SUPPLEMENTAL MATERIAL

Genetic factors explain a major fraction of the 50% lower lipoprotein(a) concentrations in Finns

Running title: Genetic factors lower Lp(a) in Finns

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Supplementary Note

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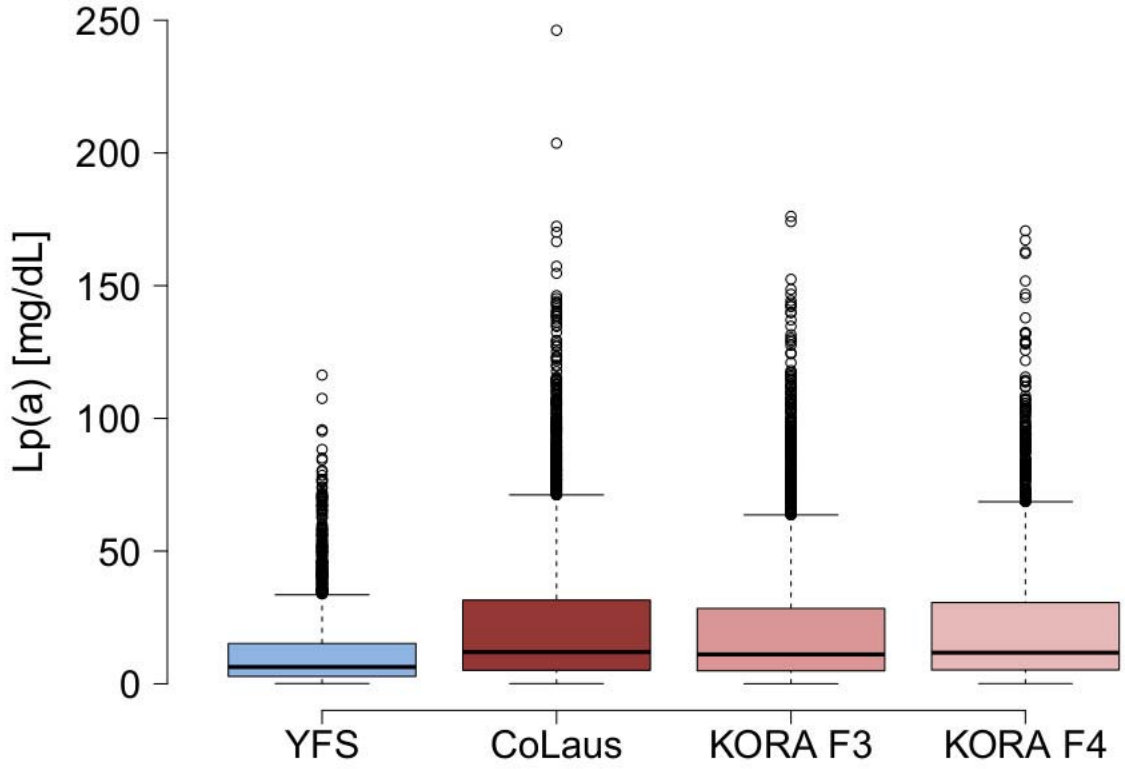
Supplementary Figures

Supplementary Figure I:

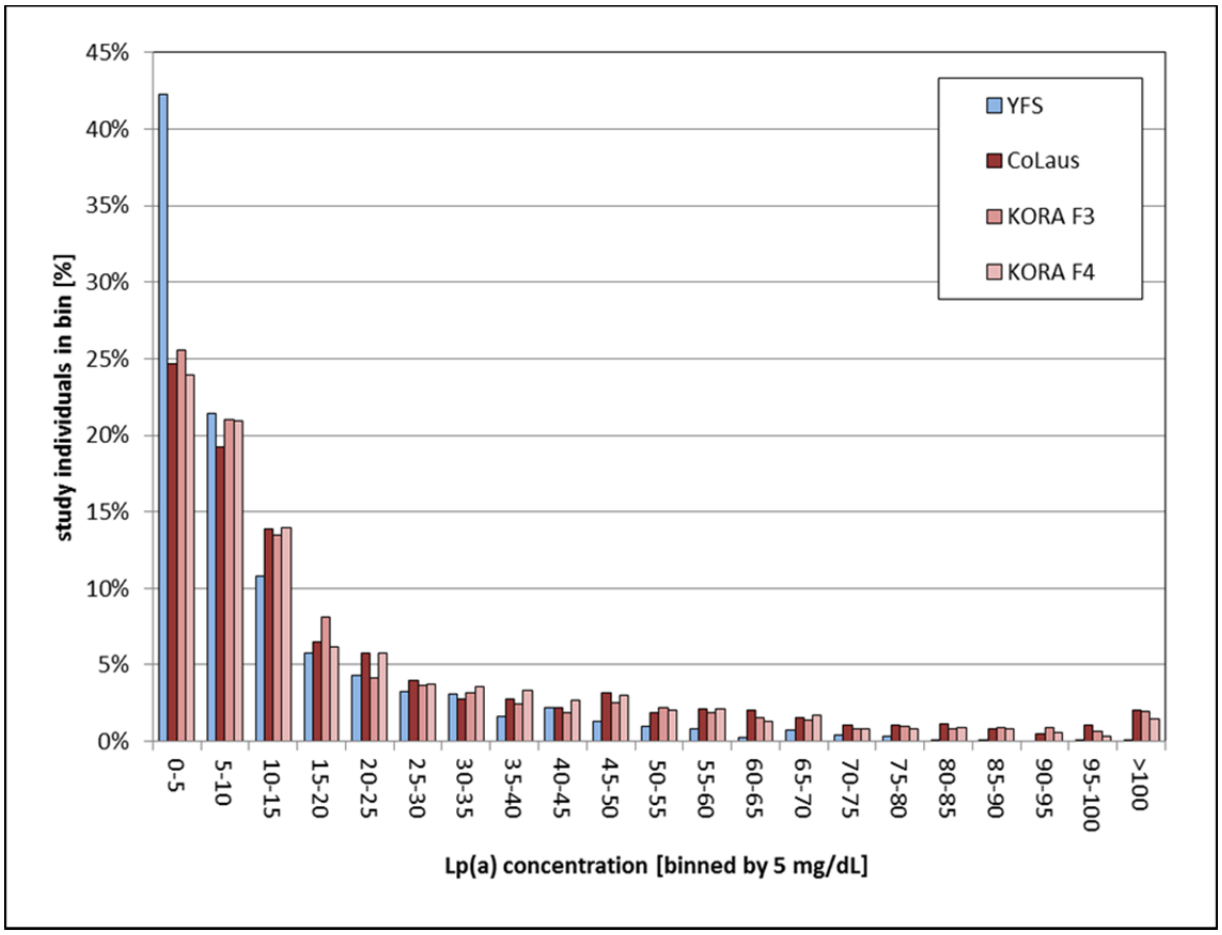
Full boxplots of Lp(a) concentrations for each population.



Supplementary Figure II:

Distribution of Lp(a) concentrations

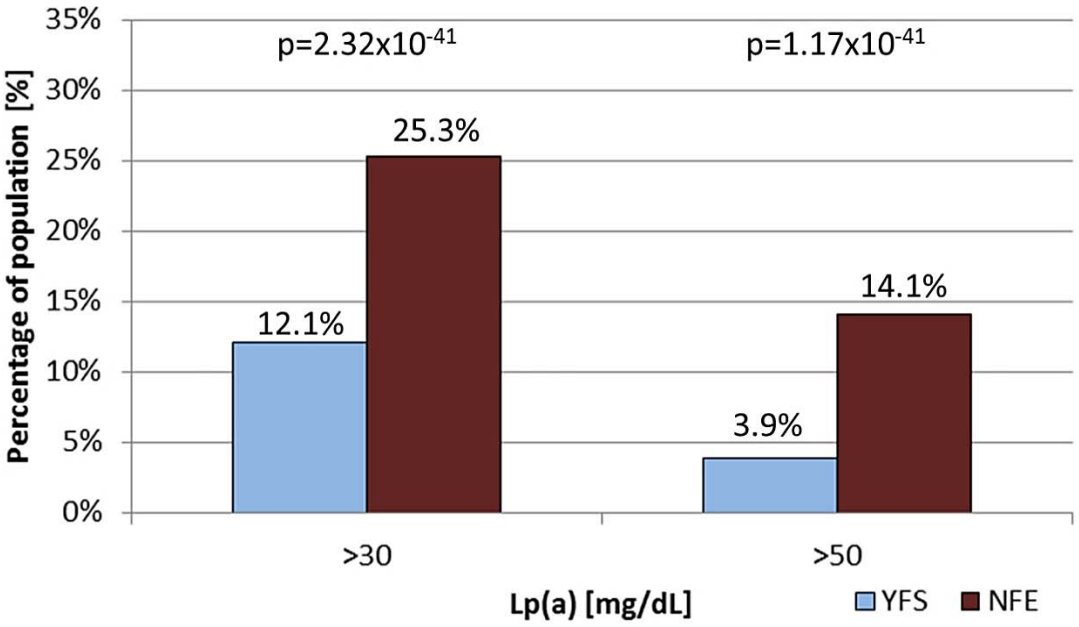
Frequencies of Lp(a) concentrations in studies. Percent of individuals of each study in the bins of 5 mg/dL Lp(a) are shown. An elevated proportion of YFS shows Lp(a) concentrations of 0-5 mg/dL.



Supplementary Figure III:

Percentage of populations with Lp(a) concentrations >30 mg/dL and >50 mg/dL

Percentage of YFS and NFE individuals presenting Lp(a) concentrations increasing CVD risk (>30[1] and >50[2] mg/dL).



Supplementary Figure IV:

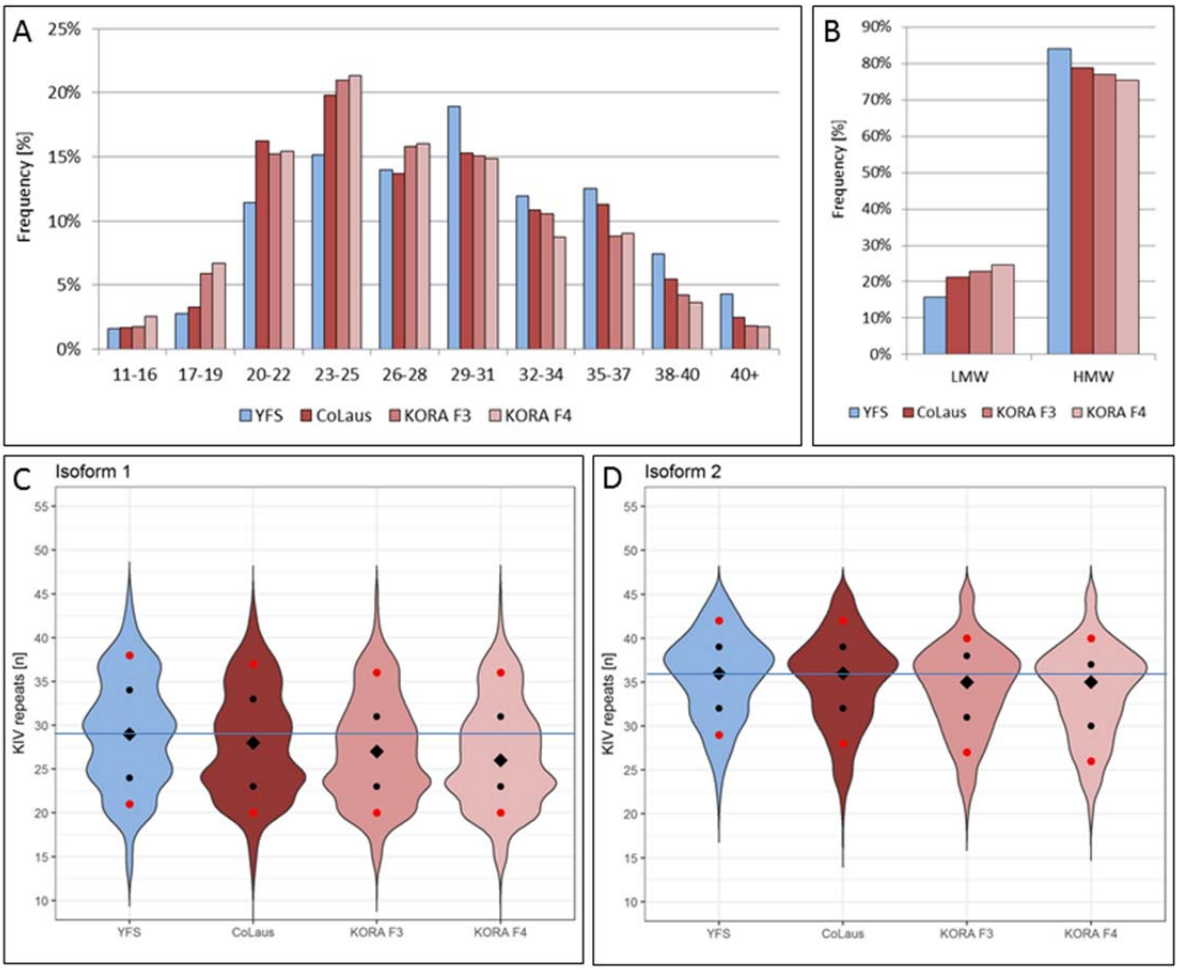
Apo(a) isoform distribution in the populations.

A: Apo(a) isoform 1 distribution in the populations. Panel A shows the apo(a) isoform 1 distribution in the different populations. YFS has markedly higher frequencies of carriers of isoforms containing >28 KIV repeats in isoform 1, so subsequently in YFS is also a higher frequency of probands grouped into HMW, which is shown in panel B. Table with the numbers of probands in each group is given in Figure 3 of the main manuscript.

B: Frequencies LMW vs. HMW. Frequencies of probands in each study grouped into LMW or HMW are shown. YFS show reduced LMW frequency and accordingly a higher HMW frequency compared to the NFE-populations.

C and D: Apo(a) isoform distribution of the two alleles. The Violin plots show distributions of the smaller allele (Isoform 1, panel C) and the larger allele (if detectable on the Western blot, Isoform 2, panel D) in the populations. In both panels the distribution of the apo(a) isoforms is shifted towards larger alleles in YFS compared to the other populations. In the Isoform 2, the samples in the CoLaus study have the same median apo(a) isoform as YFS.

diamonds: median; black dots: 25th, 75th percentile; red dots: 10th and 90th percentiles



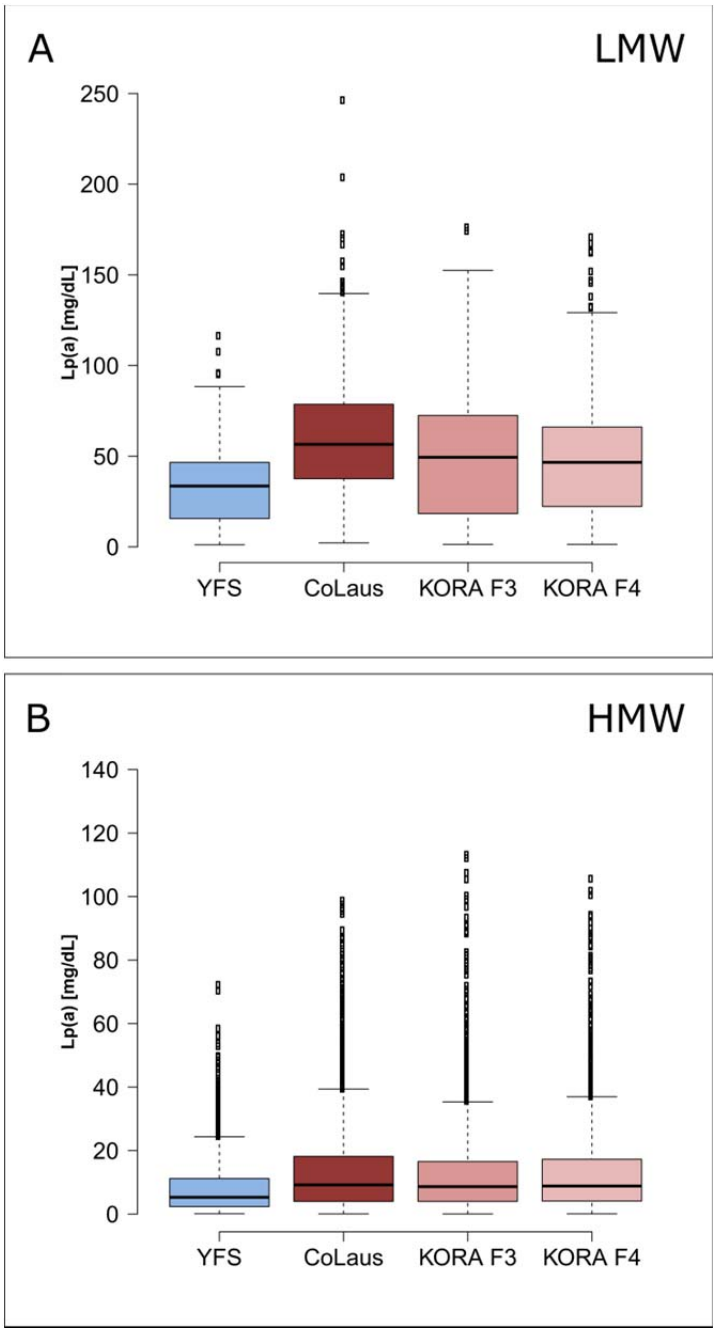
Supplementary Figure V:

Boxplots of Lp(a) concentrations by LMW/HMW status.

A: Lp(a) in LMW carriers. The boxplots of Lp(a) concentrations are shown for all LMW isoform carriers in each population.

B: Lp(a) in HMW carriers. The boxplots of Lp(a) concentrations are shown for all HMW isoform carriers in each population.

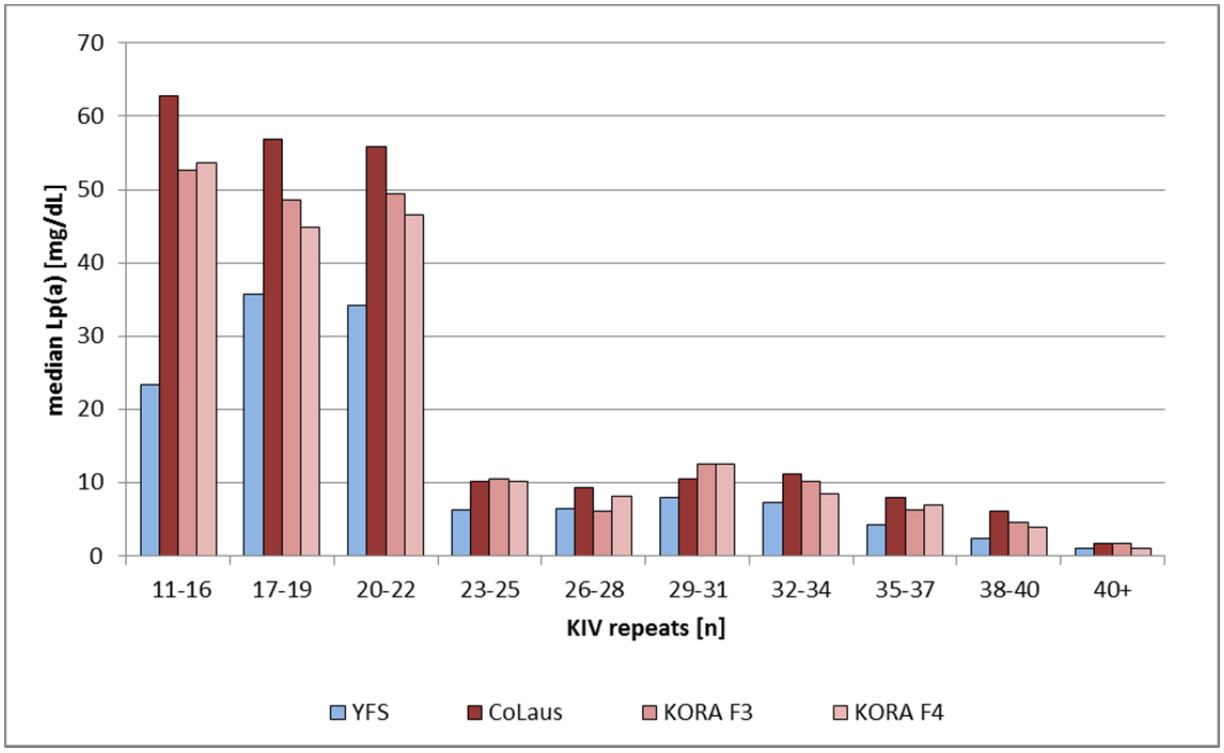
The exact median and quartile values are reported in Table 1 of the main document.



Supplementary Figure VI:

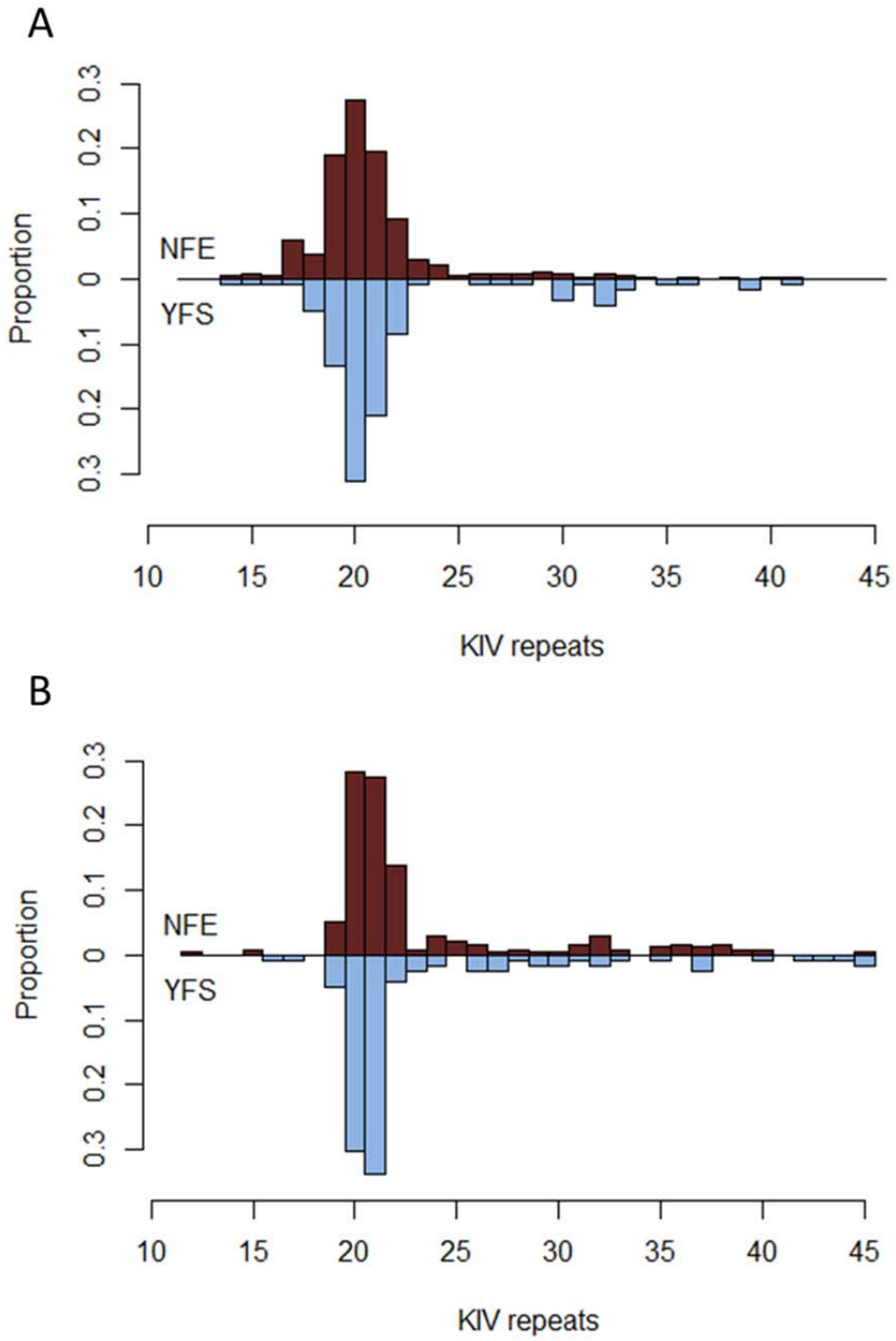
Median Lp(a) concentrations.

Histogram showing the median Lp(a) concentration in each population stratified by KIV repeats. YFS have lower Lp(a) concentrations than the NFE subgroups over the entire isoform range. The number of probands in each group is given in Supplementary Table IV and the exact values are given in Supplementary Table V.



Supplementary Figure VII:

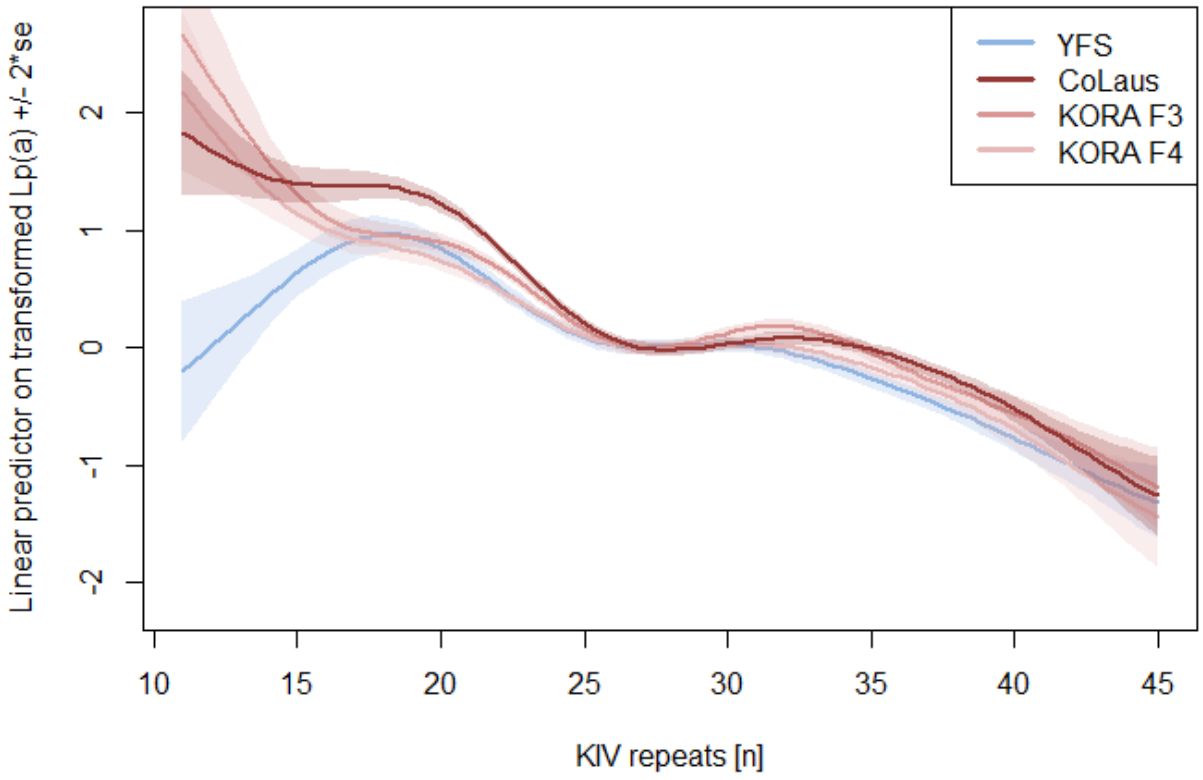
Histograms showing the distribution of rs10455872 (A) and rs3798220 (B) in the different populations. No differences in the distribution were observed (p=0.20 and p=0.61).The



Supplementary Figure VIII:

Nonlinear Spline

Spline showing the effect of the small isoform (isoform 1) on inverse normal transformed Lp(a) levels. The spline are centered at 0 at isoform 1 = 27 (median on the NFE studies) and is derived from the multiple regression model additionally adjusting for the variables age, sex, eGFR, rs143411368, rs41272114, rs11591147, rs10455872, rs3798220, APOE2 and APOE4-carriers (Supplementary Table VI). se: standard error.



Supplementary Tables

Supplementary Table I:

Lp(a) concentrations [mg/dL] stratified by (a) sex and (b) additionally including only participants in the age range ≥32 to ≤39 years, where all studies overlap.

Study	25th percentile	Median	Mean	75th percentile	Wilcoxon-test p-value
All participants					
Men, YFS (n= 1,026)	2.62	6.09	12.15	14.39	$9.66x10^{-36}$
Men, NFE (n= 4,773)	4.46	10.65	20.98	28.16	
Women, YFS (n= 1,255)	2.86	6.56	12.70	15.74	$5.61x10^{-59}$
Women, NFE (n= 5,230)	5.62	12.64	23.83	32.51	
Age range ≥32 to ≤39 years.					
Men, YFS (n=528)	2.75	6.42	12.79	15.19	$3.083x10^{-05}$
Men, NFE (n=311)	4.01	9.58	17.96	21.27	
Women, YFS (n=658)	2.80	6.58	12.67	15.59	$1.42x10^{-07}$
Women, NFE (n=354)	4.80	10.04	17.89	22.94	

Supplementary Table II:

Lp(a) concentrations in percentiles.

Lp(a) concentration percentile data is shown in YFS and NFE - both grouped and split up in single populations.

	Percentiles Lp(a) [mg/dL]						
Study	**5**	**10**	**25**	**50**	**75**	**90**	**95**
YFS (n=2,281)	0.96	1.33	2.78	6.32	15.19	33.05	45.7
NFE (n=10,003)	1.57	2.29	5.07	11.59	30.43	60.35	79.84
CoLaus (n=3,998)	1.42	2.17	5.1	11.94	31.51	62.74	81.71
KORA F3 (n=3,089)	1.82	2.52	4.89	11.07	28.4	59.48	81.26
KORA F4 (n=2,916)	1.46	2.13	5.23	11.73	30.6	56.36	73.19

Supplementary Table III:

Apo(a) isoform percentiles of both isoforms

Table shows percentiles of the apo(a) isoform size stratified in the smaller and – if determinable – the larger isoform in YFS and NFE, both grouped and in single populations. In YFS both isoforms are larger than in NFE.

		Percentiles KIV repeats						
Isoform	**Study**	**5**	**10**	**25**	**50**	**75**	**90**	**95**
Isoform 1	**YFS (n=2,281)**	20.0	21.0	24.0	29.0	34.0	38.0	40.0
	NFE (n=10,003)	19.0	20.0	23.0	27.0	32.0	36.0	38.0
	CoLaus (n=3,998)	20.0	20.0	23.0	28.0	33.0	37.0	39.0
	KORA F3 (n=3,089)	19.0	20.0	23.0	27.0	32.0	36.0	38.0
	KORA F4 (n=2,916)	19.0	20.0	23.0	26.0	31.0	36.0	38.0
Isoform 2	**YFS (n=2,281)**	27.0	29.0	32.0	36.0	39.0	42.0	43.0
	NFE (n=10,003)	25.0	27.0	31.0	35.0	38.0	40.0	42.0
	CoLaus (n=3,998)	25.0	28.0	32.0	36.0	39.0	42.0	43.0
	KORA F3 (n=3,089)	25.0	27.0	31.0	35.0	38.0	40.0	42.0
	KORA F4 (n=2,916)	24.0	26.0	30.0	35.0	37.0	40.0	41.0

Supplementary Table IV:

Numbers of probands in isoform 1 strata of all studies

	Probands in each group [n]									
KIV-repeats (grouped)	**11-16**	**17-19**	**20-22**	**23-25**	**26-28**	**29-31**	**32-34**	**35-37**	**38-40**	**40+**
YFS (n=2,281)	37	63	261	345	319	431	273	286	169	97
NFE (n=10,003)	194	510	1568	2061	1502	1510	1013	985	455	205
CoLaus	66	131	649	793	548	610	433	450	218	100
KORA F3	54	183	470	647	487	466	325	272	130	55
KORA F4	74	196	449	621	467	434	255	263	107	50

Supplementary Table V:

Median [25%/75% percentiles] Lp(a) concentrations per isoform group

Table shows the median and the 25%/75% percentiles for each apo(a) isoform group.

	Isoform group									
Lp(a) [mg/dL]	**11-16**	**17-19**	**20-22**	**23-25**	**26-28**	**29-31**	**32-34**	**35-37**	**38-40**	**40+**
YFS (n=2,281)	23.41 [4.45 / 39.80]	35.79 [15.40 / 45.58]	34.15 [20.22 / 50.68]	6.32 [4.18 / 14.08]	6.53 [2.35 / 16.08]	8.02 [2.89 / 14.05]	7.24 [3.59 / 11.10]	4.21 [2.29 / 6.55]	2.49 [1.58 / 4.46]	1.05 [0.69 / 1.83]
NFE (n=10,003)	56.43 [42.17 / 78.23]	48.54 [27.89 / 67.57]	51.23 [25.72 / 73.09]	10.33 [6.30 / 22.68]	8.19 [2.97 / 22.03]	11.62 [3.92 / 20.85]	10.26 [5.30 / 15.96]	7.05 [4.00 / 11.71]	4.91 [2.71 / 8.27]	1.44 [0.71 / 2.82]
CoLaus (n=3,998)	62.76 [48.54 / 88.28]	56.94 [40.93 / 73.15]	55.86 [35.07 / 78.53]	10.20 [6.38 / 23.30]	9.39 [3.17 / 23.56]	10.59 [3.28 / 21.37]	11.27 [5.27 / 18.18]	7.94 [4.19 / 12.61]	6.08 [2.98 / 9.61]	1.68 [0.85 / 3.39]
KORA F3 (n=3,089)	52.62 [41.14 / 70.87]	48.55 [16.42 / 68.00]	49.35 [18.28 / 73.97]	10.50 [6.46 / 22.07]	6.08 [2.94 / 19.62]	12.64 [4.49 / 20.11]	10.19 [5.60 / 15.53]	6.24 [3.78 / 9.70]	4.64 [2.74 / 7.40]	1.75 [0.73 / 2.28]
KORA F4 (n=2,916)	53.66 [34.59 / 70.04]	44.87 [30.76 / 60.85]	46.59 [16.21 / 66.09]	10.16 [6.20 / 23.03]	8.21 [2.79 / 21.88]	12.49 [4.62 / 20.26]	8.54 [4.65 / 14.35]	7.00 [3.95 / 11.69]	4.01 [2.34 / 7.11]	1.00 [0.59 / 1.81]

Supplementary Table VI:

Results of multiple regression analysis in all studies individually. The effect of the isoforms (isoform 1) on Lp(a) and inverse normally transformed Lp(a) levels in all individual studies is shown as nonlinear spline in Figure 5 in the main document.

Variable	Results from multiple regression model on Lp(a)* in							
	YFS		KORA F3		KORA F4		CoLaus	
	β	p	β	p	β	p	β	p
Age	0.07	0.3962	0.13	0.0025	0.1	0.0002	0.14	$9.26x10^{-06}$
Sex (f)	0.62	0.0368	2.72	$2.21x10^{-09}$	2.46	$2.61x10^{-05}$	2.84	$5.40x10^{-09}$
Isoforms[$]	--	$2.60x10^{-124}$	--	$1.19x10^{-165}$	--	$1.51x10^{-132}$	--	$1.10x10^{-242}$
eGFR	-0.03	0.1899	-0.04	0.0073	-0.03	0.2565	-0.02	0.4521
rs143411368[#]	-2.6	$5.33x10^{-09}$	-3.57	0.3511	-8.19	0.0093	1.29	0.5796
rs41272114[#]	-2.45	$6.38x10^{-19}$	-4.4	$2.28x10^{-14}$	-4.66	$5.69x10^{-14}$	-6.55	$4.17x10^{-32}$
rs11591147[#]	0.53	0.9545	-4.11	0.0056	0.66	0.5601	1.87	0.5118
rs10455872[#]	11.68	$1.33x10^{-13}$	24.12	$6.68x10^{-39}$	20.98	$1.17x10^{-28}$	13.14	$8.59x10^{-17}$
rs3798220[#]	28.03	$3.37x10^{-14}$	41.13	$2.42x10^{-26}$	43.83	$4.44x10^{-31}$	44.3	$6.95x10^{-35}$
APOE2 carrier	-2.34	0.0071	-5.02	$3.80x10^{-11}$	-2.19	0.0026	-3.01	$8.44x10^{-06}$
APOE4 carrier	-0.21	0.6147	-1.96	0.0100	0.48	0.4403	0.06	0.8923

*β estimates are derived from models on Lp(a); p-values are derived from models on inverse normal transformed Lp(a) values to ensure normal distribution assumption

[$] p-values for isoforms refers to the significance of a nonlinear spline of isoform 1 on inverse-normal transformed Lp(a); for effect size: see nonlinear spline in Figure 4 and Supplementary Figure VIII

[#] For SNPs, an additive inheritance model was assumed

Supplementary Table VII:

Mediation analysis results on inverse normal transformed Lp(a) including only those variables, which qualify for mediation analysis

Variable	YFS		Identified as mediator	Relative effects	
	P-value 1	P-value 2		estimate §	95 % CI*
Explained effects†				0.718	[0.634, 0.806]
Age	<0.001	<0.001	✓	0.264	[0.185, 0.348]
Sex (f)	<0.001	0.019	✓	-0.006	[-0.013, -0.001]
Apo(a) isoforms	<0.001	<0.001	✓	0.273	[0.235, 0.310]
eGFR	<0.001	<0.001	✓	0.104	[0.052, 0.157]
rs143411368	<0.001	<0.001	✓	0.038	[0.024, 0.055]
rs41272114	<0.001	<0.001	✓	0.040	[0.024, 0.054]
rs11591147	0.601	--	--	--	--
rs10455872	<0.001	0.020	✓	0.025	[0.010, 0.039]
rs3798220	<0.001	0.164	--	--	--
APOE2 carrier	<0.001	<0.001	✓	-0.018	[-0.025, -0.011]
APOE4 carrier	0.103	<0.001	--	--	--
Unexplained effect ‡				0.282	[0.194,0.366]

P-value 1: Type-3 tests in the full model, testing, whether factors are associated with Lp(a); P-value 2: Tests of relationship of each factor with the predictor (YFS/NFE-difference)

*95%CI were derived with bootstrap samples assuming normal approximation

† "indirect effect" of the mediation analysis

‡ "direct effect" of the mediation analysis

§ estimates rounded, may not add up to exactly to 1

Supplementary Table VIII:

Imputation details

This table shows the imputation details and quality of the populations in this study.

	YFS	CoLaus	KORA F3	KORA F4
Microarray used	Illumina 670k	Affymetrix GeneChip® Human Mapping 500K	Illumina Omni 2.5/ Illumina Omni Express	Affymetrix Axiom
QC before imputation	callrate >95%, p-value HWE > 10^{-6}, MAF>1%	callrate >90%*, p-value HWE > 10^{-7}	callrate >98%, p-value HWE > 10^{-10}	callrate >98%, p-value HWE > 10^{-10}
Program used for imputation	IMPUTE	minimac	IMPUTE	IMPUTE
Reference panel for imputation	1000G phase1v3[3]	1000G phase1v3[3]	HRC panel[4]	HRC panel[4]

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