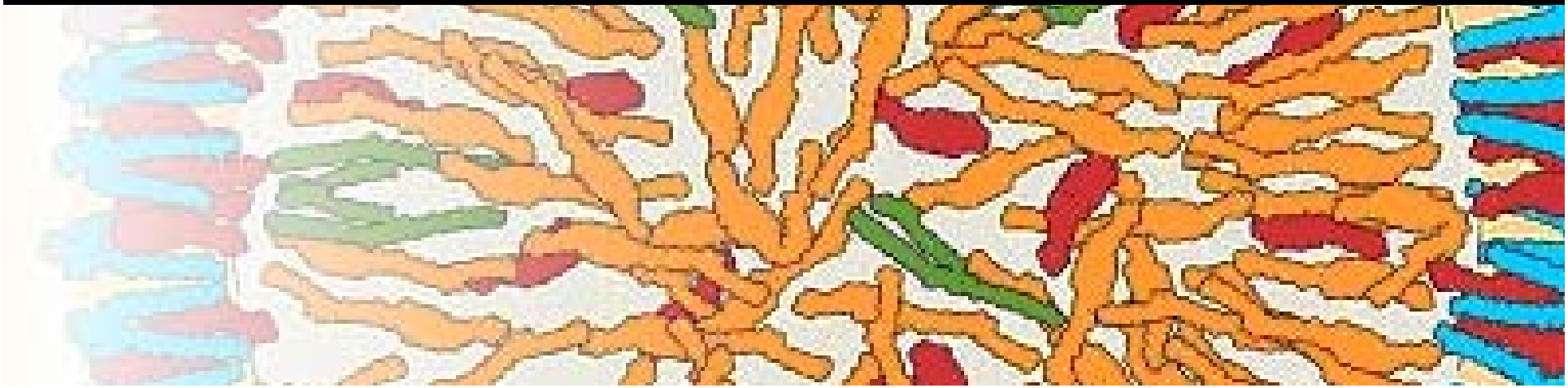
Hospital Universitario Reina Sofía. Córdoba



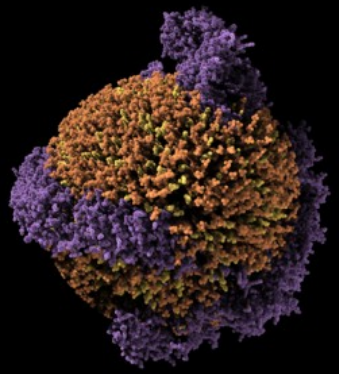
Cardiovascular risk beyond LDL-cholesterol - Lp(a) and remnant cholesterol

Marianne Benn, MD, PhD DMSc, Department of Clinical Biochemistry, Rigshospitalet,

Copenhagen, Denmark



Observational studies
In-vitro and animal studies
Genetic studies
Randomised clinical intervention trials



LDL cholesterol

Causal

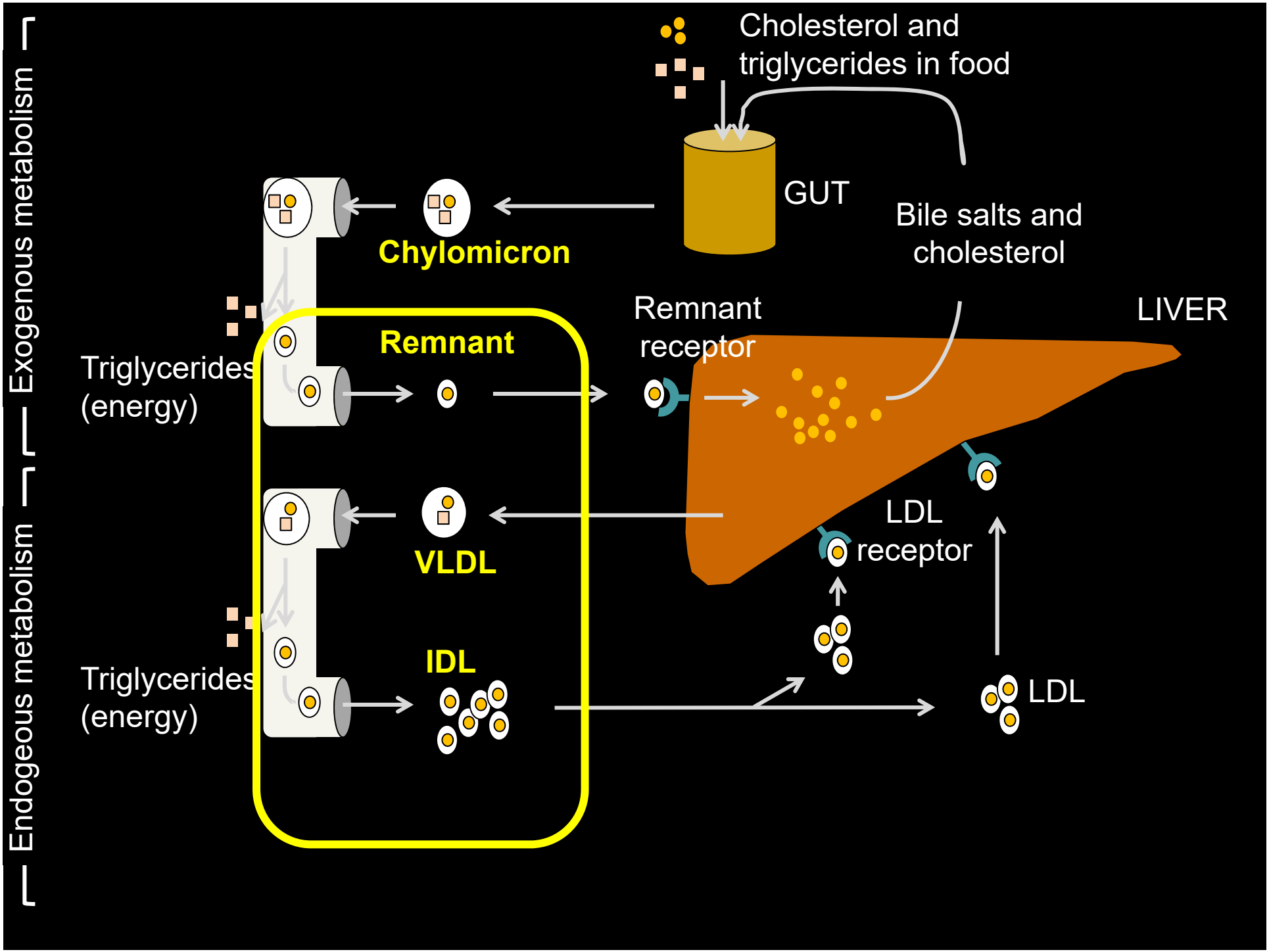
Cardiovascular disease

Residual risk of cardiovascular disease after LDL-C lowering

Cholesterol in other types of lipoproteins?

Remnant particles? Lipoprotein(a)?

Remnant cholesterol


Exogenous metabolism
Endogeous metabolism
Cholesterol and triglycerides in food
GUT
Bile salts and cholesterol
Chylomicron
Remnant
Remnant receptor
LIVER
Triglycerides (energy)
VLDL
LDL receptor
IDL
Triglycerides (energy)
LDL

Remnant cholesterol

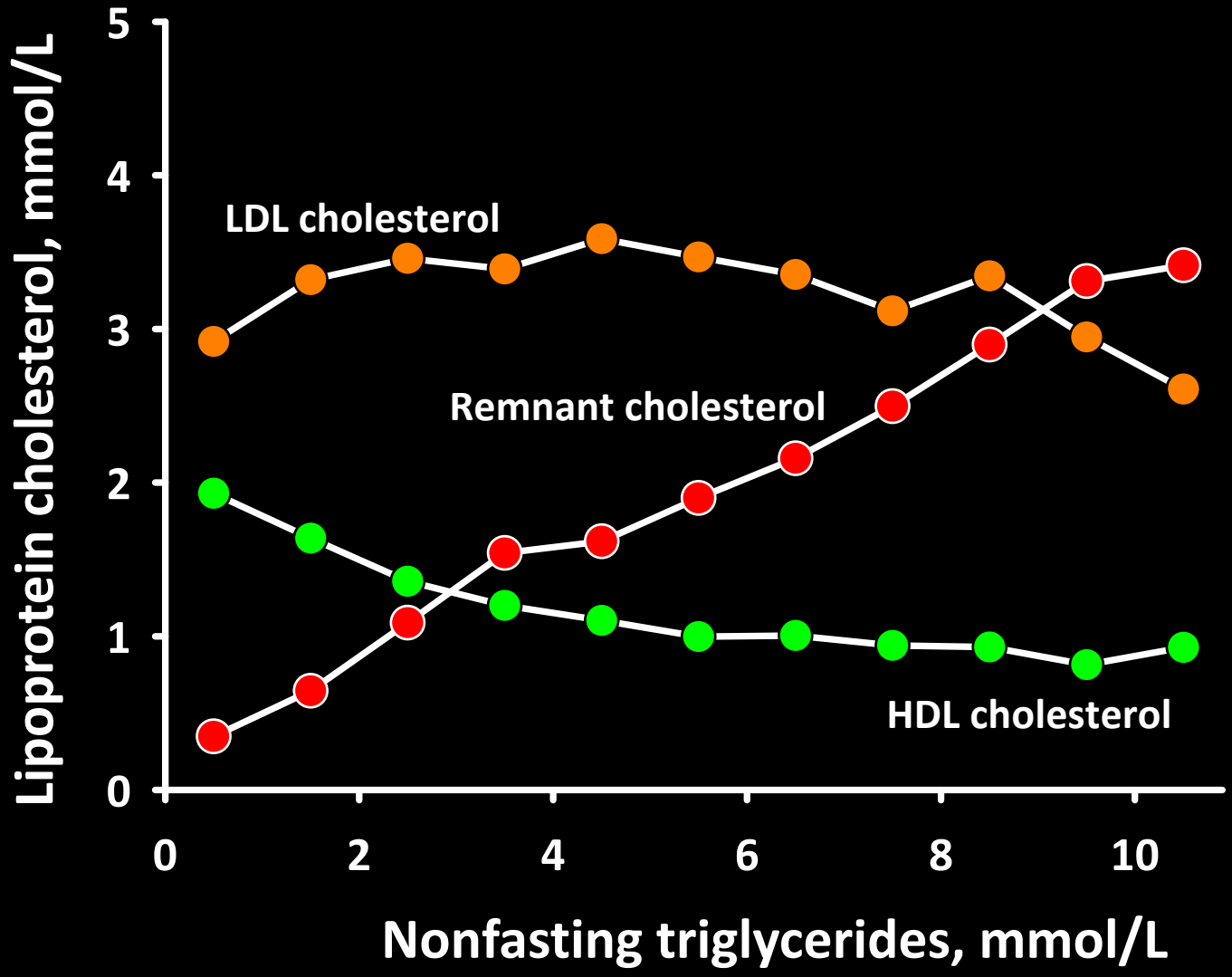
Cholesterol content of the triglyceride-rich lipoproteins (remnants)

Calculated:

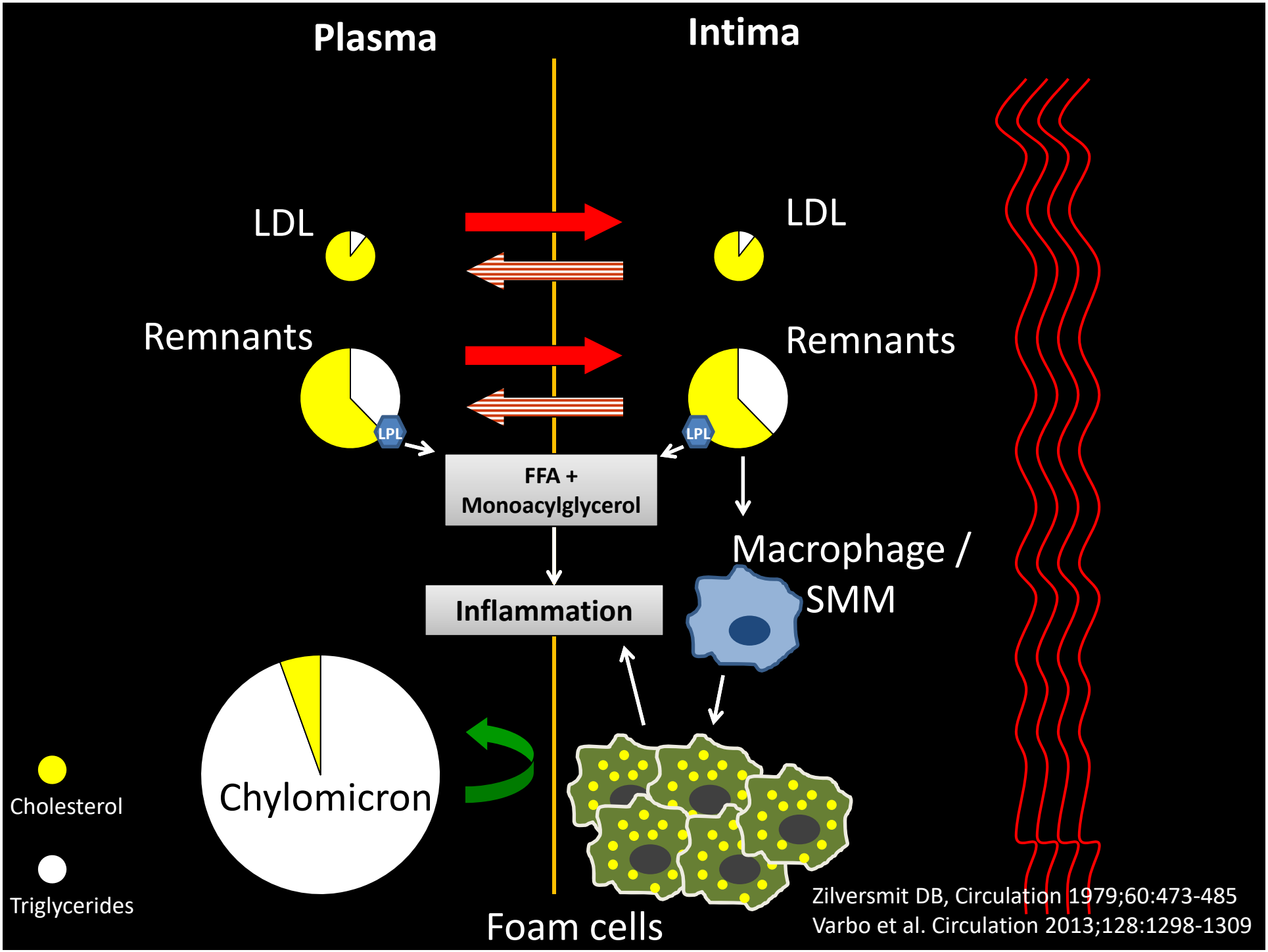
Total cholesterol – LDL cholesterol – HDL cholesterol

Copenhagen General Population Study

N = 84,177

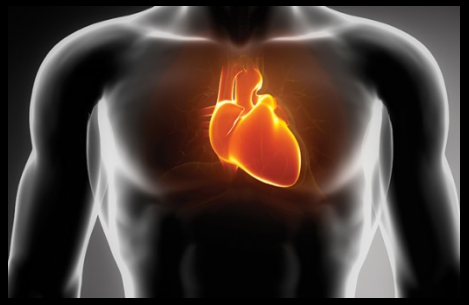


Nordestgaard et al. Lancet 2014; 384: 626-635

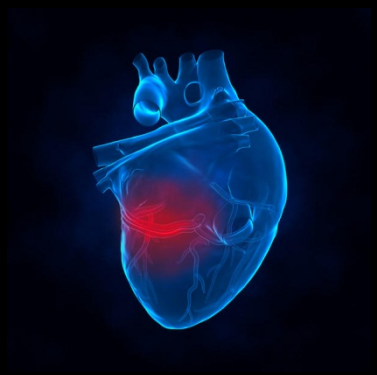

Plasma
Intima
LDL
LDL
Remnants
Remnants
LPL
LPL
FFA +
Monoacylglycerol
Macrophage /
SMM
Inflammation
Chylomicron
Cholesterol
Triglycerides
Foam cells
Zilversmit DB, Circulation 1979;60:473-485
Varbo et al. Circulation 2013;128:1298-1309

Hypotheses

Remnant cholesterol



Ischemic heart disease



Myocardial infarction

All-cause mortality

Methods

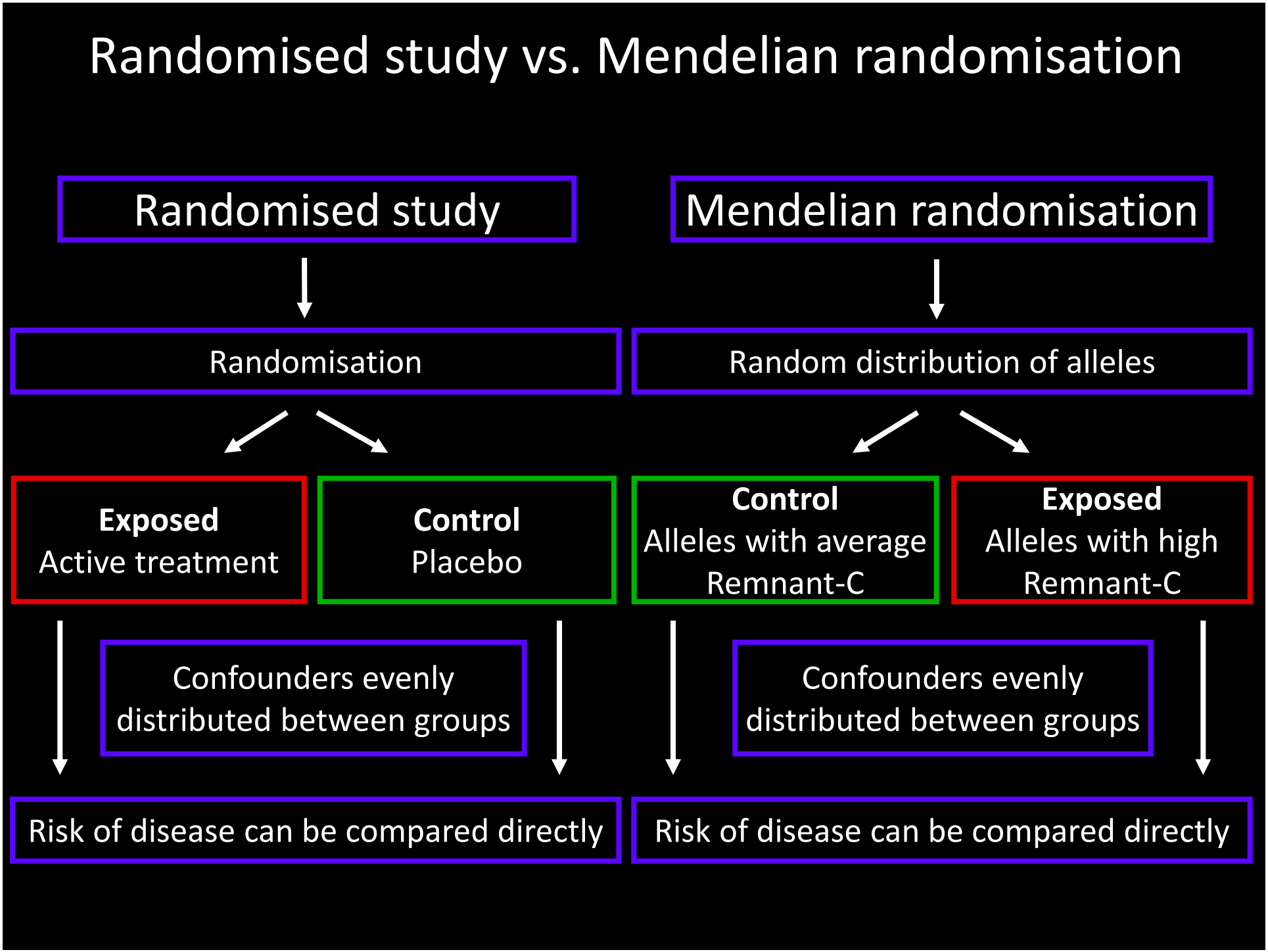
N≈14,000

Copenhagen City Heart Study 1976-78

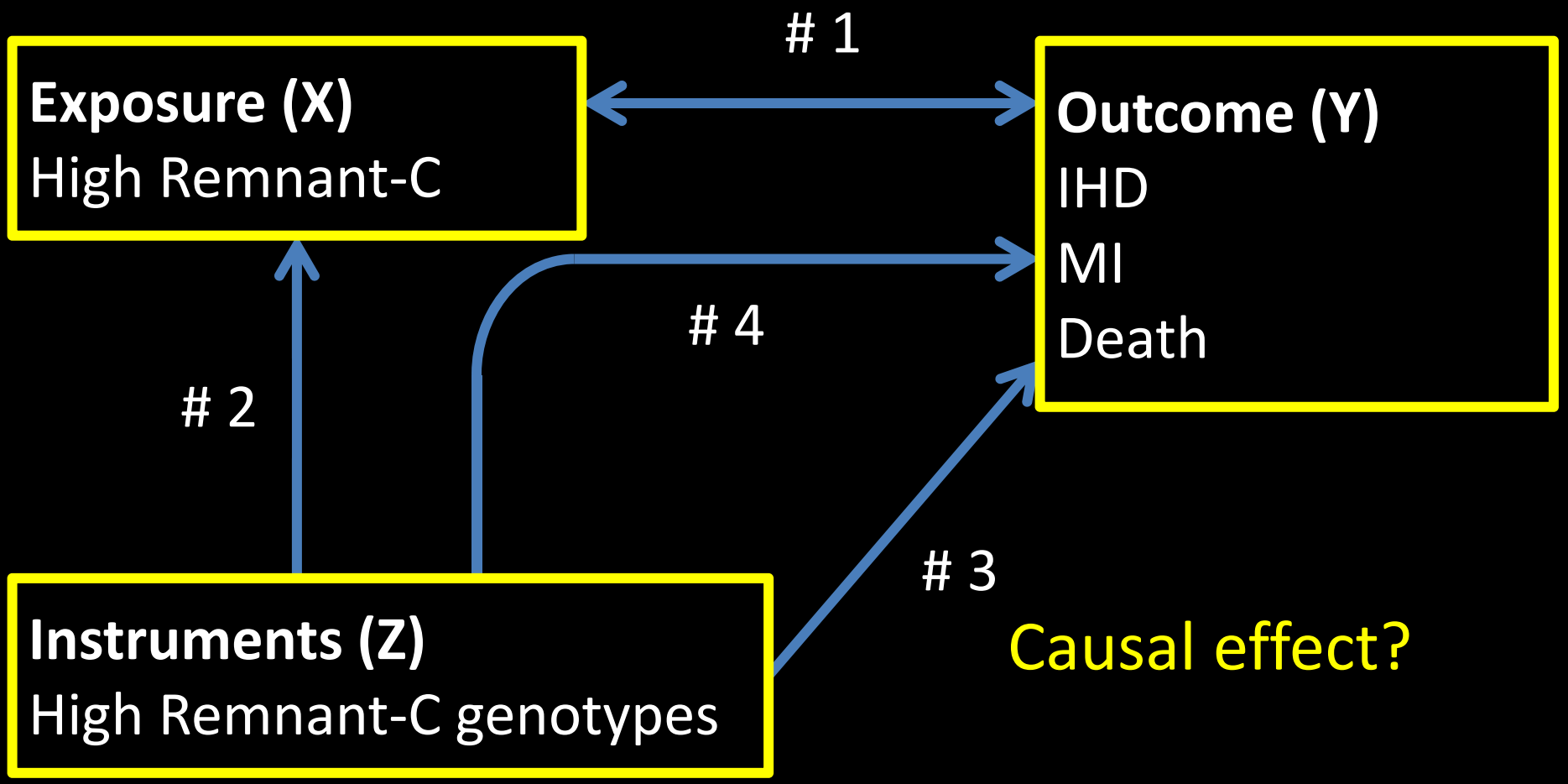
N≈110,000

Copenhagen General Population Study 2003-17

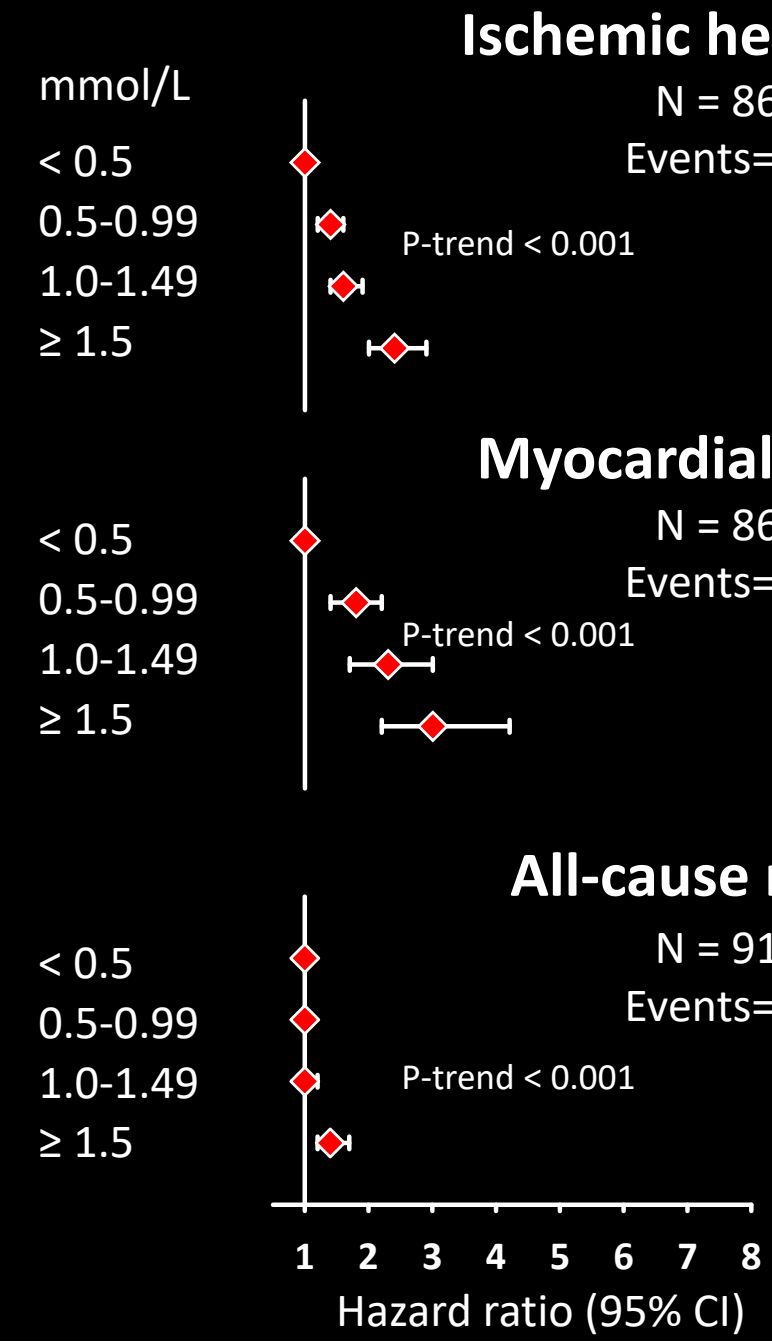
Randomised study vs. Mendelian randomisation



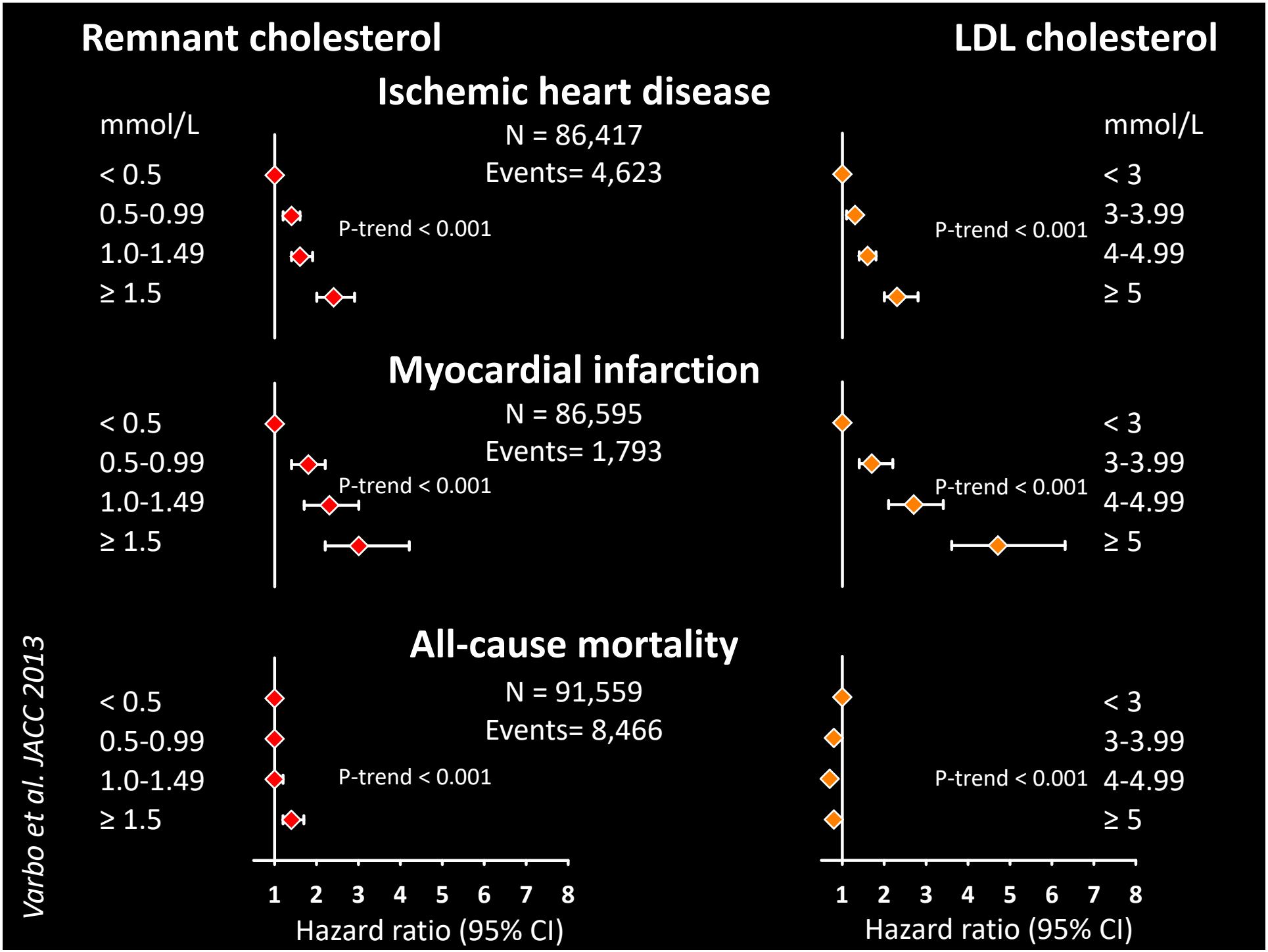
Mendelian randomisation – study design



Remnant cholesterol



Varbo et al. JACC 2013

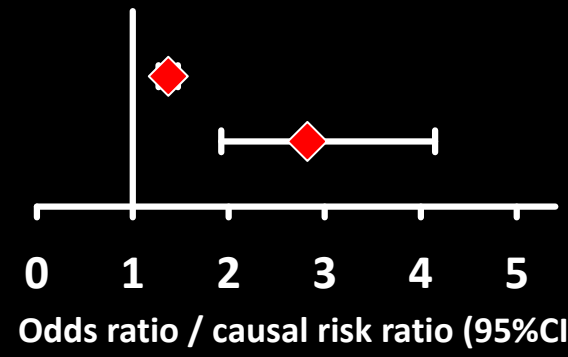

Remnant cholesterol
LDL cholesterol
Ischemic heart disease
N = 86,417
Events= 4,623
P-trend < 0.001
P-trend < 0.001
mmol/L
< 0.5
0.5-0.99
1.0-1.49
≥ 1.5
mmol/L
< 3
3-3.99
4-4.99
≥ 5
Myocardial infarction
N = 86,595
Events= 1,793
P-trend < 0.001
P-trend < 0.001
All-cause mortality
N = 91,559
Events= 8,466
P-trend < 0.001
P-trend < 0.001
1 2 3 4 5 6 7 8
Hazard ratio (95% CI)
1 2 3 4 5 6 7 8
Hazard ratio (95% CI)
Varbo et al. JACC 2013

Ischemic heart disease

Remnant cholesterol increase of 1 mmol/L

	N total	N events	Risk estimate
Observational	56,667	2,874	1.4
Using genetics	73,513	11,984	2.8

From Varbo JACC 2013; 61: 427-36

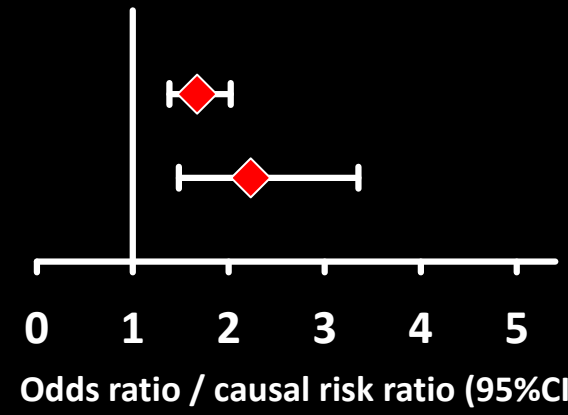


Myocardial infarction

Remnant cholesterol doubling in levels

Observational	10,391	1,098	1.7
Using genetics	60,113	5,705	2.2

From Jørgensen Eur Heart J 2013; 34: 1826-33

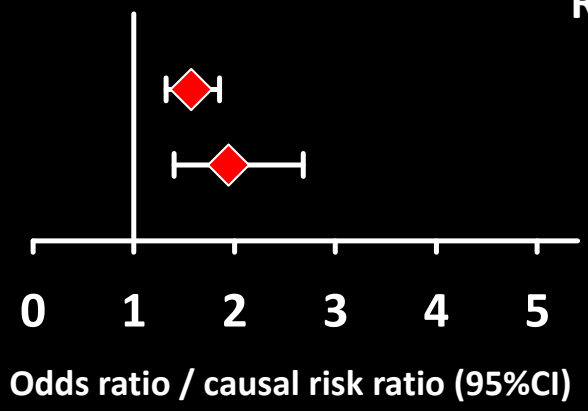


Triglyceride doubling in levels

	N total	N events
Observational	10,391	1,098
Using genetics	60,113	5,705

From Jørgensen Eur Heart J 2013; 34: 1826-33

Myocardial infarction

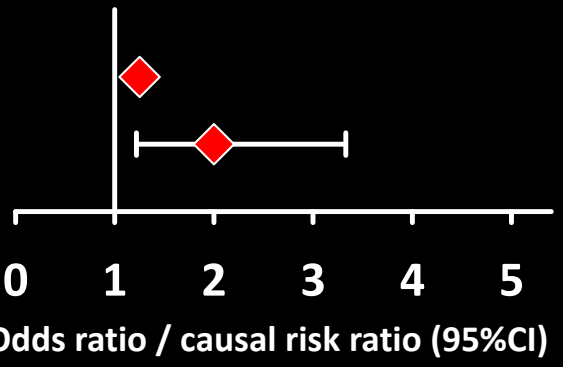


Triglyceride increase of 1 mmol/L

Observational	13,957	9,991
Using genetics	10,208	4,005

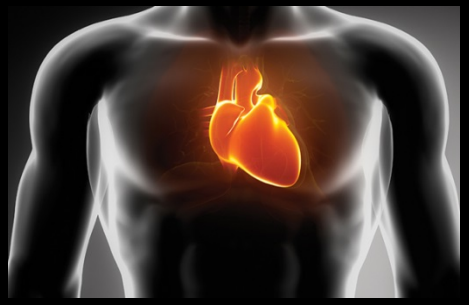
From Thomsen Clin Chem 2014; 60: 737-46

All-cause mortality



Conclusion

Remnant cholesterol
(triglycerides)



Ischemic heart disease

Myocardial infarction

All-cause mortality

Eat less

Exercise more

(reduce alcohol)

(treat diabetes)

Potent statin

Fibrate

(Fish oils / niacin)

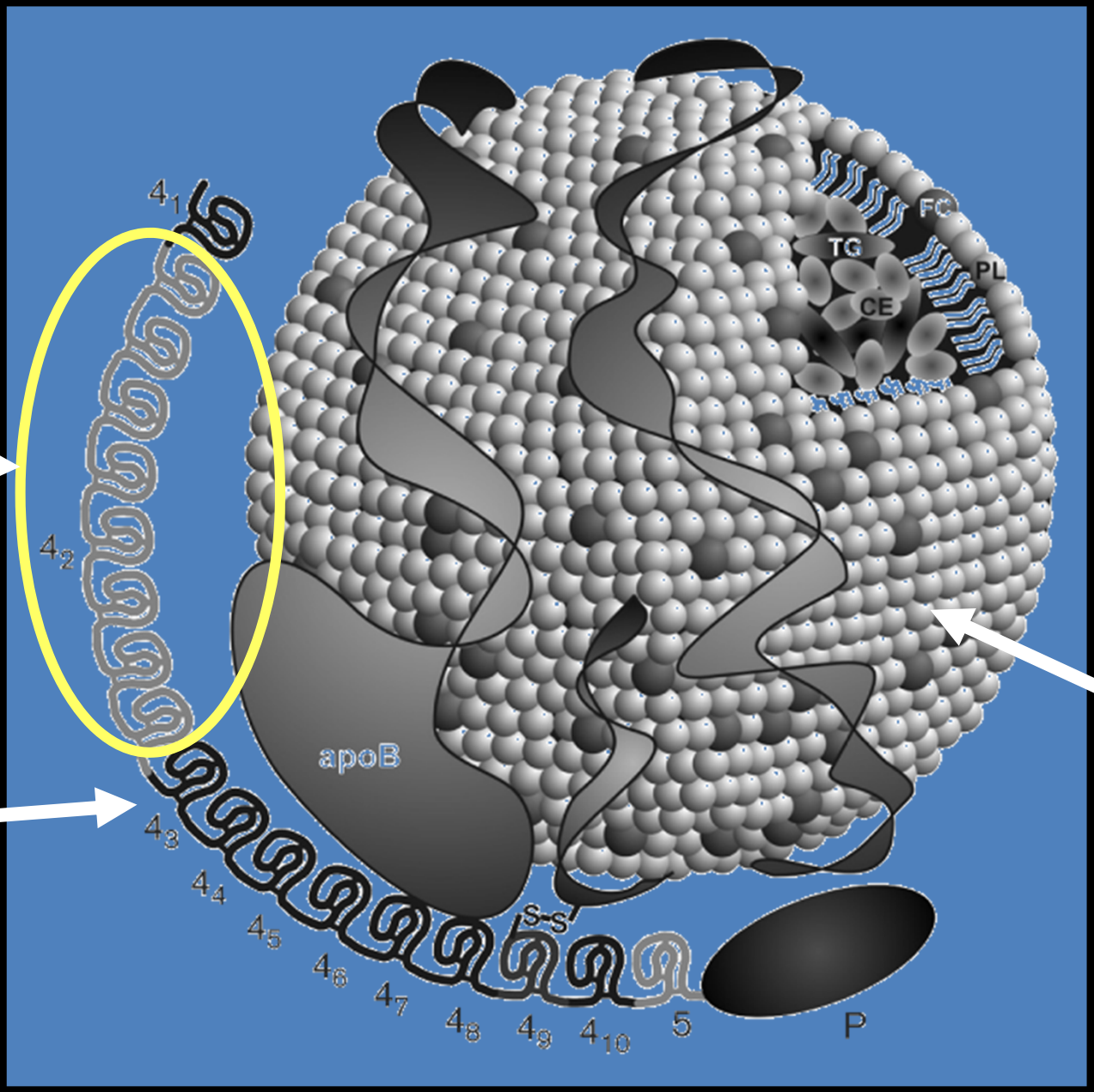
Lp(a)

Lipoprotein(a)

Danish kringle

Kringle IV-2 copy number variant: 2 to >40 repeats

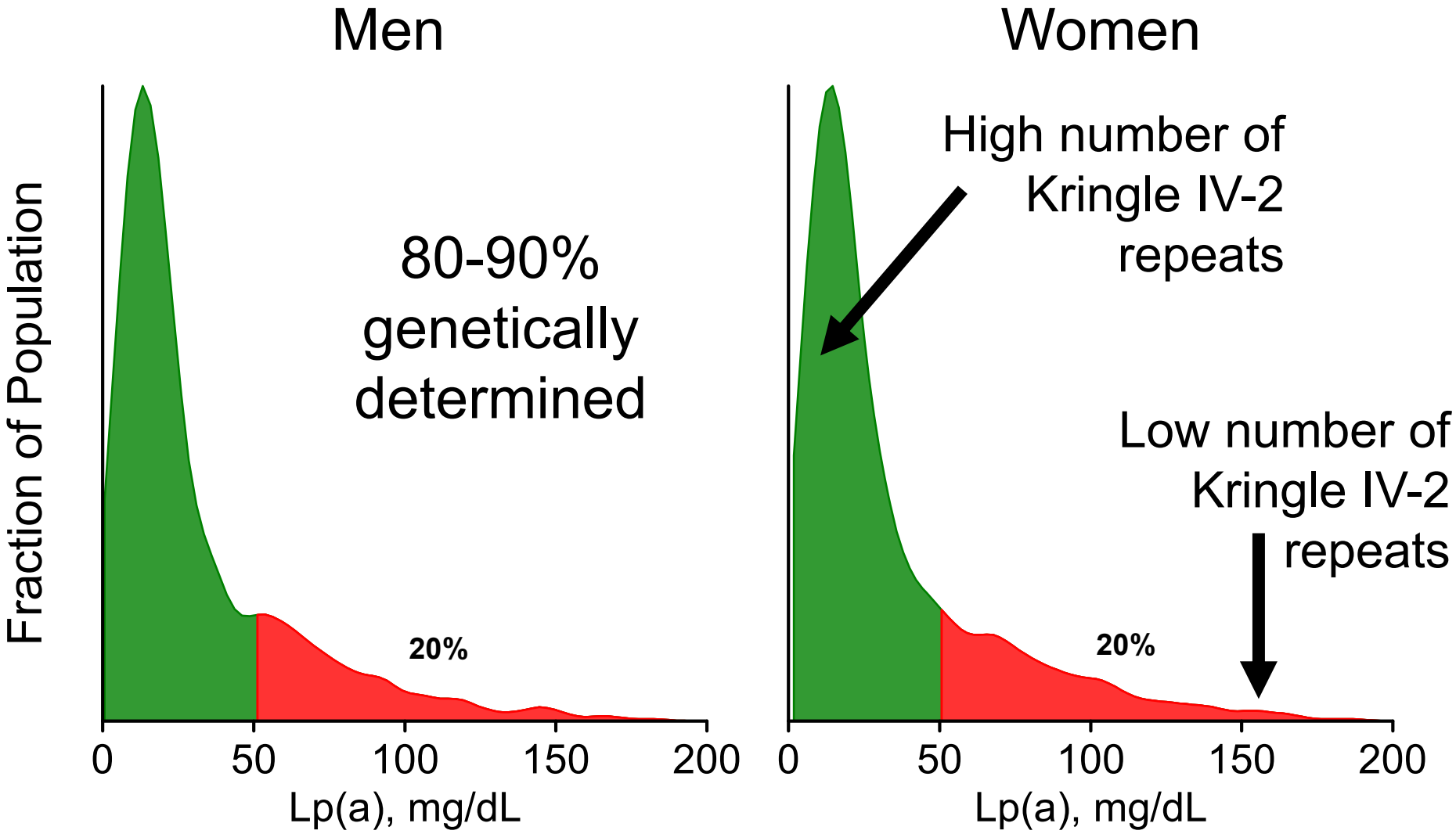
apolipo-protein(a)



LDL-like particle

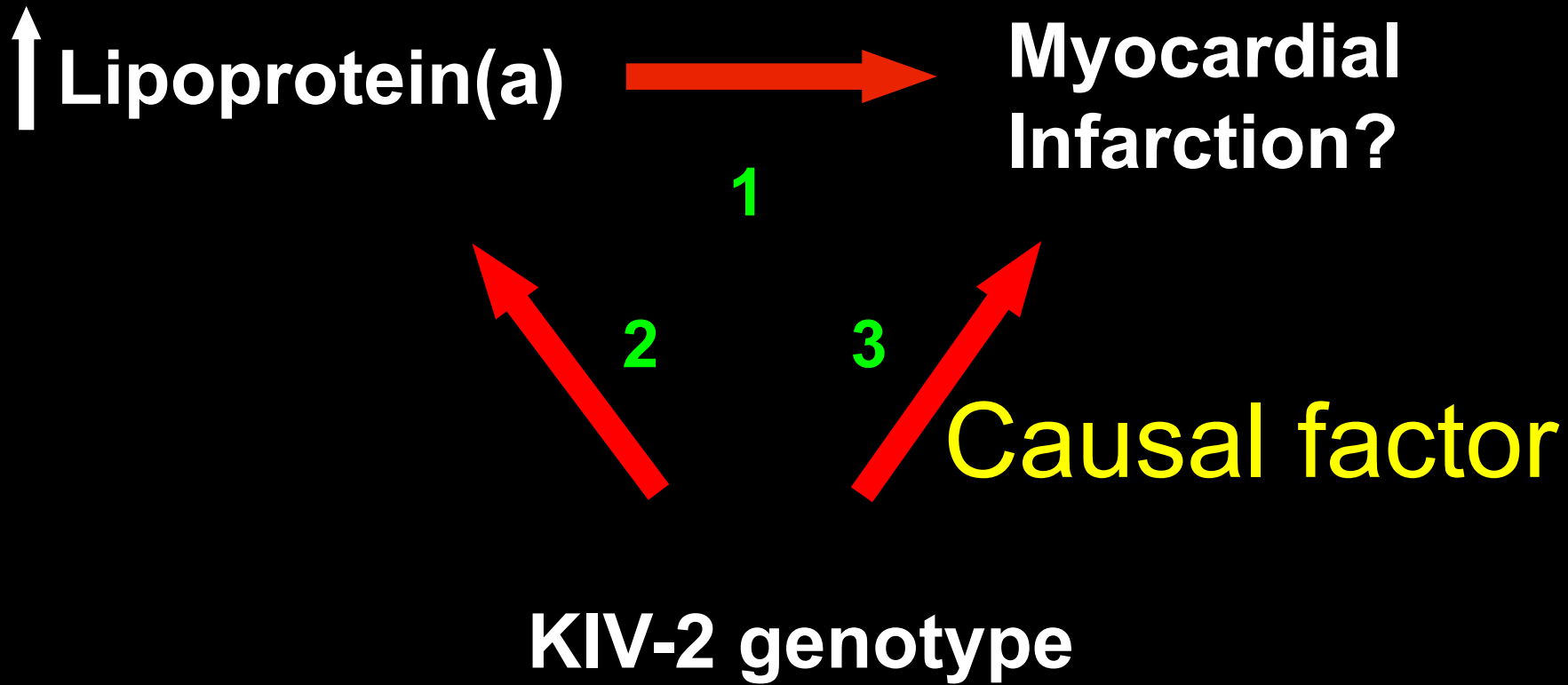
Koschinsky et al. Cur Opin Lipidol 2004;15:167-174

Copenhagen General Population Study



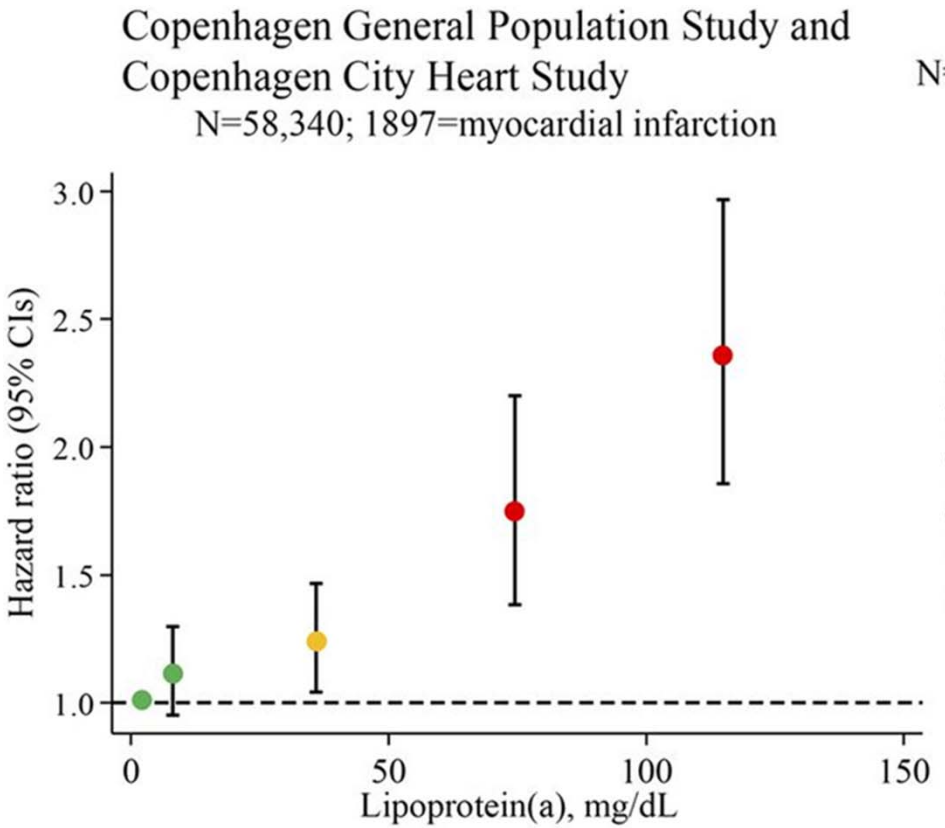
Nordestgaard et al. EAS Consensus Panel. Eur Heart J 2010;31:2844-2853

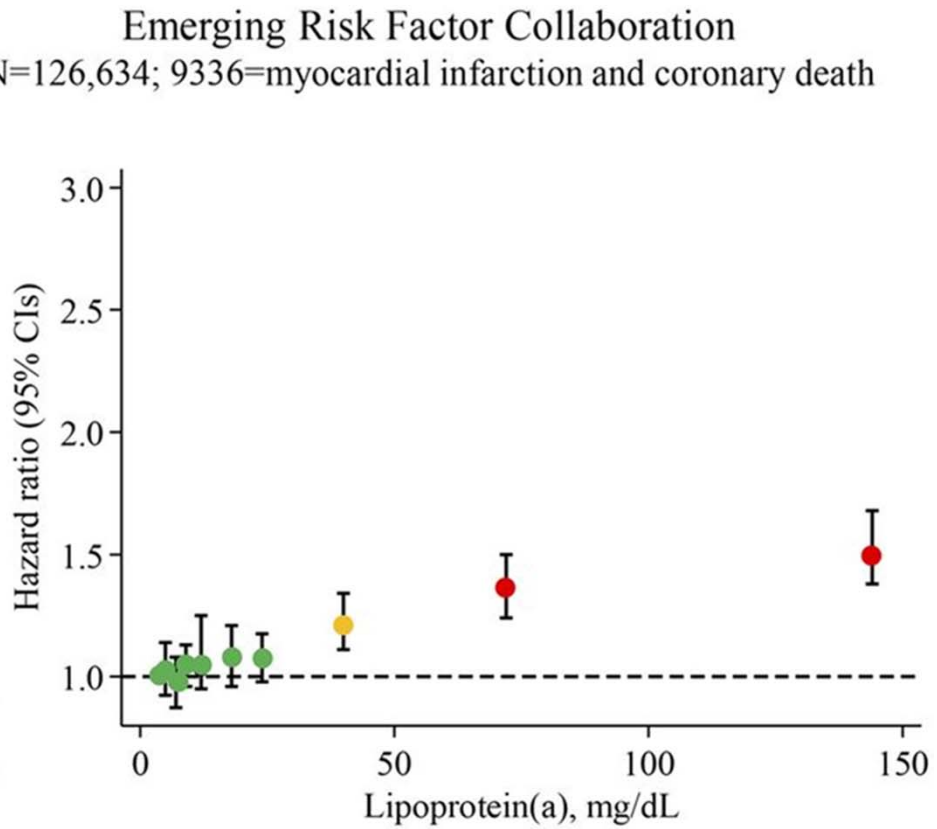
Lipoprotein(a) and risk of myocardial infarction



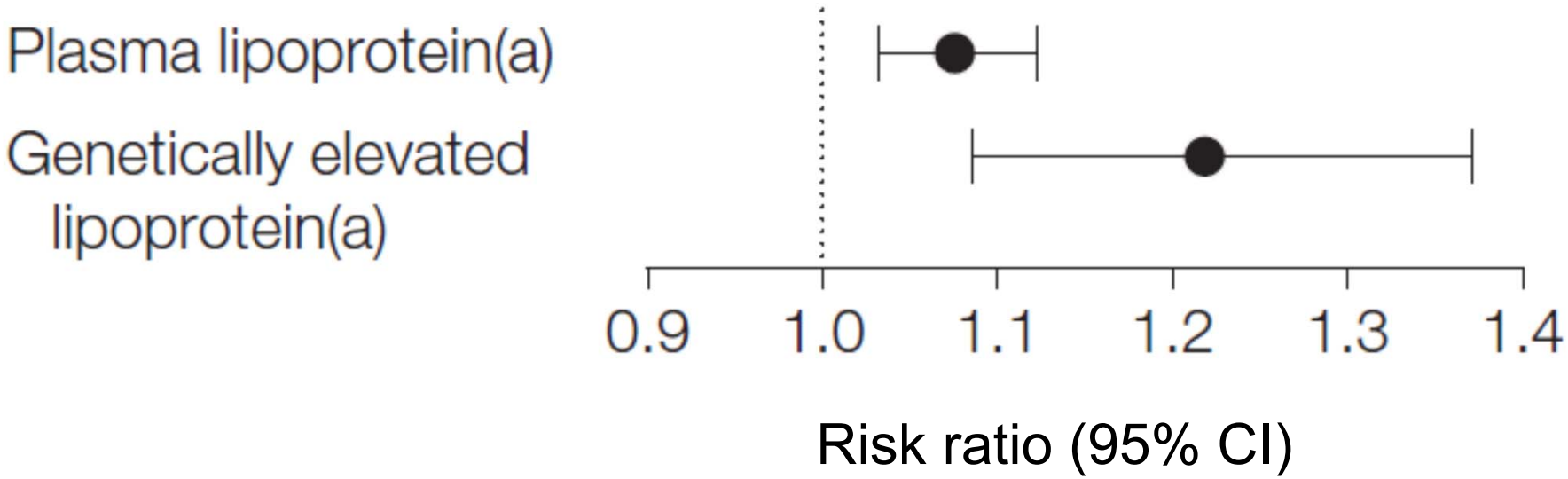
Kamstrup et al. JAMA 2009; 301: 2331-9

Risk of CVD


Copenhagen General Population Study and
Copenhagen City Heart Study
N=58,340; 1897=myocardial infarction
Hazard ratio (95% CIs)
3.0
2.5
2.0
1.5
1.0
0
50
100
150
Lipoprotein(a), mg/dL

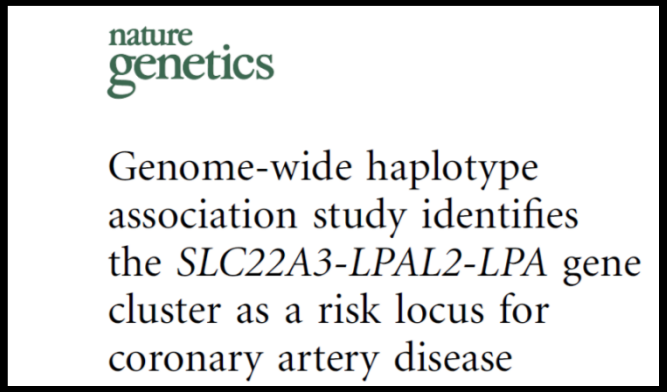

Emerging Risk Factor Collaboration
N=126,634; 9336=myocardial infarction and coronary death
Hazard ratio (95% CIs)
3.0
2.5
2.0
1.5
1.0
0
50
100
150
Lipoprotein(a), mg/dL

Risk of myocardial infarction for a doubling of lipoprotein(a) levels

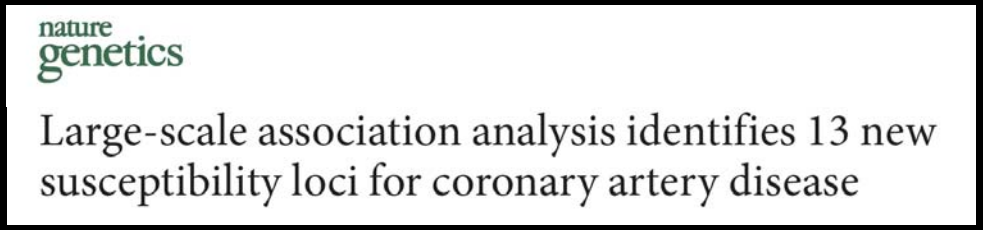


Kamstrup et al. JAMA 2009; 301: 2331-9

Consistency with custom-made chip/GWAStudies

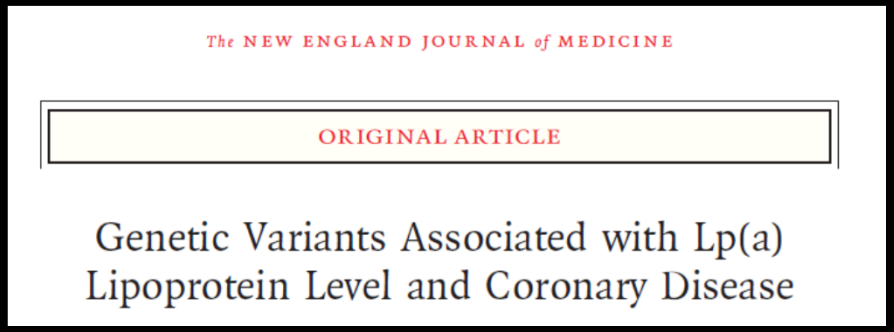


Trégouët et al. 2009



Schunkert et al. 2011

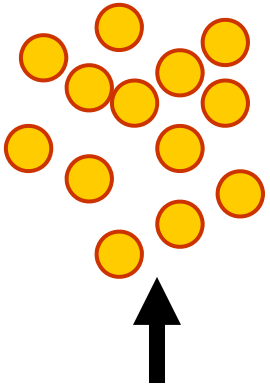
Confirmed association of *LPA* locus with CAD in CAD case-control study of 56 000 individuals



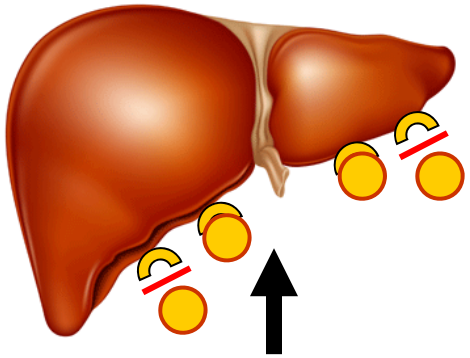
Clarke et al. 2009

LPA locus strongest association with CAD of 48 000 tested SNPs

Elevated LDL cholesterol

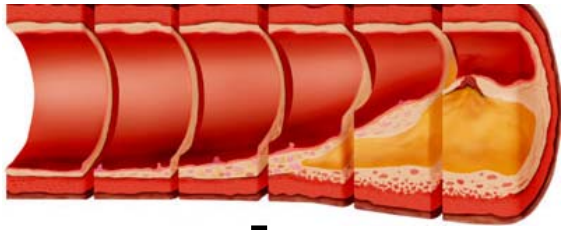


Liver with only 50% functional LDL receptors

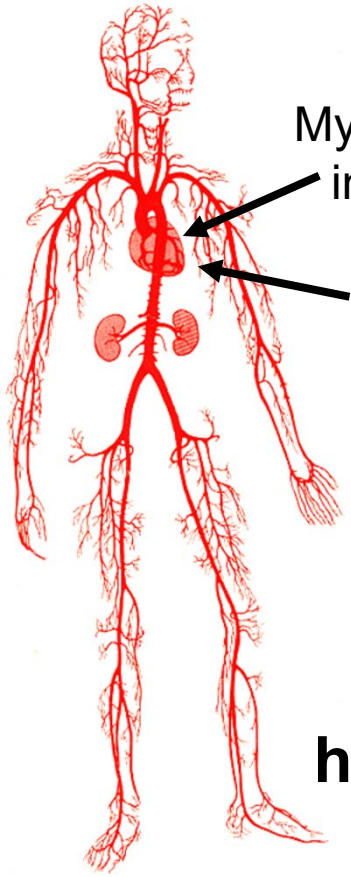


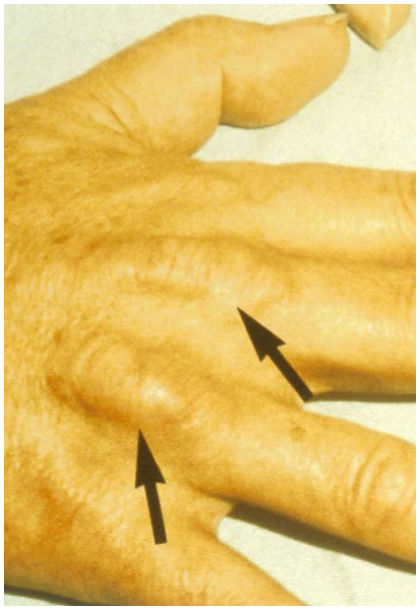
Mutations in *LDLR, APOB* or *PCSK9* genes

Atherosclerosis



Coronary heart disease





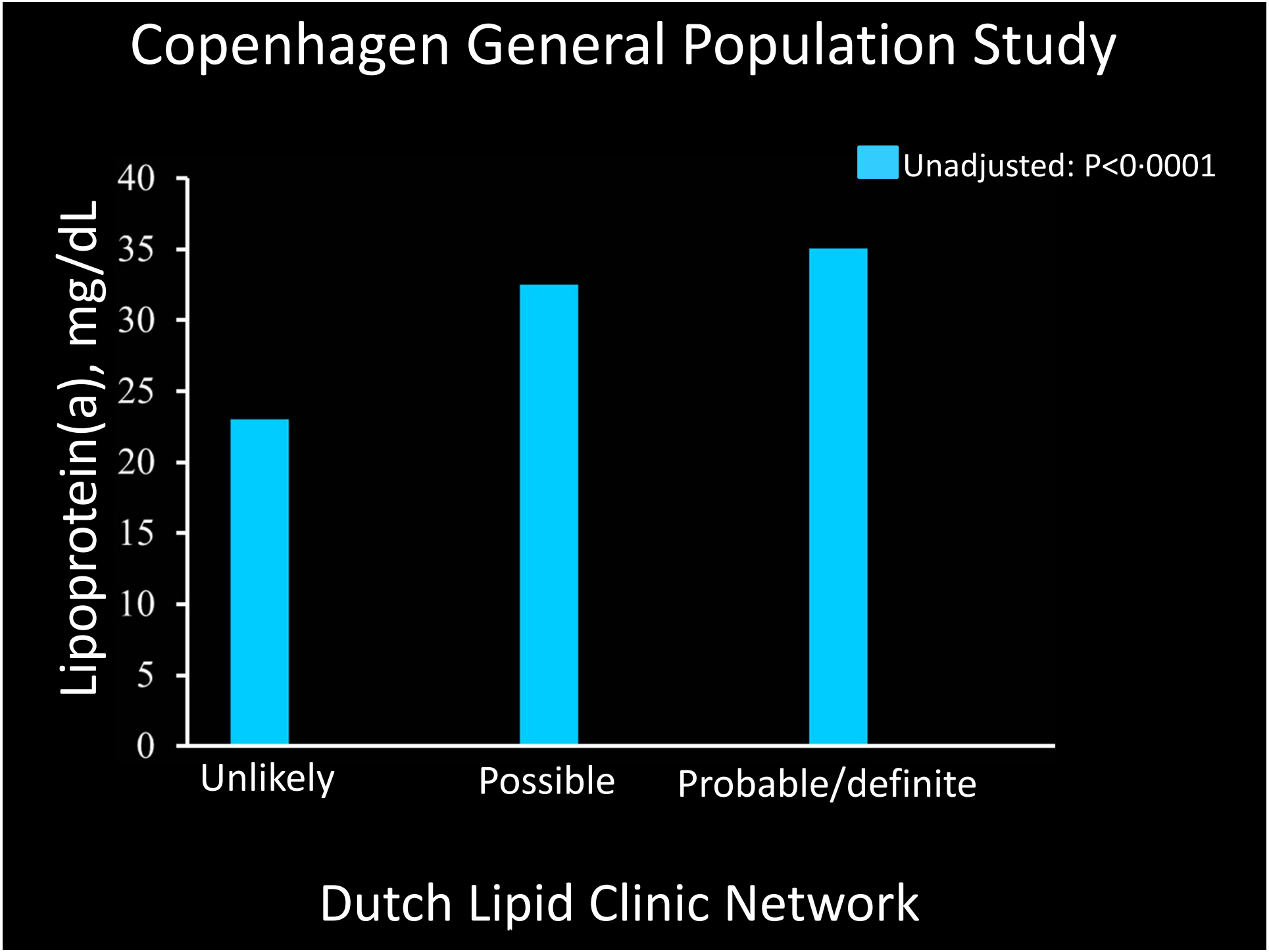
Clinical familial hypercholesterolaemia 1:200

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

Lipoprotein(a) and FH

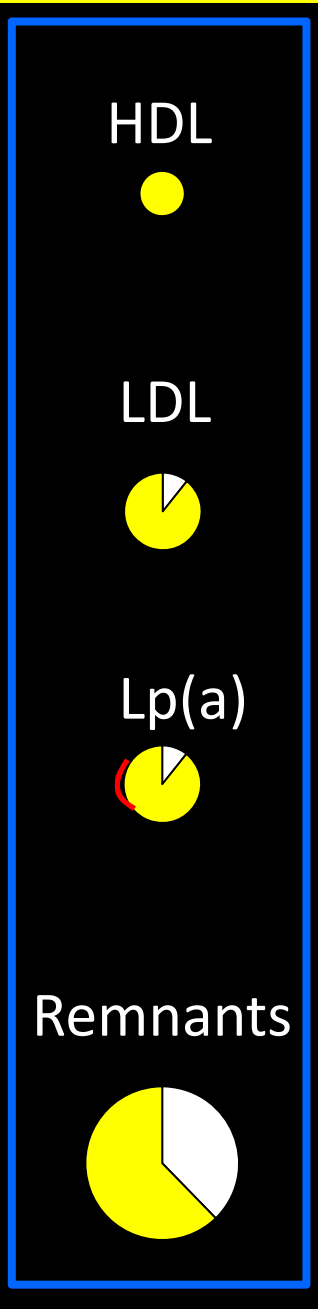
- Individuals with clinically diagnosed FH have high lipoprotein(a) levels
- Reduced LDL receptor function leads to high lipoprotein(a) concentration via decreased clearance of lipoprotein(a)?
- Is high lipoprotein(a) concentration a cause of clinical FH?

Copenhagen General Population Study



Dutch Lipid Clinic Network

Lipoprotein



Total cholesterol

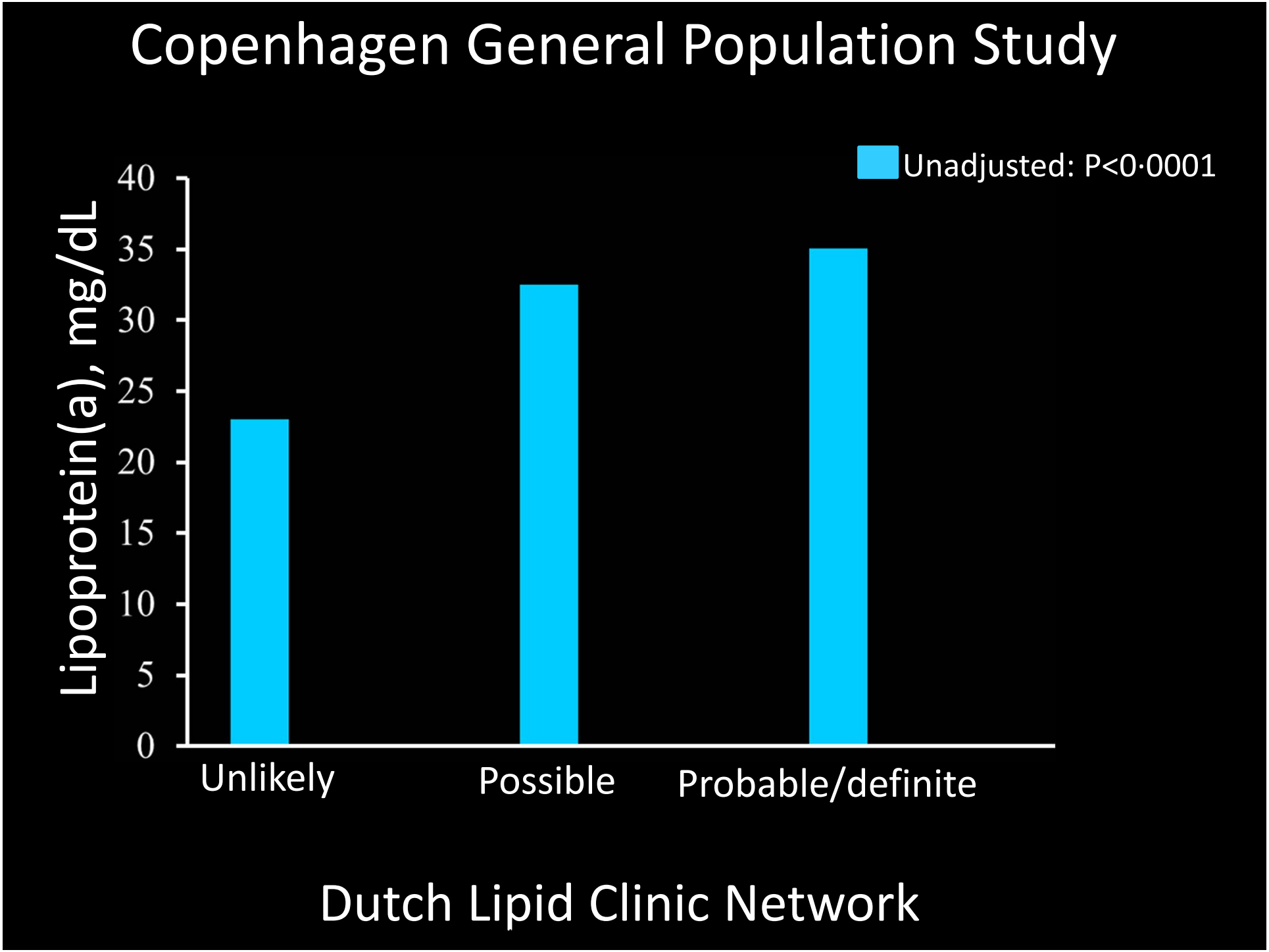
HDL cholesterol

LDL cholesterol

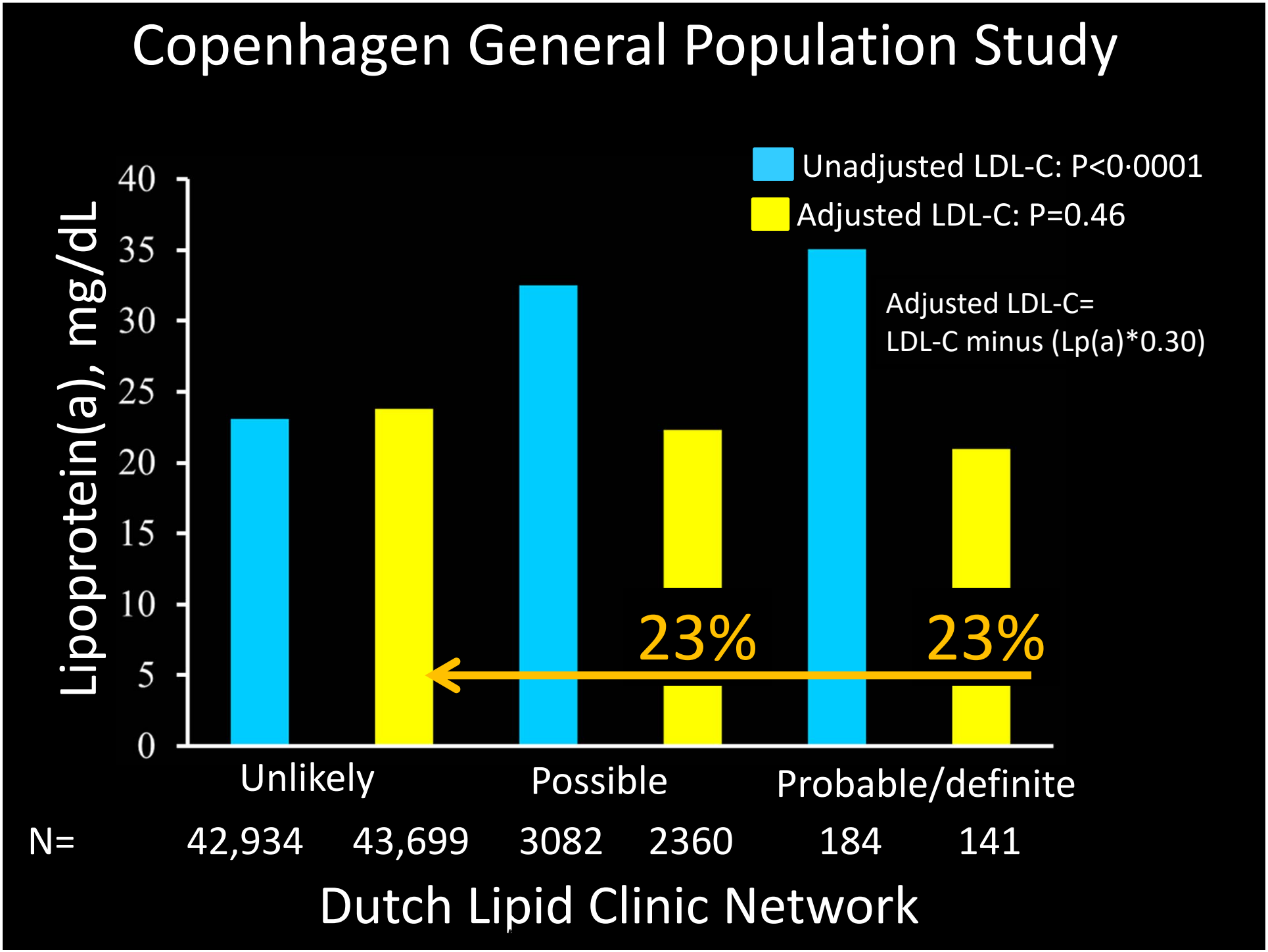
Lipoprotein(a) total mass

Remnant cholesterol

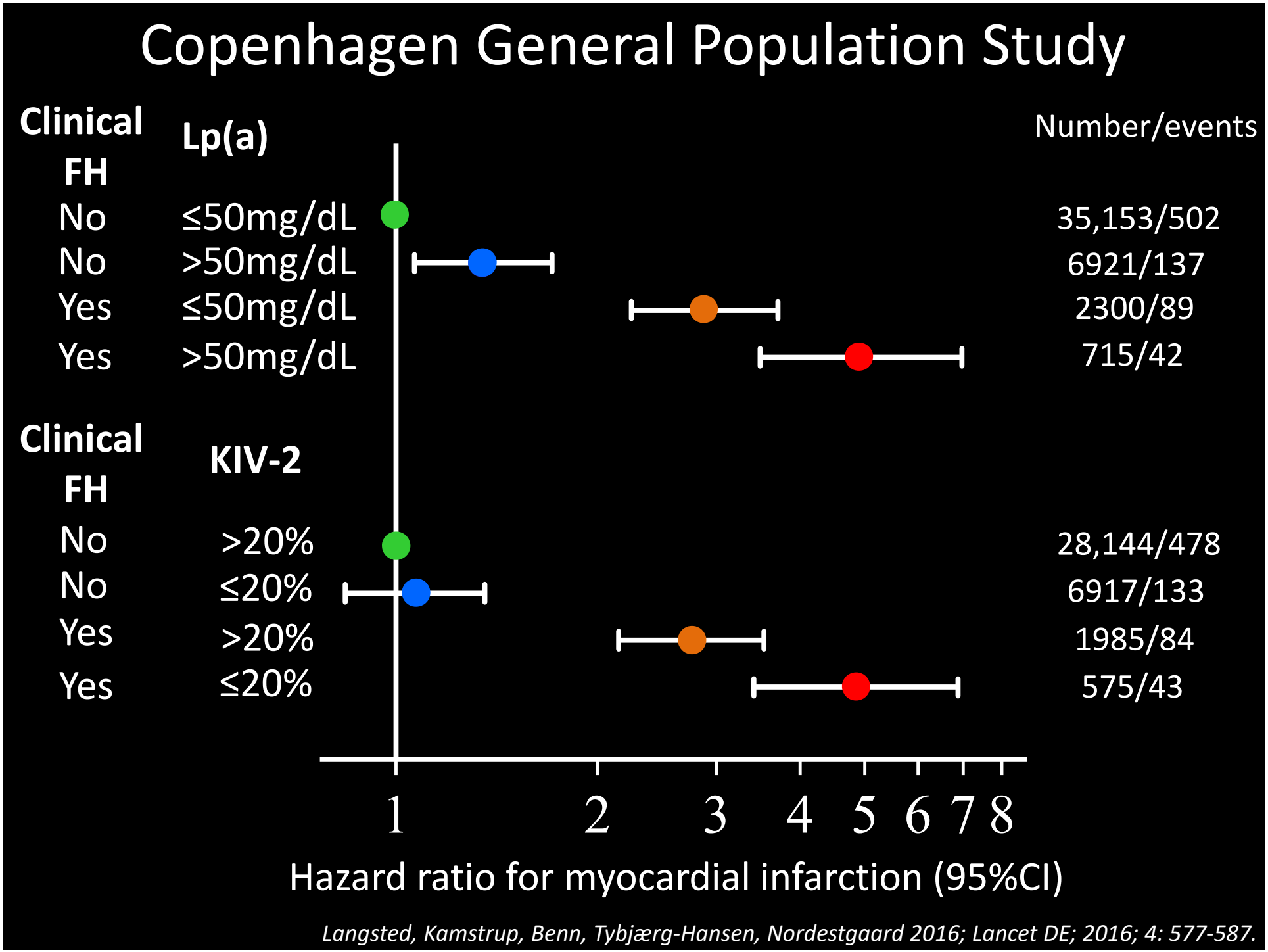
Copenhagen General Population Study



Dutch Lipid Clinic Network


Copenhagen General Population Study
Unadjusted LDL-C: P<0·0001
Adjusted LDL-C: P=0.46
Adjusted LDL-C=
LDL-C minus (Lp(a)*0.30)
Lipoprotein(a), mg/dL
40
35
30
25
20
15
10
5
0
23%
23%
Unlikely
Possible
Probable/definite
N=
42,934
43,699
3082
2360
184
141
Dutch Lipid Clinic Network

Copenhagen General Population Study

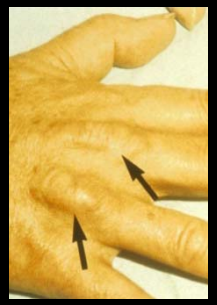


Langsted, Kamstrup, Benn, Tybjærg-Hansen, Nordestgaard 2016; Lancet DE; 2016; 4: 577-587.

High lipoprotein(a) as a cause of clinical familial hypercholesterolemia (FH)

Copenhagen General Population Study N=46,200

FH 1:200



Ranked causes of clinical FH

1. *LDLR*
2. *LPA* (23%)
3. *APOB*
4. *PCSK9*

Langsted, Kamstrup, Benn, Tybjærg-Hansen, Nordestgaard 2016; Lancet DE; 2016; 4: 577-587.

Whom to screen for Lp(a)↑

- Premature CVD
- Familial hypercholesterolemia
- Family history premature CVD or Lp(a)↑
- Recurrent CVD despite statins
- ≥3% 10-year risk of fatal CVD

Nordestgard et al. EAS Consensus Panel. Eur Heart J 2010;31:2844-2853 - updated

Treatment of Lp(a)↑ ?

- Lifestyle changes minimal effect
- Statins to lower LDL-C
- (Niacin ↓30%)
- Possibly apheresis ↓35% average

- Novel therapies?
  - PCSK9 inhibitors ↓25%?
  - CETP inhibitors ↓0-50%?
  - Apo(a) antisense oligo ↓80%?

Nordestgard et al. EAS Consensus Panel. Eur Heart J 2010;31:2844-2853 - updated

Conclusion

- Both remnant cholesterol and lipoprotein(a) have causal effect on risk of cardiovascular disease and may contribute to the residual risk

- Lipoprotein(a) should be considered a causal factor for clinical familial hypercholesterolemia

Acknowledgements

Co-workers

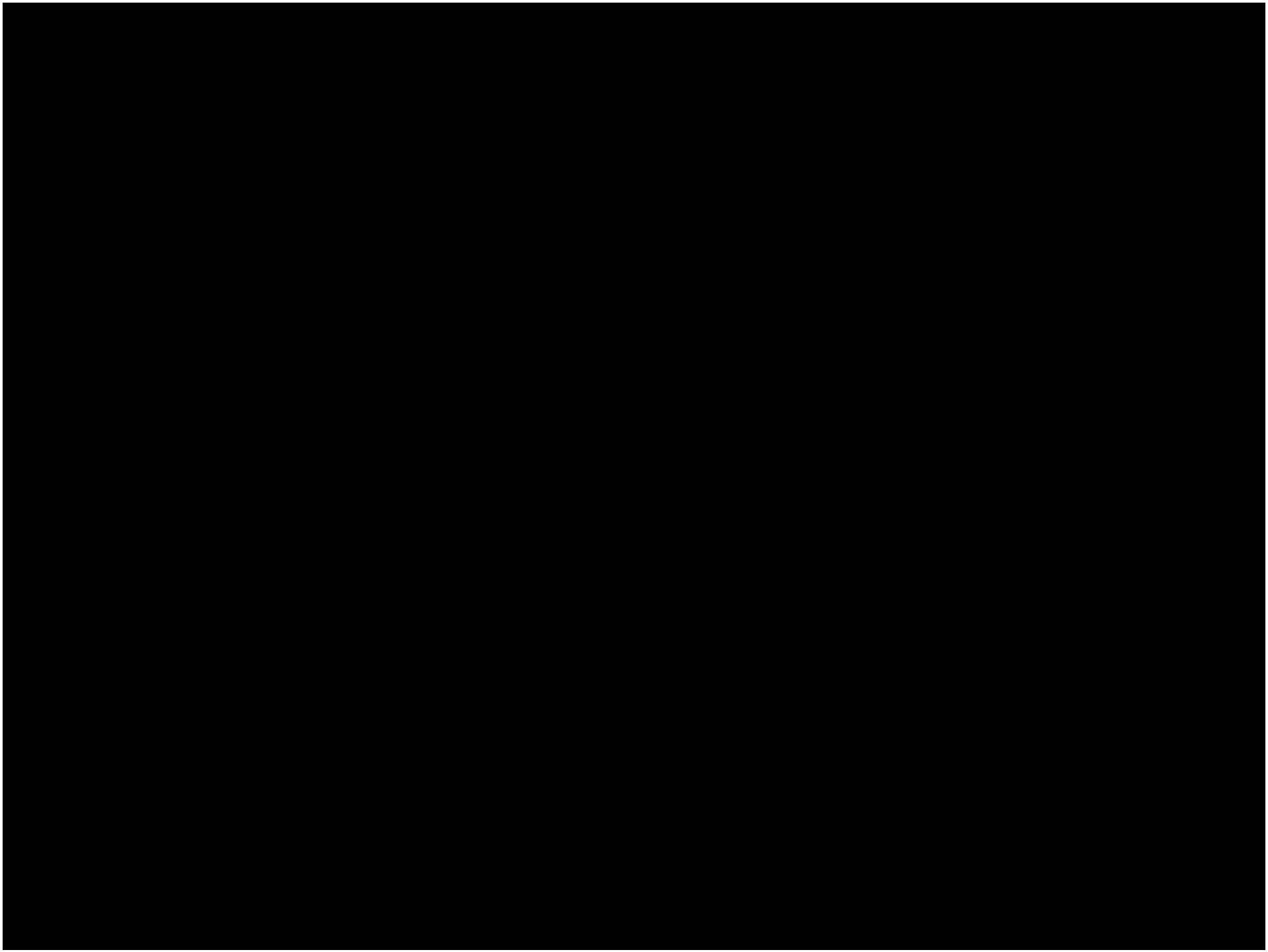
Anette Varbo
Pia Rørbæk Kamstrup
Anne Langsted
Børge G. Nordestgaard
Anne Tybjærg-Hansen

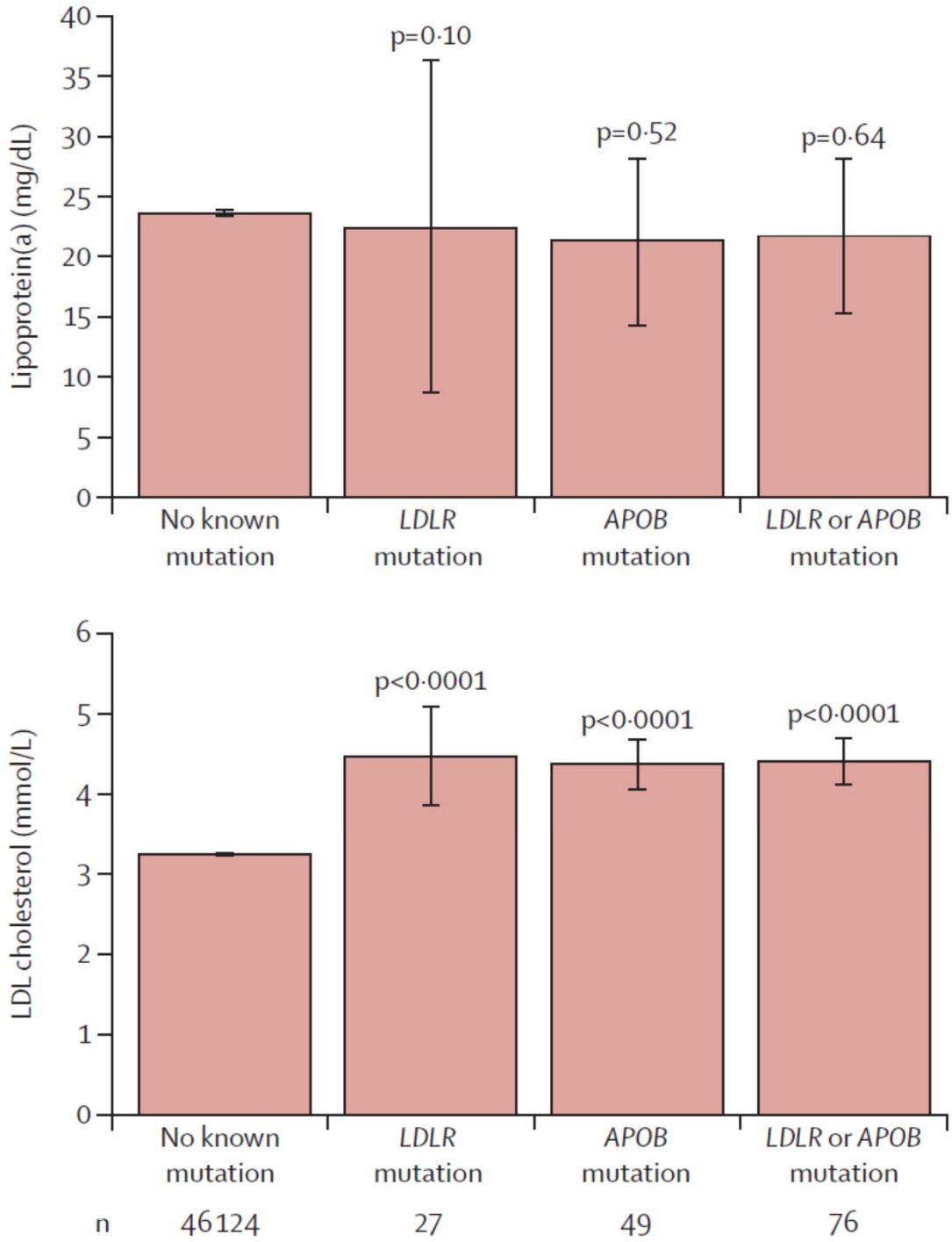
Participants and staff from

The Copenhagen City Heart Study
The Copenhagen General Population Study

Funding:

The Danish Heart Foundation
Herlev and Gentofte Hospital, Copenhagen University Hospital
Chief Physician Johan Boserup and Lise Boserup's Fund
The Danish Council for Independent Research, Medical Sciences




Lipoprotein(a) (mg/dL)
40
35
30
25
20
15
10
5
0
p=0·10
p=0·52
p=0·64
No known mutation
LDLR mutation
APOB mutation
LDLR or APOB mutation
LDL cholesterol (mmol/L)
6
5
4
3
2
1
0
p<0·0001
p<0·0001
p<0·0001
No known mutation
LDLR mutation
APOB mutation
LDLR or APOB mutation
n
46124
27
49
76