Thesis

The Role of Lipoprotein(a) in Cardiovascular Risk among Patients with Psychiatric Disorders

submitted by

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Zusammenfassung

Einleitung. Patient*innen mit schweren psychischen Erkrankungen wie Major Depression, bipolarer Störung oder Schizophrenie weisen eine signifikant reduzierte Lebenserwartung auf, welche primär auf eine erhöhte kardiovaskuläre Morbidität und Mortalität in diesem Patientenkollektiv zurückzuführen ist. Traditionelle Risikofaktoren, Lebensstil sowie psychopharmakologische Nebenwirkungen können dieses erhöhte Risiko nur teilweise erklären. Lipoprotein(a) (Lp(a)) ist ein genetisch determinierter und unabhängiger kausaler Risikofaktor für atherosklerotische kardiovaskuläre Erkrankungen. Diese Arbeit untersucht, ob Lp(a) bei psychiatrischen Erkrankungen verändert ist und ob Lp(a) zum erhöhten kardiovaskulären Risiko bei psychiatrischen Patient*innen beiträgt.
Methodik. Es wurde eine systematische Literaturrecherche auf PubMed sowie eine ergänzende manuelle Recherche durchgeführt. Die Suche konzentrierte sich auf Studien mit Veröffentlichung seit Einführung der Datenbank bis Februar 2026, welche Lp(a)-Spiegel bei psychiatrischen Patient*innen untersuchten. Die Suchstrategie basierte auf dem PICO-Schema und kombinierte Begriffe zu Lipoprotein(a), psychiatrischen Diagnosen und Psychopharmaka. Eingeschlossen wurden Studien mit erwachsenen Populationen (≥ 18 Jahre), einer nach ICD oder DSM diagnostizierten psychiatrischen Diagnose sowie quantitativen Lp(a)-Messungen und einer gesunden Kontrollgruppe. Von initial 189 identifizierten Publikationen erfüllten 9 Studien die Einschlusskriterien und wurden in das systematische Review einbezogen.
Ergebnisse. Die Studien weisen heterogene Ergebnisse auf, zeigen aber mehrheitlich eine positive Assoziation zwischen Lp(a)-Spiegeln und psychiatrischen Erkrankungen. Für depressive Störungen beschreiben vier Studien einen signifikant positiven Zusammenhang zwischen Lp(a) und Depression, während zwei Studien keine statistisch signifikanten Unterschiede feststellen. Eine weitere Studie zeigt einen bidirektionalen Zusammenhang zwischen Lp(a) und depressiven Störungen und eine Biobank-Analyse beschreibt einen positiven Zusammenhang zwischen Lp(a) und Depression, welcher durch den Entzündungsstatus (anhand hs-CRP-Werten) moduliert wird. Für Schizophrenie zeigen zwei klinische Studien signifikant erhöhte Lp(a)-Konzentrationen bei Erkrankten. Bei Patient*innen mit bipolarer Störung berichten

zwei Fall-Kontroll-Studien über höhere Lp(a)-Spiegel bei Erkrankten, wohingegen eine weitere Studie einen möglichen kausalen Zusammenhang mit niedrigeren Lp(a)-Konzentrationen darlegt. Pharmakotherapeutisch zeigt sich lediglich für Paroxetin eine signifikante Senkung der Lp(a)-Spiegel in einer Studie bei depressiven Patient*innen.

Conclusio. Mehrere Studien zeigen einen Zusammenhang zwischen erhöhten Lp(a) Konzentrationen und psychischen Erkrankungen. Aufgrund der limitierten Studiengröße der meisten Studien sowie inkonsistenten Ergebnissen in neueren Studien mit größeren Studienpopulationen kann aufgrund der aktuell limitierten Evidenz eine Rolle von Lp(a) in der Komorbidität kardiovaskulärer und psychiatrischer Erkrankungen vermutet, jedoch nicht abschließend belegt werden.

Abstract

Introduction. Patients with severe mental illness (SMI) such as major depression, bipolar disorder, or schizophrenia show a significantly reduced life expectancy, which is predominantly attributable to increased cardiovascular morbidity and mortality in this patient population. Traditional risk factors, lifestyle factors, and adverse effects of psychopharmacological medication only partially account for this elevated risk. Lipoprotein(a) (Lp(a)) is a genetically determined and independent causal risk factor for atherosclerotic cardiovascular disease (ASCVD). This thesis investigates whether Lp(a) levels are altered in psychiatric disorders and whether Lp(a) may contribute to the disproportionate cardiovascular burden in psychiatric patients.

Methods. Literature was systematically searched in the PubMed database, complemented by manual research. The search focused on studies published from database inception to February 2026 that assessed Lp(a) levels in psychiatric patients. The search strategy followed the PICO framework and combined terms related to lipoprotein(a), psychiatric diagnoses, and psychotropic medications. Studies were included if they involved adult participants (≥ 18 years), an established psychiatric diagnosis according to ICD or DSM criteria, quantitative Lp(a) measurements, and a healthy control group. A total of 189 publications were identified, and 9 studies met the inclusion criteria and were included in this systematic review.

Results. The studies observed heterogeneous, yet mainly positive associations between Lp(a) levels and psychiatric disorders. For depressive disorders, four studies reported a significant positive relationship between Lp(a) and depression, while two studies found no statistically significant differences. One additional study identified a bidirectional association between Lp(a) and depressive disorders, and a large biobank analysis suggested a positive association between Lp(a) and depression that is moderated by inflammation (assessed by hs-CRP). For schizophrenia, two clinical studies reported significantly elevated Lp(a) levels in affected individuals. For bipolar disorder, two case-control studies indicated higher Lp(a) concentrations in patients, while one study suggested a causal relationship with lower Lp(a) levels. Concerning pharmacotherapy, only paroxetine significantly lowered Lp(a) levels in depressive patients in one study.

Conclusion. Most of the included studies show an association between increased Lp(a) concentrations and mental health disorders. However, given the limited sample sizes of most studies and diverging findings from more recent studies with larger study populations, it can be suggested that Lp(a) may mediate the comorbidity of cardiovascular and psychiatric disorders, but conclusive evidence remains to be established.

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List of abbreviations

A

Apo(a) ..... Apolipoprotein(a)
ApoB ..... Apolipoprotein B
ApoB-100 ..... Apolipoprotein B-100
ASCVD ..... Atherosclerotic cardiovascular disease
AVC ..... Aortic valve calcium
AVS ..... Aortic valve stenosis

B

BDI ..... Beck Depression Inventory
BMI ..... Body mass index

C

CRP ..... C-reactive protein
CVD ..... Cardiovascular disease

D

DALYs ..... Disability-adjusted life years
DSM ..... Diagnostic and Statistical Manual of Mental Disorders

E

ELISA ..... Enzyme-linked immunosorbent assay
eNOS ..... Endothelial nitric oxide synthase

G

GFR ..... Glomerular filtration rate

H

HDL ..... High-density lipoprotein
HDL-C ..... High-density lipoprotein cholesterol
hs-CRP ..... High-sensitivity CRP

I

ICD ..... International Statistical Classification of Diseases and Related Health Problems

K

KIV ..... Kringle 4
KIV-2 ..... Kringle 4 type 2
KV ..... Kringle 5

L

LDL ..... Low-density lipoprotein
LDL-C ..... Low-density lipoprotein cholesterol
Lp(a) ..... Lipoprotein (a)

M

MACE ..... Major adverse cardiac event
MDD ..... Major depressive disorder
MR ..... Mendelian Randomization

N

NO ..... Nitric oxide

O

oxLDL ..... Oxidized LDL
OxPLs ..... Oxidized phospholipids

P

PCR ..... Polymerase chain reaction
PCSK9 ..... Proprotein convertase subtilisin/kexin type 9

R

ROS ..... Reactive oxygen species

S

SMI ..... Severe mental illness
SNP ..... Single nucleotide polymorphism
SNRI ..... Serotonin-norepinephrine reuptake inhibitor
SSRI ..... Selective serotonin reuptake inhibitor

T

tPA ..... Tissue plasminogen activator

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1 Introduction

1.1 Background and problem statement

Cardiovascular disease (CVD) is a major contributor to excess morbidity and mortality in individuals with psychiatric disorders (1), yet the underlying mechanisms of this co-morbidity are complex and the causal link remains incompletely understood (2). Life expectancy of patients with severe mental illness (SMI) - including major depressive, bipolar, and psychotic disorders such as schizophrenia – is largely reduced, mostly due to premature deaths caused by CVD (3). Traditional cardiovascular risk factors, lifestyle behaviors, psychotropic medication, and healthcare disparities account for only a part of the elevated CVD-related risk (4), suggesting that other mechanisms might contribute to the cardiovascular burden of this population. Lipoprotein(a) (Lp(a)) is an independent causal risk factor for atherosclerotic cardiovascular disease (ASCVD) predefined by genetics (5) that has also attracted attention as a potential contributor to poor mental health (6) and increased depressive symptoms (7). These findings could indicate that psychiatric disorders and their pharmacological treatment may be linked to alterations in Lp(a) levels, and that Lp(a) may contribute to the high prevalence of CVD in patients with mental health disorders.

1.2 Aim of the thesis

Therefore, the aim of this diploma thesis is to evaluate whether Lp(a) is a relevant contributor to cardiovascular risk in patients with psychiatric disorders – with focus on depressive and bipolar disorders as well as schizophrenia. To achieve a comprehensive understanding, the thesis first outlines the global burden, general determinants and development of CVD. Subsequently, Lp(a) is introduced as a specific and predisposing risk factor for CVD, detailing its genetics, biology, pathophysiological mechanisms, its relevance as a cardiovascular risk factor and its clinical implications. Building upon these foundations, the thesis explores the well-documented comorbidity between mental health disorders and CVD, highlighting potential shared pathways. In the results section, the thesis systematically synthesizes available evidence investigating the association between Lp(a) levels and psychiatric disorders and their treatment. Finally, these

findings will be critically evaluated to determine if there could be a relationship between Lp(a) and psychiatric disorders, and whether Lp(a) could potentially mediate the concomitance of increased cardiovascular risk and psychiatric disorders. Given the novelty of this field, the available evidence on the association of Lp(a) and mental health disorders is expected to be limited, and the findings may be heterogeneous. However, the well-established role of Lp(a) in CVD provides a strong rationale for investigating this topic in psychiatric populations.

1.3 Cardiovascular Risk

1.3.1 Global relevance and epidemiology

1.3.1.1 Incidence, prevalence and mortality trends

Cardiovascular diseases continue to account for the most cases of disease and death on a global scale (8). CVD cover a broad spectrum – from ischemic or structural heart diseases and degenerative valve disease to cerebrovascular diseases, ischemic stroke and peripheral arterial disease – and are the key driver of morbidity, disability and mortality worldwide (8). With 626 million people diagnosed with CVD, the latest Global Burden of Disease Study highlights the high and persistent burden of CVD being the cause of 19.2 million deaths in 2023, accounting for nearly 1/3 of all deaths globally (8,9). Compared to 1990, this is an increase of approximately 50.3% in CVD prevalence and around 31.8% in in mortality (8). In 2023, CVD also were the primary cause for disability-adjusted life years (DALYs), leading to 437 million DALYs worldwide, a 40% increase compared to CVD DALYs in 1990 (8). A prediction of future trend in cardiovascular disease by Chong et al. estimates that CVD prevalence will approach a two-fold increase by 2050 compared to 2025, corresponding to an annual increase of 3.6%, while mortality is anticipated to rise from 20.5 million in 2025 to 35.4 million in 2050 (10). CVD risk is further modified by broader health determinants including social factors, socioeconomic status and mental health conditions (11). Socioeconomically disadvantaged populations show higher rates of traditional risk factors and are more likely to engage in adverse health behaviors such as tobacco use (11). Disproportionately elevated CVD rates are furthermore observed especially in countries with the highest levels of income disparity (11). Together, these data underscore that CVD already account for the greatest burden of

morbidity and mortality worldwide and based on projections, CVD will significantly increase over the coming decades, representing the greatest challenge to healthcare systems globally.

1.3.2 Cardiovascular risk factors

1.3.2.1 Traditional risk factors

Data from the Global Burden of Disease Study, together with an extensive multinational study of the Global Cardiovascular risk Consortium, involving over 2 million participants from 39 countries, emphasize the importance of modifiable, insufficiently controlled risk factors in developing CVD in first place (8,12). Amongst all alterable risk factors for CVD, the five major classical factors include hypertension, non-high-density lipoprotein cholesterol (non-HDL-C), diabetes, smoking, and increased body mass index (BMI) (8,12,13) and explain the majority of major cardiovascular incidents in both women (2023: 57,2%) and men (2023: 52,6%) (13). Recent findings identify metabolic (BMI and fasting plasma glucose) and environmental factors as the most rapidly increasing threats to CVD, while other risk factors such as high intake of trans fats are declining (8). In absence of all mentioned classical risk factors, the estimated lifetime CVD risk is 13% in women and 21% among men before age 90 (12). In contrast, female participants with all five risk factors displayed a markedly higher risk of 24%, while male participants showed a risk of 38% (12). Furthermore, people at 50 years of age without any risk factors for CVD experience a substantially enlarged life expectancy of more than a decade as opposed to individuals presenting with all five risk factors, in both men and women (12). The international case-control INTERHEART Study also shows that these potentially preventable risk factors contribute to the largest part of myocardial infarctions globally, together with other risk factors including psychosocial factors, alcohol, poor dietary habits and insufficient physical exercise (14). In total, these factors were responsible for 94% of the population-attributable risk in women and 90% in men (14).

1.3.2.2 Non-traditional risk factors

Through research and therapeutic advances, classical risk factors such as smoking, low-density lipoprotein cholesterol (LDL-C) and hypertension show a

global progressive decline and now contribute a smaller share of the overall cardiovascular risk, largely owing to potent lipid-lowering therapies together with effective and affordable control of hypertension (15). Thus, the established risk factors nowadays contribute proportionally less to overall cardiovascular risk compared to previous years and other pro-atherogenic factors come into focus. According to data, around 11-12% of patients with acute myocardial infarction present without any traditional risk factor for CVD (16,17), whereas 21.3% present with multiple risk factors (16), underscoring the hypothesis that non-classical risk factors might significantly contribute to the pathogenesis of myocardial infarction beyond established risk factors. Moreover, a global meta-analysis including more than one million patients with acute coronary syndrome demonstrated that individuals lacking any classical risk factor even displayed a higher mortality than individuals with one or several classical risk factors (17), suggesting that non-classical risk factors might exert a greater influence in the pathogenesis of CVD than formerly believed. Given this, there is a great necessity to detect further risk modifiers in vulnerable patient populations. So even with consistent control of classical factors, a residual cardiovascular risk often persists, largely driven by non- or only partially modifiable factors. Firstly identified in 1999 (18), the described non-traditional factors included chronic inflammatory biomarkers like C-reactive protein (CRP), homocysteine, oxidative stress and endothelial dysfunction, Lp(a), negative psychosocial influences, insulin resistance markers and dysregulation of the renin-angiotensin system (19). Next to biomarkers such as high-sensitivity CRP (hs-CRP), Lp(a) and homocysteine that serve as indicators for chronic systemic inflammation and other atherogenic processes that promote CVD (20), there are several further conditions discussed to participate in the development of CVD. These include medical conditions like chronic kidney disease (CKD), cancer and its therapy, chronic obstructive pulmonary disease (COPD) along with environmental factors such as pollution or abnormal climatic conditions (21). Via increased exposure to oxidants, impaired endothelial integrity and subsequent calcification, these factors induce atherosclerotic pathogenesis and raise cardiovascular risk (21). To date, research has increasingly focused on investigating non-traditional risk factors to help explain the substantial residual amount of residual cardiovascular events among patients without classical risk

factors. Data from large randomized studies provide a convincing rationale for a causal relationship between Lp(a) levels and adverse cardiovascular outcomes, even at low LDL-C but increased hs-CRP concentrations, supporting its potential as an independent determinant conferring residual CVD risk (22). Therefore, Lp(a) now constitutes a primary research interest as a genetically determined and non-lifestyle-associated risk factor for the development of CVD. In line with that, evidence indicates that dietary interventions only have minor or heterogeneous effects on Lp(a) and levels might even diverge from LDL-C levels, which showed persistent reductions following the substitution of saturated fat with carbohydrate, monosaturated or polyunsaturated fat (23). Thus, both the 2021 Canadian Cardiovascular Society Guidelines and the 2022 European Atherosclerosis Society advise Lp(a) measurement at least once for primary prevention, even without a positive family history for CVD (24,25).

1.3.3 Pathophysiology of atherosclerosis and thrombosis

Atherosclerosis is defined by an accumulation of lipids and fibrous components in large arterial vessels (26), primarily promoted by traditional risk factors (27). Amongst all lipoproteins, the most important carrier of cholesterol in blood plasma is LDL-C (28). Disorders of lipid metabolism that lead to high concentrations of LDL-C, triglycerides and/or low high-density lipoprotein (HDL), significantly contribute to atherosclerotic development and progress (29). In the initiation of atherosclerosis, endothelium loses its normal function and LDL-C is retained within the arterial intima, undergoing oxidative modifications (30). During oxidization, reactive oxygen species (ROS) modify LDL-C and transform it into oxidized LDL (oxLDL) (27), which activates endothelial cells by enhancing the expression of cell surface adhesion molecules (31). Besides, accumulation of LDL-C in the arterial wall triggers a pro-inflammatory cascade and promotes monocyte recruitment, that differentiate into macrophages. These macrophages along with vascular smooth muscle cells internalize oxLDL and other apolipoprotein B (apoB)-containing lipoproteins (32), resulting in intracellular collection of lipids and subsequently promoting the development of lipid-laden foam cells (33,34), whereby they progressively accumulate and drive atheromatous plaque growth, stenosis of arterial lumen, and impaired blood flow (35). Progressive lipid entrapment in macrophages who accumulate within the arterial intima, culminates in the earl-

iest recognizable lesion of atherosclerosis, so-called fatty streaks (36). However, LDL-C alone cannot provide a conclusive explanation for the complex biology of atherosclerosis as its pathogenesis involves further core mechanisms (35). Once endothelial homeostasis is disrupted, the endothelium is predisposed to a range of atherogenic mechanisms including vasoconstriction, leukocyte adhesion, oxidative stress, platelet activation, dysregulation of hemostasis, coagulation and vascular inflammation (37). Oxidative stress induces cytokine synthesis (30) that stimulates immune cell recruitment by promoting the expression of adhesion molecules (38), providing a chronic inflammatory milieu which facilitates plaque formation and progression within the arterial walls (30,38). When endothelial function is impaired, endothelial nitric oxide synthase (eNOS) and superoxide dismutase - key determinants of antioxidant defense and supporters of endothelial barrier function – are downregulated, consequently compromising endothelial integrity and further promoting LDL-C-retention (39). eNOS produce nitric oxide (NO), which execute multiple features, including anti-thrombotic and anti-embolic effects as well as modulation of inflammation and immune regulation (40). Moreover, various conditions such as hypercholesterolemia, diabetes or hypertension enhance oxidative stress within the vascular wall and promote eNOS uncoupling, which further amplifies oxidative stress (41). In eNOS uncoupling, O2- instead of NO is produced by eNOS resulting in the formation of the peroxynitrite radical (ONOO-) following the reaction of NO with O2-. This radical oxidizes reduced glutathione (GSH), an essential antioxidant molecule for protection against ROS (42). ROS-mediated oxidative stress aggravates endothelial dysfunction and further augments instability of atherosclerotic plaques. Collectively, these mechanisms destabilize atherosclerotic plaques and may then provoke exposure of thrombogenic clots, eventually culminating in acute ischemic complications such as myocardial infarction or ischemic stroke (35).

1.4 Lipoprotein(a)

1.4.1 Structure and biology

1.4.1.1 Molecular composition

The macromolecular complex of Lipoprotein(a) was firstly documented in 1963 as part of an immunochemical study aiming at detecting antigenic heterogeneity in

human LDL-C (43). Also characterized as an LDL-like particle because of its structural similarity to low-density lipoprotein (LDL), the exact structural morphology of Lp(a) – specifically whether it adopts a spherical or discoidal configuration – has been a matter of long controversy (44). Subsequent electron microscopic analyses of rotary- and unidirectionally shadowed Lp(a) molecules showed that Lp(a) is a predominantly spherical molecule, with an apolipoprotein(a) (apo(a)) component encircling the LDL-like core through a combination of covalent and non-covalent interactions with apolipoprotein B-100 (apoB-100) (45). Apo(a) represents the most distinctive structural feature differentiating Lp(a) from LDL (45) and provides a hydrophilic outer layer to the molecule (46). A key finding was that apo(a) shows a significant similarity to plasminogen (47), which is a central component of the fibrinolytic system and contributes to blood-clot lysis and would initially point to a potential involvement of Lp(a) in atherothrombosis through inhibition of fibrinolysis (48). However, neither in vivo (48) nor translational ex vivo studies (49) have been able to confirm this function. Apo(a) contains an inactive protease or serine protease domain, whose amino acid sequence shares approximately 94% identity with plasminogen (47). In contrast to plasminogen, the serine-protease domain of apo(a) carries an arginine substitution at the activation region corresponding to the one of plasminogen, effectively preventing the transformation of Lp(a) into an active protease through tissue plasminogen activator (tPA), urokinase or streptokinase (47). This inactivity of the serine protease domain in apo(a) compared to plasminogen also gives a hint regarding their functional distinctions: whereas its function in plasminogen has to remain intact for the dissolution of fibrinous blood clots, its inactivation in apo(a) explains the elevated risk for cardiovascular events due to thrombus formation in individuals with increased levels of Lp(a) (44). Alongside its protease domain and similar to all proteins engaged in coagulation and fibrinolysis, apo(a) also comprises an N-terminal region which is composed of triple-looped structures with an approximate length of 80 amino acids (44). These three-dimensional formations are described as kringles (44) and define an unique structural feature of apo(a) and the loop-like form is retained by three internal disulfide bonds (50). Whereas plasminogen contains 5 different types of kringles (KI to KV), Lp(a)'s apo(a) merely consists of kringle 4 (KIV) and kringle 5 (KV) (46). While the KV domains of

plasminogen and apo(a) only barely differ, the KIV domains in apo(a) represent numerous copy repeats of sequences similar to the KIV domain of plasminogen, yet this domain only occurs once in plasminogen while exhibiting 10 variations in apo(a) (47). Only KIV type 2 appears repeatedly in a genetically determined quantity of copies - ranging from 2 to over 40 - whereas all other KIV variants are solely present as single copies (51). The result of these several repeats are highly polymorphic and informative variations creating multiple isoforms of apo(a) and exhibiting a heterozygosity of over 95% in most populations (52).

1.4.1.2 Biosynthesis, metabolism and determinants beyond genetics

Although Lp(a) shares substantial structural similarity with LDL, its biosynthesis and metabolism are completely independent from LDL synthesis and metabolism yet, the exact mechanisms remain to be entirely explained (53). Research has proven that the apo(a)-domain in Lp(a) mainly originates from the liver as reported in patients after liver transplantations, where the donor's isoform of apo(a) occurred in samples taken from recipients after transplantation (54). The precise site where the final Lp(a) molecule is formed from apo(a) and LDL-like particles continues to be debated (50), but in vivo studies with cultured hepatocytes suggest that apo(a) is produced by hepatocytes and the apo(a) and apoB-100 components of Lp(a) may be combined at the surface of hepatocytes (55). Early studies assumed an extracellular assembly with the apoB component originating from circulating LDL (56), whereas later studies contradicted this hypothesis and argued that apoB in Lp(a) cannot originate from extracellular LDL because of its distinct kinetic properties compared to apoB in LDL (57). A more recent review on the topic indicates that the LDL component in Lp(a) most likely originates from newly synthesized apoB-100 (58). Another study using human hepatocellular carcinoma cells proposes that the process may occur both intra- and extracellularly (59). The formation of Lp(a) most likely is a sequential process, with apo(a) initially docking onto apoB-100 of LDL, followed by the formation of a covalent disulfide link between the KIV-9 segment of apo(a) and the apoB component of LDL (44,58). Lp(a) displays a plasma half-life of 3-4 days (60) and according to early tracer studies, the regulation of plasma concentrations is mainly driven by its rate of synthesis instead of impaired catabolism (61). As hepatocytes constitutively produce apo(a) and smaller isoforms with less copy number

variations of KIV type 2 can be synthesized faster and in greater quantities compared to larger variants (58,62), median concentration of plasma Lp(a) shows an inverse association to apo(a) isoform size (63). As smaller apo(a) variants characteristically lead to elevated plasma Lp(a) concentrations (63), it can potentially be explained why Lp(a) cholesterol is the preferred determinant for the evaluation of cardiovascular risk over Lp(a) mass (64). Regarding catabolism, the liver is widely considered to be the primary organ responsible for Lp(a) clearance (65). Even though the exact mechanisms underlying Lp(a) catabolism stay unclear, studies assume greater relevance of Lp(a) levels under certain circumstances such as chronic disease (66). However, the extended plasma half-time of Lp(a) as compared with LDL might also be attributed to the covalently attached apo(a) molecule, which may exceed apoB in size, thereby interfering with the LDL binding site, reducing receptor-mediated clearance through LDL receptors and necessitates alternative clearance pathways (58).

1.4.1.3 Proposed physiology and pathophysiology of Lp(a) in cardiovascular disease

The physiological function of Lp(a) remains incompletely understood, especially considering the marked inter-individual differences of Lp(a) concentrations and its strong genetic component (50). The structural homology to plasminogen may confer a physiological advantage, as the inhibition of fibrinolysis could support wound healing by transporting cholesterol – a critical constituent of cell membrane synthesis and a precursor for molecules involved in tissue regeneration (67) – to the site of tissue damage – although supporting large-scale human data on this topic are lacking (68). Lp(a) has been suggested to connect cholesterol transport with the fibrinolytic system, therefore contributing to both atherosclerosis and thrombosis (52). From a pathophysiological perspective, Lp(a)'s atherothrombotic potential may derive from various mechanisms and different structural characteristics (Figure 1) (58). Given the similarities of apo(a) and plasminogen, an involvement of Lp(a) in antifibrinolytic and prothrombotic pathways was controversially presumed (69), as studies showed plasminogen activation and fibrinolysis to be inhibited by apo(a), but its contribution to the inhibitory mechanism seems to be of minor relevance (70). Moreover, studies have

proposed that Lp(a) blocks the interaction between plasminogen and tPA, effectively preventing the tPA-mediated transformation of plasminogen to plasmin, which is responsible for dissolving blood clots (71). Recent findings, conversely, revealed that neither genetic variants nor Lp(a) concentrations affect coagulation through platelet or thrombin pathways (72), leading to the presumption that the elevated CVD risk associated with Lp(a) is not attributable to formerly postulated prothrombotic mechanisms (73). Another current evidence likewise fails to support this hypothesis, as Lp(a) does not lead to increased risk for thrombotic events that culminate in pulmonary embolism (74). Overall, accumulating evidence indicates that only a marginally higher risk of venous thromboembolism is observed in relation to Lp(a) concentration, occurring primarily at very high levels (68) and there remains conflicting evidence to the causality between Lp(a) and thromboembolic risk because of its antifibrinolytic features. Irrespective of its controversial prothrombotic properties, Lp(a) is believed to have greater atherogenic properties than LDL as it combines all the pro-atherogenic features of LDL and additionally serves as a binding site for pro-inflammatory mediators like oxidized phospholipids (OxPLs) (75). Compared with all other apoB-containing lipoproteins, Lp(a) is the predominant carrier of OxPLs (75). At high Lp(a) concentrations, OxPLs are transported to injured vessels and aortic valve cusps and facilitate endothelial dysfunction, lipid accumulation, vascular calcification and inflammation (76). Therefore, OxPLs represent a potent pro-atherogenic component (77) and OxPL modification might constitute a central shared process that facilitates many of Lp(a)’s adverse effects (78). Lp(a) shows a stronger affinity to the extracellular matrix of the intima in comparison to LDL (77) and the high lipophilicity of Lp(a) enables greater accumulation within the arterial wall as Lp(a) primarily enriches in the extracellular intima and subintimal layer, where it adheres through interaction between its lipoprotein moiety and lysine-binding sites of the apolipoprotein component (79). After entering the intima, Lp(a) is modified and oxidized and the interaction with lipoxygenase or ROS leads to the production of OxPLs, which further promote and augment inflammation (80). Oxidation of Lp(a) further alters lipoprotein catabolism by impairing receptor recognition, catabolic rate, and promoting vascular retention, thereby accelerating the progression of atherosclerosis (81). Clinical studies demonstrated that OxPLs in Lp(a) promote

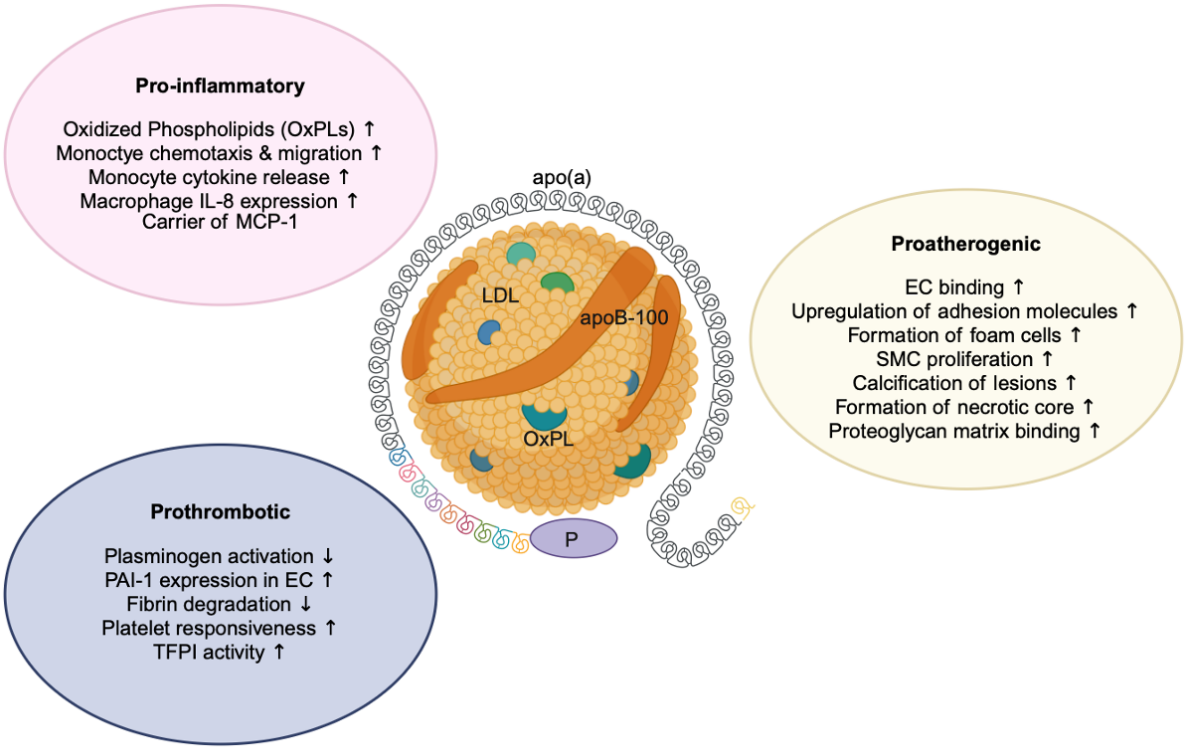

Figure 1: Structure and atherogenic features of lipoprotein(a) (created in https://BioRender.com) (58)
List of abbreviations: EC, Endothelial cell; IL, Interleukin; MCP, Monocyte chemoattractant protein; PAI, Plasminogen activator inhibitor; SMC, Smooth muscle cell; TFPI, Tissue factor pathway inhibitor; apo(a); Apolipoprotein(a); LDL, Low-density lipoprotein; apoB-100, Apolipoprotein B-100; OxPL, Oxidized Phospholipid; P, Protease domain.

inflammation as they showed enhanced inflammation and monocyte migration to the arterial wall in the setting of increased Lp(a) levels (82). Furthermore, the CASABLANCA Study demonstrated that participants with elevated OxPL linked to the apo(a) or apoB domains of Lp(a) are at a higher risk to sustain a major cardiovascular event (83). Nevertheless, the apoB-100-containing LDL-like fraction of Lp(a) only accounts for a small share of total cholesterol as the apoB-100 particle carried within Lp(a) represents only a marginal part of the total apoB-100 in the blood (84), therefore questioning its relevance for the atherogenic potential of Lp(a). Moreover, while apoB can fully explain the CVD risk linked to LDL, it does not account for the CVD risk of Lp(a) as there is residual risk remaining after adjusting for apoB (85).

1.4.2 Genetics and population distribution

1.4.2.1 *LPA* gene and kringle IV repeats

Compared to other lipoproteins, the concentration of Lp(a) is only marginally affected by environmental or lifestyle factors such as diet or physical activity and has a strong genetic component with the heterogeneity of the *LPA* gene strictly determining individual Lp(a) concentrations (52,58,73) and Lp(a) is highly heritable (86). This genetic diversity at the *LPA* locus explains the pronounced inter-individual differences of Lp(a) concentrations to over than 90% (24). Located on the long arm of chromosome 6 within 6q2.6-2.7, the gene was first cloned and sequenced in 1987 and shows large homology to the plasminogen gene, which is situated in the corresponding region (47). During the evolution of the human *LPA* gene, the *LPA* gene locus was diversified into different domain types with one domain, KV, being retained as a single copy, while another domain, KIV, was amplified and differentiated into 10 subtypes (Figure 2) (63). One subtype of KIV, KIV type 2 (KIV-2), repeats in a highly variable copy number varying from very few to over 40 repeats and therefore displays the strongest site of genetic variability within the *LPA* gene, with heterozygosity rates exceeding 95% in most human populations (52). After transcription into mRNA, this copy number variation of KIV-2 encodes for apo(a) and largely determines isoform size polymorphism of apo(a) by its particular gene sequence (52). Accordingly, fewer KIV repeats result in smaller apo(a) isoforms, leading to elevated plasma Lp(a) levels (51), potentially explained by the lower secretion of larger isoforms (87). Thus, individuals carrying variants with 22 or less KIV repeats present higher average Lp(a) concentrations compared to those with a high (> 22) number of KIV copy number repeats (88,89). This finding was corroborated by data identifying individuals with low KIV-2 repeats as having a higher risk of myocardial infarction (90). In context of the INTERHEART Study, this inverse association between Lp(a) concentration and isoform size was similarly confirmed amongst 7 ethnic groups, but no significant correlation with risk of myocardial infarction was observed (91). A review on 40 studies further demonstrated that carrying smaller apo(a) isoforms leads to an approximate two times higher risk for coronary heart disease or ischemic stroke (92). Opposing to this, a large case-control study showed that people with fewer

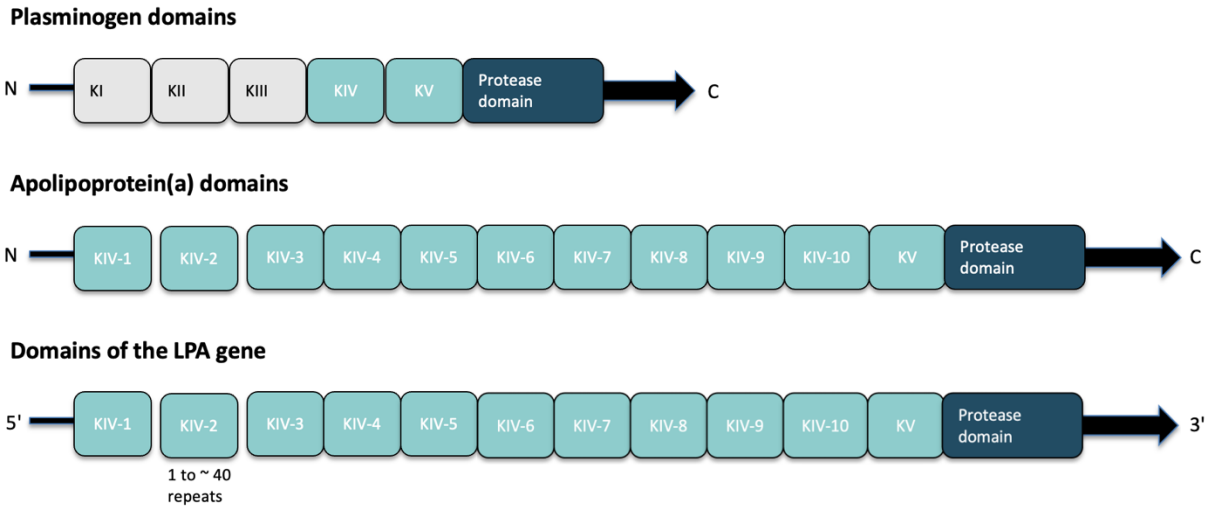

Figure 2: Evolution and structural organization of the *LPA* gene (63)

KIV type 2 repeats and consequently smaller apo(a) isoforms, yet low Lp(a) levels did not exhibit a greater risk of coronary artery disease (93). Furthermore, studies demonstrated striking variations in inter-individual Lp(a) concentrations with same isoform sizes, but not as large differences with the same allele (94), suggesting other factors influencing the concentration of Lp(a) besides the size of apo(a). Overall, copy number variations as determinants of apo(a) isoform size are estimated to only partially account for Lp(a) diversity (50). Besides the KIV-2 domain, Lp(a) concentration is also genetically influenced by other sequence variations such as promoter-region pentanucleotide repeats - variants which alter RNA splicing - and single nucleotide polymorphisms (SNPs) located in structural and functional regions of the *LPA* gene (89). Apo(a) isoforms undergo modification by functional SNPs, which range in allele frequency from 0.1% to over 20% within the *LPA* gene, which may largely affect Lp(a) levels (63). SNPs might possibly account for parts of the population-specific distinctions in Lp(a) concentrations (51,95,96) and a study on risk loci for coronary disease identified two SNPs at the *LPA* gene locus which are responsible for over 30% of differences in Lp(a) concentrations and furthermore constitute an independent risk determinant for coronary disease (97). A further study revealed that carriers of a splice-variant termed G4925A with small apo(a) isoforms, yet low molar Lp(a) levels, showed no increased CVD risk (93). These observations indicate that Lp(a) risk prediction should preferably base on molar concentration instead of apo(a) isoform size and that treatment should target molar concentration irrespective of isoform size (93).

1.4.2.2 Ethnicity-related differences and implications for thresholds

Lp(a) concentrations vary substantially within populations (from 0 mg/dl to > 200 mg/dl), while average concentrations across populations diverge by as much as fourfold (51). It has been shown that different KIV-2 subtypes appear more or less frequently in different populations (98) and that apo(a) isoform sizes and Lp(a) concentrations largely differ between ethnic groups (91). Accumulating evidence reports highest average Lp(a) concentrations in individuals of Black African origin, whereas progressively lower concentrations were reported in Asians, White Europeans and Hispanics (99). Consistent with this, a study demonstrated that the impact of the apo(a) genotype on isoform-specific Lp(a) concentrations differs between ethnicities (100). Notably, the cardiovascular risk linked to higher Lp(a) levels is prevalent amongst all ethnicities, however, the pronounced inter-ethnic differences in mean concentrations highlight the need to evaluate appropriate threshold values across populations (99). Interestingly, data from the previously mentioned INTERHEART Study further indicates that Lp(a) mainly increases the risk for myocardial infarction among Chinese, European, Latin American, South Asian, and Southeast Asian populations, but not in African or Arab cohorts (91). It should be noted, however, that these two groups had the smallest sample sizes in the study.

1.4.2.3 Non-genetic factors, gender aspects, and intra-individual variability

It is commonly believed that non-genetic factors only barely affect Lp(a) concentrations (51). It has been assumed that Lp(a) concentrations were mostly independent of sex (101), whereas age-dependent alterations of Lp(a) levels were solely documented in women (66,102). As recently demonstrated in the Copenhagen General Population Study with more than 70.000 participants, Lp(a) concentrations rise with age in both sexes, and there is a sex-related distinction in the rate of increase (103). This was particularly observed in women around the age of 50, where Lp(a) levels slightly increased, even though there were no substantial deviations in Lp(a)-related morbidity and mortality compared to men (103). However, given the association between onset of menopause and CVD risk in women described in various populations (104), Lp(a) as a potential factor

mediating this surge requires further investigation. A meta-analysis involving studies with nearly 13.000 women also suggests that menopause may be linked to elevated Lp(a) by showing significantly lower Lp(a) concentrations in premenopausal women than in postmenopausal women (105). However, no differences were detected between same age pre- and postmenopausal women, suggesting age as potential confounder (105). In this context, data also indicates a potential association between hormones and Lp(a) (66). A study reported lower Lp(a) levels in women undergoing hormone replacement therapy, with the therapy appearing to even impact cardiovascular risk in women (106). Another meta-analysis of 24 studies supports this observation by demonstrating a substantial reduction of Lp(a) in post-menopausal women in comparison with placebo or no-treatment (107). Overall, these results indicate that decreasing sex hormone production might be linked to higher Lp(a) concentrations. Additionally, numerous conditions have been proposed to affect Lp(a) concentrations (66). In a study including patients with terminal kidney disease, higher Lp(a) levels were reported compared to healthy individuals, even though apo(a) isoform distributions were comparable between the groups (108). Reduced renal function results in increased Lp(a) concentrations, demonstrating an inverse relationship between glomerular filtration rate (GFR) and Lp(a) levels (109), although the influence of estimated GFR on Lp(a) apparently is larger in female compared to male individuals (103). Accumulating evidence confirms that declining renal function causally affects Lp(a) levels and Lp(a) catabolism and even suggests Lp(a) as risk enhancing for the progression of kidney disease (110). Population studies identified age and estimated GFR as the second most important contributors to population variations in Lp(a) levels, whereas apo(a) isoforms still constituted the largest contributor (111). Since Lp(a) is mainly synthesized in the liver (112), liver diseases may be also expected to influence Lp(a) concentrations. Indeed, evidence shows that individuals with impaired hepatic function present with lower Lp(a) concentrations, a reduction that also correlates with the severity of liver disease (113). With respect to diabetes, there may be a relationship between low Lp(a) levels and onset of diabetes: The prospective Women's Health Study reported higher Lp(a) levels to be negatively correlated with the incidence of the disease (114), a paradoxical relationship that was also observed in Danish women

and men with diabetes (114), demonstrating that low Lp(a) concentrations might serve as a predictor the onset of type 2 diabetes. Concerning dietary habits, research has shown that high intake of saturated fats favors high Lp(a) levels, although dietary interventions alone may not substantially influence Lp(a) levels (115).

1.4.3 Association and causality of Lipoprotein(a) and cardiovascular outcomes

Compelling evidence established a strong correlation between Lp(a) and CVD - specifically, myocardial infarction, atherosclerotic stenosis, and aortic valve stenosis (AVS) - and therefore constitutes a determinant for elevated CVD risk and deaths caused by CVD (24,68). Large data from the UK Biobank confirmed the predictive value of Lp(a) concentrations for prevalence of ASCVD, showing that its associated risk for ASCVD is comparable to that of the established risk factors HDL and LDL (116). Findings from the JUPITER trial further demonstrated the relationship between baseline Lp(a) levels and CVD was independent of LDL-C concentrations, validating Lp(a) as an essential factor for remaining cardiovascular risk (22). Consideration of high versus low plasma Lp(a) concentrations across the population indicates that the associated cardiovascular risk ranges from 1.2-fold to the maximum risk observed in the top 5^{th} percentile (Figure 3) (5). The Copenhagen City Heart Study, a 10-year prospective study with a cohort of 9.330 people from general Danish population, observed a concentration-dependent relationship between Lp(a) and MI risk and further stated a 3- to 4-fold increase of MI in individuals with exorbitantly high levels over 120 mg/dl (117). Consistent increases of risk for myocardial infarction linked to high Lp(a) were also shown in an analysis of three large-scale studies, which, in addition to the Copenhagen City Heart Study, also included the Copenhagen General Population Study and the Copenhagen Ischemic Heart Disease Study (90). According to these Danish studies' data, the relative risk was highest for MI and AVS (5). Moreover, since Lp(a) and aortic valve stenosis show a robust association, *LPA* might be the only known monogenetic determinant for AVS (76,118). Evidence from the Copenhagen City Heart Study and the Copenhagen General Population Study further indicates elevated Lp(a) concentrations are accompanied by a consider-

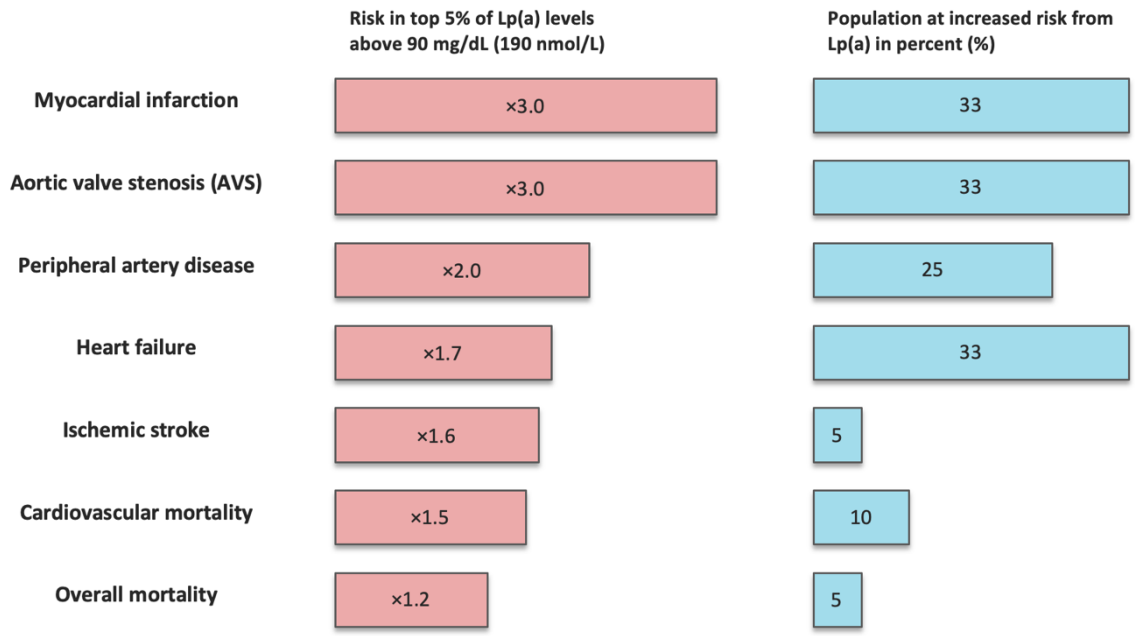

Figure 3: Cardiovascular risk in relation to high lipoprotein(a) levels (5)

able risk for AVS, with individuals in the top 5th percentile (> 90 mg/dl) even showing a three times greater risk for AVS (119). Another study shows that high Lp(a) levels were also closely related with aortic valve calcium (AVC), which serves as a predictor for the development of AVS (120). AVC shows a high prevalence in younger patients having Lp(a) levels above the 80th percentile, where Lp(a) leads to progression of calcific burden in individuals with pre-existing AVC (120). Further data associates Lp(a) with higher risk for cerebrovascular accidents: Findings from the Copenhagen City Heart Study and the Copenhagen General Population Study demonstrate a relationship between increased Lp(a) concentrations and higher incidence of ischemic stroke both in observational studies and via genetic analyses (121). A large Mendelian Randomization (MR) study furthermore corroborates these findings by showing that elevated Lp(a) levels independently enhance the risk of large artery stroke (122). Moreover, the BIOSIGNAL Study highlights that Lp(a) is associated with an increased chance of developing large artery atherosclerosis, subsequent stroke and recurrent stroke, whereas no such association was observed in patients with atrial fibrillation, likely accounting for a greater risk of Lp(a)-related stroke in younger individuals (123). In line with these findings, the ARIC Study also indicates that elevated Lp(a) concentrations confer an augmented risk for non-cardioembolic stroke, yet shows

Lp(a) is not linked to atrial fibrillation (124). Regarding stroke outcomes, a meta-analysis further indicated high Lp(a) concentrations to confer a greater risk of stroke-related cognitive impairment and disability (125). As previously described, there currently is no conclusive evidence linking Lp(a) to venous thromboembolism by promotion of coagulation or inhibition of fibrinolysis (69). There was no correlation between Lp(a) concentrations or KIV-2 repetitions and venous thrombosis, but rather underscored its role as risk factor for ASCVD (126).

1.4.4 Current and emerging therapies targeting Lp(a)

1.4.4.1 Conventional therapies and limitations

There currently is no available medication to specifically target Lp(a) and existing pharmacological agents only have marginal, if any influence on Lp(a) (73). Therefore, therapy of choice for individuals with high Lp(a) levels is considered to be the early and aggressive treatment of other established factors that increase risk for cardiovascular disease (5,24) following general guideline advise. Specific interventions aim for reducing cardiovascular risk and include lifestyle modification (smoking abstinence, weight reduction, physical exercise, healthy plant-based foods), pharmacological approaches to lower triglycerides, LDL and remnant cholesterol, reduction of blood pressure and diabetes control (5,127). As these interventions cannot directly affect Lp(a) concentrations, their primary aim is the reduction of absolute cardiovascular disease risk and thereby indirectly lowering the genetically determined, Lp(a)-associated cardiovascular risk (5). Conventional LDL-lowering therapy should be implemented, such as initial high-intensity statin therapy, and - if necessary - further escalation to a combined treatment of ezetimibe and proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors to reach recommended LDL-targets (5).

1.4.4.1.1 Statins

Aggressive statin therapy is the essential pharmacological approach to lower cardiovascular risk attributable to high Lp(a) concentrations (24). Accumulating evidence has shown that statin therapy compared to placebo does not result in a clinically relevant alteration in Lp(a) concentrations (128,129). Another meta-analysis pooling multiple randomized, placebo-controlled, statin outcome trials has

also demonstrated no influence of statins on Lp(a) levels (130) whereas smaller studies suggest that statin therapy might even slightly increase Lp(a) (131). Nevertheless, the benefits of lowering overall cardiovascular risk via lowering LDL widely exceeds any potential adverse consequences associated with minor increases of Lp(a) (130).

1.4.4.1.2 PCSK9 inhibitors

Unlike statins, which target LDL reduction, PCSK9 inhibitors also lower Lp(a) levels (73,132). While the underlying mechanism is not completely clarified, evidence suggests they augment clearance and reduce production rates of Lp(a) (73,132). Two large studies demonstrated decreases in Lp(a) by PCSK9 inhibitors: In the FOURIER trial, the cohort with a median baseline Lp(a) of 37 nmol/l (≈ 18 mg/dl) achieved approximately 27% Lp(a) lowering following evolocumab therapy and conferred risk reduction of 23% for cardiovascular events such as death by coronary heart disease, myocardial infarction, or urgent revascularization among patients with baseline Lp(a) higher than median compared to a non-significant 7% reduction in individuals with baseline concentrations lower than median Lp(a) (133). In ODYSSEY OUTCOMES, treatment with alirocumab led to a median 23% decline in Lp(a) levels, however, when considering the relative contribution of Lp(a) reduction to mitigate the risk of major adverse cardiac event (MACE), Lp(a) showed a minimal influence in individuals with non-elevated Lp(a) levels and only became considerable in those with elevated baseline levels (134,135).

1.4.4.1.3 Lipoprotein apheresis, niacin and aspirin

Lipoprotein apheresis may be a relevant therapeutic option for individuals with markedly increased Lp(a) concentrations and progressive cardiovascular disease despite adequately controlled other risk factors, although evidence on its benefit derives from uncontrolled studies (24). Apheresis yields a mean Lp(a) reduction of 35%, while reductions up to 70% were observed immediately after treatment (5). Nevertheless, compared to pharmacological strategies, apheresis is constrained by limited availability at specialized centers, high treatment frequency demands and considerable annual treatment costs and is therefore primarily indicated in specific patient populations with Lp(a) concentrations ≥ 60 mg/dl despite optimization of other lipid-lowering therapies (5,136).

Niacin lowers Lp(a) by approximately 25% and additionally reduces LDL-C, remnant cholesterol, and triglyceride concentrations (5). However, given its various adverse effects and the lack of incremental cardiovascular benefit in two outcome studies (137,138) when combined with statins, it is currently not recommended (5).
Aspirin is indicated for people with manifest atherosclerotic cardiovascular disease, yet there is no evidence or guideline that provides a solid basis on its use for lowering Lp(a) levels in primary prevention for ASCVD (5,24).
Overall, pharmacological approaches to reduce Lp(a) levels with established drugs can be regarded as modest and will likely not result in considerable cardiovascular benefit for patients, except for those with elevated baseline Lp(a) (73).
Accordingly, this circumstance has driven research to develop new agents aimed to specifically target Lp(a).

1.4.4.2 Emerging therapies and clinical trial endpoints

By now, there is no approved medication to specifically treat elevated Lp(a), although numerous agents are in development that can achieve Lp(a) plasma concentration reductions of up to 90% and above (Figure 4) (73). These drugs in development include antisense oligonucleotides (pelacarsen), small interfering RNA (olpasiran, lepodisiran, zerlasiran) and a small oral inhibitor (muvalaplin) (73), with maximum Lp(a) reductions observed for small interfering RNA agents of 98% (5).

1.4.4.2.1 Antisense nucleotide

Pelacarsen, an antisense oligonucleotide firstly introduced as AKCEA-APO(a)-L_{Rx}, inhibits hepatic mRNA transcription from the *LPA* gene encoding for apo(a) and is given via monthly subcutaneous injection (5,139). In early trials, 98% of participants receiving 60 mg monthly and 81% of those receiving 20 mg monthly have reached Lp(a) concentrations < 125 nmol/l (≈ 60 mg/dl) (139). Currently, the Lp(a)HORIZON trial (NCT04023552) - a phase 3 trial in progress with anticipated completion in March 2030 - assesses the effect of pelacarsen therapy on cardio-vascular events in patients with diagnosed CVD and Lp(a) levels ≥ 70 mg/dl (5).

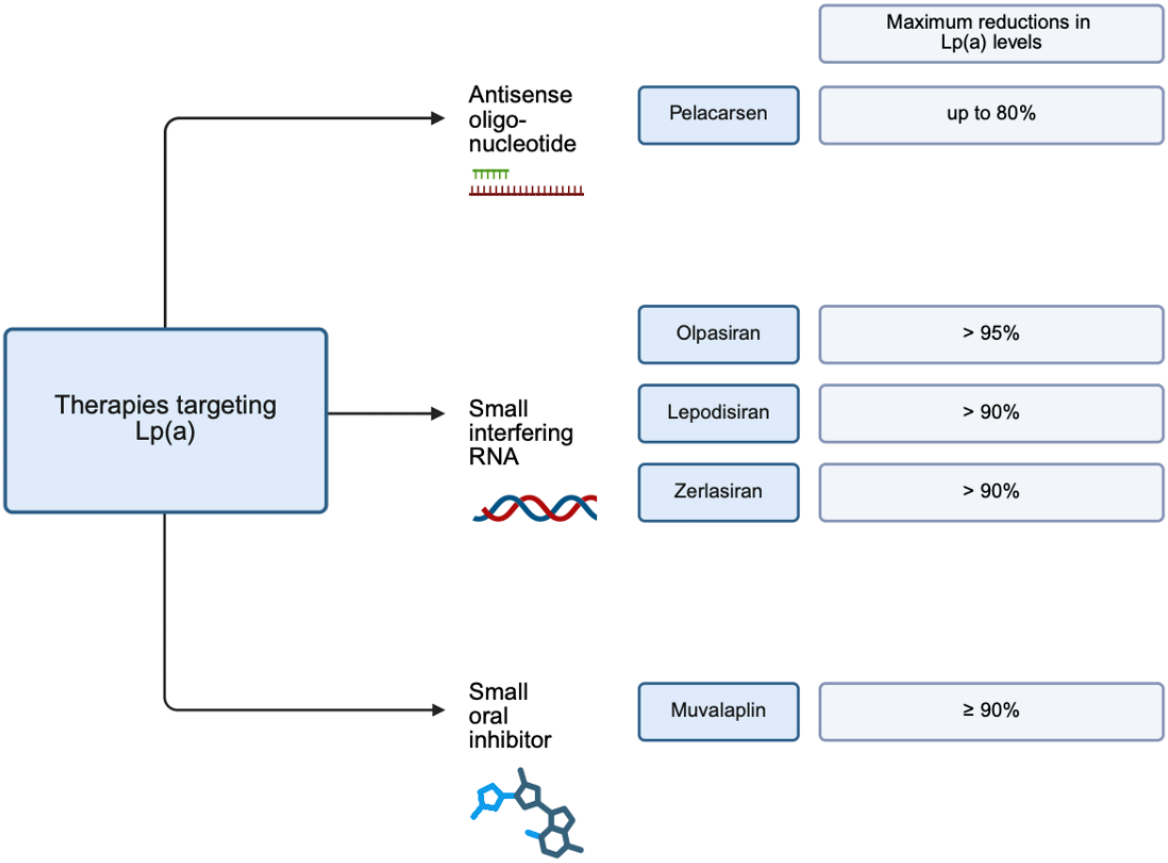

Figure 4: Drugs targeting Lp(a) in clinical testing (created in https://BioRender.com) (73)

1.4.4.2.2 Small interfering RNA (siRNA)

The three siRNAs olpasiran, zerlasiran and lepodisiran target *LPA* mRNA production and are recommended to be administered subcutaneously once every 3 to 6 months (5). In OCEAN(a)-DOSE, a dose-finding trial involving ASCVD-patients with Lp(a) > 150 nmol/l (≈ 71 mg/dl), olpasiran lowered Lp(a) significantly in relation to individuals without treatment and, moreover, higher doses conferred with greater reductions in Lp(a) concentration (140). Two additional ongoing trials are currently evaluating siRNA therapy: The OCEAN(a)-OUTCOMES trial (NCT05581303) assesses Lp(a) levels in adults with Lp(a) concentrations of ≥ 200 nmol/l (≈ 95 mg/dl) and positive history of ASCVD after treatment with olpasiran and is anticipated to conclude in December 2026 (73). Furthermore, the ACCLAIM-Lp(a) trial (NCT06292013) investigates the reduction of cardiovascular events in adults with ASCVD and increased Lp(a) levels of ≥ 175 nmol/l (≈ 83 mg/dl) induced by lepodisiran and aims for completion in March 2029 (73).

1.4.4.2.3 Small oral molecule

Muvalaplin is a small molecule administered orally and impacts Lp(a) synthesis via selectively attaching to apo(a) kringle domains 7 and 8, consequently inhibiting the non-covalent interaction binding of apo(a) and apoB-100, which is a critical step in Lp(a) formation (73,141). As part of a phase 2 trial, individuals with Lp(a) concentrations of ≥ 175 nmol/l (≈ 83 mg/dl) and manifest CVD, diabetes, or familial hypercholesterolemia received treatment with muvalaplin in different doses for 12 weeks (142). Administration of muvalaplin in the treatment group resulted in Lp(a) reductions as high as 85.8% when assessed with an Lp(a) assay and as much as 70.0% when assessed with an assay for apo(a) (142). Further research in this field includes a phase 2 study with completion in September 2025 (NCT06816264) that evaluates the therapeutic efficiency and safety of another small oral molecule, HRS-5346, in adults with increased Lp(a) levels and elevated risk for CVD (73).

1.4.5 Lp(a) measurement in clinical practice

1.4.5.1 Guideline recommendations and clinical cut-offs

In their 2019 guidelines for the management of dyslipidemias, the European Society of Cardiology (ESC) together with the European Atherosclerosis Society (EAS) suggests to consider an at least once Lp(a) measurement in every adult (143). However, some studies found Lp(a) concentrations to already approach levels comparable to those of adults within the first 14-16 months of life (144) and ischemic strokes in children and adolescents associated with Lp(a) levels > 30 mg/dl (24) could possibly be prevented. Controversially, other studies found that there are severe fluctuations in Lp(a) levels during childhood which could result in inadequate management of evolving Lp(a) levels (128). Generally, Lp(a)-related risk for CVD starts to increase at around 30-50 mg/dl (≈ 62-105 nmol/l) and with levels exceeding 50 mg/dl (≈ 105 nmol/l), Lp(a) is believed to be a clinically relevant factor for increasing the risk for ASCVD, with the risk rising proportionally with higher concentrations (145). Moreover, a MR study demonstrated this proportional relationship by showing a three to four times higher risk for coronary heart disease linked to substantially elevated Lp(a) levels of ≥ 200 mg/dl (146). Furthermore, this study suggested that patients with specific genetic predispositions that lead to extremely high Lp(a) concentrations carry a similar

lifetime risk for coronary heart disease as individuals with heterozygous familial hypercholesterinemia, yet the prevalence of these predispositions is assumed to be two times higher (146). Generally, evidence most strongly supports Lp(a) screening for patients with known ASCVD or positive family history, whereas in selected cases, additional cascade screening are recommended (118).

1.4.5.2 Assay standardization issues and measurement methods

Lp(a)'s great heterogeneity due to the numerous apo(a) isoforms largely differing in size and molecular mass (147) posed difficulties for developing accurate immunoassays measuring Lp(a) (148). Immunochemical methods for measurement are enzyme-linked immunosorbent assay (ELISA), nephelometry, immunoturbidimetry and dissociation-enhanced lanthanide fluorescent immunoassay (148). A known issue with these assays was that they were not standardized, potentially explaining widely ranging median Lp(a) concentrations in studies (147). Alternative physicochemical approaches such as mass spectrometry-based methods showed no isoform bias when quantifying Lp(a) but are limited, resource- and time-intensive (147). However, the most widely used commercial measurement methods are ELISA, immunonephelometric, and immunoturbidimetric assays (149). Amongst these, the turbidimetric methods which base on the Denka reagent are considered as reliable, largely unaffected by isoform size and applicable for high-quantity analysis and is therefore established as the standard method for Lp(a) measurement (147,148).

1.5 Co-morbidity of cardiovascular and psychiatric disease

Beyond the contribution of biomarkers such as Lp(a), it is assumed that psychosocial determinants and mental health disorders also predispose individuals to CVD: Increasing evidence suggests that psychological disorders and related exposures such as chronic stress or adverse health behaviors may contribute to an elevated cardiovascular risk profile, which may account for more cardiovascular events in psychiatric patients (1,21,150). Individuals with CVD show a high prevalence of mental health diseases, with up to 40% of patients being affected and the reasons underlying this comorbidity are considered multifactorial: In addition to higher rates of classical cardiovascular risk factors in psychiatric populations, side effects of psychotropic drugs, disparities in access

to and utilization of specialized treatment for cardiovascular diseases, biological mechanisms – including subclinical chronic inflammation in psychiatric disorders – as well as genetic determinants have been proposed as plausible factors (1,4).

1.5.1 Global burden of psychiatric disease

Mental health disorders remain a major public health issue with globally rising incidence, as data from the Global Burden of Disease Study shows (151). By prevalence, mental health disorders rank among the top 10 diseases worldwide, with pronounced regional and gender-specific disparities (151). In high-income countries, mental health disorders constitute the second most prevalent disease category after CVD (152). Among all subtypes of mental health disorders, depression and anxiety disorders represent the two most prevalent on a global scale and furthermore account for the highest DALYs in 2021 (151). Given the widely unresolved pathogenesis and underlying neurobiology (153) and the concomitant rising worldwide burden of psychiatric diseases, there is a strong need to identify the mechanisms underlying these complex diseases.

1.5.2 Epidemiology of cardiovascular risk in psychiatric disorder

There is a close association between mental health disorders and increased incidence of cardiovascular diseases and CVD constitutes the predominant cause of death in psychiatric patients (4). Together, CVD and mental health disorders constitute the two most important contributors to disability globally (152). Data from a meta-analysis on the coincidence of CVD in patients with SMI highlights that approximately one in ten individuals with SMI at an average age of 50 years is affected by at least one cardiovascular comorbidity (3). Individuals with mental health disorders furthermore show a 53% higher prevalence of CVD, a 78% higher risk for developing CVD, and a 85% higher risk of CVD-related mortality (3). Accordingly, the American Heart Association acknowledged SMIs as a predisposing risk factor promoting progression of atherosclerosis and premature CVD in young patients (154). Within the first 15 years after initial diagnosis, the absolute risk for patients with psychiatric disease for subsequently developing CVD was 54.1% (155). A large-scale meta-analysis of 92 studies with 3.211.768 individuals by Correll et al. with diagnosed mental illness – including major depression, bipolar disorder and schizophrenia – showed a 78% chance of

developing CVD, a 53% higher prevalence of CVD, and an 85% higher CVD-related mortality in comparison to overall population (3). A systematic review including over 30 million participants showed, that the rate ratio of mortality attributable to CVD approximately doubled in association with SMI (156), another review indicates that risk of sudden cardiac death and death resulting from cardiac arrest or CVD is amplified by as much as five times in patients with SMI (157). Being the most extensively studied mental health disorder linked to CVD (158), depressive disorder is associated with increases up to 72% regarding risk for CVD (3). Schizophrenia confers an approximately 50% higher risk for CVD in comparison to people without mental health disorder (3,159). Also, the life expectancy of schizophrenic patients is substantially reduced up to 20 years, with CVD-related mortality constituting the major contributor (156,160). For bipolar disorder, the pooled increase of CVD is 57% (3) whereas post-traumatic stress disorder (PTSD) is linked with a 61% greater risk of coronary heart disease and associated deaths in a meta-analysis (1,161). Regarding the affiliation of anxiety disorders and CVD, results have been very heterogenous due to definition disparities (1), although chronic systemic inflammation in patients with PTSD (162) may also increase CVD risk. However, in a meta-analysis, anxiety correlates with an estimated risk increase of 41% for coronary heart disease (163), whereas panic disorder exhibits a 47% elevated risk for the same outcome in a systematic review (164).

1.5.3 Mechanisms linking psychiatric to cardiovascular diseases

1.5.3.1 Behavioral factors and metabolic risk

Across the vast majority of mental health disorders, unhealthy lifestyle patterns such as dietary and poor sleeping habits, diminished physical activity levels and increased prevalence of tobacco use prevail (165). Patients with psychiatric disorder demonstrate substantially higher rates of smoking, reaching rates even double to five times greater among individuals with multiple psychiatric diseases (166). Further evidence shows schizophrenic patients that smoke experience a 86% higher 20-year cardiovascular mortality than non-smoking patients (167), underscoring the importance of smoking cessation to decrease overall CVD risk in patients with SMI. Moreover, individuals with SMI are more likely to have

comorbidities like diabetes, dyslipidemia, hypertension or metabolic syndrome than non-affected individuals (168). This might be caused by manifold factors such as the high rates of outlined CVD risk factors, positive family history of diabetes, antipsychotic medication which further promotes obesity, respectively worsens other metabolic risk factors as well as limited access to healthcare (168).

1.5.3.2 Healthcare system factors and access-to-care disparities

Patients with mental health disorders experience widespread stigma and discrimination, leading to major restrictions in access to cardiovascular care (169,170) as well as diagnostic overshadowing, whereby clinical symptoms are misattributed to previously diagnosed comorbidities and furthermore results in compromised care for patients with mental illness (171). Therefore, risk factors for CVD might be disregarded and treated poorly, amplifying the probability of CVD and associated adverse events (4). Patients with SMI predominantly receive care from psychiatric specialists whose expertise in somatic diseases is limited, resulting in insufficient physical health screening and poorer treatment of CVD (172). Additionally, a Norwegian study demonstrated that the probability of patients with SMI receiving specialized cardiovascular treatment for vascular and coronary diseases or arrythmia is significantly less than in patients without SMI, even though there was no disparity in the prevalence of diagnostic screenings (173). Notably, despite similar mortality benefits of revascularizing interventions in schizophrenic patients and healthy individuals, schizophrenic patients face worse outcomes after myocardial infarction, and this group also receives less evidence-supported diagnostic tests and appropriate medical interventions (174).

1.5.3.3 Psychotropic medications: Antipsychotics, antidepressants and mood stabilizers

Antipsychotics, antidepressants and mood stabilizers all show unfavorable side effects like metabolic or endocrine dysregulation, with the strongest effects being observed with antipsychotics, but effects largely differ depending on specific agents and patient's individual factors (175). A meta-analysis on long-term metabolic and cardiovascular adverse effects of antipsychotics did not show a correlation between antipsychotic therapy and risk for stroke or myocardial infarction (176). Conversely, other studies identified a short-term risk effect of

typical antipsychotics and acute myocardial infarction (177). Despite the potential adverse side effects associated with antipsychotic medications, their therapeutic benefits substantially outweigh these negative effects with respect to cardiovascular mortality (159). This advantage can primarily be attributed to a healthier lifestyle, reduced stress caused by psychotic episodes, and greater therapy adherence (178). Adherence to medication is crucial for SMI patients to improve impaired perception of symptoms, cognitive deficits and inadequate self-care and to promote social participation (157), which may lead to better access to healthcare (4). Moreover, co-administration of medication for cardiovascular and psychiatric diseases is common, especially in older individuals (179). The most frequent drug-drug interactions involve cytochrome P450 (CYP450) metabolism, leading to a modification of the pharmacokinetic or pharmacodynamic of a drug. Additionally, serotonin-norepinephrine reuptake inhibitors (SNRIs) and selective serotonin reuptake inhibitors (SSRIs) lead to bleeding risk by enhancing anticoagulant activity (179).

1.5.3.4 Biological and genetical pathways

Among potential common biological mechanisms, inflammation could be involved in the pathogenesis of psychiatric diseases and might represent a link to CVD (180). Elevated inflammatory biomarkers including cytokines and acute-phase reactants – which have been linked to heterogeneous psychopharmacologic responsiveness and unfavorable clinical outcomes - are consistently observed in some individuals with unipolar and bipolar depression, anxiety-related disorders, and schizophrenia (181). Moreover, chronic inflammation promotes obesity, insulin resistance and metabolic dysfunction (182) - factors which further augment risk for CVD. Additionally, genetic determinants appear to contribute to the observed comorbidity. Evidence proposes that specific genetic predispositions might link schizophrenia but not bipolar disorder to cardiovascular and metabolic diseases, although the exact mechanisms remain uncertain (183). This is supported by findings among first-degree relatives in individuals with psychotic mental disorders, who are more likely to be affected by CVD and metabolic diseases, indicating a potential overlapping genetic contribution in these diseases and psychotic disorders (184). However, a cross-sectional study involving over 200 patients with recent diagnosis of bipolar disorder and 50 unaffected relatives, no increased

incidence of metabolic syndrome was shown among first-degree relatives (185). There has also been evidence from analysis on large-scale meta-analyses of genome-wide association studies identifying overlapping pathways and SNPs between schizophrenia, bipolar disorder and cardiometabolic features involved in inflammation and immune activation (183), suggesting a genetic predisposition of patients with SMI to cardiometabolic diseases. Overall, the comorbidity is influenced by a complex interplay of various determinants, suggesting that less well-studied factors may also represent important mechanistic links.

1.5.3.5 Current evidence on the association of lipoproteins and mental health disorders

Given the mounting comorbidity as well as the incompletely understood linking mechanisms of cardiovascular and psychiatric disease, the question arises whether Lipoprotein(a) - as an established contributor to cardiovascular risk – might also be associated with the development of psychiatric diseases and consequently to the enlarged cardiovascular risk in psychiatric patients. To address this assumption, evidence from research indicates a possible link: About half of the brain's dry mass consists out of lipids – more than any other organ except adipose tissue - and the central nervous system (CNS) contains the largest amount of unesterified cholesterol of all organs (186). Early studies detected these especially high concentrations of cholesterol in the nervous system and suggested reduced levels as a possible reason for altered mental state or personality (187), a finding consistent with other studies that associated lower cholesterol levels and synapses with mood disorders (188). As in any tissue, cholesterol is delivered to the brain via LDL (186), which may imply one potential interaction between lipoproteins and disorders of the brain. As recent evidence shows, different lipid categories are associated to mental health disorders and could be of potential use as clinical markers (189). Furthermore, a study on non-high-density lipoprotein cholesterol to high-density lipoprotein cholesterol ratio (NHHR) and symptoms of depression revealed elevated NHHR levels as a determinant for the onset of depression (190). Accordingly, a meta-analysis showed that lower levels of LDL-C and depressive disorder were consistently associated (191). Mendelian Randomization (MR) analysis also showed less cases of major depression in

individuals with higher levels of LDL-C, but found no significant associations for high-density lipoprotein cholesterol (HDL-C) (192). Regarding HDL-C, studies found higher concentrations to correlate with a reduced risk for psychiatric disorders (193), which has been verified by other studies that show low HDL levels in depression (194). In line with that, evidence indicates higher HDL-C concentrations in individuals with suicidal thoughts and similarly, patients with anhedonia had lower LDL levels in this study (195). However, a large UK Biobank analysis showed both HDL-C and LDL-C to be inversely associated with subsequent depression (196), questioning whether HDL-C and depression are positively or negatively associated. Regarding Lp(a), a retrospective, observational study on mental health in male participants with premature coronary heart disease reported a co-occurrence of impaired mental health and elevated Lp(a) (6). Further data from the prospective MESA cohort study reported more cases of depression during follow-up in participants with elevated baseline Lp(a), yet they found no significant discrepancies in Lp(a) concentrations in individuals with new elevated depressive symptoms when applying widely used clinical cut-off points (7). Notably, this study used a self-reported questionnaire for depressive symptomatic, limiting the study's relevance to patients with clinically diagnosed psychiatric disorders. Overall, there are many uncertainties remaining about the relationship between lipoproteins and psychiatric disorders and further research is needed. Unfortunately, most studies prioritized investigating the possible connection between traditional lipoproteins and mental health disorders rather than concerning a broader spectrum of lipoproteins, resulting in a limited body of evidence on this topic. However, given the potential associations of other lipoproteins and mental health disorders, evidence on the relationship between psychiatric diseases and Lp(a), as an evolving factor for various conditions, is of great interest as there is lack of established review literature addressing this topic. Therefore, aim of this systematic review is to synthesize the existing evidence on Lp(a) levels in psychiatric disorders, to evaluate the associations and to discuss the role of Lp(a) as a potentially modifying factor to more conclusively understand high CVD prevalence in psychiatric populations.

2 Methods

2.1 Type of review

Literature was systematically searched to identify studies on psychiatric disorders, their treatment, and lipoprotein(a) levels. The aim of this approach was to provide a structured synthesis of the available evidence and to assess the quality and consistency of the existing literature. Given the anticipated heterogeneity in study designs and reported outcomes, a quantitative meta-analysis was not considered feasible across all domains. Nevertheless, a systematic synthesis of the available evidence allows the identification of current knowledge gaps and priorities for future research.

2.2 Aims and scope

The focus of this systematic review is to examine whether psychiatric disorders and their treatment are associated with elevated Lp(a) levels based on existing studies, and whether such alterations could contribute to the increased cardiovascular risk observed in individuals with psychiatric disorders. This review was conducted in accordance with the PICO (Population, Intervention, Comparison and Outcome) framework. The population includes individuals diagnosed with psychiatric disorders - including depressive disorder, bipolar disorder, schizophrenia and other mental health conditions. The intervention or exposure under investigation is twofold: First, the presence of a psychiatric disorder itself, reflecting the hypothesis that psychiatric conditions may be associated with altered Lp(a) levels. Second, the use of psychotropic medication – particularly antipsychotics, mood stabilizers, and antidepressants – is investigated as a pharmacological exposure that may modulate Lp(a) levels. The comparator groups consist of healthy controls, general population reference values or untreated individuals. The primary outcome of interest is the serum Lp(a) concentration in individuals with psychiatric disorders compared to control groups, as well as in response to psychotropic treatment compared to untreated controls.

2.3 Search strategy and sources

Literature was systematically searched to identify research work articles and papers addressing Lipoprotein(a), psychiatric disorders and psychopharmaceuticals, which were combined via Boolean operators. The search was conducted on the electronic database PubMed as well as Internet research from other sources with dates from database inception to 23rd of February 2026. A total of 189 titles was revealed (184 from PubMed, 5 publications from other sources). The search strategy included the following terms:
("Lp(a)" OR "Lipoprotein(a)" OR "lipoprotein(a)") AND (psychiatric OR psychiatry OR "psychiatric disorder" OR "psychiatric disorders" OR "psychiatric illness" OR "psychiatric illnesses" OR "mental health" OR "mental disorder" OR "mental disorders" OR "mental illness" OR "mental illnesses" OR depression OR "depressive disorder" OR "depressive disorders" OR "mood disorder" OR "mood disorders" OR bipolar OR "bipolar disorder" OR "bipolar disorders" OR schizophrenia OR schizophrenias OR "personality disorder" OR "personality disorders" OR "substance use disorder" OR "substance use disorders" OR "alcohol use disorder" OR "alcohol use disorders" OR psychotic OR psychotics OR psychosis OR psychoses OR anxiety OR "anxiety disorder" OR "anxiety disorders" OR PTSD OR "posttraumatic stress" OR panic OR "panic disorder" OR "panic disorders" OR phobic OR phobics OR "affective disorder" OR "affective disorders" OR "psychiatric medication" OR "psychiatric medications" OR "psychiatric drug" OR "psychiatric drugs" OR psychopharmacology OR psychopharmacologies OR antidepressant OR antidepressants OR antipsychotic OR antipsychotics OR "mood stabilizer" OR "mood stabilizers" OR anxiolytic OR anxiolytics OR psychotropic OR psychotropics OR "psychotropic drug" OR "psychotropic drugs" OR "psychotropic medication" OR "psychotropic medications").

2.4 Eligibility criteria and study selection logic

This review included studies examining Lp(a) levels in individuals with psychiatric disorders and in control groups without psychiatric diagnoses. Titles and abstracts were screened, and full versions of potentially appropriate publications were obtained for further evaluation. Study selection was based on predefined eligibility criteria. Merely publications in English language and studies with human

populations were considered. Eligible participants were adults (≥ 18 years) with a psychiatric disorder diagnosed according to established diagnostic criteria and with available quantitative assessment of lipoprotein(a) levels. Eligible diagnoses for all psychiatric conditions were defined according to Diagnostic and Statistical Manual of Mental Disorders (DSM) or International Statistical Classification of Diseases and Related Health Problems (ICD). Studies were required to include a comparison group without psychiatric disorders. No restrictions were applied regarding study design. Studies were excluded during the initial screening if psychiatric diagnoses were unclear or not based on established criteria, if they focused on conditions other than psychiatric disorders, if lipoprotein(a) data were missing or insufficient, if they involved animal populations, or if methodological descriptions were inadequate. Studies were selected in a two-step process (first: screening of title and abstract; second: full-text review). Exclusion criteria used at each stage are presented in Figure 5. Data extraction was performed according to predefined criteria.

2.5 Data extraction approach and synthesis plan

All search results were transferred to a reference managing database (Zotero 8). The initial search identified 189 publications from the published literature that fulfilled the prespecified eligibility criteria established in this systematic review. After de-duplication, titles and abstracts of 188 publications were eligible for screening in two steps. First, abstracts were assessed for relevance – focusing on studies with Lp(a) measurements in psychiatric patients. 164 papers were excluded because they had no relevance to the topic.

In the second step, 24 potentially relevant texts were retrieved and evaluated carefully for quality and fit. After further assessment, 15 articles were excluded for common reasons: Insufficient diagnostic characterization (n = 7), lack of non-psychiatric comparison group (n = 3), cohort with adolescent individuals (n = 2), non-humane studies (n = 1), absent or inadequately described Lp(a) measurement (n = 2). After removal, 9 studies met all criteria and were included in the review. Figure 5 summarizes the identification and selection of studies included in this review, following the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines (197).

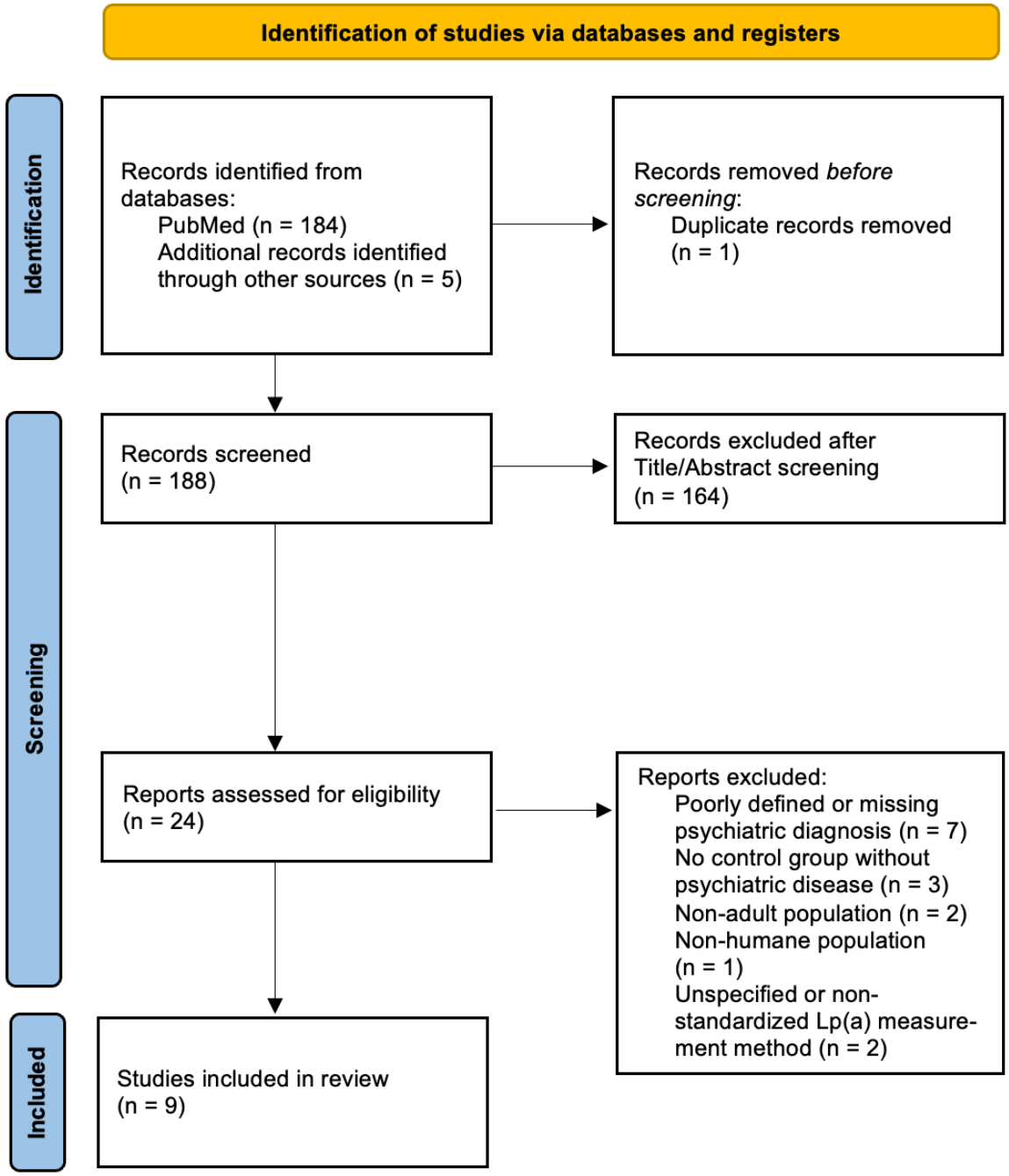

Figure 5: PRISMA Flow Diagram

3 Results

3.1 Characteristics of included studies

All results are summarized in Table 1. The nine included studies were published between 2006 and 2025. The countries where the studies were conducted included China, United Kingdom (n = 2) (195,197), United States (n = 1) (198), Denmark (n = 1) (199), Germany (n = 1) (200), Italy (n = 1) (201), Iran (n = 1) (202), Tunisia (n = 2) (203,204), Turkey (n = 1) (205). Regarding study design, five were clinical case-control or cross-sectional studies conducted in psychiatric inpatient or outpatient settings, with sample sizes ranging from 70 to 259 individuals (201–205). These studies focused on comparing Lp(a) levels between specific psychiatric patient cohorts and healthy control groups. One study by Paslakis et al. (200) was an intervention trial assessing the effects of a 4-week double-blind randomized treatment with two different antidepressants on Lp(a) levels in 35 inpatients with major depression compared to 33 healthy controls. The remaining three studies utilized large-scale population or biobank data: Langsted et al. (199) included 109.440 individuals from the Copenhagen General Population Study, using both observational (plasma Lp(a) quartiles) and genetic analyses (*LPA* genotypes) to assess morbidity risks, including a not further specified “mental disorders” category according to ICD-10. This study was included despite this broad and heterogeneous definition of mental disorders (ICD-10 codes F00-F99), given the limited available evidence on this topic. Li et al. (196) applied a mixed graphical model (MGM) network analysis of 87.636 UK Biobank participants to estimate prospective associations between baseline lipid parameters and subsequent depression, incorporating hs-CRP as a moderator. Pan et al. (198) combined retrospective matched case-control study using electronic health records (90.542 matched patients) and data on major depressive disorder (MDD) from the National Health and Nutrition Examination Survey III (NHANES III) with a bidirectional MR analysis using large genome-wide association study (GWAS) datasets to assess causality between Lp(a) and mental health disorders. Lp(a) measurement techniques varied across the studies, primarily utilizing immunoturbidimetric or ELISA assays, with results reported in mg/dl, mg/l, g/l, or

nmol/l. Diagnostic criteria in clinical studies used ICD codes, structured clinical interviews (e.g. DSM-III), or self-report questionnaires (e.g. PHQ-9).

Table 1: Summarizing table of the included studies

Author	Study design	Psychiatric diagnosis	Diagnostic criteria	Lp(a) measurement method	Results
Emanuele et al. (2006) (201)	Cross-sectional (n = 148; 74 patients, 74 controls)	Schizophrenia (n = 39); Bipolar disorder (n = 13); Personality disorder (n = 12); Major depressive disorder (n = 10)	DSM-IV-TR	ELISA	Lp(a) significantly elevated in schizophrenia, major depression and bipolar disorder compared to healthy controls. No significant differences in personality disorder patients. Median Lp(a) comparable to post-athero-thrombotic event cohorts.
Sarandol et al. (2006) (205)	Case-control study (n = 122; 86 patients, 36 controls)	Major depressive disorder	DSM-IV	Immuno-nephelometry	No significant differences in Lp(a) levels between the group with major depressive disorder and healthy control group.
Hamidifard et al. (2009) (202)	Case-control, cross-sectional (n = 70; 35 patients, 35 controls)	Major depressive disorder	DSM-IV	Immuno-turbidimetry	Lp(a) significantly higher in patients with major depression and without atherothrombotic history vs. healthy controls; positive correlation of Lp(a) levels with severity of illness (measured by BDI).

Author	Study design	Psychiatric diagnosis	Diagnostic criteria	Lp(a) measurement method	Results
Ezzaher et al. (2010) (203)	Cross-sectional study (n = 130; 66 patients, 64 controls)	Bipolar I disorder	DSM-IV	Immuno-turbidimetry	Bipolar I patients had significantly higher Lp(a) levels and perturbations in their lipid profile compared to control subjects.
Paslakis et al. (2011) (200)	Randomized double-blind study (n = 68; 35 patients, 33 controls)	Major depressive disorder	DSM-IV; Hamilton Depression Rating Scale score	Photometric system	Before treatment, Lp(a) levels were higher in patients than controls, but not statistically significant. Treatment with the SSRI paroxetine significantly decreased Lp(a) levels in depressed patients.
Mabrouk et al. (2014) (204)	Cross-sectional study (n = 259; 140 patients, 119 controls)	Schizo-phrenia	DSM-IV	Immuno-turbidimetric techniques	Schizophrenic patients had significantly higher Lp(a) levels and perturbations in their lipid profile compared to controls.
Langsted et al. (2021) (199)	General population cohort study (n = 109.440)	Mental and behavioral disorders	ICD-10	Immuno-turbidimetric assays	Low Lp(a) levels were observationally associated with mental disorders, but genetic analysis (*LPA* genotypes) did not support a causal link.

Author	Study design	Psychiatric diagnosis	Diagnostic criteria	Lp(a) measurement method	Results
Pan et al. (2025) (198)	Combined retrospective study (case-control; n = 7.028; 2.537 patients, 4.491 controls) and MR analysis	Major depressive disorder (n = 583); depression (n = 670); Anxiety (n = 1284)	DSM-III, Hamilton Depression Rating Scale (Chinese Version), Hamilton Anxiety Rating Scale	Latex-enhanced Immuno-turbidimetry; ELISA	MR shows a positive causal effect of Lp(a) on longest depression period and number of depressive episodes; Positive causal association of bipolar disorder and major depressive disorder status with reduced Lp(a) levels in MR; No association of low Lp(a) with depression and anxiety in MR. Retrospective study showed lower Lp(a) is associated with higher risk of depression, major depression and anxiety.
Li et al. (2025) (196)	UK Biobank network analysis within a prospective cohort (n = 87.636; 3.180 patients, 84.456 controls)	Depression	ICD-10; Patient Health Question-naire	Immunoturbi-dimetry	Lp(a) was positively associated with subsequent depression after controlling for other lipids; association was moderated by inflammation (measured by hs-CRP); positive correlation persists at low inflammation levels (non-elevated hs-CRP) and was weakened or shifted with increased inflammation.

Table 1. Overview of the nine included studies, listing first author and year of publication (column 1), study design (column 2), psychiatric diagnoses observed in each study (column 3), methods of Lp(a) measurement (column 4), and a short summarization of outcomes (column 5). List of abbreviations: ELISA, Enzyme-linked Immunosorbent Assay; Lp(a), Lipoprotein(a); BDI, Beck Depression Inventory; MR, Mendelian Randomization; hs-CRP, high-sensitivity C-reactive protein.

3.2 Findings for Lipoprotein(a) levels in different psychiatric disorders

3.2.1 Lp(a) and depressive disorder

In a clinical case-control study, Emanuele et al. (201) observed median Lp(a) levels to be significantly higher in 10 patients with major depression (41 mg/dl) compared to 74 healthy controls (12 mg/dl) ($p = 0.039$). This study undertook a multivariate logistic regression analysis, using Lp(a) levels ≥ 25 mg/dl as outcome variable, while clinical (age, sex, BMI) and biochemical (white blood cells, erythrocytes sedimentation rate, creatinine, plasma glucose, total cholesterol and triglycerides) findings of participants were applied as predictor variables to adjust for potential confounders. Results of this analysis indicated that the odds of increased Lp(a) levels (> 25 mg/dl) were 6.61 times higher for major depression. Similarly, Hamidifard et al. (202) corroborated these findings in a focused study on major depressive disorder, reporting mean Lp(a) levels of 34.94 mg/dl in 35 patients with MDD versus 20.08 mg/dl in matched controls ($p < 0.0001$). Furthermore, they noted a positive association between Lp(a) concentration and severity of disease as measured by the Beck Depression Inventory (BDI) score ($r = 0.571$, $p < 0.0001$). In this cohort, 68.6% of MDD patients exceeded the previously established cardiovascular risk threshold of 25 mg/dl, compared to only 28.6% of controls. Paslakis et al. (200) documented elevated baseline Lp(a) concentrations in 35 MDD inpatients (0.25 g/l = 25 mg/dl) compared to 33 controls (0.20 g/l = 20 mg/dl), however, the result was not statistically significant. In contrast, Sarandol et al. (205) observed no significant differences in Lp(a) levels between 86 MDD patients and 36 healthy controls, although they noted higher total cholesterol and LDL-C in the patient group. In a large-scale UK Biobank network analysis, Li et al. (196) identified a robust positive association between baseline Lp(a) levels and the subsequent development of depression in the overall sample (edge weight 0.012). Interestingly, they found this association to be moderated by inflammation, as the positive association of Lp(a) with depression was only consistent in the group with non-elevated hs-CRP (< 3.0 mg/l) (edge weight 0.017). In the elevated hs-CRP group (> 3.9 mg/l), however, this association was no longer observed (edge weight -0.007).

The study by Pan et al. (198) presented complex, bidirectional findings. In their retrospective study, low Lp(a) levels were associated with a significantly higher risk of depression (OR 1.273 (1.007, 1.609), 95 CI, p = 0.044) and major depression (OR 1.364 (1.012, 1.841), 95 CI, p = 0.042). Conversely, their Mendelian Randomization (MR) analysis indicated that genetically predicted Lp(a) had a positive causal effect on the longest period of depression (OR 1.05 (1.02-1.08), 95 CI, p = 0.0001) and the number of depressive episodes (OR 1.03 (1.01-1.06), 95 CI, p = 0.009), suggesting high Lp(a) levels as a risk factor for duration and frequency of depression. Furthermore, the MR analysis showed that MDD status was causally associated with significantly lower Lp(a) levels (OR 0.96 (0.93-0.98), 95 CI, p = 0.003). Overall, six studies examined the relationship between Lp(a) and MDD, with four studies (196,198,201,202) reporting a statistically significant positive association of Lp(a) and depression. However, findings were inconsistent as two studies found no significant difference (200,205) and evidence from MR and Biobank network analysis suggests the association may be bidirectional (198) or modulated by inflammatory status (196).

3.2.2 Lp(a) and schizophrenia

Two clinical studies consistently reported elevated Lp(a) levels in patients with schizophrenia. Emanuele et al. (201) found that median Lp(a) was significantly increased in 39 schizophrenic patients (26 mg/dl) compared to 74 health controls (12 mg/dl) (p = 0.021), and these patients had 5.12 times higher odds of elevated Lp(a) above 25 mg/dl in multivariate logistic regression analyses. Mabrouk et al. (204) also reported significantly higher Lp(a) levels in 140 schizophrenic patients (349 mg/l = 34.9 mg/dl), compared to 119 healthy controls (188 mg/l = 18.8 mg/dl) (p = 0.0001), alongside other lipid perturbations. There was no information provided whether there were any differences in Lp(a) levels in each clinical sub-type of schizophrenia. Taken together, these two studies demonstrate significantly elevated Lp(a) concentrations in schizophrenic patients compared to healthy controls, suggesting a positive association between Lp(a) levels and schizophrenia.

3.2.3 Lp(a) and bipolar disorder

Similar to the findings in schizophrenia, elevated Lp(a) concentrations were observed in clinical bipolar disorder samples. Emanuele et al. (201) reported significantly higher median Lp(a) levels in 13 patients with bipolar disorder (32 mg/dl) compared to controls ($p = 0.0027$) and 7.01 times higher odds of Lp(a) levels > 25 mg/dl. Ezzaher et al. (203) found that 66 Bipolar I patients had significantly higher Lp(a) levels (243 mg/l = 24.3 mg/dl) compared to healthy controls (156 mg/l = 15.5 mg/dl) ($p = 0.001$), an association that remained significant after adjusting for confounders like gender, BMI, and alcohol consumption. However, genetic evidence provided a different perspective. Pan et al. (198) observed in their bidirectional MR analysis that, like in MDD, bipolar disorder status was causally associated with significantly lower Lp(a) levels (OR 0.96 (0.93-0.98), 95 CI, $p = 0.003$). In summary, two case-control studies found elevated Lp(a) concentrations to be associated with bipolar disorder, whereas data from MR shows lower Lp(a) levels in bipolar patients.

3.2.4 Lp(a) and other psychiatric outcomes

In the present review, two studies specifically addressed other psychiatric outcomes than MDD, bipolar disorder and schizophrenia. For personality disorders, Emanuele et al. (201) found no significant differences in Lp(a) levels among 12 patients compared to healthy controls (19 mg/dl vs. 12 mg/dl, $p = 0.119$). Regarding anxiety, Pan et al. (198) found in their retrospective matched cohort that low Lp(a) levels were associated with a significantly higher risk of anxiety (OR 1.231, $p = 0.015$). In a broader assessment of mental disorders diagnosed according to ICD-10, Langsted et al. (199) analyzed 109.440 individuals and found an observational hazard ratio of 1.12 (95% CI: 1.03-1.12) for mental disorders. This reflects a 12% increased risk of mental disorders in individuals within the first quartile (lowest levels) of plasma Lp(a) compared to those in the fourth quartile (highest levels), suggesting low Lp(a) levels as a risk factor for mental disorders. However, in the same study they found no concordant genetic association of *LPA* genotypes that correspond to low or high Lp(a) levels (KIV-2 repeats via real-time PCR and rs10455872/rs3798220 carriers via TaqMan assays) and mental disorders, leading the authors to classify the observational

findings as either incidental or as a result of reverse causality, where the disease state itself causally lowers Lp(a) levels through yet unknown mechanisms.

3.3 Findings for Lp(a) and psychotropic medication

The study by Paslakis et al. (200) directly investigated the impact of antidepressant treatment of Lp(a) levels in 35 inpatients with MDD. After a 4-week randomized, double-blind treatment, depressive patients receiving 40 mg paroxetine daily (n = 21) contributed to a significant reduction of approximately 17% in mean serum Lp(a) levels (from 0.33 g/l to 0.28 g/l = 33 mg/dl to 28 mg/dl; p = 0.024), whereas those receiving amitriptyline (n = 14) showed no significant change (from 0.13 g/l to 0.19 g/l = 13 mg/dl to 19 mg/dl, p = 0.107). Notably, the difference in baseline levels between the paroxetine group (0.33 g/l) and the amitriptyline group (0.13 g/l) was not statistically significant (0.072). Furthermore, the study reported a significant Lp(a)-course x medication interaction (p = 0.007) that was independent of the change in Hamilton Depression Rating Scale (HAMD) scores. Interestingly, Mabrouk et al. (204) found no statistically significant difference (p = 0.606) in the variation of Lp(a) levels between schizophrenic patients treated with typical antipsychotics (n = 120) (338 g/l = 33.8 mg/dl) and atypical antipsychotics (n = 6) (373 g/l = 37.3 mg/dl) or both (n = 14) (431 g/l = 43.1 mg/dl). Notably, the standard deviation was very high suggesting a large divergence of single levels. In observational data regarding treatment, Ezzaher et al. (203) reported significantly lower paraoxonase 1 (PON1) activity in bipolar I patients compared to healthy controls. PON1 is a serum esterase that has shown to decrease lipid peroxidation (206) and therefore has anti-atherosclerotic properties. Among the different treatment subgroups – comprising lithium (n = 5), valproic acid (n = 31), carbamazepine (n = 8) and antipsychotics (n = 22) - patients under lithium therapy (n = 5) showed the significantly lowest levels of PON1 activity. In patients taking antipsychotics (n = 22), mean PON1 activity was modestly higher than mean of the patient group, without reaching statistical significance. No data on treatment and Lp(a) levels was documented in this study. Overall, evidence on the effect of psychopharmacological treatment on Lp(a) levels is sparse, with only one study directly suggesting a positive drug-specific

effect on Lp(a) levels. Table 2 provides a summary of the observed treatment effects in the three studies.

Table 2: Psychotropic medication and outcomes

Author	Treatment	Dosage	Indication	Outcomes
Ezzaher et al. (2010) (203)	Lithium, Carbamazepine, Valproic acid, Mood stabilizers, Antipsychotics	Not mentioned	Bipolar I disorder	Lithium therapy was associated with lowest PON1 activity; no significant differences for other drugs.
Paslakis et al. (2011) (200)	Paroxetine (SSRI), amitriptyline (tricyclic antidepressant	Paroxetine: 40 mg (final dosage) Amitriptyline: 150 mg (final dosage)	MDD	Paroxetine significantly lowered Lp(a); Amitriptyline showed no significant effect on Lp(a) levels.
Mabrouk et al. (2014) (204)	Typical antipsychotics, atypical antipsychotics	Not mentioned	Schizophrenia	No significant differences were found between patients with typical, atypical or combined therapy.

Table 2. Overview of studies reporting the effects of psychotropic medication, including first author and year of publication (column 1), psychotropic medication administered to participants (column 2), reported dosages where available (column 3), clinical indication for drug administration (column 4), and a summary of outcomes (column 4). List of abbreviations: PON1, Paraoxonase 1; SSRI, Selective Serotonin Reuptake Inhibitor; MDD, Major depressive disorder; Lp(a), Lipoprotein(a).

4 Discussion

To our best knowledge, this present work is the first attempt to systematically review the contemporary evidence on Lp(a) levels in psychiatric patients. Amongst all psychiatric diseases, depression was the most frequently addressed condition, with six out of nine included studies providing data on Lp(a) and depression. Overall, evidence from four of those studies (196,198,201,202) suggests that higher Lp(a) levels may be associated with depression. These results indicate that CVD risk in this patient group could possibly be mediated by Lp(a). However, the patient groups in two of those studies (201,202) ranged from 10 to 35 individuals, which limits the interpretability of the findings due to the large underlying inter-individual heterogeneity of Lp(a) levels, especially in studies with small cohorts (51). Small sample size may also have limited the statistical power of the study by Paslakis et al. (200) (n = 35), potentially explaining the lack of statistically significant findings for Lp(a) levels between depressive patients and controls in this study. Moreover, standard deviation for Lp(a) levels in the patient group was very high (25 ± 36 mg/dl), suggesting a large inter-individual variation of Lp(a) levels. Additionally, the wash-out period of only 6 days may have been insufficient to eliminate residual medication effects, potentially confounding baseline Lp(a) levels. In contrast, Sarandol et al. (205) reported no differences for Lp(a) levels in depressive compared to healthy individuals. Although this study represents the largest clinical MDD sample (n = 86), the control group was markedly small (n = 36), therefore limiting the comparability of the two groups. Furthermore, this study did not report exclusion of confounders such as previous history of atherothrombotic events or comorbid conditions, which have been shown to potentially influence Lp(a) levels (113). Another possible explanation for the null finding in this study may be the stage of disease represented in the patient group, as 69% of patients presented with a first depressive episode and short duration of illness. As findings from Hamidifard et al. (202) indicate, Lp(a) levels may be directly correlated with severity of depression, potentially reflecting the absence of detectable differences at early stages of disease. Finally, sex distribution in this study may be a potential source of bias, as evidence from a study of patients with depression and anhedonia suggests significantly lower Lp(a) levels in male patients compared to female patients (207). Accordingly, the

considerable imbalance between female (n = 64) and male (n = 24) patients in the MDD group of Sarandol et al. (205) may therefore have an affected the results of the study. Another recent, large analysis by Li et al. (196) found the positive association between Lp(a) and the subsequent development of depression to be influenced by inflammatory status. However, studies showed that following an inflammatory response, Lp(a) as well as apo(a) synthesis primarily increases, given their role as acute phase proteins in the inflammatory process (208,209). Notably, the BiomarCaRE project, which included over 150.000 individuals from general European population, observed no modifying effect of inflammation on Lp(a)-related risk for coronary heart diseases, although this effect might differ in high-risk populations (210). More evidence that Lp(a) does not mediate depression through CRP is also provided in the MR study by Pan et al. (198) where no difference in the frequency or duration of depressive episodes via this pathway was demonstrated. Interestingly, the observational results in the study by Pan et al. (198) contrasted with the genetic findings from the MR approach.

A comparable discrepancy can be observed in the context of bipolar disorder, where two case-control studies (201,203) reported a positive association between Lp(a) and bipolar disorder, whereas Pan et al. (198) reported low Lp(a) concentrations in these patients in their retrospective observational data. These results are largely consistent with those for depression in the same study, which might be explained by the study design: as MR analysis shows, genetically predicted higher Lp(a) is associated with longer duration and higher number of depressive episodes, whereas patients with manifest disease show lower Lp(a) levels. However, these findings might not be completely contradictory to the findings of other case-control studies: High Lp(a) may therefore contribute to depression onset or chronicity, while the depressive state itself could lead to a reduction of Lp(a), although there is no evidence to support this hypothesis so far. Another explanation by the authors for this discrepancy is that low Lp(a) levels in anxious and depressed patients are caused by reduced nutrition, potentially leading to lower lipid levels. However, as Lp(a) levels are primarily determined by genetics (51) and nutrition only shows minimal effects on Lp(a) levels (115,211), this explanation only insufficiently accounts for these findings. However, since there is no information about the treatment-status of patients included in this study,

the potential influence of pharmacotherapy on Lp(a) levels in the patient group warrants consideration, as discussed further below.

Merely two studies (201,204) assessing Lp(a) levels in schizophrenic patients were identified in this review, with both studies reporting significantly elevated Lp(a) levels in patients. In particular, the study by Mabrouk et al. (204) strengthens the hypothesis that Lp(a) may be elevated in schizophrenia, given the larger study cohort compared to the small patient group of Emanuele et al. (201) (n = 140 vs. n = 39) and adjustment for multiple confounders. However, medication status represents an important uncontrolled confounder in both studies. It is worth noticing that Mabrouk et al. (204) reported significantly higher triglyceride and Triglyceride/HDL-C levels in patients under treatment with atypical antipsychotics, suggesting an influence on lipid metabolism that may extend to Lp(a). Moreover, both studies used different measurement methods for Lp(a), which further limits comparability (212). Nevertheless, the results of these two studies support the assumption of elevated Lp(a) levels in schizophrenic patients and provide a solid foundation for future research.

The available evidence for other psychiatric outcomes - besides depression, schizophrenia and bipolar disorder - is very sparse. Evidence for personality disorders is limited to a single study by Emanuele et al. (201) which reported no significant difference in Lp(a) compared to controls. Given the sample size limitation (n = 12) and diagnostic heterogeneity subsumed under personality disorders (213), no definite conclusion can be drawn. Same applies to anxiety disorders, which was only addressed by Pan et al. (198), reporting that low Lp(a) was associated with significantly higher anxiety risk in their retrospective cohort. Here too, however, the lack of comparative studies limits conclusions that can be made on this topic. In line with that, the large-scale study Langsted et al. (199) finds observationally low Lp(a) levels to be associated with mental disorders, strengthening the observations of Pan et al. (198) in large population studies. Conversely, the genetic analyses showed no correlation between Lp(a) and mental disorders at all. However, the heterogeneity of diseases subsumed in the “mental disorders” category applied in this study includes all mental and behavioral disorders according to ICD-10 – from dementia syndromes, mental disorders due to substance use and unspecified disorders, amongst others (214). This

inhomogeneous diagnostic range of conditions probably masks disorder-specific associations and limits the ability to make precise statements on specific psychiatric disorders that are predisposed to elevated CVD risk. Importantly, despite the differences in study design and population, both studies (198,199) associated mental disorders with lower Lp(a) levels, suggesting that Lp(a) levels may change over the course of a mental health disorder. Therefore, repeated Lp(a) measurements in a long-term follow-up study would better reflect the dynamics of Lp(a) levels in this context, as retrospective data from a cohort study regarding Lp(a)-associated CVD risk suggests temporal changes of Lp(a) (215). Overall, two studies (200,204) assessed the relationship between psychotropic medication and Lp(a) levels and another one study only observed PON1 activity (203). Only the randomized, double-blind trial by Paslakis et al. (200) investigated specific agents and proposed a direct effect of drug treatment on Lp(a) concentrations. The study design of this study is a great strength compared to the two other studies by Ezzaher et al. (203) and Mabrouk et al. (204), which do not permit causal conclusions regarding the influence of medication on Lp(a) levels due to their cross-sectional design. It should be noted that the patient sample of the study by Paslakis et al. (n = 35) was considerably smaller than those of Mabrouk et al. (n = 140) and Ezzaher et al. (n = 66), and the distribution between the therapy groups (n = 14 vs. n = 21) was uneven, limiting its statistical power. However, despite the relatively large overall patient cohort in the study by Mabrouk et al. (204), the subgroup receiving atypical antipsychotics was very small (n = 6) as was the group receiving combination therapy (n = 14), making it difficult to draw reliable conclusions for these treatment groups. Additionally, there was lack of information on dosage or specific drugs. This equally applies to the study by Ezzaher et al. (203), which found a statistically significant result regarding PON1 activity only for the lithium subgroup, suggesting this group at higher risk for atherosclerotic diseases caused by low PON1 activity. However, this group was once again very small (n = 5), so this finding should be interpreted with considerable caution. Moreover, comparability of baseline Lp(a) values across the studies is further limited by differences in medication management: while Paslakis et al. (200) implemented a wash-out period, patients in both other studies continued their ongoing pharmaco-therapy, meaning that measured Lp(a) levels

could possibly already reflect pharmacological rather than purely disease-related effects. Consequently, the influence of medication on Lp(a) remains largely unproven by now. Furthermore, methodological heterogeneity in Lp(a) measurement adds lack of comparability, as Paslakis et al. (200) employed a photometric system, whereas Ezzaher et al. (203) and Mabrouk et al. (204) used immunoturbidimetric methods. However, a recent in-vitro study by Deo et al. (216) supported the findings of Paslakis et al. (200) by demonstrating that specific selective serotonin reuptake inhibitors (SSRIs) – particularly citalopram and paroxetine – as well as the tricyclic antidepressant imipramine induce macropinocytosis at a cellular level. This process promotes enhanced membrane binding and the subsequent active cellular internalization, effectively clearing Lp(a) from the systemic circulation. Overall, particularly based on the findings from Paslakis et al. (200), which were supported by recent evidence, promising effects on lowering Lp(a) levels are expected especially from SSRIs, suggesting them as potential key agents to decrease CVD risk in psychiatric patients. To confirm this suggestion, more and larger, randomized placebo-controlled trials are needed in the future. Moreover, given this evidence, medication status may represent an important confounder in psychiatric cohorts across the included studies in this review. Notably, amongst all included studies in this review, only one study restricted inclusion to patients free of psychiatric medication for a minimum of six months (202), while most of the remaining studies either did not account for medication status or involved patients in treatment.

Collectively, the findings across all included studies predominantly suggest that patients with psychiatric disorders – including MDD, schizophrenia, and bipolar disorder – tend to have higher Lp(a) levels compared to healthy individuals. However, the results throughout the studies were not entirely consistent with some notable differences between smaller case-control studies and more recent large-scale studies. Taken together, this review found seven studies (196,198,200–204) reporting a positive association between Lp(a) – whether genetically determined or directly measured - and mental health disorders. Based on these findings, Lp(a) could represent a relevant contributor to the high prevalence of CVD in psychiatric populations. Additionally, effective antidepressant treatment may confer a dual benefit with the potential to target both psychiatric disease and Lp(a)-associated

CVD risk, yet the evidence remains limited. However, none of the currently available studies directly links elevated Lp(a) levels to cardiovascular outcomes in psychiatric patients, as most studies rely on Lp(a) concentrations as a marker for estimated risk rather than providing any outcome data. This fundamental methodological gap underscores the need for prospective studies in larger, well-characterized psychiatric cohorts alongside complementary MR studies to clarify the directionality of the relationship and to establish whether Lp(a) contributes to the excess cardiovascular morbidity and mortality in psychiatric populations.
In conclusion, this review highlights the urgent need for more comprehensive research in this area, which is essential to improve our understanding of this complex relationship and to potentially reduce the high cardiovascular burden that disproportionately affects this vulnerable patient population.

5 Limitations

The main strength of this review is that it constitutes the first systematic review on this topic. However, certain limitations should be acknowledged. The inconsistencies in some findings may be largely due to small sample sizes of most studies and variation in patient selection (e.g., inpatient vs. outpatients, duration of untreated illness). Also, there are several methodological limitations to consider when interpreting the findings of this systematic review. Smaller studies recruited participant exclusively from single psychiatric wards, which may introduce selection bias. Additionally, inconsistent confounder adjustment leads to heterogeneity across the studies. Differences in diagnostic precision further limits comparability: while clinical cohort studies applied DSM-IV criteria by experienced psychiatrists, large-scale studies relied on ICD-10 or combined them with self-administered questionnaires. In addition, most of the included studies have a cross-sectional study design, which cannot establish direct causality between Lp(a) and mental health disorders, a limitation only recently addressed by MR studies. Furthermore, large underlying inter-individual heterogeneity of Lp(a) levels in the study cohorts limits the interpretability and comparability of findings. Most of the included studies also did not determine apo(a) isoform size, which accounts for the largest part of variation in Lp(a) concentrations (86) and would be of high interest for CVD risk prediction in psychiatric populations. Moreover, small cohorts from the same region imply a high chance of significant genetic overlap within the study population, which leads to less pronounced inter-individual differences in Lp(a) levels (86). With respect to ethnicity, most study subjects are European or Tunisian descent, which may limit generalizability to other ethnic groups as there are large differences in different ethnicities (113). Finally, the thresholds applied in some of the included studies, are no longer consistent with updated recommendations. Whereas current guidelines define elevated Lp(a) levels as ≥ 30 mg/dl (145), some earlier studies considered concentrations ≥ 25 mg/dl as elevated. When applying this updated threshold, documented Lp(a) levels by Emanuele et al. (201) in patients with schizophrenia (26 mg/dl) would not be considered as increased anymore. Nevertheless, the difference in Lp(a) concentrations between patients and healthy controls (12 mg/dl) was still significant ($p = 0.021$). This also applies to the study by Ezzaher et al. (203), in

which substantially higher Lp(a) levels were reported in patient with bipolar disorder (24.3 mg/l) compared to controls (15.6 mg/l), however, these patients would also not be classified as at elevated cardiovascular risk according to current guidelines. Irrespective of the established cutoffs, the documented Lp(a) levels in these studies are comparable to those in patients with prior atherothrombotic events according to recent data of a multicenter cross-sectional epidemiological study (217).

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The following AI tools were used to edit language and style of the text:

Notebook LM
Provider: Google LLC
Accessed: 20.03.2026
URL: https://notebooklm.google.com

Claude Sonnet 4.6
Provider: Anthropic
Accessed: 23.03.2026 (via Perplexity Pro: https://perplexity.ai)
URL: https://anthropic.com/claude/sonnet