

Thematic Review Series: Lipoprotein (a): Coming of Age at Last

Lipoprotein (a) as a cause of cardiovascular disease: insights from epidemiology, genetics, and biology

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Abstract Human epidemiologic and genetic evidence using the Mendelian randomization approach in large-scale studies now strongly supports that elevated lipoprotein (a) [Lp(a)] is a causal risk factor for cardiovascular disease, that is, for myocardial infarction, atherosclerotic stenosis, and aortic valve stenosis. The Mendelian randomization approach used to infer causality is generally not affected by confounding and reverse causation, the major problems of observational epidemiology. This approach is particularly valuable to study causality of Lp(a), as single genetic variants exist that explain 27–28% of all variation in plasma Lp(a). The most important genetic variant likely is the kringle IV type 2 (KIV-2) copy number variant, as the apo(a) product of this variant influences fibrinolysis and thereby thrombosis, as opposed to the Lp(a) particle per se. We speculate that the physiological role of KIV-2 in Lp(a) could be through wound healing during childbirth, infections, and injury, a role that, in addition, could lead to more blood clots promoting stenosis of arteries and the aortic valve, and myocardial infarction. Randomized placebo-controlled trials of Lp(a) reduction in individuals with very high concentrations to reduce cardiovascular disease are awaited. ■ Recent genetic evidence documents elevated Lp(a) as a cause of myocardial infarction, atherosclerotic stenosis, and aortic valve stenosis.—Nordestgaard, B. G., and A. Langsted. **Lipoprotein (a) as a cause of cardiovascular disease: insights from epidemiology, genetics, and biology.** *J. Lipid Res.* 2016. 57: 1953–1975.

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The first articles on lipoprotein (a) [Lp(a)] were published in 1963 by Kåre Berg from Norway, describing Lp(a) in human plasma as a heritable trait (1–3). Over the next more than 20 years, the scientific interest in this lipoprotein was modest. Then in 1987, Richard Lawn, Angelo

Scanu, and colleagues cloned and sequenced the *LPA* gene coding for apo(a) (4, 5), a protein with homology to plasminogen, which accounts for the difference between an Lp(a) particle and an LDL particle. These observations generated a huge scientific interest in Lp(a), leading to an exponential growth in the number of articles published, which then later declined again.

Renewed interest in Lp(a) came in 2009 from Pia Kamstrup et al. (6) with genetic evidence from Mendelian randomization that high Lp(a) is causally associated with cardiovascular disease, from the Emerging Risk Factors Collaboration led by John Danesh that Lp(a) epidemiologically is continuously and independently associated with cardiovascular disease risk (7), and from Robert Clarke et al. (8) that of 2,100 candidate genes for cardiovascular disease, genetic variation in the *LPA* gene was the strongest genetic cardiovascular risk factor. Following the publication of these studies, high concentrations of Lp(a) have been considered to be a direct cause of cardiovascular disease, just like high LDL cholesterol concentrations. Genetic evidence largely free of confounding and fully free of reverse causation, two major problems of observational epidemiology, is what has cemented the understanding of causality of Lp(a) for cardiovascular disease.

These novel and important findings led the European Atherosclerosis Society to publish a 2010 consensus panel statement recommending screening for elevated Lp(a) in individuals at intermediate, high, or very high cardiovascular risk, and suggested a desirable plasma concentration of less than 50 mg/dl (9). Of note, we naturally were fully aware that the risk of cardiovascular disease increases already at Lp(a) levels above 30 mg/dl, but to get the attention of the clinical community, we believed it was the best strategy to start focusing on individuals with the highest cardiovascular risk, that is, the 20% of individuals with concentrations above 50 mg/dl.

Abbreviations: CI, confidence interval; FH, familial hypercholesterolemia; KIV-2, kringle IV type 2; Lp(a), lipoprotein (a).

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Although some cardiologists suspected for many years, as far back as the mid-1990s, that Lp(a) was a risk factor for aortic valve stenosis, a further novel development was the documentation by George Thanassoulis et al. (10) in 2013 that genetic variation in the *LPA* gene is strongly associated with aortic valve calcification and stenosis. It was later shown that high plasma Lp(a) concentrations are likewise causally associated with high risk of aortic valve stenosis (11). Taken together therefore, the genetic evidence now firmly demonstrates that high plasma Lp(a) concentration is a direct cause of cardiovascular disease, that is, myocardial infarction, atherosclerotic stenosis, and aortic valve stenosis (Fig. 1).

Although mainly recent genetic research has firmly established the claim for causality for high Lp(a) concentrations to cardiovascular disease, these findings have only been possible due to the many other excellent scientific works on Lp(a) published from 1963 until today, produced by a large number of dedicated researchers within this field. In this review, it will not be possible to do justice to all the important scientific discoveries on Lp(a) in relation to cardiovascular disease published during the 50 years. That said, with our own personal touch to the story and with focus on evidence from human studies, we will try our best, in a historical perspective, to cover insights in epidemiology, genetics, and biology that led to the understanding of Lp(a) as a cause of cardiovascular disease. Many classic and more recent reviews, viewpoints, and meta-analyses cover related areas (5, 7, 9, 12–40), include even more references, and, together with the present review, provide a comprehensive coverage of Lp(a) as a cause of cardiovascular disease.

Lp(a) IN NORMAL, ATHEROSCLEROTIC, AND INJURED INTIMA

A necessary condition for Lp(a) to cause cardiovascular disease is its ability to enter into and accumulate in the

intima of arteries and aortic valve leaflets. Lp(a) or apo(a) is indeed found within the lesioned intima of human arteries and coronary artery bypass vein grafts removed at reoperation (41–46), as well as within the lesioned intima of monkey arteries (47) and arteries in rabbits and mice after intravenous injection of human Lp(a) (48, 49) or after transgenic modification with human Lp(a) (50). Likewise, apo(a) is found within early to end-stage lesions of human aortic valve stenosis (51).

In vivo kinetic studies show that radiolabeled human Lp(a) enters the intima at similar rates to LDL in normal and atherosclerotic arteries in humans and rabbits (49, 52, 53), which appears to be like other lipoproteins, through a simple molecular sieving not involving any receptors, but dependent on lipoprotein plasma concentrations and on lipoprotein particle size, blood pressure, and on arterial wall permeability (54). Importantly, however, as the plasma concentration of LDL is much higher than that of Lp(a) in most individuals, the mass intimal influx of LDL was 15-fold that of Lp(a) in humans (52). Again using kinetic studies in vivo, the rates of relative removal of Lp(a) and LDL from the arterial intima were similar, while the trapping of both lipoproteins was higher in lesioned compared with normal intima (53); it cannot entirely be excluded that there may be preferential trapping of Lp(a) in settings where lesion formation is ongoing and/or more advanced. Also, degradation in vivo of human Lp(a) was higher in atherosclerotic compared with nonlesioned rabbit intima (55).

Surprisingly, when the arterial intima in a rabbit model was subjected to a balloon injury, radiolabeled human Lp(a) accumulated in vivo 2- to 3-fold greater than that of radiolabeled human LDL in the balloon-injured aortic intima, but not in the adjacent uninjured arterial intima (56). As removal of intact endothelial cells would not explain why Lp(a) preferentially accumulates, because entry into the intima would be enhanced for LDL and Lp(a) equally, this can most likely occur because of prolonged

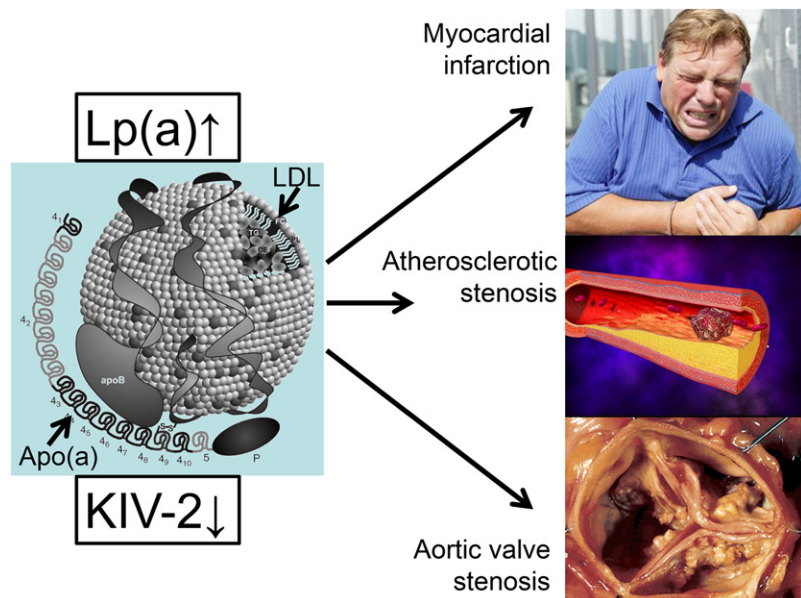


Fig. 1. Summary of the strongest causal genetic evidence linking high Lp(a) concentrations with corresponding small apo(a) size due to low number of KIV-2 repeats to risk of disease.

residence time, e.g., enhanced binding of Lp(a) selectively to the matrix in the intima. A simple explanation for this observation could be that the balloon-injury removes the endothelial cells and thus exposes the intima directly to flowing blood, favoring deposition of fibrin. Thereby Lp(a), unlike LDL, can bind to small blood clots rapidly forming at the injured sites, or to exposed glycosaminoglycans (21, 56, 57). Preferential accumulation of Lp(a) compared with LDL at injured sites could thus be related to the greater capacity of Lp(a) than LDL to bind to fibrin (58) or glycosaminoglycans (59). Indeed, Lp(a) compared with LDL appeared to be preferentially immobilized via fibrin binding in human arterial tissue (44).

Taken together, these data suggest that Lp(a) accumulation at sites of injury could be a primary mechanism by which elevated Lp(a) causes cardiovascular disease. That said, there is also evidence that Lp(a) can be taken up by macrophages to produce foam cells (60–62), a mechanism by which LDL and triglyceride-rich lipoproteins are believed to cause the development of atherosclerosis (63–65). Interestingly, in coronary artery bypass vein grafts and relative to plasma concentrations, Lp(a) accumulated 2.4-fold more than all apoB-containing lipoproteins combined, that is, LDL, Lp(a), and triglyceride-rich lipoproteins, and unlike apoB that was found mainly at atherosclerotic core regions, this was not the case for Lp(a) (43). The latter suggests that the intimal accumulation of Lp(a) is by a different mechanism than that of other apoB-containing lipoproteins, and that Lp(a) accumulation is throughout the intima, while other apoB-containing lipoproteins mainly are found at atherosclerotic lesions.

PLASMA CONCENTRATIONS AND GENETICS

The fact that plasma concentrations of Lp(a) are mainly genetically determined (14, 39) has been instrumental in the study of causality of Lp(a) for cardiovascular disease. Because of this, the genetic evidence for causality in cardiovascular disease is much stronger for Lp(a) than for most other cardiovascular risk factors (8, 30, 66). It is also of huge importance for Mendelian randomization studies that single genetic variants exist that explain 27–28% of all variation in plasma Lp(a), and that these variants can be genotyped in large-scale studies (6, 8, 10, 11, 67). Therefore, a brief discussion of plasma Lp(a) concentrations and the genetic principles used in Mendelian randomization studies is given below. An in depth review of this topic is presented elsewhere in this Thematic Review Series (39, 68).

In the general population, plasma concentrations of Lp(a) vary to a great extent among individuals (14). Concentrations also differ between different ethnicities, with higher concentrations in individuals of African compared with European and Asian descent (14, 68–74). In Europeans and Asians, Lp(a) concentrations are highly skewed with a tail toward higher concentrations (Fig. 2, top panel), and in the Copenhagen General Population Study, we observed concentrations as high as 387 mg/dl. Concentrations

of other lipoproteins are often affected by life-style and physiological factors, whereas Lp(a) concentrations remain stable inter-individually throughout life, indirectly suggesting that Lp(a) concentrations are mostly genetically determined.

In very early studies, Lp(a) was suggested to be an inherited trait with autosomal dominant inheritance (2, 3, 75–77) and a major gene and polygenic factors were proposed as contributors to the variation in Lp(a) concentrations (78–80). Hasstedt et al. (78) found that the major gene and the polygenic factors accounted for 95% of the variation in plasma Lp(a) concentrations. Following this, a number of studies primarily led by Gerd Utermann and colleagues revealed that apo(a) varied in size due to kringle IV type 2 (KIV-2) copy number variation, and that the number of KIV-2 copies were inversely correlated to plasma Lp(a) concentrations (81–87) (Fig. 2, middle and lower panel). However, the correlation between the apo(a) size polymorphism and Lp(a) plasma concentrations was found to vary greatly among individuals of different ethnicity, as do plasma Lp(a) concentrations (69, 70, 73, 74, 88). One study found that the apo(a) allele frequencies were different among different populations (69). In that study, the size variation of apo(a) explained from 19% in Sudanese to 77% in Malays of the variability in plasma Lp(a) concentrations.

In 49,615 individuals from the Copenhagen General Population Study, the KIV-2 number of repeats in the *LPA* gene coding for the apo(a) size polymorphism explained 27% of the variation in plasma Lp(a) concentrations (Fig. 2, lower panel); however, the KIV-2 number of repeats was measured as both alleles combined and does not take different expression of alleles into account, suggesting that the 27% should be viewed as a minimal estimate for Danes. Therefore, the measurements of KIV-2 in these studies do not necessarily reflect the dominant isoform that is associated with the highest Lp(a) concentrations. For Mendelian randomization studies, the most important genetic variant is likely the KIV-2 copy number variation, or corresponding apo(a) size polymorphism, as this causal variant possibly is the direct cause of cardiovascular disease (39). However, although genotyping of this variant can be done in large-scale-studies, it requires, at present, quantitative polymerase chain reaction (6) or even more complicated techniques (39). Importantly, for now, it is not possible to determine for sure whether it is the KIV-2 copy number variation or the associated plasma Lp(a) concentration that is causally associated with cardiovascular disease.

In 2009, Robert Clarke et al. (8) published an article using a gene chip with 48,742 SNPs in 2,100 candidate genes examining individuals with coronary disease and controls. They found that the rs10455872 and rs3798220 SNPs in the *LPA* gene explained 25% and 8% of the variation in plasma Lp(a) concentrations, and each was associated with high risk of coronary heart disease. Importantly, in numerous other studies, including genome-wide linkage and association studies, multiple genetic variants in or around *LPA* on chromosome 6q27 were also found to be major determinants of plasma Lp(a) concentrations (39, 89–93). For Mendelian

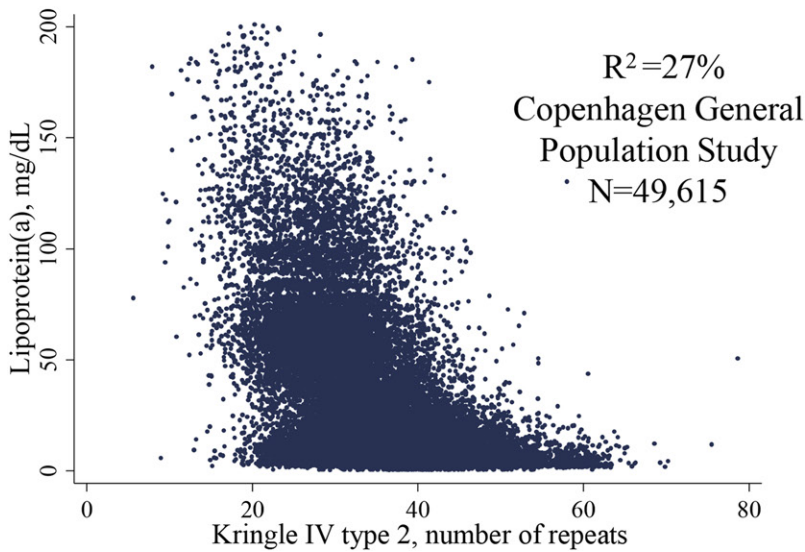
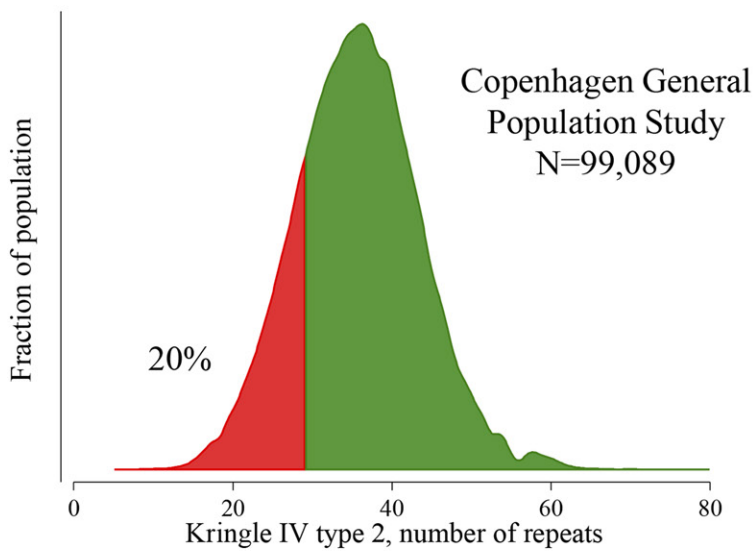
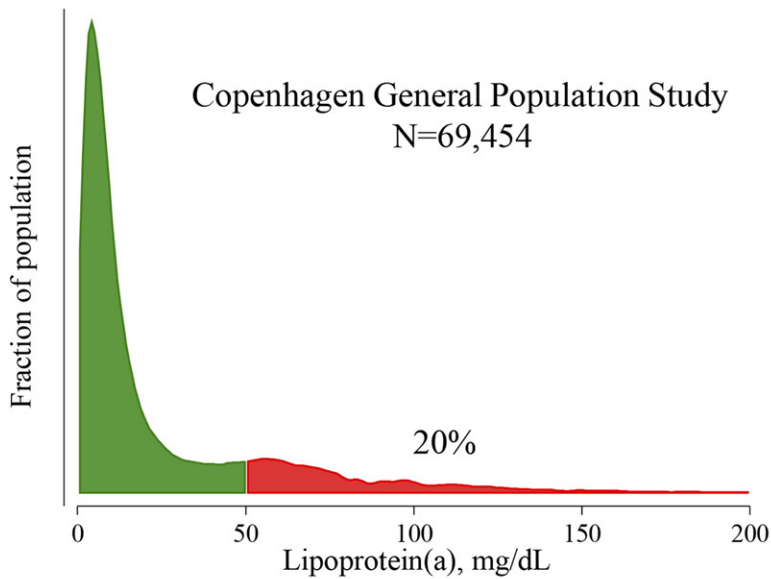


Fig. 2. Distribution of and correlation between plasma Lp(a) concentrations and KIV-2 number of repeats in the Danish general population.

randomization studies, however, the most important SNP is *LPA* rs10455872, as this variant explains up to 28% of variation in plasma Lp(a) concentrations in the general population of Whites (11, 67), and this variant, unlike the KIV-2

copy number variation, is very easy to genotype in large-scale studies. Even though this SNP is not causal for high Lp(a) (39), it can still be an excellent instrument to examine causality of high Lp(a) concentrations per se.

Taken together, the *LPA* KIV-2 copy number variation and the *LPA* rs10455872 SNP have so far been the best genetic instruments in large-scale Mendelian randomization studies, each explaining 27–28% variation in plasma Lp(a) concentrations. Because KIV-2 copy number variation directly measures apo(a) size differences as opposed to rs10455872, which marks both apo(a) size differences and Lp(a) concentrations unrelated to this genetic variation (67), the combined use of both has the potential to explore whether it is the KIV-2 copy number variation or the Lp(a) particle, per se, that is the direct cause of cardiovascular disease.

While KIV-2 number of repeats above 40 and rs10455872 noncarrier state both mark very low Lp(a) concentrations, heterozygosity and homozygosity for rs10455872 mark very different plasma Lp(a) concentration profiles than intermediate or low number of KIV-2 number of repeats (Fig. 3). Using these two genetic variants simultaneously has previously been used by us to suggest that the well-documented slightly higher risk of type 2 diabetes in those with the lowest Lp(a) concentration (67, 94–96) is possibly explained by the KIV-2 copy number variation rather than the Lp(a) particle per se (67). In other words, these data indirectly suggest that lowering of Lp(a) pharmacologically

is unlikely to lead to increased risk of diabetes. Importantly however, more evidence using even better genetic instruments is needed before this can be concluded definitively (67, 97).

GENETIC STUDIES TO INFER CAUSALITY: THE MENDELIAN RANDOMIZATION APPROACH

Genetic studies, like randomized intervention trials, are completely free of reverse causation and largely free of confounding. Therefore, if a genetic variant or a drug leads to higher or lower concentrations of a lipoprotein and this further leads to higher or lower risk of cardiovascular disease, then it is quite likely that it is the lipoprotein that causes the effect on cardiovascular disease. In essence, this is the principle of the Mendelian randomization approach. In contrast, results from observational epidemiology can mislead through confounding and reverse causation. Confounding is when a third factor influences both lipoprotein concentrations and cardiovascular disease risk, while reverse causation implies that cardiovascular disease leads to changes in lipoprotein concentrations, rather than vice versa.

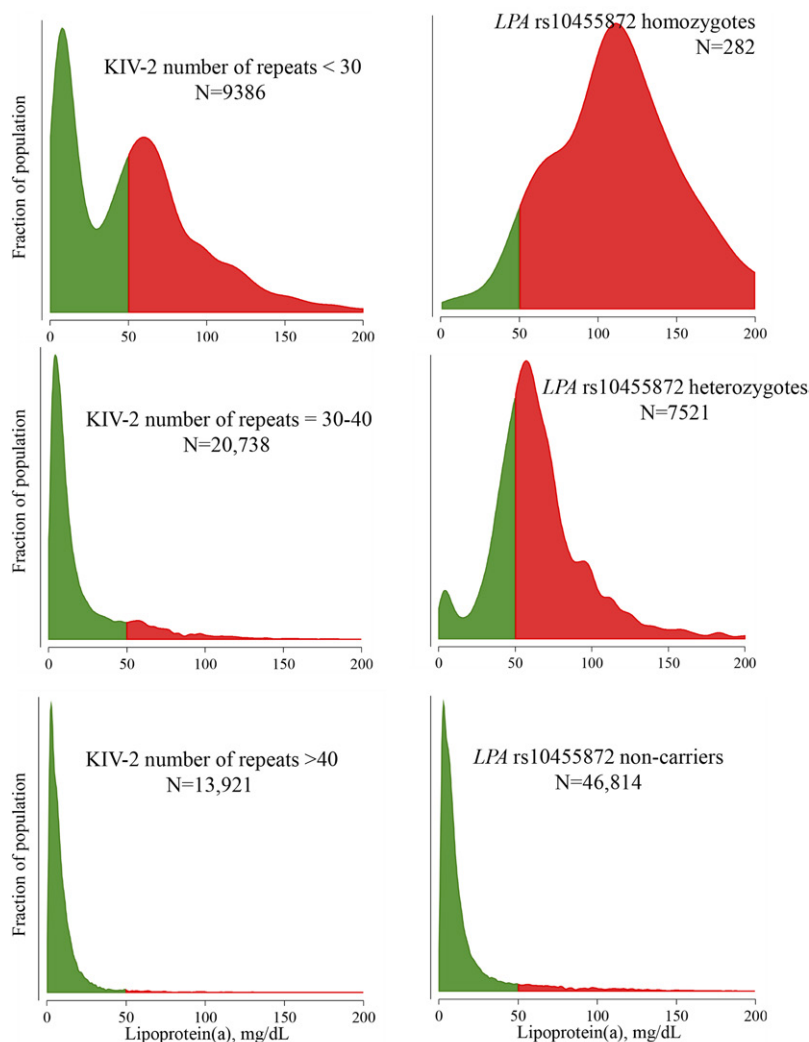


Fig. 3. Distribution of plasma Lp(a) concentrations as a function of *LPA* KIV-2 number of repeats and of *LPA* rs10455872 in the Copenhagen General Population Study. Green and red parts correspond to the bottom 80% and top 20% of the entire population distribution of plasma Lp(a) concentrations (see Fig. 3).

There are several early examples of studies that suggest the idea that if a risk factor is elevated or reduced due to genetic variation, and if such genetic variation is or is not associated with a disease of interest, then it would be possible to infer or exclude causality of the risk factor (98–100). This idea involving the causal genetic influence of high Lp(a) concentrations on risk of coronary heart disease was already presented in 1992 by Gerd Utermann and colleagues (101, 102). However, the concept of the Mendelian randomization approach, including in-depth discussion of strengths and limitations, mainly crystallized due to many insightful publications from George Davey Smith and colleagues (103–108), publications that can be used as a “starter’s kit” to understand the Mendelian randomization approach. Growing out of the awareness of the limitations of observational epidemiology, it was suggested that Mendelian randomization, that is, the random assortment of genes from parents to offspring that occurs during gamete formation and conception, would provide a method for assessing the causal nature of risk factors on disease. The clear formulation of these ideas has substantially influenced thinking on how to understand disease causality, especially in cardiovascular medicine and most importantly for the role of Lp(a) as a cause of cardiovascular disease.

Epidemiology alone cannot determine causality due to potential problems with confounding and reverse causation (Fig. 4, double-pointed arrow #1). Thus, potential confounders, including life-style factors, may be unevenly distributed between those with high and low Lp(a) concentrations, and such confounders may be the real explanation for the high risk of cardiovascular disease in those with high Lp(a) (Fig. 5, left panel). In contrast, in the Mendelian randomization study design, such confounders are always evenly distributed between those with high and low Lp(a), and therefore, cannot explain the high cardiovascular risk in those with genetically high Lp(a) concentrations (Fig. 5, middle and right panels). The other major

potential limitation of observational studies is reverse causation, that is, the possibility that cardiovascular disease leads to high Lp(a) concentrations, rather than vice versa (Fig. 5, left panel). In the Mendelian randomization study design, reverse causation is simply not possible, as cardiovascular disease cannot change your genes (Fig. 5, middle and right panels). In other words, the Mendelian randomization study design can be used to infer causality just like a randomized double-blind placebo-controlled Lp(a)-reducing trial and these two types of studies share many advantages and have similar limitations [see Fig. 5 in (65)]. Unfortunately however, so far no randomized double-blind placebo-controlled Lp(a)-reducing trials to prevent cardiovascular disease have been published or even initiated. Therefore, for now, the human evidence to suggest that high Lp(a) causes cardiovascular disease has to depend on genetics and the Mendelian randomization approach. While these approaches are powerful, it is naturally the totality of evidence that counts in understanding causality.

Another limitation of observational studies is the problem of regression dilution bias (109, 110) because risk factors typically are only measured once, and therefore the association observed will only represent a single point estimate (Fig. 5, left panel). Regression dilution bias means that the effect size of the risk estimate is underestimated, although this bias does not influence statistical significance. In contrast, SNPs used in the Mendelian randomization design generally are measured precisely and have less of a problem with regression dilution bias (Fig. 5, right panel). The exception here is KIV-2 number of repeats measured using quantitative polymerase chain reaction, as this measurement will vary due to measurement error just like plasma Lp(a) concentrations and likewise is affected by regression dilution bias (Fig. 5, middle panel), suggesting that the effect sizes for KIV-2 number of repeats for causal associations with cardiovascular disease should be viewed as minimal estimates (6, 11, 67, 111–113).

Mendelian randomization studies using human genetics have many similarities with randomized double-blind placebo-controlled trials and, thus, advantages over traditional observational studies (Fig. 5). Like in randomized trials, Mendelian randomization studies are double-blind and confounding and reverse causation are circumvented due to nature’s own randomization method during distribution of alleles at meiosis. Mendelian randomization studies have the additional advantage over conventional epidemiology that genetics typically capture a life-long effect (Fig. 5, middle and right panels), while observational studies only include the time between risk factor assessment and end of follow-up. Like a drug in randomized trials, genetics can have the problem of pleiotropic effects; however, while this can be a problem with SNPs as markers of high Lp(a) concentrations, direct measurement of KIV-2 number of repeats or corresponding apo(a) size polymorphism will not have this problem (Fig. 5, right and middle panels).

Another potential problem of Mendelian randomization studies includes linkage disequilibrium with other causative genetic variants in other genes; however, this is not a

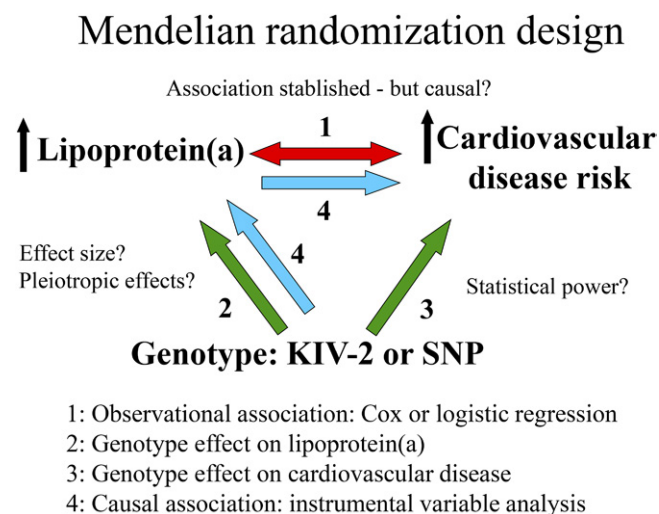


Fig. 4. The four different statistical parts of a complete Mendelian randomization study design to examine causality from high plasma Lp(a) concentrations to high risk of cardiovascular disease. Potential limitations are shown with question marks.

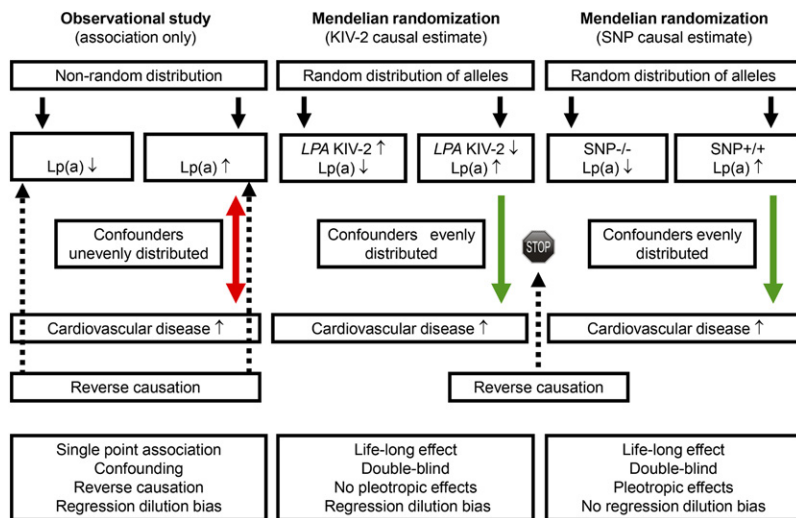


Fig. 5. Comparison of observational studies and Mendelian randomization studies to help understand causality from high plasma Lp(a) concentrations to high risk of cardiovascular disease.

problem for KIV-2, although it can be a problem for SNPs associated with high Lp(a) concentrations. Also, population admixture can be a major problem if both genotype and the disease studied are found preferentially in certain subpopulations; however, this potential problem can be largely circumvented by studying ethnically homogeneous populations or by adjusting for different ethnicity using genetic information. Finally, it is essential to use genetic variation with sufficiently large effect sizes, which has been done in Lp(a) causality research more than for any other cardiovascular risk factor: the *LPA* KIV-2 copy number variation and the *LPA* rs10455872 SNP, which can be used for genotyping large-scale studies, each explain 27–28% of the variation in plasma Lp(a) concentrations.

Technically, what is done in a complete Mendelian randomization study is depicted in Fig. 4. Published examples of this complete design that are easy to follow for the non-specialist include that low concentrations of vitamin D are causally associated with high all-cause mortality (114), and that low concentrations of nonfasting triglycerides are causally associated with low all-cause mortality (115).

First, the well-known observational association is shown in the study population (Fig. 4, double-pointed arrow #1). Second, the causal association between *LPA* genotype

(KIV-2 or a SNP) on Lp(a) concentration is documented and the extent of variation on plasma concentrations determined by genotype is quantified. This allows assessment of the value of the genotype as an instrument in the Mendelian randomization study design (Fig. 4, single-pointed arrow #2). At this stage, it is also important to exclude pleiotropic effects, that is, genotype should not be associated with any other factor that might cause cardiovascular disease (Table 1). Third, genotype is then directly associated with cardiovascular disease, using a study with sufficient statistical power to document or reject the causal association (Fig. 4, single-pointed arrow #3). Fourth, the formal test of causality involves running an instrumental variable analysis (Fig. 4, single-pointed arrows #4) that integrates the effect of genotype on Lp(a) concentrations (arrow #2) with the effect of genotype on cardiovascular disease risk (arrow #3). Observational and genetic causal risk estimates can then be compared directly, as arrows #1 and #4 will be on the same scale, that is, for Lp(a) per, for example, a 30 mg/dl higher concentration either observationally or genetically.

For research on Lp(a) as a cause of cardiovascular disease, it can be argued that even conventional epidemiology will suffice in understanding causality of Lp(a), as the

TABLE 1. Baseline characteristic in individuals from the Copenhagen General Population and the Copenhagen City Heart Study combined

Characteristic	Observational (N = 58,232), Plasma Lp(a)		Genetic (N = 98,941), <i>LPA</i> KIV-2 Number of Repeats		Genetic (N = 104,366), <i>LPA</i> rs10455872 SNP	
	High 80%	Low 20%	Low 20%	High 80%	Non-carrier 86%	Carrier 14%
Age, years	58 (49–68)	59 (50–68)	58 (48–67)	58 (48–67)	58 (48–67)	58 (48–67)
Women, %	54	57	55	55	55	55
Hypertension, %	67	68	66	66	66	66
Diabetes, %	4	4	4	4	4	4
Smoking, %	17	17	17	19	17	17
Cholesterol-lowering therapy, %	11	17	13	11	11	14
Body Mass Index, kg/m ²	26 (23–28)	26 (23–28)	26 (23–28)	26 (23–29)	26 (23–28)	26 (23–28)
Total cholesterol, mmol/l	5.5 (4.8–6.2)	5.7 (5.0–6.4)	5.6 (4.9–6.3)	5.5 (4.8–6.3)	5.5 (4.8–6.3)	5.6 (4.9–6.4)
Triglycerides, mmol/l	1.4 (1.0–2.0)	1.4 (1.0–2.1)	1.4 (1.0–2.1)	1.4 (1.0–2.1)	1.4 (1.0–2.1)	1.4 (1.0–2.1)

Values are median (interquartile range).

concentrations of this lipoprotein are largely genetically determined (14, 39) and minimally confounded by environmental variables (Table 1). Although this seems to be a valid statement, experience has shown that it was mainly the large-scale genetic Mendelian randomization studies published from 2009 and onwards that paved the path for a general understanding that high concentrations of Lp(a) are a direct cause of myocardial infarction, atherosclerotic stenosis, and aortic valve stenosis (Fig. 1).

MYOCARDIAL INFARCTION AND ISCHEMIC HEART DISEASE

Early retrospective case-control studies found that Lp(a) concentrations were higher in patients with myocardial infarction and ischemic heart disease (coronary heart disease), than in individuals without these diseases (116–118). Later on, many similar studies followed (102, 119–130), the majority with the same conclusion that Lp(a) was higher in those with than in those without myocardial infarction and ischemic heart disease. On hindsight, with the current understanding of the Mendelian randomization approach, this is an impressive set of studies; however, at the time of publication of these studies evidence from prospective population-based studies was needed.

Early population-based prospective cohort and nested case-control studies (131–140) were summarized in a meta-analysis by Wendy Craig et al. (141) in 1998. In these studies dominated by White participants, 12 of 14 prospective studies found that Lp(a) concentrations were higher in subjects who later developed ischemic heart disease than in those who did not. After addition of six more prospective population-based studies (142–147), John Danesh and colleagues updated the meta-analysis in 2000 to show that after including 4,044 deaths from coronary heart disease or nonfatal myocardial infarction during a mean follow-up of 10 years in 18 studies, individuals in the top versus bottom third of the Lp(a) concentration distribution had a combined risk ratio of 1.7 [95% confidence interval (CI): 1.4–1.9] (23).

Different results in some of the early studies could be because measurement of Lp(a) is complicated by the varying isoform sizes of apo(a), that is, assays that are not isoform independent might overestimate Lp(a) plasma concentrations when large isoforms are present and underestimate

concentrations when small isoforms are present (148–150). Further, many of these early studies used Lp(a) samples that had been frozen for several years, which might affect the structure of Lp(a) and thereby lead to incorrect measurement of plasma Lp(a) concentrations (151). Also, most previous studies did not estimate risk in individuals with extremely high Lp(a) concentrations, the concentrations that would seem most relevant clinically. Finally, many early studies did not correct for regression dilution bias (109, 110) and, therefore, effect sizes for risk of myocardial infarction and ischemic heart disease likely were underestimated.

After publication of yet another six prospective population-based studies (152–157), we published in 2008 the results of the Copenhagen City Heart Study with 9,330 individuals followed for 10 years during which time 498 developed a myocardial infarction (158). We measured Lp(a) concentrations in 1991–1994 shortly after sampling using an apo(a) isoform-insensitive assay. Risk estimates were corrected for regression dilution bias, and we focused on the risk of myocardial infarction in those with the extremely high concentrations. Specifically, we chose myocardial infarction as the endpoint, as this disease is registered correctly 99.5% of the time in the Danish registries and the follow-up in this population is 100% complete (6). In women, multifactorially adjusted hazard ratios for myocardial infarction for high Lp(a) concentrations were 1.1 (95% CI: 0.6–1.9) for 5–29 mg/dl, 1.7 (95% CI: 1.0–3.1) for 30–84 mg/dl, 2.6 (95% CI: 1.2–5.9) for 85–119 mg/dl, and 3.6 (95% CI: 1.7–7.7) for above 120 mg/dl versus concentrations below 5 mg/dl (158). Corresponding hazard ratios in men were 1.5 (95% CI: 0.9–2.3), 1.6 (95% CI: 1.0–2.6), 2.6 (95% CI: 1.2–5.5), and 3.7 (95% CI: 1.7–8.0), respectively. Also, absolute 10 year risks of myocardial infarction were 10 and 20% in smoking hypertensive women aged above 60 years with Lp(a) concentrations of below 5 mg/dl and above 120 mg/dl, respectively, with corresponding values in men of 19 and 35%.

The Emerging Risk Factors Collaboration included individual records for 126,634 participants from 36 prospective studies, recorded 9,318 myocardial infarctions and coronary deaths, corrected for regression dilution bias, and also focused on the risk of myocardial infarction and coronary death in those with the extremely high Lp(a) concentrations (7) (Fig. 6, right panel). In that study, risk was higher after approximately 30 mg/dl and the age- and sex-adjusted

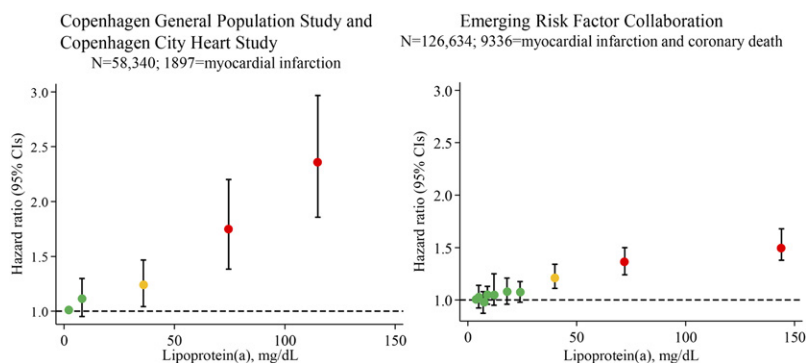


Fig. 6. Observational associations between high plasma Lp(a) concentrations and risk of cardiovascular disease in the Copenhagen City Heart Study and Copenhagen General Population Study combined (left panel) and in the Emerging Risk Factors Collaboration (right panel). Hazard ratios in the left panel were estimated by Cox proportional hazard regression models and were adjusted for age and sex and corrected for regression dilution bias. Right panel was adapted from (7).

risk ratio was 1.5-fold in those with Lp(a) above 100 mg/dl versus below 4 mg/dl. There were continuous, independent, and modest associations of Lp(a) concentration with risk of coronary heart disease that appeared exclusive to vascular outcomes. Importantly however, this meta-analysis included many former studies using frozen samples and nonoptimal Lp(a) assays, likely partly explaining the relatively modest overall effect sizes observed. Also, this may partly be explained by nondifferential misclassification of events from study to study, as myocardial infarction and coronary death events were classified according to the International Classification of Diseases or, where this was not available, on study-specific classification systems.

For use specifically in this review, we updated our former epidemiological studies (6, 112, 158) based on the Copenhagen City Heart Study and the Copenhagen General Population Study combined to achieve maximal statistical power (Fig. 6, left panel). We included 58,340 individuals, measured Lp(a) concentrations in fresh samples using apo(a)-insensitive assays, corrected for regression dilution bias, recorded 1,897 validated myocardial infarctions, and also focused on the risk in those with the extremely high Lp(a) concentrations. In this new analysis, the risk was again higher after approximately 30 mg/dl and the age- and sex-adjusted hazard ratio for myocardial infarction was 2.4-fold in those with Lp(a) above 100 mg/dl versus below 5 mg/dl, and thus more pronounced than in the Emerging Risk Factors Collaboration (compare Fig. 6, left and right panels).

A complete large-scale Mendelian randomization study was first published by us in 2009 (6), although the basic idea had been suggested previously (101, 102). For use specifically in this review, we updated our former Mendelian randomization studies (6, 67, 112) based on the Copenhagen City Heart Study and the Copenhagen General

Population Study combined to achieve maximal statistical power (Fig. 7, top panel). In instrumental variable analyses, a doubling in plasma Lp(a) concentrations caused a 15% (95% CI: 11–20%) higher risk ratio for myocardial infarction using *LPA* KIV-2 number of repeats and a 10% (95% CI: 6–13%) higher risk ratio using *LPA* rs10455872 SNP. This should be compared with the corresponding observational estimate of 9% (95% CI: 7–12%). Importantly, as Lp(a) concentrations vary up to a 1,000-fold between individuals (14), then Lp(a) can double many times. *LPA* genotypes were largely unconfounded by conventional cardiovascular risk factors (Table 1), which was also close to being the case for plasma Lp(a) concentrations.

Many recent large-scale genetic studies also strongly supported high Lp(a) concentrations as a cause of myocardial infarction and ischemic heart disease (8, 66, 159, 160); however, these publications did not include a complete Mendelian randomization approach, but mainly provided data for the direct association between genotypes and risk of disease (Fig. 4, arrow #3). Most importantly, Robert Clarke et al. (8) identified two common *LPA* variants, rs10455872 with a per allele odds ratio for coronary heart disease of 1.70 (95% CI: 1.49–1.95; allele frequency 0.07) and rs3798220 with a per allele odds ratio of 1.92 (1.48–2.49; allele frequency 0.02).

Also important was a 2010 meta-analysis on apo(a) isoforms and risk of coronary heart disease (24). The 34 included studies of mainly White and Asian individuals used either phenotyping (69, 70, 102, 127, 139, 156, 161–182), that is, gel migration speed of plasma Lp(a) and molecular weight determination of apo(a), or genotyping of KIV-2 number of repeats (6, 183). For the 30 studies using phenotyping and including 7,382 cases and 8,514 controls, relative risk of coronary heart disease for smaller versus larger apo(a) isoforms was 2.08 (95% CI: 1.67–2.58). The

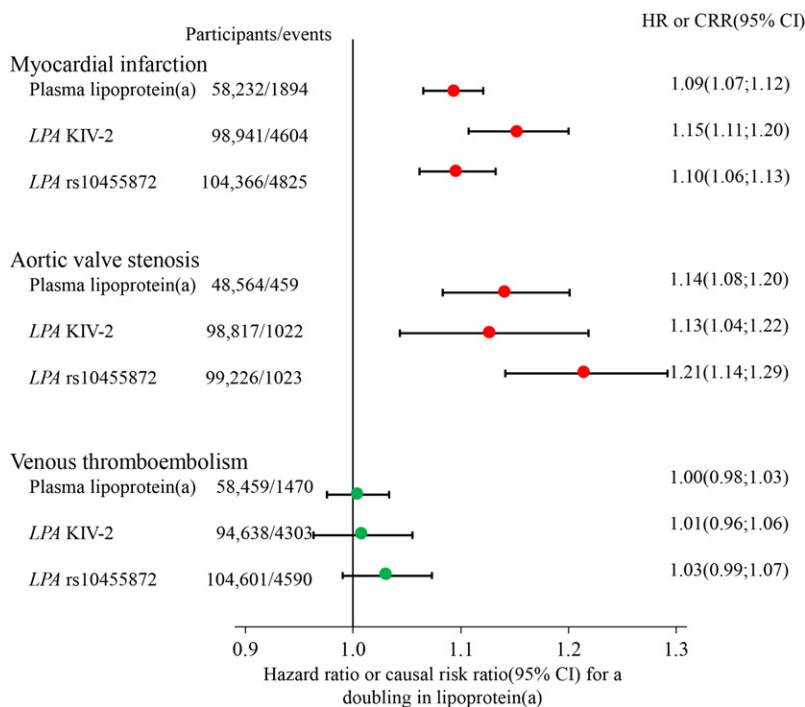


Fig. 7. Observational and causal genetic associations between high plasma Lp(a) concentrations and risk of cardiovascular disease in the Copenhagen City Heart Study and Copenhagen General Population Study combined. Hazard ratios for observational analyses of plasma Lp(a) concentrations were estimated by Cox proportional hazard regression models and were adjusted for age and sex. Causal risk ratios for analyses of genetically determined plasma Lp(a) concentrations were estimated by instrumental variable analyses and were adjusted for age and sex.

genotyping studies were dominated by our own study mentioned above in the complete Mendelian randomization study design (6). It is also important to note that individuals carrying *LPA* loss-of-function alleles with low Lp(a) concentrations have low risk of cardiovascular disease (184, 185). Although relatively few Blacks have been studied in the past, a study in 2012 documented that risk of coronary heart disease is also higher in Black individuals with high plasma Lp(a) concentrations (186).

Taken together, there is now overwhelming evidence from epidemiology and genetics that high Lp(a) concentrations cause high risk of myocardial infarction. It could be argued that the same is true for ischemic and coronary heart disease, but the findings for these disease endpoints could be driven largely by that for myocardial infarction and for atherosclerotic stenosis as described below.

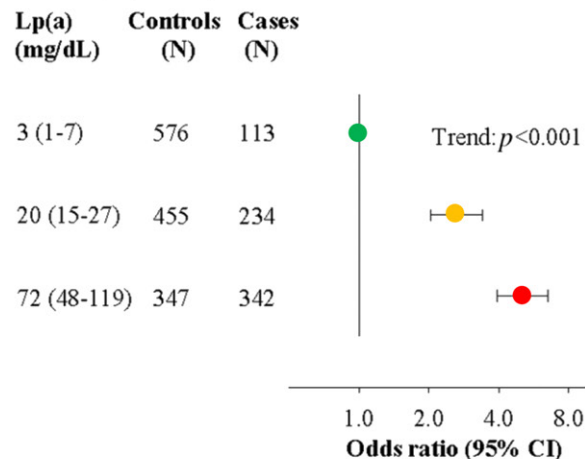
ATHEROSCLEROTIC STENOSIS

When high Lp(a) concentrations lead to high risk of myocardial infarction and ischemic heart disease, then automatically almost everybody will think that this must be because Lp(a) is atherogenic. However, there are other possible explanations and one could be that high Lp(a) leads to thrombosis causing myocardial infarction and to atherosclerotic stenosis causing angina pectoris, rather than Lp(a) causing atherosclerosis per se (111, 187, 188). To us, the latter idea became more plausible when it was suddenly documented that high Lp(a) concentrations also cause aortic valve stenosis (10, 11). However, it can be argued that this is a poor analogy. Indeed, the pathophysiology of “stenosis” in a coronary artery is complex and due to atherosclerotic mediated narrowing of the arterial lumen, some smooth muscle cell proliferation, and likely some element of thrombosis. Thus, the process of atherosclerotic stenosis is very complex and possibly very different than what goes on in aortic valve stenosis. Nevertheless, let us review the human evidence for this idea.

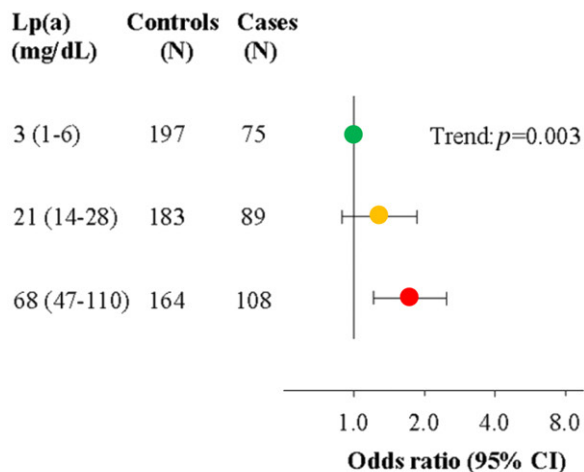
In a study by Kamstrup, Tybjaerg-Hansen, and Nordestgaard (111) in the Copenhagen Ischemic Heart Disease Study, the Copenhagen Carotid Stroke Study, and the Copenhagen City Heart Study, the highest versus lowest tertile of Lp(a) was associated with high risk of coronary, carotid, and femoral atherosclerotic stenosis; that the findings were similar for the lowest versus highest tertile of KIV-2 number of repeats supports that these findings represent causal relationships. For risk of coronary atherosclerotic stenosis, the age- and sex-adjusted odds ratio for highest versus lowest tertile of Lp(a) was 5.0 (95% CI: 3.9–6.5) (Fig. 8, top panel). Corresponding odd ratios were 1.7 (95% CI: 1.2–2.5) for carotid atherosclerotic stenosis (Fig. 8, middle panel) and 1.6 (95% CI: 1.3–2.0) for femoral atherosclerotic stenosis (Fig. 8, bottom panel).

Many other studies have also found an association between high concentrations of Lp(a) or *LPA* risk genotypes and high risk of coronary, carotid, and femoral atherosclerotic stenosis (101, 102, 121, 160, 189–207). For example, in a cohort of 504 patients, Sam Tsimikas, Joe Witztum, and

Coronary (CIHDS): case-control



Carotid (CCSS): case-control



Femoral (CCHS): case-control

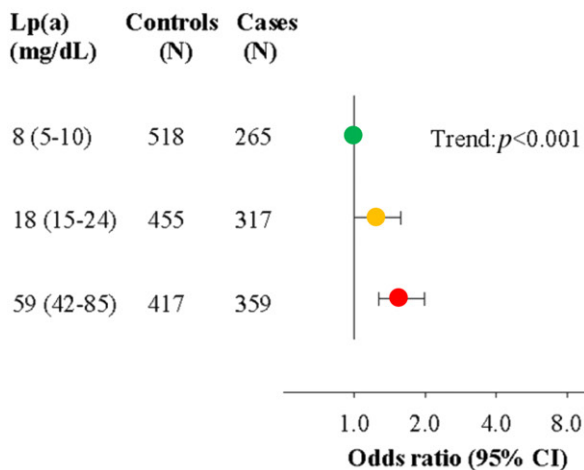


Fig. 8. Observational associations between high plasma Lp(a) concentrations and risk of coronary, carotid, and femoral atherosclerotic stenosis in the Copenhagen Ischemic Heart Disease Study, Copenhagen Carotid Stroke Study, and Copenhagen City Heart Study, respectively. Odds ratios were estimated by logistic regression models and were adjusted for age and sex. CIHDS, Copenhagen Ischemic Heart Disease Study; CCSS, Copenhagen Carotid Stroke Study; CCHS, Copenhagen City Heart Study. Adapted from (111).

colleagues showed a strong association between high oxidized phospholipids and high Lp(a) concentrations with the presence and extent of coronary artery disease, detected by coronary angiography as the number of vessels with a stenosis of more than 50% of the luminal diameter (190). Also, in the InCHIANTI Study, 1,002 individuals aged above 60 years had their ankle-brachial index assessed over a 6 year period, and the authors found that high Lp(a) was an independent risk factor for peripheral arterial disease of the lower limbs (192). Finally, in a large case-control study, the odds ratio per *LPA* rs10455872 or rs3798220 risk alleles was 1.47 (95% CI: 1.33–1.62) for peripheral arterial disease (N = 5,215 cases) (160).

In contrast, high Lp(a) concentrations or *LPA* risk alleles have not been associated with early atherosclerosis measured as modest intima-media thickening in carotid or femoral arteries (160, 208–213); however, there is controversy as to whether such intima-media thickness represents atherosclerosis per se. For example, in the Young Finns Study, including 939 men and 1,141 women, data from observational and Mendelian randomization analyses provided no support for early atherogenic effects of high Lp(a) concentrations (211). Also, after pooling two studies and including 3,714 individuals, *LPA* rs10455872 or rs3798220 risk alleles were not associated with carotid intima-media thickness (160).

Taken together, a large number of studies unanimously show that high plasma Lp(a) concentrations are associated with high risk of coronary, carotid, and femoral atherosclerotic stenosis, with concordance between observational and causal genetic risk estimates. In contrast, there is no human evidence to support that high Lp(a) concentrations should cause early atherosclerosis in the form of increased intima-media thickness. That said, many researchers likely disagree with us on this topic, and many view aortic stenosis and carotid, femoral, or coronary stenosis as separate pathological entities.

AORTIC VALVE STENOSIS

In a 1995 study from Japan, it was observed in 347 men and 437 women that high age and high plasma Lp(a) concentrations were the best risk factors for aortic valve stenosis (sclerosis) (214). Likewise, in 1997, it was observed in 5,201 US individuals aged 65 and above, that age, male sex, and high plasma Lp(a) concentrations were the most important factors to discriminate between individuals with and without calcific aortic valve stenosis (disease) (215). High Lp(a) concentration as an important risk factor for aortic valve stenosis was later confirmed (216, 217), and interestingly, in individuals with both high Lp(a) and high *Chlamydia pneumoniae* IgG antibodies the risk was particularly high (216). Probably not too many noticed these early findings, and after all, this was observational evidence believed to be prone to confounding and reverse causation.

Then in 2013, Thanassoulis et al. (10) discovered that the *LPA* rs10455872 SNP, well-known as a high risk factor for myocardial infarction and coronary heart disease, was

also found to be the best genetic causal risk factor for aortic valve calcification and stenosis: the per allele odds ratio for aortic valve calcification was 2.05 (95% CI: 1.63–2.57). This finding was replicated in additional White European, African-American, and Hispanic-American cohorts. In prospective analyses, this *LPA* SNP had a per allele hazard ratio for incident aortic valve stenosis of 1.68 (95% CI: 1.32–2.15) and 1.60 (95% CI: 1.12–2.28) in Swedish and Danish cohorts of the general population.

In a subsequent study in 2014 based on the Copenhagen City Heart Study and the Copenhagen General Population Study combined, we showed a stepwise higher risk of aortic valve stenosis with stepwise higher extreme concentrations of Lp(a) (Fig. 9) (11). Multivariable adjusted hazard ratios for aortic valve stenosis were 1.2 (95% CI: 0.8–1.7) for 5–19 mg/dl, 1.6 (95% CI: 1.1–2.4) for 20–64 mg/dl, 2.0 (95% CI: 1.2–3.4) for 65–90 mg/dl, and 2.9 (95% CI: 1.8–4.9) for above 90 mg/dl, versus Lp(a) concentrations below 5 mg/dl. Also, combining *LPA* rs10455872, rs3798220, and KIV-2 number of repeats, instrumental variable analysis yielded a genetic causal risk ratio for aortic valve stenosis of 1.6 (95% CI: 1.2–2.1) for a 10-fold higher Lp(a) concentration, comparable to the observational hazard ratio of 1.4 (95% CI: 1.2–1.7) for a 10-fold higher plasma Lp(a) concentration. Interestingly, as observed in the same individuals from Copenhagen and for a comparable doubling in Lp(a) concentrations, the risk estimated for aortic valve stenosis appeared slightly higher than for myocardial infarction, with concordance between observational and causal genetic risk estimates (Fig. 7, compare middle and upper panels).

Even more studies have now confirmed that high Lp(a) concentrations observationally and genetically represent strong causal risk factors for aortic valve calcification, stenosis, and stenosis progression (218–223). This is true for Whites and Asians alike.

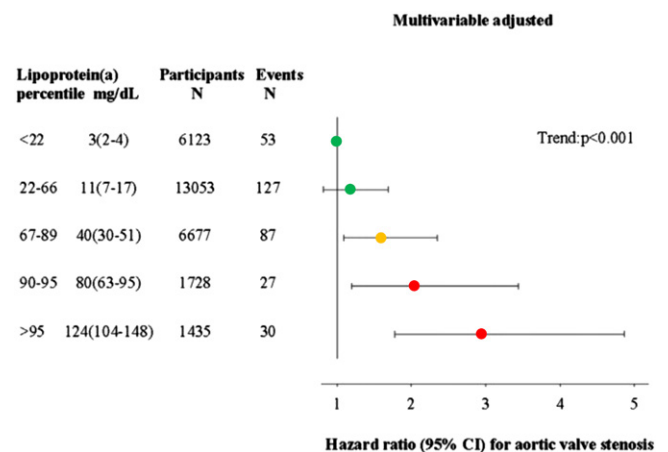


Fig. 9. Observational associations between high plasma Lp(a) concentrations and risk of aortic valve stenosis in the Copenhagen City Heart Study and Copenhagen General Population Study combined. Hazard ratios were estimated by Cox proportional hazard regression models and were multivariable adjusted for age, sex, total cholesterol, HDL cholesterol, systolic blood pressure, smoking, and diabetes. Lp(a) in milligrams per deciliter is shown as median (interquartile range). Adapted from (11).

Together, these studies document high Lp(a) concentrations as one of the strongest causal risk factors for aortic valve stenosis, with risk estimates slightly higher than for myocardial infarction. As both these diseases are among the main causes of heart failure, high Lp(a) concentrations may also be a strong causal risk factor for this condition.

HEART FAILURE

Given the role of high Lp(a) concentrations in myocardial infarction and aortic valve stenosis, it seemed natural to explore the impact of Lp(a) on the end product of these two diseases in the form of heart failure. We combined the Copenhagen City Heart Study and the Copenhagen General Population Study with 98,097 Danish individuals, of whom 4,122 were diagnosed with heart failure from 1976 through 2013. High Lp(a) concentrations were associated with multivariable adjusted hazard ratios for heart failure of 1.10 (95% CI: 0.97–1.25) for 8–19 mg/dl, 1.24 (95% CI: 1.08–1.42) for 20–67 mg/dl, 1.57 (95% CI: 1.32–1.87) for 68–153 mg/dl, and of 1.79 (95% CI: 1.18–2.73) for concentrations above 153 mg/dl, versus Lp(a) concentrations below 8 mg/dl. Of all heart failure in the population, high Lp(a) had a population-attributable fraction of 9%. This means that if high Lp(a) was not present in the Danish population, then heart failure prevalence would be 9% lower than current levels.

By combining all *LPA* risk genotypes, instrumental variable analysis yielded a genetic causal risk ratio for heart failure of 1.18 (95% CI: 1.04–1.34) per 10-fold higher Lp(a) concentrations, which was comparable to the corresponding observational hazard ratio of 1.22 (95% CI: 1.11–1.35). Finally, in mediation analysis, 63% (95% CI: 45–99%) of heart failure risk due to high Lp(a) was mediated via myocardial infarction and aortic valve stenosis combined. Although 63% is a very high number in a mediation analysis, we naturally cannot exclude that high Lp(a) could lead to heart failure via yet another mechanism, e.g., through occlusion of small blood vessels in the myocardium.

VENOUS THROMBOEMBOLISM

Because high Lp(a) is a causal factor for myocardial infarction, and as there is ample evidence that Lp(a) interferes

with fibrinolysis and likely promotes thrombosis (34), it seems logical that high Lp(a) should also be a strong causal risk factor for venous thromboembolism, that is, deep venous thrombosis and pulmonary embolism. Interestingly however, this is probably not the case except at extremely high Lp(a) concentrations (111). Importantly, Lp(a) likely does not have inherent pro-thrombotic properties, but it may be anti-fibrinolytic, i.e., a clot has to be forming for Lp(a) to potentially affect growth. This implies a first hit of some other pro-thrombotic risk factor that is worsened by Lp(a), which might explain why different results on venous thromboembolism have been reported.

Kamstrup, Tybjaerg-Hansen, and Nordestgaard (111) found that highest versus lowest tertile of Lp(a) did not associate with high risk of venous thrombosis; however, the extreme top 5% versus the lowest 22% of the concentration distribution of Lp(a) yielded an odds ratio of 1.7 (95% CI: 1.2–2.3) for risk of venous thrombosis. For the purpose of the present review, we updated this analysis and now included 53,908 individuals from the Copenhagen General Population Study and the Copenhagen City Heart Study with a total of 2,501 events of venous thromboembolism, and correspondingly found at extremely high Lp(a) concentrations above 100 mg/dl compared with concentrations below 5 mg/dl, a hazard ratio of 1.33 (95% CI: 1.06–1.69) for risk of venous thromboembolism (Fig. 10).

A meta-analysis from 2007, including six case-control studies with 1,826 patients with venous thromboembolism and 1,074 controls, found an odds ratio for venous thromboembolism of 1.8 (95% CI: 1.1–2.8) for Lp(a) concentrations above versus below 30 mg/dl (224). Three of the studies in the meta-analysis found individually higher risk of venous thromboembolism (225–227), whereas three studies had insignificant results (228–230). Further, the Longitudinal Investigation of Thromboembolism Etiology (LITE) study, including 19,921 participants with no venous thromboembolism at baseline, observed 327 venous thromboembolic events in Whites and 83 in African Americans during follow-up: the hazard ratio for risk of venous thromboembolism at Lp(a) above versus below 30 mg/dl was 1.12 (95% CI: 0.55–2.27) for Whites and 1.31 (95% CI: 0.69–2.47) for African Americans (231). In addition, several studies have been carried out in children with respect to high Lp(a) concentrations and risk

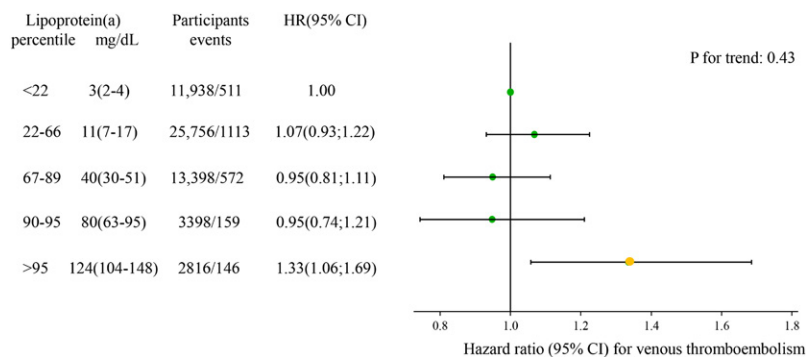


Fig. 10. Observational associations between high plasma Lp(a) concentrations and risk of venous thromboembolism in the Copenhagen City Heart Study and Copenhagen General Population Study combined. Hazard ratios were estimated by Cox proportional hazard regression models and were adjusted for age and sex. Lp(a) in milligrams per deciliter is shown as median (interquartile range). HR, hazard ratio.

of venous thromboembolism, with conflicting results (232–242).

As for genetic association of high Lp(a) with venous thromboembolism, one study found that after combining the *LPA* rs10455872 and rs3798220 SNPs, both of which are associated with high Lp(a) concentrations, there was no association of the *LPA* risk score with venous thromboembolism (N = 4,607 cases) (160). Also, another study among 21,483 women found similar results (243).

Calculated for the present review, among 104,601 individuals in the Copenhagen General Population Study and the Copenhagen City Heart Study combined, we find, using instrumental variable analyses, that the *LPA* rs10455872 SNP has a causal risk ratio of 1.03 (95% CI: 0.99–1.07) per doubling in Lp(a) for risk of venous thromboembolism (Fig. 7, bottom panel). A recently published study, including 516 patients with venous thromboembolism and 1,117 healthy controls, found that *LPA* KIV-2 number of repeats was independently associated with venous thromboembolism and that KIV-2 number of repeats was lower in patients than in controls (244). This is in contrast to what we find in 94,638 individuals in the Copenhagen General Population Study and the Copenhagen City Heart Study combined, where the *LPA* KIV-2 in instrumental variable analysis had a causal risk ratio of 1.01 (95% CI: 0.96–1.06) per doubling in Lp(a) concentrations for risk of venous thromboembolism (Fig. 7, bottom panel), also in accordance with previously published data on our studies (111).

Taken together, it seems likely that extremely high Lp(a) concentrations lead to modestly higher risk of venous thromboembolism. However, over the major part of the concentration range of Lp(a), risk of venous thromboembolism does not seem to be higher. Certainly, when compared directly using the same roughly 100,000 individuals from Copenhagen, then high Lp(a) is a much stronger causal factor for risk of myocardial infarction and aortic valve stenosis than for risk of venous thromboembolism, with concordance between observational and causal genetic risk estimates (Fig. 7).

SPECULATIONS ON POSSIBLE MECHANISMS IN PHYSIOLOGY AND PATHOPHYSIOLOGY

Given the evidence presented above, it is worth considering what human epidemiologic and genetic evidence can teach us about mechanisms, that is, how high Lp(a) concentrations can cause disease and, conversely, whether that will tell us something about the physiological role of Lp(a). Certainly, as Lp(a) has developed twice in evolution in two different forms, around 140 million years ago in the hedgehog and around 40 million years ago in Old World monkeys, apes, and humans (14), Lp(a) likely must have had an important function on survival.

Physiologically, it was proposed by Michael Brown and Joe Goldstein (12) in 1987 that Lp(a) may play a role in wound healing, an idea that has been elaborated on (14, 27, 245–247). The physiological mechanism suggested is that Lp(a) binds to fibrin by its kringle structures and thereby specifically is transported to sites of injury, to facilitate wound healing via fibrinolysis inhibition and perhaps providing cholesterol for cell proliferation during tissue repair. If the latter hypothesis is true, it would seem natural that high Lp(a) concentrations should lead to low risk of bleeding.

From an evolutionary perspective in a context without modern medicine, it is easy to envision how protection from major fatal bleeds at a young age facilitated by high plasma Lp(a) concentration could have had a positive influence on survival (Fig. 11, left part). Improved survival due to reduced bleeding would seem highly likely for mother and child during childbirth, during infectious diseases, including tuberculosis, and from injuries during war or from dangerous animals and insects, or just in ordinary everyday life.

Until now, no convincing large-scale human data have been presented to support the hypothesis of improved wound healing at high Lp(a) concentrations. However, in a study including 109,169 individuals from the Copenhagen City Heart Study and the Copenhagen General Population study combined, we found that high Lp(a) concentrations

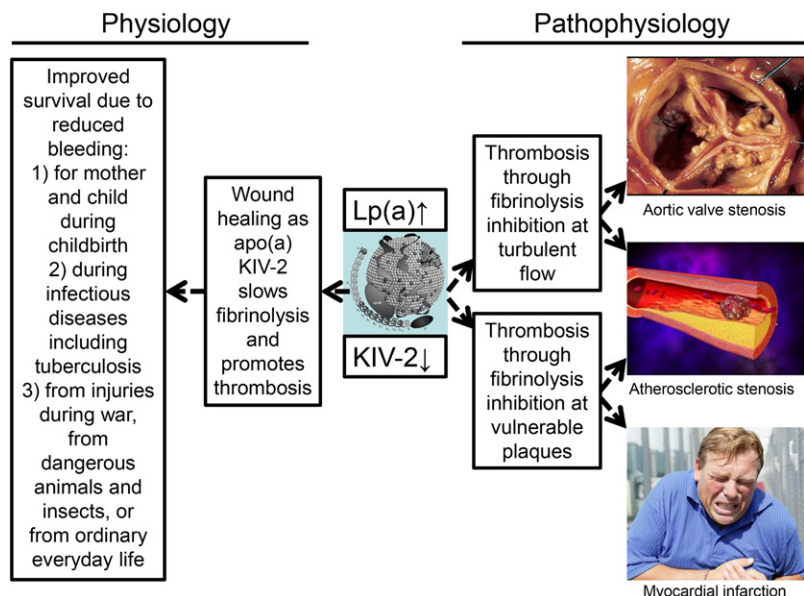


Fig. 11. Speculations on physiological role and pathophysiology of high plasma Lp(a) concentrations, with corresponding small apo(a) size due to low number of KIV-2 repeats.

were associated with low risk of major bleeding observationally and causal, genetically (A. Langsted, P.R. Kamstrup, B.G. Nordestgaard, unpublished observations). To us, this supports that Lp(a) physiologically may play a role in wound healing, although the hypothesis, at present, is mainly speculative.

In support of our findings, a prospective cohort study of the Japanese general population, including 10,494 individuals, found that the highest versus the lowest tertile of Lp(a) was associated with a hazard ratio for risk of cerebral hemorrhage of 0.34 (95% CI: 0.15–0.76) for men and of 0.44 (95% CI: 0.21–0.96) for women (249). Also, a previous study showed that Lp(a) particles with small apo(a) isoforms [and thus high Lp(a) concentrations] may inhibit fibrinolysis (250), and another study showed that high Lp(a) concentrations or small apo(a) sizes were associated with the formation of dense fibrin clots of reduced clot permeability and prolonged clot lysis time (251).

Further, a proteomic study identified Lp(a)-associated proteins to be assigned to wound healing, including the processes of coagulation, complement activation, and inflammatory response, implying that Lp(a) might have a role in the wound healing process (252). Interestingly though, although high Lp(a) concentrations may be involved in inflammation locally at sites of injury, e.g., locally in the arterial wall (253), genetically high Lp(a) concentrations (like genetically high LDL cholesterol concentrations) were not associated with high concentrations of C-reactive protein in individuals in the general population (**Fig. 12**) (112); in contrast, high triglyceride-rich lipoproteins measured as high remnant cholesterol led to low-grade inflammation on a whole body level (254).

The exact molecular mechanism by which high Lp(a) concentrations and small apo(a) size inhibit fibrinolysis and thereby possibly may promote thrombosis and facilitate wound healing, is discussed in another article in this Thematic Review series (34). If wound healing is indeed promoted by high Lp(a) concentrations, then it could even be speculated that the higher Lp(a) concentrations in individuals of African descent compared with individuals of European or Asian descent (14), could specifically, in an African context, present a survival advantage, e.g., through less bleeding during childbirth, infectious diseases, and injury, as speculated in Fig. 11.

An evolutionary advantage at a young age, like wound healing, could at an old age lead to more thrombosis and related diseases (Fig. 11, right part). As apo(a) has homology with plasminogen (4, 39), Lp(a) may promote thrombosis by competing with plasminogen and thereby inhibiting the role of plasmin in dissolving fibrin clots (34, 255–257). This could then, through fibrin deposition, lead to progressive aortic valve and atherosclerotic stenosis. We speculate that Lp(a) could bind to fibrin and be transported to and accumulate at sites of vulnerable plaques, and thereby deliver cholesterol via its LDL-component to sites of tissue healing, and as such is part of a wound healing process leading to progressive narrowing at atherosclerotic stenoses in coronary, carotid, and femoral arteries. If Lp(a) accumulates at sites of wound healing during rupture of vulnerable plaques, then it can further be speculated that Lp(a) might also accumulate at sites of minor injury during turbulent blood flow with beginning aortic valve and atherosclerotic stenosis, enhancing the deposition of cholesterol and possibly thrombi (12, 258), each of which may lead to further stenosis.

In support of this idea, Lp(a), compared with LDL, preferentially accumulates at sites of arterial injury, but not in adjacent uninjured arteries (56). Also, high Lp(a) concentration was a strong predictor of vein graft stenosis after coronary artery bypass surgery (259), although this was not the case after percutaneous transluminal coronary angioplasty (260). The exact molecular mechanism by which high Lp(a) concentrations and small apo(a) size may cause aortic valve and atherosclerotic stenosis, e.g., by oxidized phospholipids through pro-inflammatory and pro-calcifying effects, is discussed in other articles in this Thematic Review series (34, 261). Importantly, a recent study suggests that Lp(a) induces monocyte trafficking to the arterial wall and mediates pro-inflammatory responses through its oxidized phospholipid content, pointing at a possible novel mechanism by which Lp(a) mediates cardiovascular disease (253).

As Lp(a) consists of a LDL cholesterol-rich particle covalently bound to an apo(a) glycoprotein, another possible mechanism involves that Lp(a), after transfer from the blood stream into the wall of aortic valve leaflets and the arterial intima (49, 52, 53), leads to cholesterol deposition in the manner similar to LDL and remnant cholesterol

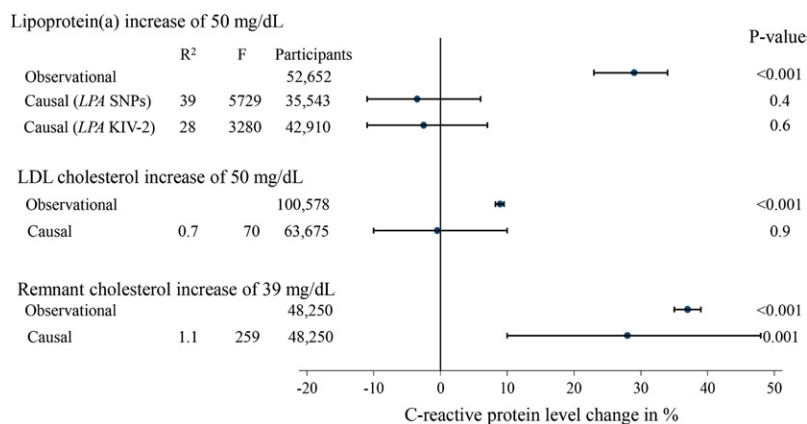


Fig. 12. Observational and causal genetic associations between high Lp(a) cholesterol, high LDL cholesterol, and high remnant cholesterol with C-reactive protein concentrations. Observational changes were by linear regression and causal genetic estimates were by instrumental variable analyses. Adapted from (112, 254).

(63, 65). This would then cause a thickening of aortic valve leaflets and the arterial intima. However, as mentioned above, there is no human evidence to support that high Lp(a) concentrations promote early atherosclerosis (160, 208–213), at least in the form of increased intima-media thickness.

We speculate that the physiological role of KIV-2 in Lp(a) could be through wound healing during childbirth, infections, and injury, a role that at an old age could lead to more blood clots promoting stenosis of arteries and the aortic valve, and to myocardial infarction at sites of vulnerable plaques. Although many speculations are involved in this chain of events, this scenario seems to us to be the most straightforward explanation for the human data available today. We recognize that many experts in the field of Lp(a) research will find the proposed function of Lp(a) to promote wound healing as overemphasized here; nevertheless, we feel this subject should be presented in this Thematic Review so that the full range of ideas may be presented. The many other possible functions that might be equally or even more important are discussed in other articles in this Thematic Review series.

FAMILIAL HYPERCHOLESTEROLEMIA

Many early studies have demonstrated that Lp(a) concentrations are particularly high in those with clinically diagnosed heterozygous or homozygous familial hypercholesterolemia (FH) (122, 262–267), while others have not been able to document this (268, 269). FH with genetically very high LDL cholesterol is an autosomal dominant condition found in almost 1 in 200 individuals (270–274). Kinetic studies in subjects with homozygous FH found that Lp(a) is not catabolized via the LDL-receptor (275), demonstrating that the mechanism for high Lp(a) concentrations in FH is not the same as that for high LDL concentrations. In fact, plasma Lp(a) concentrations are mainly determined by production rates (276). Studies of genetic variation in both the *LDLR* and *LPA* genes have nevertheless supported that the observed high Lp(a) in those with clinically diagnosed FH is biologically based (268, 277).

Individuals diagnosed clinically with FH are prone to ascertainment bias (278), that is, individuals with the most extreme risk factors are most likely to be referred to hospital clinics. It is therefore possible that the high Lp(a) concentrations in individuals with clinically defined FH simply is the additional risk factor making the person attend a lipid clinic. In accordance with this idea, nonaffected family members of clinically diagnosed FH patients had higher Lp(a) concentrations than individuals in a reference population (267).

As reviewed above, it is now well demonstrated that high Lp(a) concentration is a causal risk factor for cardiovascular disease in the average person (6, 8, 9), irrespective of the concentration of LDL cholesterol (7, 158), and studies in FH patients demonstrate that high Lp(a) is also an important cardiovascular risk factor in this population (125,

279). In other words, high Lp(a) concentrations make risk of cardiovascular disease even worse in those already at extremely high risk due to the high LDL associated with FH. In accordance with this, European Atherosclerosis Society consensus panel statements made it a priority to screen all FH patients for high Lp(a) concentrations (9, 271, 280, 281).

On this background, we recently tested the hypotheses that high Lp(a) cholesterol and *LPA* risk genotypes are a cause of clinical FH, and that individuals with both high Lp(a) and clinical FH have the highest risk of myocardial infarction (113). In 46,200 individuals from the Copenhagen General Population Study, we used the Dutch Lipid Clinic Network criteria to diagnose FH clinically.


It should be recognized that the conventional measurement of “LDL cholesterol” contains the cholesterol content of both LDL as well as that found in the LDL component of Lp(a). Using routine LDL cholesterol measurements, e.g., unadjusted LDL cholesterol, mean Lp(a) concentrations were 23 mg/dl in individuals unlikely to have FH, 32 mg/dl in those with possible FH, and 35 mg/dl in those with probable or definite FH ($P < 0.0001$ for trend) (113). However, when adjusting LDL cholesterol for Lp(a) cholesterol content by subtracting 30% of the total Lp(a) mass from LDL cholesterol, the corresponding values were 24, 22, and 21 mg/dl, respectively ($P = 0.46$ for trend). Thus, the contribution of high Lp(a) cholesterol to the unadjusted LDL cholesterol measurement accounted for a quarter of all individuals diagnosed with clinical FH. Further, *LPA* risk genotypes were more frequent in clinical FH, whereas Lp(a) concentrations were similar in those with and without FH mutations in *LDLR* and *APOB* genes.

The hazard ratios for myocardial infarction compared with individuals unlikely to have FH and Lp(a) concentration below 50 mg/dl were 1.4 (95% CI: 1.1–1.7) in those unlikely to have FH and Lp(a) concentrations above 50 mg/dl, 3.2 (95% CI: 2.5–4.1) in those with possible, probable, or definite FH and Lp(a) concentration below 50 mg/dl, and 5.3 (95% CI: 3.6–7.6) in those with possible, probable, or definite FH and Lp(a) concentration above 50 mg/dl (113). In analyses using Simon Broome or MEDPED criteria, results were similar to those using Dutch Lipid Clinic Network criteria to diagnose clinical FH.

Taken together, plasma Lp(a) concentrations are higher in individuals with clinically diagnosed FH, but this is not due to FH mutations in *LDLR* and *APOB* genes. Rather, because Lp(a) cholesterol contributed to LDL cholesterol in the clinical diagnosis of FH, 25% of all clinically defined FH is due to high Lp(a) concentrations. The combined evidence strongly supports that all individuals with FH should have their Lp(a) measured in order to identify those with the highest concentrations, and as a result, the highest risk of myocardial infarction.

CONCLUSION AND PERSPECTIVES

Research and clinical interest in Lp(a) has had its ups and downs since its initial discovery in 1963 (1). The first

golden age in Lp(a) research started in 1987 with the cloning and sequencing of the *LPA* gene coding for apo(a) in Lp(a) (4), leading to a huge increase in scientific interest in Lp(a). Then 22 years later in 2009, new genetic evidence that Lp(a) was a direct cause of cardiovascular disease just like LDL, started the second golden age in research and clinical interest in Lp(a) (6, 8), an interest that is only unraveling right now. We hope to experience a third golden age, a period in which, hopefully, randomized trials of Lp(a) reduction in individuals with very high concentrations can document reduction in cardiovascular disease. Only then will the clinical interest in Lp(a) become widespread. Certainly, for LDL cholesterol this is what happened after the 4S trial of statin therapy documented that reduction in LDL cholesterol lead to reduced cardiovascular disease and reduced all-cause mortality (282).

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