Sequence variants in apolipoprotein(a) gene associate with systemic atherosclerosis and coronary atherosclerotic burden but not with venous thromboembolism

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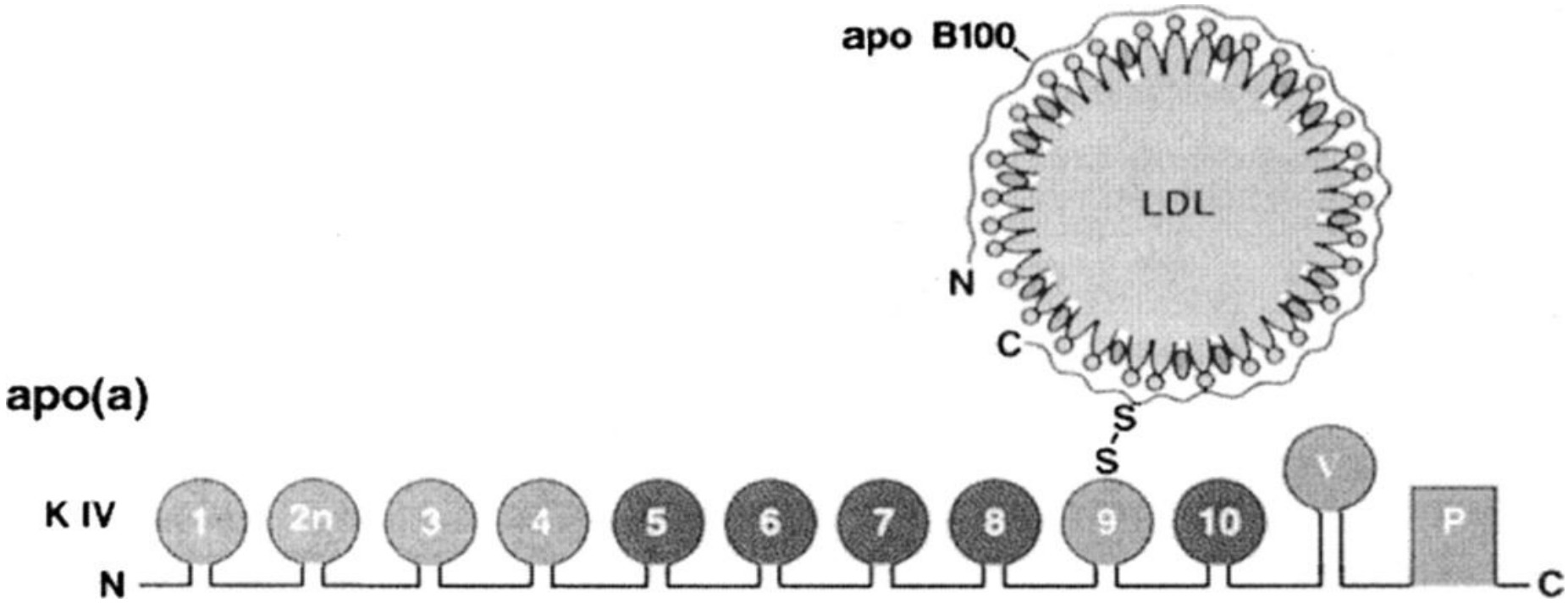
Lipoprotein (a) = Lp(a)



Plasma lipoprotein first identified 1963

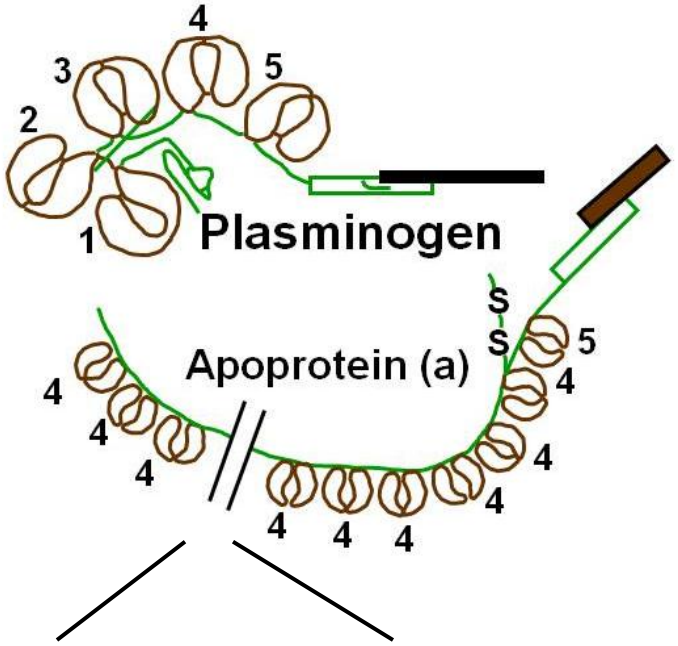
Lipoprotein (a) = LDL cholesterol + Apo(a)

Apolipoprotein (a)

Structural homology with plasminogen, a fibrinolytic pro-enzyme

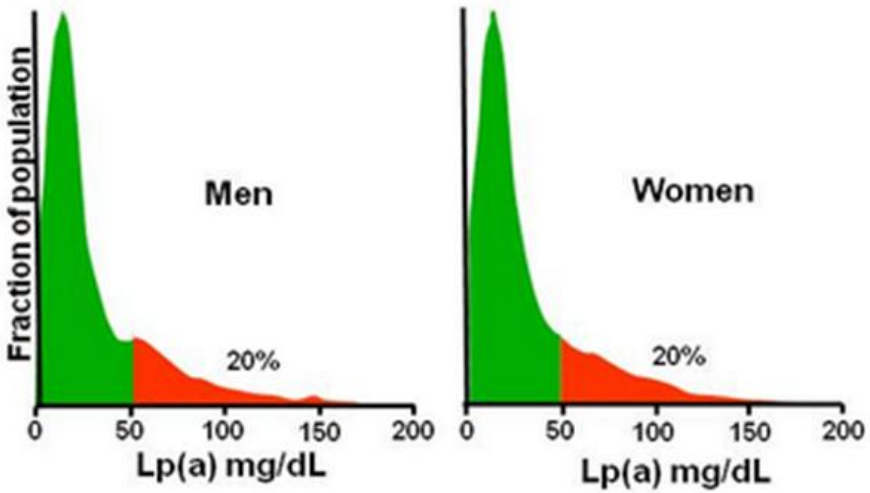
Unlike plasminogen which has five kringles, apo(a) consists of only two plasminogen-like kringles (K-IV and K-V).

Exon 2 of the apo(a) gene (*LPA*), that encodes for kringle IV type 2, has a copy number variation, resulting in a large number of protein size isoforms



$(KIV\text{-}2)_n$
The number of KIV-2 domains per apo(a) particle can vary from ~5-50 copies.

Distributions of Lp(a) levels in the general population



Eur Heart J 2010,Dec 31(23):2844-53

In individuals of European origin the isoform size accounts for approximately one-half of the interindividual variability of Lp(a) plasma levels

Smaller apo(a) isoforms associated with higher concentrations

Diet or lipid-lowering drugs (statins and fibrates) have little or no impact on Lp(a) levels

Niacin (nicotinic acid=vitamin B3) decrease Lp(a) levels by 20-30%

Lp(a) and cardiovascular disease

- Many prospective epidemiological studies have reported positive associations of baseline Lp(a) concentration with coronary artery disease (CAD) risk
    - A systemic review (*JAMA 2009*) including data from 36 prospective studies assessed the association of Lp(a) concentration with the risk of CAD and stroke
    - The adjusted risk ratio for CAD, was 1.13 per 1 SD increase in Lp(a), and the corresponding risk ratios were 1.10 for ischemic stroke
- A systematic review (*JACC 2010*) studying the effects of isoform size, showed a two-fold increase in the risk for MI and stroke among Caucasian subjects with small versus large isoforms of apo(a)

Lp(a) and cardiovascular disease

Genetic Variants Associated with Lp(a)Lipoprotein Level and Coronary Disease *(N Engl J Med 2009;361:2518-28)*

- Two independent SNPs in the *LPA* gene, rs10455872 and rs3798220, were shown to associate with high plasma levels of Lp(a) and CAD

- Both SNPs also correlate with small apo(a) isoforms

- Together the variants explain about 36% of the variance in Lp(a) levels

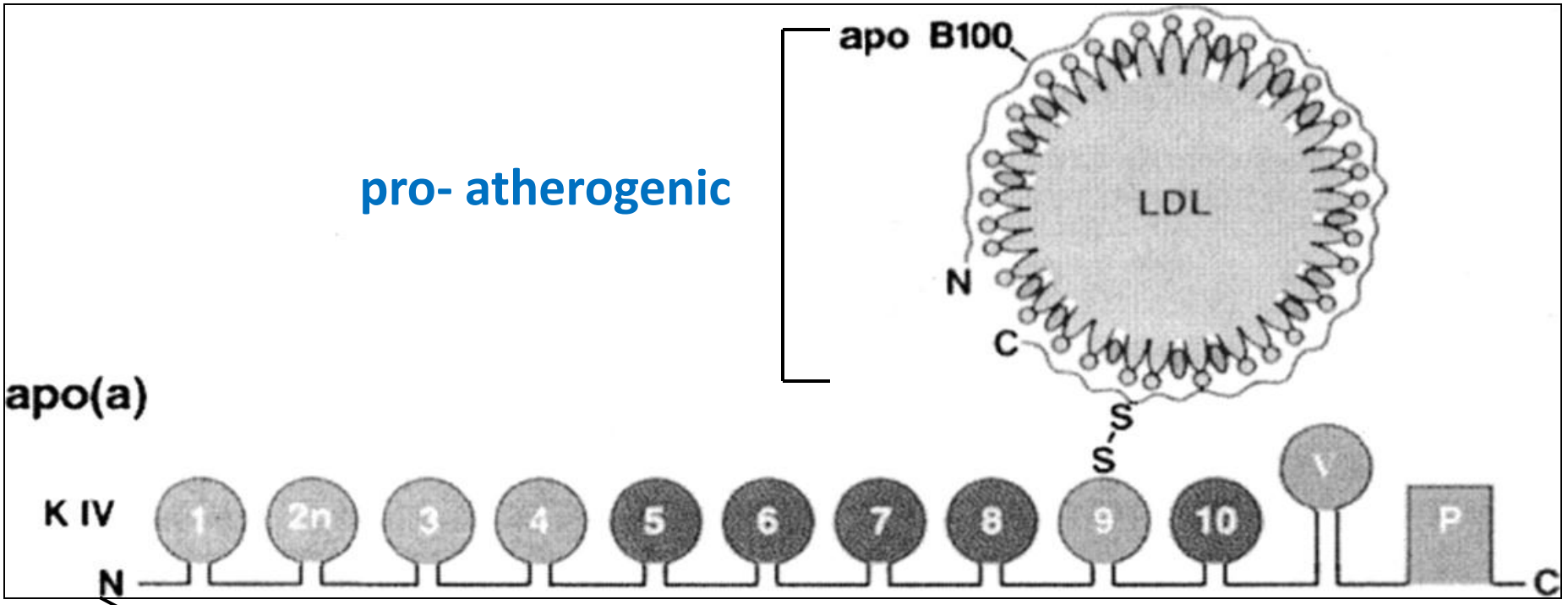
- Adjusting for Lp(a) levels the association with CAD was abolished, indicating that the association of the SNPs with CAD was mediated through increased levels of Lp(a)

Lp(a) and cardiovascular disease

- The genetic results, together with results from large meta-analyses of observational studies provide firm evidence of a causal role of Lp(a) in CAD

- Evidence for the association between plasma Lp(a) and other cardiovascular diseases is weaker
  - fewer studies
  - smaller sample sizes
  - contradictory findings

Plausible mechanisms linking Lp(a) to the expression of cardiovascular disease

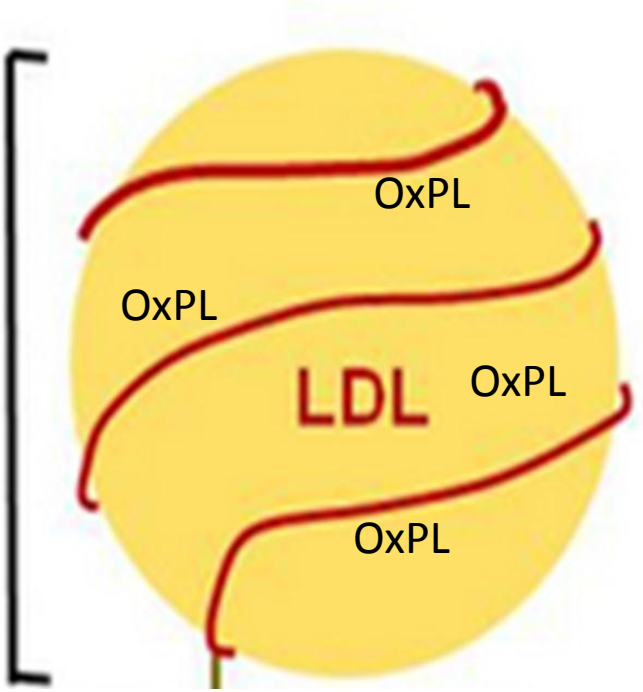


pro- atherogenic

pro-thrombogenic properties of the apo(a)

Support for pro-atherosclerotic role

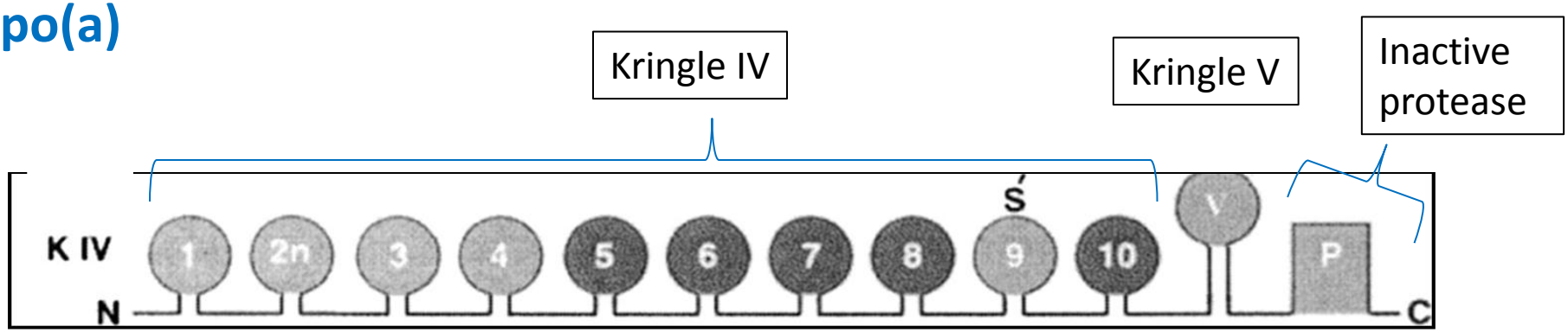
- Lp(a) accumulate in plaques
- Levels in plaques correlate with levels in plasma
- Is oxidised within the vascular wall leading to foam cell formation
- Stimulation of various proinflammatory actions:
  - chemotaxis of macrophages
  - expression of adhesion molecules by endothelial cells
  - proliferation of smooth muscle cells



Lp(a) is a preferential carrier of proinflammatory oxidized phospholipids

Support for prothrombotic role

apo(a)



↓fibrinolysis

- Striking homology between apo(a) and plasminogen
- Competes with plasminogen for binding to fibrin
- Inhibits production of tissue-type plasminogen activator (tPA)
- Stimulates synthesis of plasminogen activator inhibitor-1 (PAI-1)

↑ coagulation

- by inhibiting the function of tissue factor pathway inhibitor (a regulator of thrombin generation)
- May be a risk factor for venous thrombosis (supported by meta-analysis of 6 case-control studies)

Study objectives

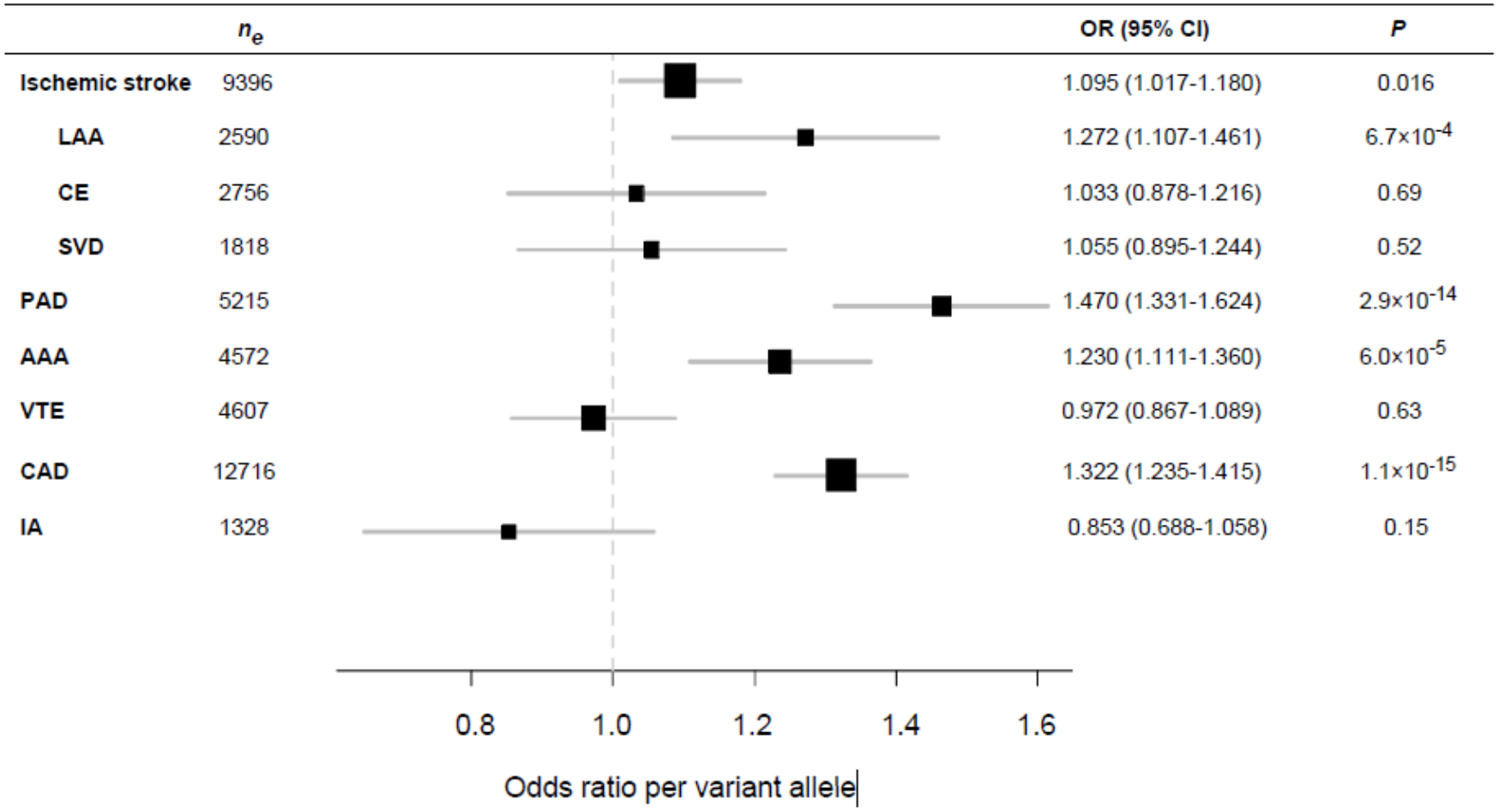
To provide insight into the mechanism by which Lp(a) confers susceptibility by investigating the effects of *LPA* genetic variants (and thus Lp(a) levels), on vascular diseases with different atherosclerotic and thrombotic components

Methods

We genotyped and tested the association of *LPA* genetic variants (rs10455872 and rs3798220 -analysed jointly as *LPA* score) with:

- **Ischemic stroke** (n_e=9396)
  subtypes: **LAA, cardioembolism, small vessel disease**
- **Peripheral arterial disease** (PAD) (n_e=5215)
- **Abdominal aortic aneurysm** (AAA) (n_e=4572)
- **Intracranial aneurysm** (IA) (n_e=1328)
- **Venous thromboembolism** (VTE) (n_e=4607)
- **Carotid intima media thickness** (IMT) (n=3714)
- **Coronary artery disease angiographic severity** (n=5588)

Association of *LPA* score with vascular diseases



No association with MI among patients with angiographic CAD

To test whether *LPA* variants associated with thrombotic events among CAD patients:

We compared (in a logistic regression model) patients with angiographic CAD with MI (N=1,817) or without (N=1,908)

=> the *LPA* score did not associate with MI
(OR = 0.99, P = 0.90)*

*After adjusting for gender, age at angiography, study site and ethnicity, and the age at first CAD diagnosis

Strengthening the view that the risk is mediated through atherogenic rather than thrombogenic mechanisms

No association of *LPA* score with carotid intima media thickness

Study group	*N*	IMT_{log} (mm) β	SE	*P*	P_{het}
IMPROVE	2984	-0.0064	0.0036	0.076	-
Oxfordshire Family Blood Pressure Study	730	-0.0002	0.0224	0.99	-
Combined	3714	-0.0060	0.0036	0.083	0.70

Linear regression coefficients (β) with corresponding standard errors (SE) and P-values (*P*), assuming additive allelic effects. The model included age, sex, body mass index and physical exercise as covariates. Additional adjustments were made for study site (country) for the IMPROVE study. *N* is the number of subjects.

Suggesting that Lp(a) mediates its effects at later stages in the atherosclerosis process

Association between *LPA* score and the age at diagnosis of CAD

		Age at diagnosis (years)		
	N	**β**	**SE**	***P***
European ancestry				
Age at first CAD diagnosis	9275	-1.581	0.295	8.2×10^{-8}
Age at first MI	5148	-0.918	0.416	0.028
Age at first CAD diagnosis for MI cases	5148	-1.334	0.400	0.00085
African Americans				
Age at first CAD diagnosis	333	-3.541	2.521	0.16
Age at first MI	185	-2.221	3.249	0.50
Age at first CAD diagnosis for MI cases	185	-6.009	3.159	0.059

Linear regression coefficients (β) with corresponding standard errors (SE) and P-values (*P*), assuming additive allelic effects. N=the number of subjects.

Association of *LPA* score with angiographic CAD severity

		Number of affected coronary index vessels		
Study group	***N***	**β**	**SE**	***P***
Iceland	2330	0.245	0.061	5.8×10^{-5}
Atlanta-European American	2718	0.281	0.052	6.3×10^{-8}
Atlanta-African American	540	0.396	0.219	0.071
Combined	5588	0.267	0.038	4.8×10^{-12}

Linear regression coefficients (β) with corresponding standard errors (SE) and P-values (*P*), assuming additive allelic effects. Age at angiography and sex were included as covariates in the model for each study group. In the combined analysis additional adjustments were made for study group (site/ethnicity). *N* is the number of subjects.

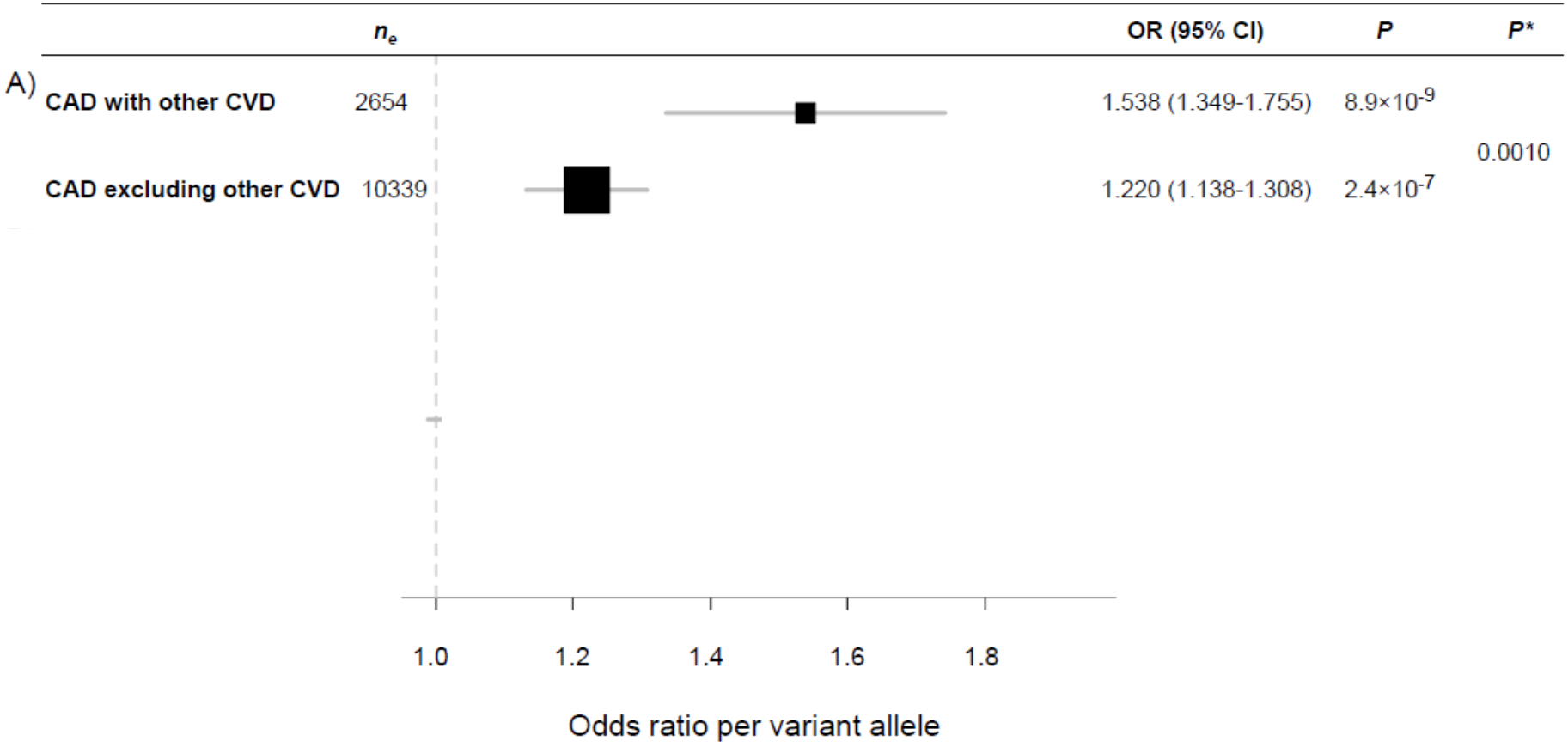
Carriers are more likely to have a widespread coronary disease than non-carriers

Comparison of the association of *LPA* score with atherosclerotic diseases, with and without concomittant CAD

Study population	ne	OR (95% CI)	P
AAA with CAD	1960	1.523 (1.313-1.766)	2.7×10-8
AAA without CAD	2700	1.100 (0.963-1.257)	0.16
PAD with CAD	2752	1.557 (1.354-1.791)	5.4×10-10
PAD without CAD	1397	1.174 (0.960-1.434)	0.12
LAA with CAD	639	0.985 (0.729-1.332)	0.92
LAA without CAD	1137	1.297 (1.056-1.592)	0.013

Suggesting that carriers of the *LPA* variants were more likely to have atherosclerotic manifestations in more than one vascular bed (↑atherosclerotic severity)

CAD cases carrying *LPA* risk alleles have increased risk of atherosclerosis in vascular beds outside the coronary tree



Summary

The two variants in the *LPA* gene, previously shown to correlate with Lp(a) levels and CAD, associate with three atherosclerosis related diseases, i.e. the LAA subtype of ischemic stroke, PAD, and AAA

We reported a correlation between the *LPA* variants and the number of obstructed coronary arteries and with earlier diagnosis of CAD

We show that CAD cases carrying *LPA* risk alleles have increased susceptibility to atherosclerotic manifestations outside the coronary tree

Summary

In contrast, we found no association with the ischemic stroke subtypes cardioembolism and small vessel disease, which have less obvious atherosclerotic components, or with cardiovascular diseases that do not have atherosclerotic aetiology, such as venous thromboembolism and intracranial aneurysm

Further, *LPA* score did not associate with thrombotic events (i.e. MI) among patients with angiographic CAD

Conclusion

These findings imply that risk conferred by high Lp(a) levels is mediated through atherosclerotic rather than thrombotic aspects of vascular disease

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