

Supplementary file to

Lipoprotein(a) in atherosclerotic cardiovascular disease and aortic stenosis: A European Atherosclerosis Society Consensus Statement

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1 Further information on the genetic control of Lp(a) concentration

2 Further to the main text and Figure 1 and detailed discussion in a recent review ¹, this section
3 summarizes the most important characteristics of the genetic regulation of lipoprotein(a)
4 [Lp(a)] concentration.

5 The *LPA* gene locus explains up to 90% of Lp(a) variance.^{2, 3} About 30-70% of Lp(a)
6 concentration is attributed to apo(a) isoform size, which is determined by the number of
7 Kringle IV (KIV) repeats. There is an inverse correlation between the number of KIV repeats and
8 Lp(a) concentration.⁴ Individuals with a low number of KIV repeats (up to 22 repeats) have small
9 apo(a) isoforms and usually have median Lp(a) concentrations 4-5 times higher than those who
10 carry only large isoforms (> 22 KIV repeats). This inverse relationship is most probably caused
11 by more efficient maturation of smaller apo(a) proteins in the endoplasmatic reticulum.^{5, 6}

12 Two well-known single nucleotide polymorphisms (SNPs), rs10455872 and rs3798220, are
13 usually observed with small apo(a) isoforms and are associated with high Lp(a) concentrations.⁷
14 However, this so-called "tagging" (meaning that they are simply proxies of the mentioned two
15 SNPs) is far from perfect since only about 50% of small isoform carriers are also carriers of one
16 or both of the mutated variants of these two SNPs.⁸ Additionally, these two SNPs might not
17 have direct functional consequences.

18 The complex relationship between apo(a) isoform and Lp(a) concentration is also modified by
19 several functional SNPs (see Figure 1 in the man manuscript for overview), resulting in a large
20 variance in individual Lp(a) concentrations within each isoform group.¹ The *LPA* gene contains a
21 large number of loss of function mutations with a wider range of allele frequencies. Some of
22 these occur only in defined isoform size ranges and concomitantly influence the Lp(a)
23 concentration trait (reviewed in ¹).

24 With the introduction of new methods, exploration of the highly repetitive KIV type-2 region for
25 mutations and polymorphisms is only now possible, more than 500 have been discovered ⁹ and
26 functional characterization is ongoing. Among these are two splice site variants, 4925G>A and
27 4733 G>A, which are highly frequent (22% and 38% are carriers, respectively) and result in a
28 pronounced decrease in Lp(a) concentration (by ≈30 and 13 mg/dL, respectively) and a lower
29 risk for cardiovascular disease.^{10, 11} These two variants are the second and third strongest
30 relative contributors to Lp(a) concentration beyond apo(a) isoform size.¹¹

31 Ethnic differences in Lp(a) concentration are partially explained by genetic variants in the *LPA*
32 gene, in particular loss of function variants such as rs41272114 ¹² or rs143431368 ¹³ which vary
33 considerably in frequency between ethnic groups.

34

1 **Extended discussion of non-genetic influences on Lp(a) concentration**

2 This is an extended discussion to information in the text and Table 1 of the main document.

3 Although Lp(a) plasma concentrations are under strong genetic regulation, non-genetic factors
4 also play a role. Some but not all studies reported that short-term (3–8 weeks) isocaloric
5 replacement of saturated fatty acids with carbohydrate or unsaturated fats increased Lp(a)
6 concentration by 10-15%.¹⁴ In a recent randomized feeding trial, a low carbohydrate-high
7 saturated fat diet lowered Lp(a) concentration moderately (by 15% compared with a high
8 carbohydrate diet) and improved insulin resistance in a dose-dependent manner.¹⁵

9 Hormones may also influence Lp(a) concentration, especially those with important roles in lipid
10 metabolism, such as thyroid hormone. In a recent systematic review and meta-analysis,
11 treatment of overt hyperthyroidism increased Lp(a) concentration, whereas treatment of overt
12 hypothyroidism decreased Lp(a) concentration.¹⁶ Growth hormone replacement therapy in
13 men also increased Lp(a) concentration.¹⁷ While endogenous sex hormones do not appreciably
14 impact Lp(a) concentration, some studies reported elevation in Lp(a) concentration during
15 pregnancy, returning to baseline concentrations postpartum. There is, however, evidence that
16 administration of exogenous androgens and oestrogen reduces Lp(a) concentration. A meta-
17 analysis of oral postmenopausal hormonal therapy showed a mean 25% reduction in Lp(a)
18 concentration independent of the type of therapy.¹⁸ Most studies suggest that physical activity
19 has no or minimal impact on Lp(a) concentration, although there are conflicting data,
20 particularly among younger or diabetic populations.^{19, 20}

21 Kidney function also impacts Lp(a) concentration.^{21, 22} Lp(a) concentration increases with
22 decreasing glomerular filtration rate, being highest in patients with end-stage kidney function
23 treated by peritoneal dialysis or in those with nephrotic syndrome.^{23, 24} In the latter group, it is
24 assumed that these very high concentrations are caused by increased hepatic synthesis of
25 several proteins triggered by the pronounced loss of proteins via urine and dialysate.²¹ In other
26 conditions, elevated Lp(a) concentration seems to be related to impaired catabolism and is
27 mainly observed in patients with large apo(a) isoforms.²¹ Following kidney transplantation,
28 Lp(a) concentration decreases independent of the modality of immunosuppressive therapy.²⁵

29 Hepatocellular damage has been associated with reduced Lp(a) concentration in parallel with
30 disease progression, leading some to suggest Lp(a) is a marker of hepatic cell damage.²⁶
31 Whether this also applies to non-alcoholic fatty liver disease is uncertain.²⁷

32 Finally, pre-clinical models suggest that inflammation influences Lp(a) concentration.²⁸
33 Clinically, reduction in Lp(a) concentration was reported in severe, life-threatening acute phase
34 conditions (sepsis, severe burns), whereas increased levels were reported in several
35 inflammatory conditions.²⁹ A modest increase related to interleukin (IL)-6 concentrations was

1 reported in population studies, with a reduction in Lp(a) concentration during treatment with a
2 monoclonal antibody targeting IL-6 (tocilizumab) in rheumatoid arthritis patients.³⁰ The latter
3 effect has been attributed to the IL-6 responsive element in the *LPA* promotor region.³¹ In
4 human immunodeficiency virus patients with baseline Lp(a) concentrations >20-30 mg/dL,
5 treatment with protease inhibitors or antiretroviral therapy was associated with increased Lp(a)
6 concentration.^{32, 33}

7 In population studies, the clinical impact of inflammation on Lp(a) concentration is small. For
8 example, among 34,829 individuals in the Copenhagen City Heart Study/Copenhagen General
9 Population Study, Lp(a) concentration was only slightly higher in those with higher C-reactive
10 protein (CRP) levels (3 mg/dL difference in Lp(a) concentration when comparing individuals with
11 CRP <1 vs > 10 mg/L), and the association of baseline Lp(a) with ASCVD risk was not modified by
12 baseline inflammation status.³⁴ In the JUPITER study, in which individuals were recruited on the
13 basis of elevated CRP concentration, Lp(a) concentration remained remarkably stable over a
14 one-year period irrespective of treatment (statin or placebo; intraclass correlation coefficient
15 0.92 and 0.93, respectively).³⁵ Moreover, there is no evidence of differences in Lp(a)
16 concentration in coronary artery disease patients with or without inflammatory disease, or of a
17 causal association with low-grade inflammation.³⁶ Given the extent of uncertainty in this area,
18 further study is indicated.

19 Finally, while air pollution has been shown to influence several cardiovascular risk factors,
20 studies investigating effects on Lp(a) are sparse. A recent US-based study which measured Lp(a)
21 regularly over a period of one year reported that long-term exposure to fine particle matter
22 (PM_{2.5}) had Lp(a)-increasing effects which were stronger than for any other
23 lipoprotein/apolipoprotein.³⁷ These fine particles cause oxidative stress and inflammation and
24 disturb the normal function of lipoproteins and apolipoproteins.

25

1 **Supplementary material on Lp(a) and diabetes mellitus**

2 Meta-analysis of studies investigating the association of Lp(a) and diabetes mellitus

3 A random effects meta-analysis was performed to estimate the pooled effect size. This analysis
4 used the generic inverse variance method for meta-analysis on estimates³⁸ that uses regression
5 estimates and standard errors as input, and the DerSimonian-Laird method to estimate the
6 between-study variance³⁹, implemented as a metagen function in meta R package. Log relative
7 risks were used as input to the meta-analysis function.^{40, 41} While most studies estimated
8 relative risk for the lowest quintile using the upper quintile as a reference, Langsted et al used
9 quartiles⁴², Kaya et al used tertiles⁴³, and Gudbjartsson et al⁴⁴ contrasted the lowest decile
10 with pooled data for the other nine deciles. To align the relative risks on the same scale, two
11 approaches could have been used – either converting all relative risks to the same scale of Lp(a)
12 measurement, or to perform rank-based conversion. Lp(a) measurements are sensitive to
13 specific calibration criteria used by the laboratories which varies across the laboratories.
14 Additionally, conversion of ranks is more conservative. Therefore, a more conservative
15 approach was adopted with conversion of the ranks. Assuming linearity of log relative risks
16 across percentile categories, non-quintiles log relative risks were converted to a quintile scale
17 using the following formulas:

- 18 • Middle percentile of the top quintile was 90%, middle percentile of the bottom quintile was
19 10%, therefore, quintile_logRR was contrasting 90%-10%=80%
- 20 • Middle percentile of the top quartile was 75+12.5=87.5%, middle percentile of the bottom
21 quartile was 12.5%, therefore quartile_logRR was contrasting 87.2%-12.5%=75% hence
22 conversion formula was: $\logRR_{\text{quintile}} = \text{quartiles}_{\logRR} \times 80 / 75$
- 23 • Middle percentile of the top tertile was 66+16.5=82.5%, middle percentile of the bottom
24 tertile was 16.5%, therefore tertile_logRR was contrasting 83.5%-16.5%=66% hence
25 conversion formula was: $\logRR_{\text{quintile}} = \text{tertile}_{\logOR} \times 80 / 66$
- 26 • Middle percentile of the top deciles was 55%, middle percentile of the bottom decile was
27 5%, therefore decile_logRR was contrasting 55%-5%=50% hence conversion formula was:
28 $\logRR_{\text{quintile}} = \text{decile}_{\logRR} \times 80 / 50$

29

30

1 **Supplementary Table 1:** Overview of studies investigating the association of Lp(a)
 2 concentration with diabetes mellitus.

Citation	Cohort	No. of subjects	No. of cases	Group comparisons and risk estimates	
				Lp(a) (mg/dL)	Relative Risk (95% CI)
Mora (2010) ⁴⁵	Women's Health Study	26,746	1,670	3.9 vs 45.3	1.28 (1.10-1.49)
Tolbus (2017) ⁴⁶	CCHS	8,390	832	1 vs 48	1.33 (1.12-1.58)
Kamstrup (2013) ⁴⁷	CCHS/CGPS	29,106	2,157	4 vs 55	1.26 (1.09-1.45)
Langsted (2021) ⁴²	CGPS	70,286	3,519	4.7 vs 29 ^b	1.39 (1.26-1.54)
Ye (2014) ⁴⁸	EPIC-Norfolk	18,490	593	5.3 vs 35.3	1.59 (1.23-2.05)
Kaya (2017) ⁴³	Turkey	1,685	90	6.5 vs 17.2 ^c	1.79 (1.01-3.23)
Paige (2017) ⁴⁹	Bruneck	815	94	3.6 vs 27.1	1.37 (0.74-2.53)
Gudbjartsson (2019) ⁴⁴	Iceland, case control	10,295	1,548	<3.5 ^d vs ≥3.5	1.44 (1.21-1.71)
TOTAL		165,813	10,503		

3 ^a This table provides the originally described estimates reported in the mentioned publications which is
 4 different for three of the studies ^{42,43,44} from those in Figure 5 of the manuscript and Supplementary
 5 Figure 1 where non-quintile log relative risks were converted to a quintile scale.

6 ^b Q, quartiles; ^c tertiles; ^d lowest decile;

7 CCHS, Copenhagen City Heart Study; CGPS, Copenhagen General Population Study

8

9

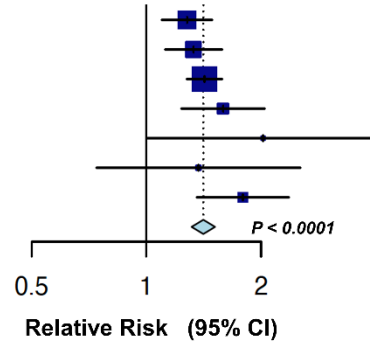
10

1 **Supplementary Figure 1: Sensitivity analysis on Lp(a) and diabetes mellitus**

- 2 Analysis as in Figure 5 of the main manuscript but excluding the Kamstrup et al study⁴⁷ (for
 3 potential overlap with the Tolbus et al.⁴⁶ and Langsted et al.⁴² studies) in **Panel A** or when
 4 excluding the case-control study by Gudbjartsson et al.⁴⁴ in **Panel B**.

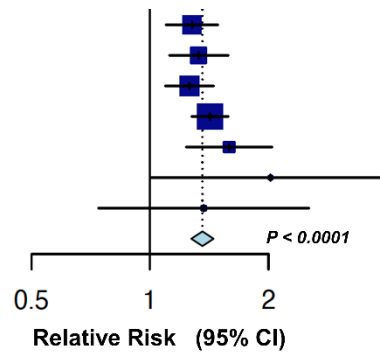
A

Study (Year)	RR [95% CI]
Mora (2010)	1.28 [1.10; 1.49]
Tolbus (2017)	1.33 [1.12; 1.58]
Langsted (2021)	1.42 [1.28; 1.58]
Ye (2014)	1.59 [1.23; 2.05]
Kaya (2017)	2.03 [1.00; 4.10]
Paige (2017)	1.37 [0.74; 2.53]
Gudbjartsson (2019)	1.79 [1.36; 2.36]
Total	1.41 [1.31; 1.52]
Heterogeneity: $\chi^2_6 = 6.80$ ($P = .34$), $I^2 = 12\%$	



B

Study (Year)	RR [95% CI]
Mora (2010)	1.28 [1.10; 1.49]
Tolbus (2017)	1.33 [1.12; 1.58]
Kamstrup (2013)	1.26 [1.09; 1.45]
Langsted (2021)	1.42 [1.28; 1.58]
Ye (2014)	1.59 [1.23; 2.05]
Kaya (2017)	2.03 [1.00; 4.10]
Paige (2017)	1.37 [0.74; 2.53]
Total	1.36 [1.27; 1.45]
Heterogeneity: $\chi^2_6 = 5.11$ ($P = .53$), $I^2 = 0\%$	



1 **Should aspirin be given to patients with high Lp(a)?**

2 Based on current data, there are no clinical indications for targeting aspirin use according to
3 Lp(a) levels. In a post hoc analysis of the Women’s Health Study, a randomized primary
4 prevention trial, treatment with aspirin (100 mg every other day) versus placebo in women
5 with Lp(a) >65 mg/dL did not significantly reduce cardiovascular events over a 10-year period
6 (age-adjusted hazard ratio 0.75 (95% CI: 0.48–1.18, p=0.22). In a subgroup analysis, carriers of
7 the rs3798220 variant with baseline median Lp(a) ≈80 mg/dL significantly benefitted from
8 aspirin treatment (HR 0.44, 95% CI: 0.20–0.94, p = 0.03).⁵⁰ This gives the impression that aspirin
9 might be beneficial at extreme Lp(a) levels. However, as this subgroup analysis was based on
10 only 19 patients with events in the carrier group, these data await replication. Individuals with
11 high Lp(a) levels might be considered for aspirin therapy if they have other indications for
12 aspirin therapy (e.g. very high ASCVD risk and low bleeding risk).

13

14

1 **Supplemental Text for Figure 2C, 2D and 2E of the main document:**

2 **Panels C and D of Figure 2** were constructed by using natural cubic splines to plot the hazard
3 ratio for increasing levels of Lp(a) and the lifetime risk of major cardiovascular events among
4 422,409 participants of the UK Biobank who self-identified as being of either White (n=415,274)
5 or Black (n=7,135) ancestry. Age was used as the time scale. Participants were censored at the
6 age of first major cardiovascular event (defined as the composite of the first occurrence of fatal
7 or non-fatal myocardial infarction, fatal or non-fatal ischemic stroke, or coronary
8 revascularization [percutaneous coronary intervention or coronary artery bypass graft
9 surgery]). The natural cubic spline analysis used knots at the 5th 10th, 25th, 50th, 75th, 90th
10 and 95th percentile of plasma Lp(a) levels, and 19.7 nmol/L as the reference value. **Panel C**
11 shows the results for 415,274 participants of European ancestry in the UK Biobank for whom
12 measured Lp(a) values were available; and **Panel D** shows the results of the same analysis
13 among 7,135 participants of Black ancestry in the UK Biobank for whom measured Lp(a) values
14 were available. Analyses were adjusted for age at enrolment, sex, and the first 10 principle
15 components of ancestry.

16 **Panel E of Figure 2** was constructed by dividing 415,274 participants of European ancestry in
17 the UK Biobank with measured Lp(a) values into six groups with increasing median Lp(a)
18 concentrations:

- 19 1. a reference group with median Lp(a) 16 nmol/L or approximately 7 mg/dL (n=290,193);
- 20 2. a group with median Lp(a) 70 nmol/L or approximately 30 mg/dL (n=34,284);
- 21 3. a group with median Lp(a) 115 nmol/L or approximately 50 mg/dL (n=32,380);
- 22 4. a group with median Lp(a) 175 nmol/L or approximately 75 mg/dL (n=32,404);
- 23 5. a group with median Lp(a) 230 nmol/L or approximately 100 mg/dL (n=14,406);
- 24 6. and a group with median Lp(a) 350 nmol/L or approximately 150 mg/dL (n=11,607).

25 The cumulative incidence curves for major cardiovascular events (MCVEs, defined as the
26 composite of the first occurrence of fatal or non-fatal myocardial infarction, fatal or non-fatal
27 ischaemic stroke, or coronary revascularization [percutaneous coronary intervention or
28 coronary artery bypass graft surgery]) up to age 80 years was then plotted for participants
29 within each group. Analyses were adjusted for age at enrolment, sex, and the first 10 principle
30 components of ancestry.

31

1 **Supplemental Text for Figure 4 of the main document:**

2 In the analyses presented in Panels A and B of Figure 4, an *LPA* instrumental variable genetic
3 score was constructed by counting the number of Lp(a)-increasing risk (minor) alleles at
4 variants rs10455872 and rs3798220 inherited by 440,368 UK Biobank participants of European
5 ancestry. Each participant was then assigned to one of three groups based on the number of
6 Lp(a)-increasing alleles they inherited:

- 7 • reference group (participants who inherited no (0) Lp(a) increasing minor alleles at either
8 rs10455872 or rs3798220);
- 9 • group 1 (participants who inherited one Lp(a) increasing minor allele at either rs10455872
10 or rs3798220);
- 11 • group 2 (participants who inherited two Lp(a) increasing minor alleles – either one minor
12 allele at both rs10455872 and rs3798220, two minor alleles at rs10455872, or two minor
13 alleles at rs3798220).

14 The median Lp(a) level (in nmol/L) was then calculated for participants in each group.

15 In **Panel A**, the hazard ratio for the risk of major cardiovascular events (MCVEs, defined as the
16 composite of the first occurrence of fatal or non-fatal myocardial infarction, fatal or non-fatal
17 ischaemic stroke, or coronary revascularization [percutaneous coronary intervention or
18 coronary artery bypass graft surgery]) is presented, both for the entire population expressed as
19 a Hazard Ratio per 100 nmol/L higher Lp(a) level; and as an ordinal analysis providing the
20 Hazard Ratio for participants in each group defined by the *LPA* instrumental variable genetic
21 score as compared to the reference group (persons without any Lp(a) increasing alleles). This
22 analysis included all major cardiovascular events (n=27,187) with a conformed date (age) at first
23 occurrence (and therefore included both events that were prevalent at the time of enrolment
24 into the UK Biobank, and incident events that occurred during a median of 11.2 years of follow-
25 up. The results were very similar when restricted to either prevalent or incident events.

26 In **Panel B**, the hazard ratio for venous thrombotic events (defined as the first occurrence of
27 either a deep venous thrombosis or a pulmonary embolism) is presented, both for the entire
28 population expressed as hazard ratio per 100 nmol/L higher Lp(a) level; and as an ordinal
29 analysis providing the hazard ratio for participants in each group defined by the *LPA*
30 instrumental variable genetic score as compared to the reference group (persons without any
31 Lp(a) increasing alleles). This analysis used age as the time scale and included all venous
32 thrombotic events (n=15,789) with a confirmed date (age) at first occurrence that were
33 prevalent at the time of enrolment into UK Biobank. Analyses were restricted to prevalent
34 analyses because the date of diagnosis for incident deep venous thrombosis was not available
35 for all incident events. The results were very similar when analyses included prevalent deep

- 1 venous thrombosis and both prevalent and incident pulmonary embolism (for which the date of
- 2 occurrence were available).
- 3 Analyses in Figure 4 were adjusted for age at enrolment, sex, and the first 10 principal
- 4 components of ancestry.
- 5

1 **Supplemental Text for Figure 6 of the main document:**

2 **Panel A** shows the estimated remaining lifetime risk of experiencing a major cardiovascular
3 event (MCVE, defined as the composite of the first occurrence of fatal or non-fatal myocardial
4 infarction, fatal or non-fatal ischaemic stroke, or coronary revascularization [percutaneous
5 coronary intervention or coronary artery bypass graft surgery]) among 415,274 participants of
6 European ancestry in the UK Biobank for whom measured Lp(a) values were available.

7 Participants were initially divided into categories of baseline estimated lifetime risk (5%, 10% ,
8 15%, 20%, and 25%) calculated using the Joint British Societies (JBS3) Lifetime Risk Estimating
9 algorithm (derived from a similar UK population). This algorithm includes age, sex, total
10 cholesterol, high-density lipoprotein cholesterol (HDL-C), systolic blood pressure (SBP), blood
11 pressure treatment (yes/no), tobacco smoking (never, former, current), type 2 diabetes, family
12 history of premature coronary heart disease, and body mass index (BMI) (using default setting
13 of mean Townsend deprivation index).

14 Within each estimated baseline lifetime risk category, participants were then further divided
15 into six categories defined by increasing baseline measured Lp(a) concentration, thus creating
16 the following groups:

- 17 • a reference group with median Lp(a) 16 nmol/L or approximately 7 mg/dL;
- 18 • a group with median Lp(a) 70 nmol/L or approximately 30 mg/dL;
- 19 • a group with median Lp(a) 115 nmol/L or approximately 50 mg/dL;
- 20 • a group with median Lp(a) 175 nmol/L or approximately 75 mg/dL;
- 21 • a group with median Lp(a) 230 nmol/L or approximately 100 mg/dL;
- 22 • a group with median Lp(a) 350 nmol/L or approximately 150 mg/dL.

23 The number of participants within each group is presented in the following Supplementary
24 Table 2:

1 **Supplementary Table 2: Number of UK Biobank Participants**

2 The number of UK Biobank Participants in groups is stratified by estimated lifetime risk of MCVE
 3 and Lp(a) level measured at time of enrolment

	Estimated Lifetime risk of Major Cardiovascular Event (%)					Total
	5%	10%	15%	20%	25%	
Number of Participants	26,257	107,357	119,863	87,987	73,809	415,274
Measured Lp(a) level mg/dl (nmol/L)						
median Lp(a) 7 mg/dl (16 nmol/L) - reference	18,349	75,021	83,760	61,485	51,578	290,193
median Lp(a) 30 mg/dl (70 nmol/L)	2,168	8,863	9,896	7,264	6,094	34,284
median Lp(a) 50 mg/dl (115 nmol/L)	2,047	8,371	9,346	6,861	5,755	32,380
median Lp(a) 75 mg/dl (175 nmol/L)	2,049	8,377	9,353	6,866	5,759	32,404
median Lp(a) 100 mg/dl (230 nmol/L)	911	3,724	4,158	3,052	2,560	14,406
median Lp(a) 150 mg/dl (350 nmol/L)	734	3,001	3,350	2,459	2,063	11,607

4 For participants within each group, the estimated lifetime risk of experiencing a MCVE was
 5 calculated using JBS4. The additional impact of measured Lp(a) level on estimated lifetime risk
 6 was calculated by including Lp(a) level as an independent exposure in the JBS3 Lifetime Risk
 7 Estimating Algorithm – assuming Lp(a) had an effect independent of all other risk factors and a
 8 constant proportional hazard of 1.35 per 100 nmol/L higher Lp(a). The validity of the estimated
 9 lifetime risk was then assessed by comparing the estimated lifetime risk for participants within
 10 each group calculated using JBS3 and the ‘observed’ lifetime risk estimated by plotting the
 11 cumulative incidence of MCVEs up to age 80 years for participants within that group.

12

1 **Supplemental Text for Figure 7 of the main document:**

2 Panel A shows the cumulative absolute life-time risk of experiencing a major cardiovascular
3 event (MACE, defined as the composite of the first occurrence of fatal or non-fatal myocardial
4 infarction, fatal or non-fatal ischaemic stroke, or coronary revascularization [percutaneous
5 coronary intervention or coronary artery bypass graft surgery]) among 440,368 UK Biobank
6 participants of European descent. For each sex, these were randomly divided into three
7 groups:

- 8 • Group 1: reference group with population average Lp(a) [16-17 nmol/L] and LDL-C levels
9 [3.5-3.6 mmol/L] who had NO Lp(a)-increasing alleles at either variants rs10455872 or
10 rs3798220;
- 11 • Group 2: a group with higher lifetime exposure to Lp(a) [136-138 nmol/L] due to inheriting
12 one copy of either the rs10455872 or rs3798220 Lp(a)-increasing alleles, but with
13 population average LDL-C levels [3.5-3.6 mmol/L];
- 14 • Group 3: a group with BOTH higher lifetime exposure to Lp(a) [136-138 nmol/L] due to
15 inheriting one copy of either the rs10455872 or rs3798220 Lp(a)-increasing alleles AND
16 lifetime exposure to 0.5 mmol/L lower LDL-C [3.0-3.1 mmol/L] due to inheriting a
17 combination of LDL-C lowering genetic variants.

18 The partitioning into these three groups is based on instrumental genetic variable scores. Thus,
19 partitioning is random because each genetic variant included in the instrumental variable
20 genetic scores is inherited randomly. As a result, the only differences between participants
21 within each group are the Lp(a) and/or LDL-C levels.

22 For participants within each group, the cumulative incidence curves for MCVes up to age 80
23 years was plotted.

24 The Figure shows that at all ages, the cumulative incidence of major cardiovascular events is
25 elevated for both men and women who have lifetime exposure to higher Lp(a) levels as
26 compared to participants who have population median Lp(a) levels – and the same LDL-C levels.
27 However, the Figure also shows that both men and women who randomly inherit
28 approximately 120 nmol/L higher Lp(a) due to carriage of a rs10455872 or rs3798220 variant,
29 AND who inherit approximately 0.5 mmol/L lower lifetime exposure to LDL-C due to a
30 combination of genetic variants – have nearly identical lifetime risk of major cardiovascular
31 events with superimposable cumulative incidence curves at all ages. This implies that the
32 increased risk of major cardiovascular events caused by lifelong exposure to 120 nmol/L higher
33 Lp(a) can be mitigated by maintaining 0.5 mmol/L lower lifetime exposure to LDL-C.

34 This finding illustrates the potential to estimate how much intensification of risk factor
35 modification, in this case LDL-C lowering, is needed to mitigate the increased risk of major
36 cardiovascular events caused by a person's Lp(a) level.

1 Clinical Practice Guidelines recommend more intense risk factor modification among persons
2 with elevated Lp(a) levels. The data in the Table of Panel B of Figure 7 provides specific
3 quantitative guidance for how risk factor modification, in this case LDL-C lowering, should be
4 intensified to mitigate the increased risk of major cardiovascular events caused by increasingly
5 higher Lp(a) levels. We note here that the proportional reduction in major cardiovascular
6 events decreases with decreasing duration of LDL-C lowering. As a result, the magnitude of LDL-
7 C lowering intensification needed to mitigate the increased risk caused by Lp(a) will increase
8 the later in life that LDL-C lowering is initiated.

9 We can calculate how much LDL-C lowering must be intensified to mitigate the increased risk
10 caused by any level of Lp(a) depending on the age at which LDL-C lowering is initiated using the
11 following process:

- 12 1. Estimate the hazard ratio for a given level of Lp(a) – assuming a fixed proportional hazard of
13 1.35 nmol/L (among both men and women)
- 14 2. Take the reciprocal of this hazard to estimate the proportional reduction in risk needed to
15 mitigate the increased risk caused by a given Lp(a) level
- 16 3. Estimate the magnitude of LDL-C lowering (in mmol/L) required to achieve this proportional
17 risk reduction as a function of the age at which LDL-C lowering is initiated and continuing
18 until age 80 years.

19 Specifically, we can use the algorithm proposed by the EAS in their 2018 Consensus Statement
20 on the Causality of LDL ⁵¹. From Table 2 of this manuscript we see that:

- 21 • The expected proportional risk reduction per mmol/L lower LDL for any specific duration
22 can be calculated as:

23 $[(1 - e^{-(0.249 + (X - 5) * (-0.0152))})]$; where X = number of years of LDL lowering

- 24 • With rearrangement and simplification, we can solve for the magnitude of LDL lowering
25 needed to achieve the proportional risk reduction required to specifically mitigate the
26 increased risk caused by a given Lp(a) level when

27 $Y = \ln(RR) \div [(X * (-0.0126)) - (-0.1601)]$

28 Where Y = magnitude of LDL lowering (in mmol/L) needed to achieve the desired
29 proportional risk reduction; X = (80 - Age at initiation of LDL lowering intensification); and
30 RR = the desired proportional risk reduction (calculated as $1 \div \text{HR}$ for specific Lp(a) level).

31 Using this process, we estimated the magnitude of intensification of LDL lowering (in mmol/L)
32 required to mitigate the increased risk of major cardiovascular events caused by Lp(a) levels in
33 the 70th, 82.5th, 90th, 93.75th, 97.5th, and 99th percentiles as compared to the population median
34 Lp(a) levels. The magnitude of the intensification of LDL-C lowering was further estimated when

1 initiating LDL-C lowering at 30, 40, 50, and 60 years of age (and extending until age 80 years).
2 The results of this analysis are presented in Panel B of Figure 7.

3 An easy-to-use online Lp(a) Risk and Benefit algorithm can provide convenient and specific
4 guidance on how much LDL-C intensification is needed to mitigate the risk caused by a person's
5 Lp(a) level depending on the age at which LDL-C lowering is initiated. A similar approach can be
6 used for other traditional risk factors, as implemented in this risk calculator. This information
7 should motivate testing of Lp(a) and inform the clinical use of measured Lp(a) levels. However,
8 where the main part of the risk is substantial and mainly attributable to Lp(a), lowering of
9 traditional risk factors such as LDL-C will be insufficient to mitigate the increased risk. In these
10 cases specific Lp(a)-lowering therapies are urgently required. The online Lp(a) Risk and Benefit
11 algorithm is available at the European Atherosclerosis Society website ([www.eas-](http://www.eas-society.org/LPA_risk_and_benefit_algorithm)
12 [society.org/LPA_risk_and_benefit_algorithm](http://www.eas-society.org/LPA_risk_and_benefit_algorithm)).

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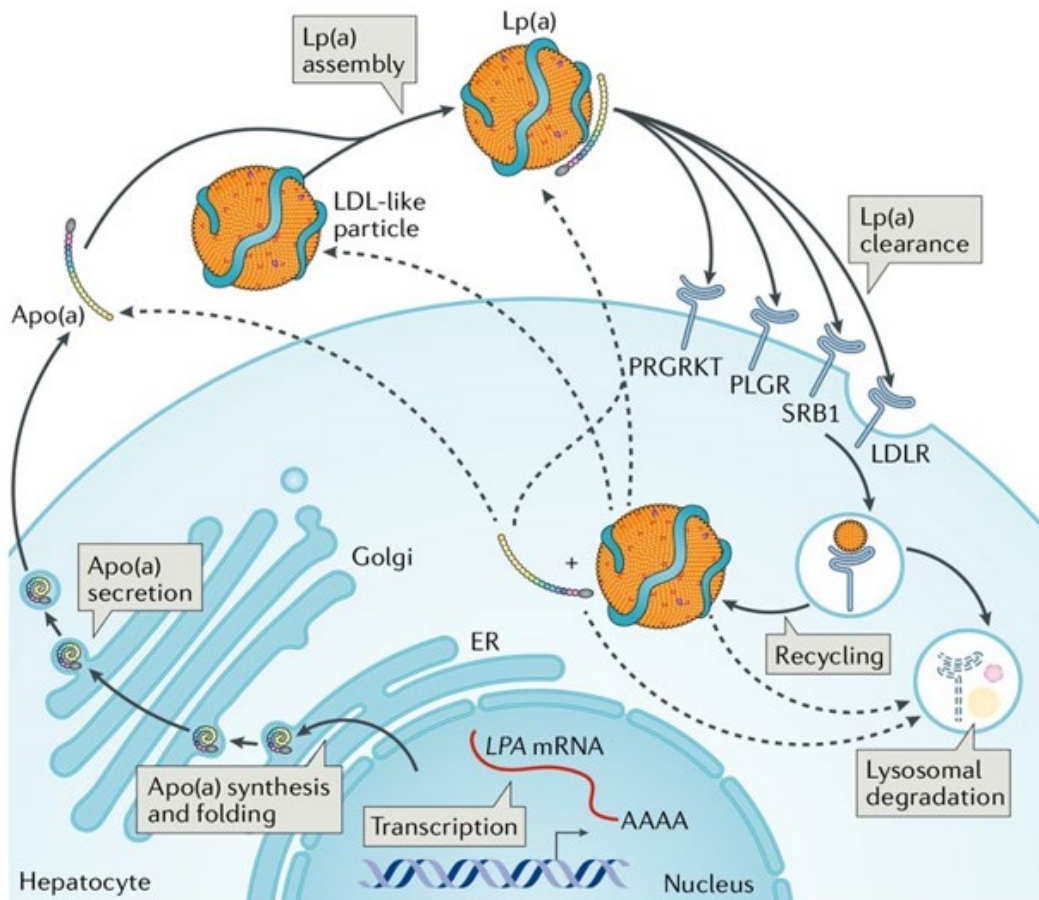
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1 **Supplementary Figure 2. Overview of lipoprotein(a) synthesis and metabolism.**

2 Lipoprotein(a) [Lp(a)] biosynthesis occurs in the liver. Apolipoprotein(a) (apo(a)) production is
3 regulated transcriptionally, with protein folding and processing in the endoplasmic reticulum
4 (ER) and possibly other compartments of the secretory system. Lp(a) assembly occurs
5 intracellularly or on the surface of hepatocytes. Non-covalent association between apo B100
6 and apo(a) occurs within hepatocytes, with a possible role for the cell membrane in supporting
7 covalent association with an LDL-like particle at the surface of hepatocytes.⁵²⁻⁵⁴

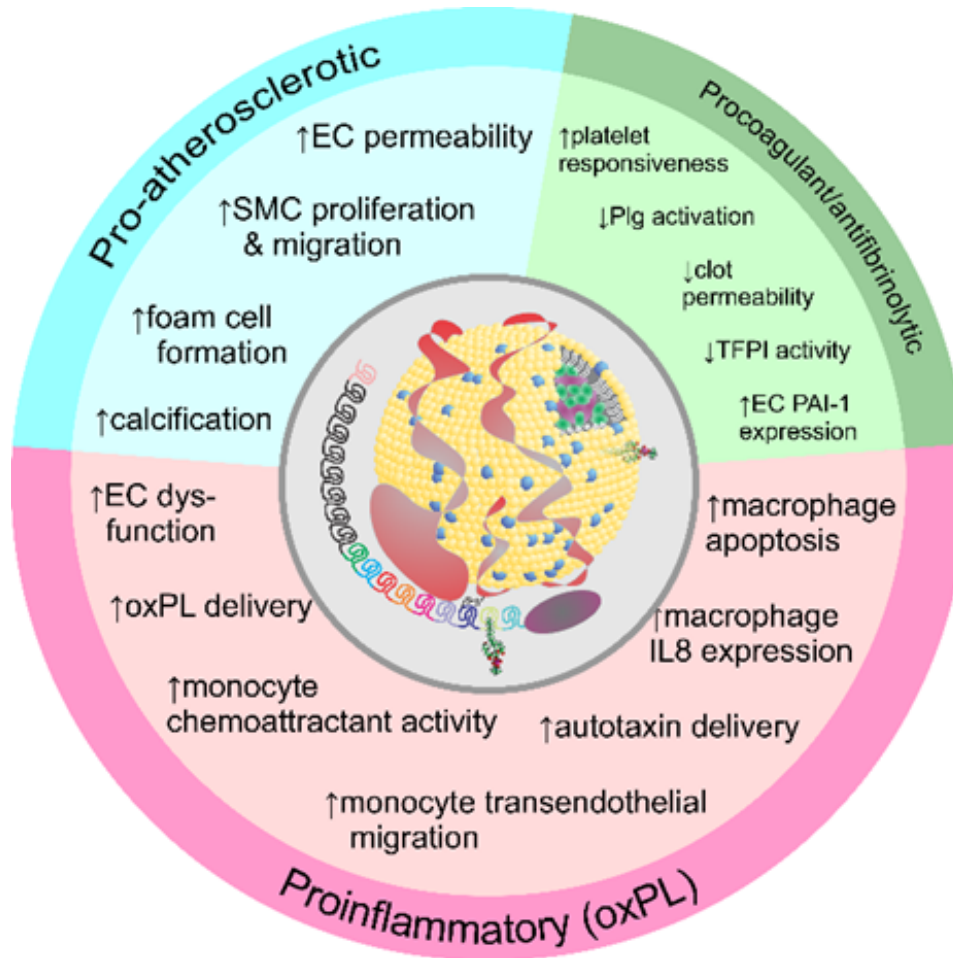
8 Lp(a) is principally cleared and catabolized by the liver (and to lesser extent the kidney) via
9 multiple putative receptor-mediated pathways. Those implicated include the LDL receptor
10 (LDLR), scavenger receptor class B member 1 (SRB1) and the plasminogen receptors PLGR and
11 PLGRKT. Internalization of Lp(a) can lead to uncoupling of apo(a) and the LDL-like moiety,
12 which in turn are degraded in the lysosome or recycled to form newly synthesized Lp(a)
13 particles. The rate of assembly and secretion of Lp(a) is mainly determined by the size of apo(a)
14 gene transcripts and hence by the *LPA* gene. Dashed arrows indicate incompletely understood
15 mechanisms. Figure reproduced from⁵⁵ with permission.



1 **Supplementary Figure 3. Summary of proposed pathogenic mechanisms for Lp(a).**

2 Proinflammatory effects of Lp(a) related to oxidized phospholipids (OxPL) may underlie both
3 atherosclerosis and aortic valve stenosis. Possible procoagulant/antifibrinolytic effects of Lp(a)
4 require further clinical validation.

5



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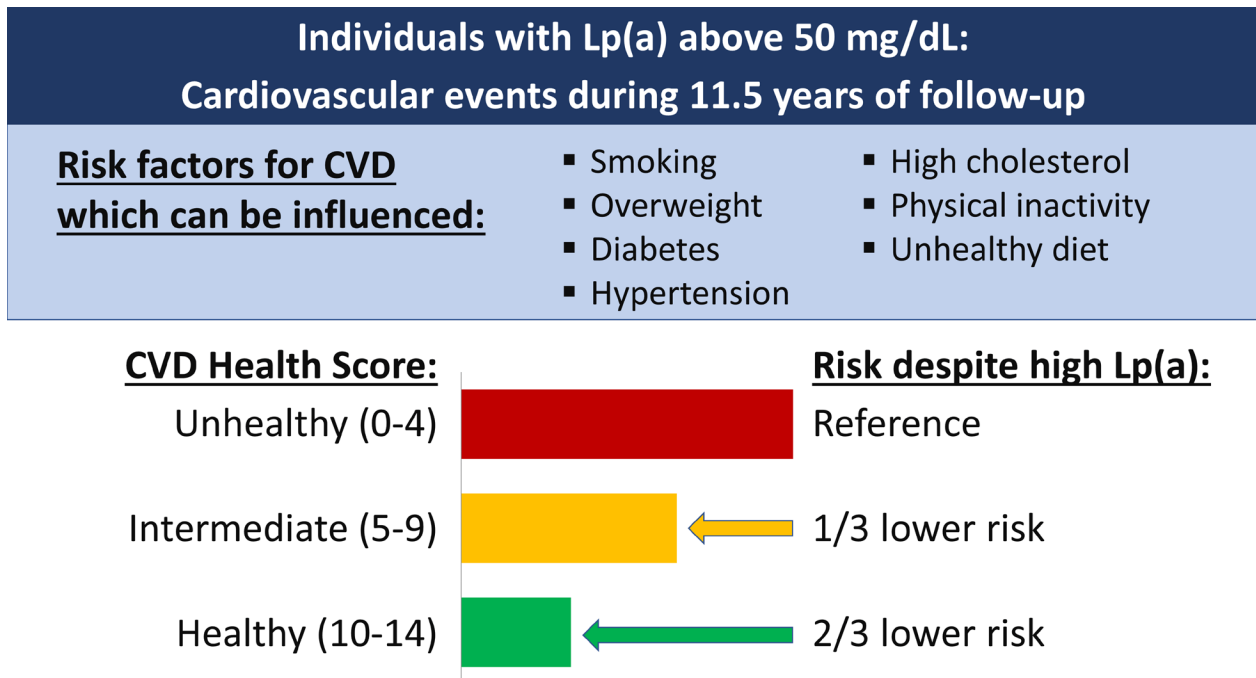
7 EC endothelial cell; IL interleukin; PAI=1 Plasminogen activator inhibitor type 1; Plg, plasminogen; SMC,
8 smooth muscle cell; TFPI, tissue factor pathway inhibitor

9

10

1 **Supplementary Figure 4. Lp(a) and global cardiovascular risk.**

2 Data from the population-based EPIC-Norfolk Study (11.5 years follow-up) for subjects with
 3 Lp(a) levels >50 mg/dL (>~125 nmol/L), were stratified according to a "Cardiovascular Health
 4 Score" with the categories "Unhealthy" (reference group with a score of 0-4), "Intermediate"
 5 (score of 5-9) and "Healthy" (score 10-14)⁵⁶. The overall score was calculated based on these
 6 seven health metrics, giving 2 points for an ideal metric, 1 point for an intermediate metric, and
 7 0 points for a poor metric, thus yielding an overall Cardiovascular Health Score between 0 and
 8 14. A detailed description of each of these health metrics is described below. Compared with
 9 an unhealthy score (reference group), those with a healthy Cardiovascular Health Score had
 10 two-thirds lower risk despite similar median Lp(a) levels (66-68 mg/dL in all three groups).
 11 Figure taken and adapted with permission from Kronenberg ⁵⁷.



12

13 The authors describe the score as follows:

14 *"Ideal cardiovascular health metrics were classified as ideal, intermediate or poor according the*
 15 *seven risk factors identified by the American Heart Association, as previously described* ⁵⁸.

- 16 • *Body mass index (BMI) was classified as ideal if < 25 kg/m², as intermediate if 25–30 kg/m²*
 17 *or as poor if ≥ 30 kg/m².*
- 18 • *A healthy diet score (HDS) was based on intake of five dietary components. The first*
 19 *component was intake of sufficient amounts of fruit and vegetables; a consumption of 4.5 or*
 20 *more cups per day was classified as meeting the guidelines. Second, the weight of estimated*

1 *daily fish consumption was multiplied by seven and divided by 3.5 oz (portion size); if the*
2 *value was ≥ 2 , the participant was considered to consume two or more servings per week.*
3 *Third, for fibre-rich whole grains, participants consuming three or more servings per day of 1*
4 *oz each were considered to meet the guidelines. The fourth and fifth HDS components were*
5 *low sodium intake (< 1500 mg per day was classified as healthy) and low consumption of*
6 *sugar-sweetened beverages (< 450 kcal per week was classified as healthy). The HDS was*
7 *calculated as the sum of the number of healthy food items, yielding a HDS range of 0–5. HDS*
8 *was categorized as ideal (≥ 4), intermediate (2–3), or poor (< 2).*

- 9 • *Physical activity was defined as ideal, intermediate and poor if the status was active,*
10 *moderately active or moderately inactive, and inactive, respectively, as previously described*
11 *⁵⁹.*
- 12 • *Smoking status was classified as ideal, intermediate or poor if the study participant had*
13 *never smoked, previously smoked, or was a current smoker, respectively.*
- 14 • *Blood pressure was defined as ideal if systolic pressure was < 120 mmHg and diastolic*
15 *pressure was < 80 mmHg, as intermediate if systolic pressure was 120–139 mmHg or*
16 *diastolic pressure was 80–89 mmHg without antihypertensive drug treatment or if the blood*
17 *pressure was at goal on treatment, or poor if systolic pressure was ≥ 140 mmHg or diastolic*
18 *pressure was ≥ 90 mmHg.*
- 19 • *Total cholesterol levels were classified as ideal (< 5.2 mmol/L), intermediate (5.2–6.2*
20 *mmol/L) or when cholesterol levels were treated to goal, or poor (≥ 6.2 mmol/L).*
- 21 • *Diabetes mellitus status was ascertained by means of (1) self-report of diabetes medication*
22 *use or (2) a Hba1c ≥ 6.5 mmol/L. Participants meeting one of these criteria were attributed a*
23 *value of 0 while individuals without diabetes mellitus were attributed a value of 2."*

24

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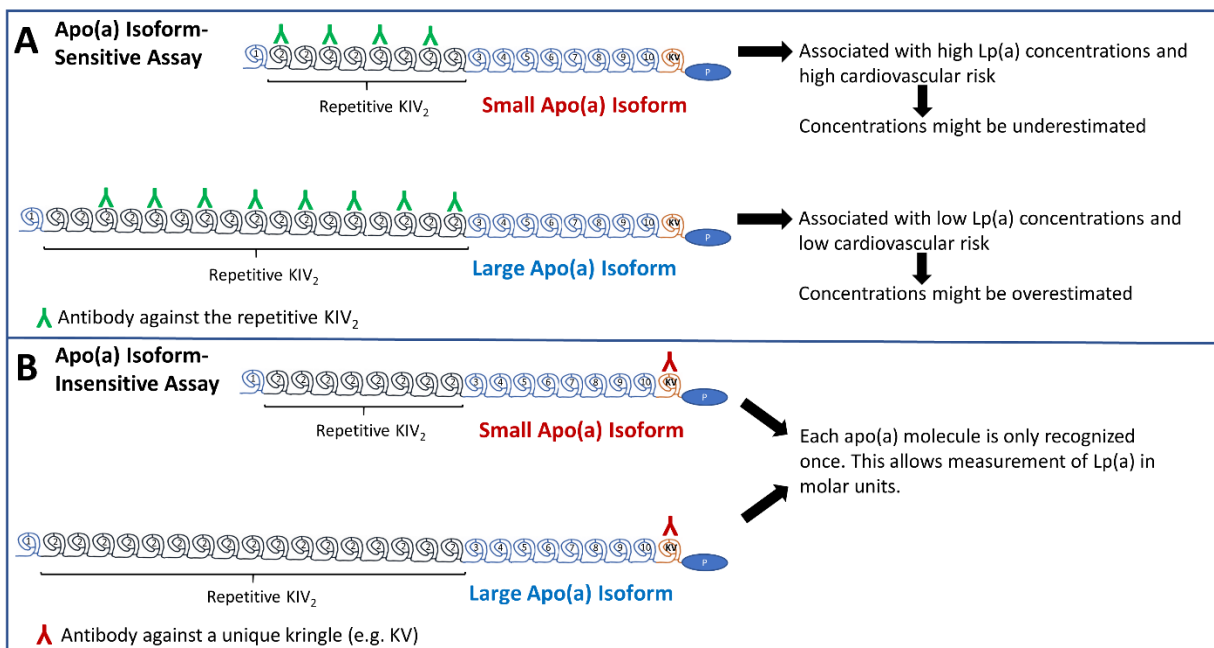
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1 **Supplementary Figure 5. Lp(a) assays.**

2 Panel A: Schematic illustration of apo(a) isoform-dependent measurement of Lp(a) concentration
3 using antibodies directed against the repeated KIV type 2 (KIV2) domain. Panel B shows an apo(a)
4 isoform-independent assay using antibodies directed against the unique apo(a) kringle V domain.
5 (Figure used and adapted with permission from reference⁶⁰).

6 In a systematic comparison of apo(a) isoform-dependent and isoform-independent assays,⁶¹
7 Lp(a) was underestimated by ~10% in samples with smaller isoforms and overestimated by up to
8 35% in samples from large isoform carriers. This relative bias, however, translates in both cases
9 to an average absolute bias of ± 10 nmol/L (or 4 mg/dL) which is - clinically speaking - not very
10 much. Comparison of the Denka immunoturbidometric assay, with quality characteristics similar
11 to the reference Northwest Lipid Metabolism and Diabetes Research Laboratories (NLMDRL)
12 assay, to six commercially available assays, showed biases between -25% and +35%⁶².

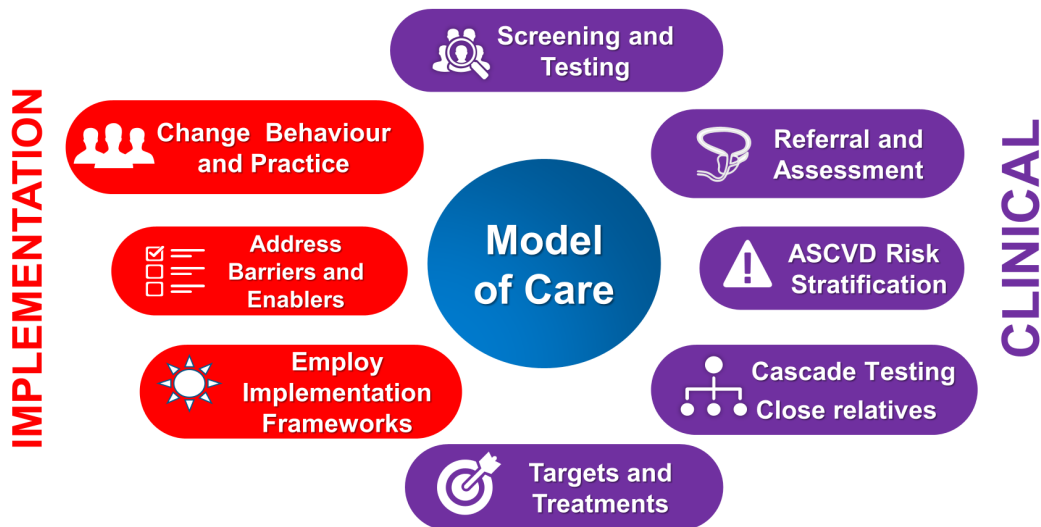
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- 1 **Supplementary Figure 6. Proposed model of care for elevated Lp(a)**
- 2 The model should incorporate clinical (detection, risk stratification, consultation, management)
- 3 and implementation (use frameworks, address barriers, leverage enablers, change behaviour
- 4 and practice) strategies.
- 5 Challenges to implementation include the lack of uniform advice on screening and Lp(a)
- 6 threshold values for clinical action; use of different Lp(a) assays and units for reporting Lp(a);
- 7 variations in reimbursement strategies for Lp(a) testing; and lack of global diagnostic codes for
- 8 elevated Lp(a).⁶³
- 9

Model of Care for Elevated Lp(a)



10

1 **Supplementary Table 3.** Baseline absolute risk for cardiovascular disease and incremental
 2 impact of elevated Lp(a) concentration.

3 The Table shows baseline risk categories (5%, 10% , 15%, 20%, and 25%) estimated from
 4 conventional risk factors and the incremental increased risk caused by increasingly greater Lp(a)
 5 concentrations of 30 to 150 mg/dL (75 to 375 nmol/L). Data are derived from UK Biobank
 6 participants of European ancestry assuming constant proportional hazards of the effect of Lp(a)
 7 on the risk of ASCVD at all levels of baseline risk.

8

	Plasma Lp(a) Level				
Baseline ASCVD Risk (%) without Lp(a)	30 mg/dL (70 nmol/L)	50 mg/dL (115 nmol/L)	75mg/dL (175 nmol/L)	100 mg/dL (230 nmol/L)	150 mg/dL (350 nmol/L)
5	6.1% ($\Delta=1.1\%$)	7.0% ($\Delta=2.0\%$)	8.3% ($\Delta=3.3\%$)	9.8% ($\Delta=4.8\%$)	13.6% ($\Delta=8.6\%$)
10	12.2% ($\Delta=2.2\%$)	14.0% ($\Delta=4.0\%$)	16.5% ($\Delta=6.5\%$)	19.5% ($\Delta=9.5\%$)	27.2% ($\Delta=17.2\%$)
15	18.3% ($\Delta=3.3\%$)	20.9% ($\Delta=5.9\%$)	24.8% ($\Delta=9.8\%$)	29.3% ($\Delta=14.3\%$)	40.8% ($\Delta=25.8\%$)
20	24.4% ($\Delta=4.4\%$)	27.9% ($\Delta=7.9\%$)	33.0% ($\Delta=13.0\%$)	39.0% ($\Delta=19.0\%$)	54.5% ($\Delta=34.5\%$)
25	30.5% ($\Delta=5.5\%$)	34.9% ($\Delta=9.9\%$)	41.3% ($\Delta=16.3\%$)	48.8% ($\Delta=23.8\%$)	68.1% ($\Delta=43.1\%$)
	Baseline ASCVD Risk (%) including plasma Lp(a) levels				

9

1 References

- 2 1. Coassin S, Kronenberg F. Lipoprotein(a) beyond the kringle IV repeat polymorphism: the complexity
3 of genetic variation in the LPA gene. *Atherosclerosis* 2022:(in press) DOI:
4 10.1016/j.atherosclerosis.2022.04.003.
- 5 2. Kraft HG, Köchl S, Menzel HJ, Sandholzer C, Utermann G. The apolipoprotein(a) gene: a transcribed
6 hypervariable locus controlling plasma lipoprotein(a) concentration. *Hum Genet* 1992;**90**:220-230.
- 7 3. Boerwinkle E, Leffert CC, Lin J, Lackner C, Chiesa G, Hobbs HH. Apolipoprotein(a) gene accounts for
8 greater than 90% of the variation in plasma lipoprotein(a) concentrations. *J Clin Invest* 1992;**90**:52-
9 60.
- 10 4. Utermann G, Menzel HJ, Kraft HG, Duba HC, Kemmler HG, Seitz C. Lp(a) glycoprotein phenotypes:
11 inheritance and relation to Lp(a)-lipoprotein concentrations in plasma. *J Clin Invest* 1987;**80**:458-
12 465.
- 13 5. White AL, Hixson JE, Rainwater DL, Lanford RE. Molecular basis for null lipoprotein(a) phenotypes
14 and the influence of apolipoprotein(a) size on plasma lipoprotein(a) level in the baboon. *J Biol Chem*
15 1994;**269**:9060-9066.
- 16 6. Brunner C, Lobentanz EM, Pethö-Schramm A, *et al.* The number of identical kringle IV repeats in
17 apolipoprotein(a) affects its processing and secretion by HepG2 cells. *J Biol Chem* 1996;**271**:32403-
18 32410.
- 19 7. Clarke R, Peden JF, Hopewell JC, *et al.* Genetic variants associated with Lp(a) lipoprotein level and
20 coronary disease. *N Engl J Med* 2009;**361**:2518-2528.
- 21 8. Kronenberg F. Genetic determination of lipoprotein(a) and its association with cardiovascular
22 disease. Convenient does not always mean better. *J Intern Med* 2014;**276**:243-247.
- 23 9. Coassin S, Schoenherr S, Weissensteiner H, *et al.* A comprehensive map of single base
24 polymorphisms in the hypervariable LPA Kringle IV-2 copy number variation region. *J Lipid Res*
25 2019;**60**:186-199.
- 26 10. Coassin S, Erhart G, Weissensteiner H, *et al.* A novel but frequent variant in LPA KIV-2 is associated
27 with a pronounced Lp(a) and cardiovascular risk reduction. *Eur Heart J* 2017;**38**:1823-1831.
- 28 11. Schachtl-Riess JF, Kheirkhah A, Grüneis R, *et al.* Frequent LPA KIV-2 Variants Lower Lipoprotein(a)
29 Concentrations and Protect Against Coronary Artery Disease. *J Am Coll Cardiol* 2021;**78**:437-449.
- 30 12. Di Maio S, Grüneis R, Streiter G, *et al.* Investigation of a nonsense mutation located in the complex
31 KIV-2 copy number variation region of apolipoprotein(a) in 10,910 individuals. *Genome Medicine*
32 2020;**12**:74.
- 33 13. Lim ET, Wurtz P, Havulinna AS, *et al.* Distribution and Medical Impact of Loss-of-Function Variants in
34 the Finnish Founder Population. *PLoS Genet* 2014;**10**:e1004494.
- 35 14. Enkhmaa B, Petersen KS, Kris-Etherton PM, Berglund L. Diet and Lp(a): Does Dietary Change Modify
36 Residual Cardiovascular Risk Conferred by Lp(a)? *Nutrients* 2020;**12**:2024.
- 37 15. Ebbeling CB, Knapp A, Johnson A, *et al.* Effects of a low-carbohydrate diet on insulin-resistant
38 dyslipoproteinemia—a randomized controlled feeding trial. *Am J Clin Nutr* 2022;**115**:154-162.
- 39 16. Kotwal A, Cortes T, Genere N, *et al.* Treatment of Thyroid Dysfunction and Serum Lipids: A
40 Systematic Review and Meta-analysis. *J Clin Endocrinol Metab* 2020;**105**:dgaa672.

- 1 17. Edén S, Wiklund O, Oscarsson J, Rosén T, Bengtsson B-Å. Growth hormone treatment of growth
2 hormone-deficient adults results in a marked increase in Lp(a) and HDL cholesterol concentrations.
3 *Arterioscler Thromb* 1993;**13**:296-301.
- 4 18. Salpeter SR, Walsh JM, Ormiston TM, Greyber E, Buckley NS, Salpeter EE. Meta-analysis: effect of
5 hormone-replacement therapy on components of the metabolic syndrome in postmenopausal
6 women. *Diabetes Obes Metab* 2006;**8**:538-554.
- 7 19. Theodorou AA, Panayiotou G, Volaklis KA, *et al.* Aerobic, resistance and combined training and
8 detraining on body composition, muscle strength, lipid profile and inflammation in coronary artery
9 disease patients. *Res Sports Med* 2016;**24**:171-84.
- 10 20. Austin A, Warty V, Janosky J, Arslanian S. The relationship of physical fitness to lipid and
11 lipoprotein(a) levels in adolescents with IDDM. *Diabetes Care* 1993;**16**:421-425.
- 12 21. Kronenberg F. Causes and consequences of lipoprotein(a) abnormalities in kidney disease. *Clin Exp*
13 *Nephrol* 2014;**18**:234-237.
- 14 22. Hopewell JC, Haynes R, Baigent C. The role of lipoprotein (a) in chronic kidney disease. *J Lipid Res*
15 2018;**59**:577-585.
- 16 23. Kronenberg F, König P, Neyer U, *et al.* Multicenter study of lipoprotein(a) and apolipoprotein(a)
17 phenotypes in patients with end-stage renal disease treated by hemodialysis or continuous
18 ambulatory peritoneal dialysis. *J Am Soc Nephrol* 1995;**6**:110-120.
- 19 24. Kronenberg F, Lingenhel A, Lhotta K, *et al.* The apolipoprotein(a) size polymorphism is associated
20 with nephrotic syndrome. *Kidney Int* 2004;**65**:606-612.
- 21 25. Kronenberg F, König P, Lhotta K, *et al.* Apolipoprotein(a) phenotype-associated decrease in
22 lipoprotein(a) plasma concentrations after renal transplantation. *Arterioscler Thromb*
23 1994;**14**:1399-1404.
- 24 26. Feely J, Barry M, Keeling PWN, Weir DG, Cooke T. Lipoprotein(a) in cirrhosis. *BMJ* 1992;**304**:545-
25 546.
- 26 27. Jung I, Kwon H, Park SE, *et al.* Serum lipoprotein(a) levels and insulin resistance have opposite
27 effects on fatty liver disease. *Atherosclerosis* 2020;**308**:1-5.
- 28 28. Reyes-Soffer G, Westerterp M. Beyond Lipoprotein(a) plasma measurements: Lipoprotein(a) and
29 inflammation. *Pharmacol Res* 2021;**169**:105689.
- 30 29. Missala I, Kassner U, Steinhagen-Thiessen E. A Systematic Literature Review of the Association of
31 Lipoprotein(a) and Autoimmune Diseases and Atherosclerosis. *Int J Rheumatol* 2012;**2012**:480784.
- 32 30. Schultz O, Oberhauser F, Saech J, *et al.* Effects of inhibition of interleukin-6 signalling on insulin
33 sensitivity and lipoprotein (a) levels in human subjects with rheumatoid diseases. *PLoS ONE*
34 2010;**5**:e14328.
- 35 31. Wade DP, Clarke JG, Lindahl GE, *et al.* 5' control regions of the apolipoprotein(a) gene and members
36 of the related plasminogen gene family. *Proc Natl Acad Sci U S A* 1993;**90**:1369-1373.
- 37 32. Enkhmaa B, Anuurad E, Zhang W, *et al.* Effect of antiretroviral therapy on allele-associated Lp(a)
38 level in women with HIV in the Women's Interagency HIV Study. *J Lipid Res* 2018;**59**:1967-1976.
- 39 33. Enkhmaa B, Anuurad E, Zhang W, *et al.* HIV disease activity as a modulator of lipoprotein(a) and
40 allele-specific apolipoprotein(a) levels. *Arterioscler Thromb Vasc Biol* 2013;**33**:387-92.

- 1 34. Langsted A, Kamstrup PR, Nordestgaard BG. Lipoprotein(a): fasting and nonfasting levels,
2 inflammation, and cardiovascular risk. *Atherosclerosis* 2014;**234**:95-101.
- 3 35. Khera AV, Everett BM, Caulfield MP, *et al.* Lipoprotein(a) concentrations, Rosuvastatin therapy, and
4 residual vascular risk: an analysis from the JUPITER Trial (Justification for the Use of Statins in
5 Prevention: An Intervention Trial Evaluating Rosuvastatin). *Circulation* 2014;**129**:635-642.
- 6 36. Holm S, Oma I, Hagve TA, *et al.* Levels of Lipoprotein (a) in patients with coronary artery disease
7 with and without inflammatory rheumatic disease: a cross-sectional study. *BMJ Open*
8 2019;**9**:e030651.
- 9 37. Wu XM, Broadwin R, Basu R, *et al.* Associations between fine particulate matter and changes in
10 lipids/lipoproteins among midlife women. *Sci Total Environ* 2019;**654**:1179-1186.
- 11 38. Borenstein M, Hedges LV, Higgins JP, Rothstein HR. A basic introduction to fixed-effect and random-
12 effects models for meta-analysis. *Res Synth Methods* 2010;**1**:97-111.
- 13 39. DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials* 1986;**7**:177-188.
- 14 40. Annesi I, Moreau T, Lellouch J. Efficiency of the logistic regression and Cox proportional hazards
15 models in longitudinal studies. *Stat Med* 1989;**8**:1515-21.
- 16 41. Stare J, Maucort-Boulch D. Odds ratio, hazard ratio and relative risk. *Advances in Methodology and*
17 *Statistics* 2016;**13**:59-67.
- 18 42. Langsted A, Nordestgaard BG, Kamstrup PR. Low lipoprotein(a) levels and risk of disease in a large,
19 contemporary, general population study. *Eur Heart J* 2021;**42**:1147-1156.
- 20 43. Kaya A, Onat A, Yuksel H, Can G, Yuksel M, Ademoglu E. Lipoprotein(a)-activated immunity, insulin
21 resistance and new-onset diabetes. *Postgrad Med* 2017;**129**:611-618.
- 22 44. Gudbjartsson DF, Thorgeirsson G, Sulem P, *et al.* Lipoprotein(a) Concentration and Risks of
23 Cardiovascular Disease and Diabetes. *J Am Coll Cardiol* 2019;**74**:2982-2994.
- 24 45. Mora S, Kamstrup PR, Rifai N, Nordestgaard BG, Buring JE, Ridker PM. Lipoprotein(a) and risk of
25 type 2 diabetes. *Clin Chem* 2010;**56**:1252-1260.
- 26 46. Tolbus A, Mortensen MB, Nielsen SF, Kamstrup PR, Bojesen SE, Nordestgaard BG. Kringle IV Type 2,
27 Not Low Lipoprotein(a), as a Cause of Diabetes: A Novel Genetic Approach Using SNPs Associated
28 Selectively with Lipoprotein(a) Concentrations or with Kringle IV Type 2 Repeats. *Clin Chem*
29 2017;**63**:1866-1876.
- 30 47. Kamstrup PR, Nordestgaard BG. Lipoprotein(a) concentrations, isoform size, and risk of type 2
31 diabetes: a Mendelian randomisation study. *Lancet Diabetes Endocrinol* 2013;**1**:220-227.
- 32 48. Ye Z, Haycock PC, Gurdasani D, *et al.* The association between circulating lipoprotein(a) and type 2
33 diabetes: is it causal? *Diabetes* 2014;**63**:332-342.
- 34 49. Paige E, Masconi KL, Tsimikas S, *et al.* Lipoprotein(a) and incident type-2 diabetes: results from the
35 prospective Bruneck study and a meta-analysis of published literature. *Cardiovasc Diabetol*
36 2017;**16**:38.
- 37 50. Chasman DI, Shiffman D, Zee RY, *et al.* Polymorphism in the apolipoprotein(a) gene, plasma
38 lipoprotein(a), cardiovascular disease, and low-dose aspirin therapy. *Atherosclerosis* 2009;**203**:371-
39 376.

- 1 51. Ference BA, Ginsberg HN, Graham I, *et al.* Low-density lipoproteins cause atherosclerotic
2 cardiovascular disease. 1. Evidence from genetic, epidemiologic, and clinical studies. A consensus
3 statement from the European Atherosclerosis Society Consensus Panel. *Eur Heart J* 2017;**38**:2459-
4 2472.
- 5 52. Koschinsky ML, Côté GP, Gabel B, Van der Hoek YY. Identification of the cysteine residue in
6 apolipoprotein(a) that mediates extracellular coupling with apolipoprotein B-100. *J Biol Chem*
7 1993;**268**:19819-19825.
- 8 53. Callow MJ, Rubin EM. Site-specific mutagenesis demonstrates that cysteine 4326 of apolipoprotein
9 B is required for covalent linkage with apolipoprotein(a) *in vivo*. *J Biol Chem* 1995;**270**:23914-23917.
- 10 54. Youssef A, Clark JR, Marcovina SM, Boffa MB, Koschinsky ML. Apo(a) and ApoB Interact
11 Noncovalently Within Hepatocytes: Implications for Regulation of Lp(a) Levels by Modulation of
12 ApoB Secretion. *Arterioscler Thromb Vasc Biol* 2022;**42**:289-304.
- 13 55. Boffa MB, Koschinsky ML. Oxidized phospholipids as a unifying theory for lipoprotein(a) and
14 cardiovascular disease. *Nat Rev Cardiol* 2019;**16**:305-318.
- 15 56. Perrot N, Verbeek R, Sandhu M, *et al.* Ideal cardiovascular health influences cardiovascular disease
16 risk associated with high lipoprotein(a) levels and genotype: The EPIC-Norfolk prospective
17 population study. *Atherosclerosis* 2017;**256**:47-52.
- 18 57. Kronenberg F. Measuring lipoprotein(a): do it without ifs and buts. *Eur J Prev Cardiol* 2022; **29**:766-
19 768.
- 20 58. Lachman S, Peters RJ, Lentjes MA, *et al.* Ideal cardiovascular health and risk of cardiovascular
21 events in the EPIC-Norfolk prospective population study. *Eur J Prev Cardiol* 2016;**23**:986-994.
- 22 59. Wareham NJ, Jakes RW, Rennie KL, *et al.* Validity and repeatability of a simple index derived from
23 the short physical activity questionnaire used in the European Prospective Investigation into Cancer
24 and Nutrition (EPIC) study. *Public Health Nutr* 2003;**6**:407-13.
- 25 60. Kronenberg F, Tsimikas S. The challenges of measuring Lp(a): A fight against Hydra? *Atherosclerosis*
26 2019;**289**:181-183.
- 27 61. Marcovina SM, Albers JJ, Gabel B, Koschinsky ML, Gaur VP. Effect of the number of
28 apolipoprotein(a) kringle 4 domains on immunochemical measurements of lipoprotein(a). *Clin*
29 *Chem* 1995;**41**:246-255.
- 30 62. Scharnagl H, Stojakovic T, Dieplinger B, *et al.* Comparison of lipoprotein(a) serum concentrations
31 measured by six commercially available immunoassays. *Atherosclerosis* 2019;**289**:206-213.
- 32 63. Tsimikas S, Stroes ESG. The dedicated “Lp(a) clinic”: A concept whose time has arrived?
33 *Atherosclerosis* 2020;**300**:1-9.
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