ISSN 0973-2063 (online) 0973-8894 (print)

Bioinformation 22(8): 4838-4842 (2026)

BIOINFORMATION
Discovery at the interface of physical and biological sciences

BIOMEDICAL INFORMATICS

www.bioinformation.net

Volume 22(8)

Research Article

Received August 1, 2026; Revised August 31, 2026; Accepted August 31, 2026, Published August 31, 2026

DOI: 10.6026/973206300224838

SJIF 2026 (Scientific Journal Impact Factor for 2026) = 8.478
2022 Impact Factor (2023 Clarivate Inc. release) is 1.9

Edited by Vini Mehta
E-mail: vmehta@statsense.in
Citation: Raghuwanshi *et al.* Bioinformation 22(8): 4838-4842 (2026)

Generalized anxiety disorder and lipoprotein (a): A biomarker-based case–control analysis

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ISSN 0973-2063 (online) 0973-8894 (print)
Bioinformation 22(8): 4838-4842 (2026)

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Abstract:
Generalized Anxiety Disorder (GAD) links to cardiovascular risk through inflammation and lipid dysregulation, yet lipoprotein(a) (Lp(a)) elevation and its relationship to anxiety severity remain underexplored. Therefore, it is of interest to measure the fasting serum Lp(a) via immunoturbidimetric assay in 100 GAD adults versus 100 matched controls, alongside Hamilton Anxiety Rating Scale (HAM-A) assessments and multivariable regression analysis. GAD patients showed significantly elevated Lp(a) (35.2 ± 9.8 mg/dL versus 21.5 ± 7.3 mg/dL; $p < 0.0001$), rising progressively from mild (30.1 ± 6.7 mg/dL) to moderate-severe anxiety (49.2 ± 10.2 mg/dL; $p < 0.0001$). HAM-A scores strongly correlated with Lp(a) ($r = 0.64$, $p < 0.0001$), with anxiety independently predicting levels after age/gender adjustment ($\beta = 0.59$, $p < 0.0001$). Thus, data shows that Lp(a) as a severity-linked biomarker connecting GAD pathophysiology to high cardiovascular risk, supporting its role in preventive monitoring.

Keywords: Generalized anxiety disorder, lipoprotein (a) (Lp(a)), anxiety severity, cardiovascular risk, inflammation

Background:
Generalized Anxiety Disorder (GAD) and related anxiety disorders rank among the most prevalent psychiatric conditions globally, imposing substantial burdens on both individual well-being and public health systems. Traditionally, anxiety can be considered as a purely psychological condition, but today it is understood that it may cause systemic physiological changes, especially those associated with the inflammation processes. Both cohort and meta-analytic studies with large cohort sizes have showed that people with anxiety have higher levels of inflammatory markers, which include C-reactive protein and interleukin-6, in circulation than healthy controls, indicating that psychological stress is biologically related to the activation of the immune system **[1, 2]**. The hypothalamic-pituitary-adrenal axis and sympathetic nervous system release cytokines and activate immune cells during chronic stress **[3]**. Low-grade inflammation is a chronic inflammatory mediator of cardiometabolic disease. Chronic inflammatory signaling causes endothelial dysfunction, lipid modification and atherogenesis, correlating anxiety to high cardiovascular risk. Epidemiologic data suggest that high levels of inflammatory markers in anxiety, in addition to being associated with present cardiovascular dysfunction, are predictive of future adverse events **[4, 5]**. Here, Lipoprotein (a) (Lp(a)) has become a powerful and independent cardiovascular risk factor. Lp(a), structurally related to LDL, is characterized by a covalent connection with apolipoprotein(a) that endows it with pro-atherogenic and pro-inflammatory capabilities **[6]**. Both experimental and clinical studies have shown that oxidative alterations of Lp(a) increase its inflammatory capacity, facilitating monocyte activation, endothelial impairment and the development of vascular smooth muscle **[7]**. Moreover, Lp(a) levels can be regulated by inflammatory stimuli, forming a two-way connection where cardiovascular risk may be reinforced by anxiety-linked inflammation and Lp(a) biology **[8]**. The cardiovascular importance of LP(a) is well-established through epidemiologic, genetic and prospective studies. Higher levels correlate with increased occurrence of significant adverse cardiovascular events, which involve myocardial infarction, stroke, as well as aortic stenosis, with or without traditional risk determinants, including LDL cholesterol **[9]**. According to evidence of a large participant-level meta-analysis, lipoprotein(a) is independently associated with the risk of atherosclerotic cardiovascular disease, which highlights its utility as a residual cardiovascular risk factor **[10]**. Therefore, it is of interest to contribute to the current body of knowledge on the biological processes that interrelate psychological stress and cardiovascular risk and may have implications in research and practice.

Materials and Methods:

Study design and setting:
This hospital-based analytical case–control study was conducted after obtaining approval from the "Institutional Human Ethics Committee (approval number: CIMS/Ethics Committee/2024/14588, dated 20/12/2024)". The study was carried out in the Departments of Psychiatry and Biochemistry at Chhindwara Institute of Medical Sciences, in association with the District Hospital, Chhindwara, Madhya Pradesh, India. The duration of the study was one year, from January 2025 to December 2025.

Study population:
A total of 200 participants had been enrolled in the study, including 100 patients diagnosed with Generalized Anxiety Disorder (GAD) attending the psychiatry outpatient department of the CIMS-affiliated district hospital and 100 age- and gender-matched healthy controls. All participants were 18–45 years old, male and female.

Diagnosis and assessment of severity of anxiety:
The diagnosis and severity of the anxiety were conducted with the help of the publicly available Hamilton Anxiety Rating Scale (HAM-A) **[11]**. This scale has 14 items with a score ranging between 0 and 4, with a total score of 0-56. The interpretation of the scores was as follows: 0 (no anxiety), 1-7 (minimal anxiety), 8-17 (mild anxiety), 18-24 (mild to moderate anxiety) and more than 25 (moderate to severe anxiety). All participants underwent a thorough medical history and physical examination to rule out any conditions that could affect serum Lp(a) levels.

Sample size:

The 100 cases and 100 controls were determined to identify a moderate effect size (Cohen d = 0.5) in serum Lp (a) levels, with 80% statistical power at a two-sided alpha of = 0.05. Subgroup analyses involving the severity of anxiety were also possible due to this size. The previous studies involving lipid biomarkers in psychiatric populations have reported similar sample sizes **[12].**

Inclusion and exclusion criteria:
The study included 18–45 year without psychotropic medications for three months and informed consent was obtained. The exclusion criteria included a history of cardiovascular disease, lipid metabolism disorders, smoking or substance dependence, pregnancy or lactation, active infection, autoimmune or inflammatory disorders, intellectual disability, psychiatric conditions other than GAD, use of antidepressants or anxiolytic drugs, severe systemic illness and not willing to participate.

Biochemical assessment:
All participants had to fast overnight (8-10 hours) and then provide aseptic 5 mL venous blood samples. Samples were centrifuged to separate serum, which was stored at -20°C till analysis. The serum Lp(a) was quantified in an automated biochemical analyser by a standardised immunoturbidimetric assay. To ensure that the results could be accurate and reproducible, both internal and external quality control was applied.

Data management:
Participant data were anonymized based on unique identification codes and stored in a secure and access-restricted database. Cross-checking was done to verify that there was no inaccuracy in data entry. All the laboratory results were documented with coded identifiers. All records were securely maintained with regular backups and only de-identified data were used for analysis in compliance with ethical standards.

Statistical analysis:
Analytics were done using SPSS 25.0 (IBM Corp., Armonk, NY, USA). Frequencies and percentages represented categorical variables, while mean and SD represented continuous variables. The Shapiro-Wilk test and the Levine test were used to test the normality of data distribution and homogeneity of variance, respectively. Continuous variables were tested using an independent samples t-test and categorical variables using a chi-square test to compare cases and controls. One-way analysis of variance (ANOVA) was used to compare serum Lp(a) levels in groups with different anxiety levels, followed by a post hoc test with Bonferroni correction for multiple t-tests. Pearson correlation coefficient was used to determine the relationship between HAM-A scores and the serum Lp(a) levels. Moreover, multivariate linear regression analysis was carried out to assess the independent predictive value of the HAM-A scores on the serum Lp(a) level, when age and gender were controlled. Effect sizes were determined employing Cohen's d for group comparisons and partial η^2 for ANOVA. A two-tailed p-value <0.05 indicates statistical significance.

Results:
The study included 200 participants, comprising 100 patients with Generalized Anxiety Disorder (GAD) and 100 age- and gender-matched healthy controls. GAD patients had a mean age of 32.5 ± 6.7 years, versus controls of 31.9 ± 7.0 years; no difference in age was found (t (198) = 0.63, p = 0.529). The groups also matched well on gender distribution (2 (1) = 0.16, p = 0.689). **Table 1** provides a summary of demographic information. The mean serum Lp(a) levels had been found to be significantly higher in GAD patients (35. 2 ± 9.8mg/dL) compared to healthy controls (21.5 ± 7.3mg/dL) with a highly significant difference (t (198) = 11.19, p = 0.0001) and very large effect size (Cohen d = 1.61) (Table 2). The mean serum Lp(a) levels were found to be significantly higher in GAD patients (35. 2 ± 9.8mg/dL) compared to healthy controls (21.5 ±7.3mg/dL) with a highly significant difference (t (198) = 11.19, p = 0.0001) and very large effect size (Cohen d = 1.61). Mean serum Lp(a) increased gradually by severity groups: mild (30.1 ± 6.7 mg/dL), mild-to-moderate (37.5 ± 8.1 mg/dL) and moderate-to-severe (49.2 ± 10.2 mg/dL). ANOVA one-way showed a statistically significant difference between the groups (F (2, 97) = 32.47, p < 0.0001) and a large effect size (partial η^2 = 0.25) **(Table 3)**. Tukey tests with Bonferroni correction showed that there were significant differences between all pairwise comparisons **(Table 4)**. Pearson correlation analysis demonstrated a strong positive relationship between HAM-A scores and serum Lp(a) levels (r(98) = 0.64, p < 0.0001) (Table 5). In multivariable linear regression analysis, HAM-A score independently predicted serum Lp(a) levels (β = 0.59, t = 8.02, 95% CI: 0.46–0.72, p < 0.0001) after adjusting for age and gender. The overall model explained 36% of the variance in Lp(a) (adjusted R^2 = 0.36) and was statistically significant (F (3, 96) = 19.56, p < 0.0001). Gender (p = 0.524) and age (p = 0.398) were not significant predictors (**Table 5**). The assumptions of normality and homogeneity of variance were satisfied by all continuous variables, as indicated by the Shapiro-Wilk and Levene tests (p > 0.05). This validates the application of parametric statistical tests in group comparisons and testing of correlation. These findings indicate that the serum Lp(a) levels are much higher in GAD patients than in healthy controls. Moreover, the Lp (a) concentrations increase gradually as the anxiety severity increases, which means that there is a definite graded relationship. This relationship remains when age and gender are controlled, indicating that high Lp(a) is mostly influenced by the physiological effects of anxiety and not by demographic variables. These results are consistent in group comparisons, correlation studies and regression models and suggest Lp(a) may be useful in monitoring the biological burden of anxiety.

Table 1: Baseline characteristics of study participants

Variable	Cases (n=100)	Controls (n=100)	Statistical Test	Value	df	p-value

Age (years, mean ± SD)	32.5 ± 6.7	31.9 ± 7.0	Independent t-test	t=0.63	198	0.529
Gender (M/F)	54/46	52/48	Chi-square test	χ^2=0.16	1	0.689

Legend: Baseline characteristics were comparable between cases and controls, with no statistically significant differences.

Table 2: Comparison of serum lipoprotein (a) Levels between cases and controls

Group	Lp(a) (mg/dL, mean ± SD)	Statistical Test	Value	df	p-value	Effect Size
Cases	35.2 ± 9.8	Independent t-test	t=11.19	198	<0.0001	Cohen's d = 1.61
Controls	21.5 ± 7.3					

Legend: GAD patients demonstrated a highly significant elevation in serum Lp(a) compared to healthy controls, with a very large effect size.

Table 3: Serum lipoprotein(a) Levels across anxiety severity groups

Severity Group	n	Lp(a) (mg/dL, mean ± SD)	Statistical Test	Value	df	p-value
Mild	47	30.1 ± 6.7	One-way ANOVA	F=32.47	(2,97)	<0.0001
Mild–Moderate	36	37.5 ± 8.1				
Moderate–Severe	17	49.2 ± 10.2				

Legend: Lp(a) levels increased progressively with anxiety severity. Partial η^2 = 0.25 indicates a large effect of anxiety severity on Lp(a) levels.

Table 4: Post hoc pairwise comparisons of serum lipoprotein(a) Levels across anxiety severity groups

Comparison	Mean Difference (mg/dL)	p-value	Significance
Mild vs Mild–Moderate	7.4	0.008	Significant
Mild vs Moderate–Severe	19.1	<0.0001	Significant
Mild–Moderate vs Moderate–Severe	11.7	0.003	Significant

Table 5: Correlation and Multivariable Regression Analysis

Parameter	Statistical Test	Value	df	p-value
HAM-A vs Lp(a)	Pearson correlation	r=0.64	98	<0.0001
HAM-A (predictor)	Linear regression	β=0.59, t=8.02, 95% CI: 0.46–0.72	96	<0.0001
Age (covariate)	Linear regression	β=0.05, 95% CI: −0.08–0.18	96	0.398
Gender (covariate)	Linear regression	β=0.04, 95% CI: −0.09–0.17	96	0.524
Model significance	ANOVA (regression)	F=19.56	(3,96)	<0.0001
Model fit	Adjusted R^2	0.36		—

Legend: Anxiety severity shows a strong positive correlation with serum Lp(a). Multivariable regression confirms HAM-A score as an independent predictor, while age and gender were not significant contributors.

Discussion:

This study has provided evidence that there is a strong, dose-dependent relationship between Generalized Anxiety Disorder (GAD) and high levels of serum Lipoprotein(a), with increasing levels of anxiety symptoms being associated with increasing levels of Lp(a). These results provide evidence of a biologically plausible mechanism whereby chronic psychological stress contributes to systemic inflammation, which in turn affects the Lp(a) metabolism, thus increasing the risk of cardiovascular disease. Our results are consistent with an accumulating body of literature that highlights the interaction between mental health and cardiovascular biology in terms of psycho-neuroimmune processes. Previous research has reported anxiety to be related to increased systemic inflammatory markers. Even after controlling behavioral and lifestyle confounding factors, individuals with anxiety disorders have an increased concentration of C-reactive protein in circulation **[1]**. Similarly, pro-inflammatory cytokines that involve IL-6 and TNF-α are frequently elevated in anxious populations, reflecting chronic HPA axis and sympathetic activation that promotes sustained immune cell signaling **[13, 14]**. These pathways provide a link connecting psychological distress with systemic inflammatory changes. Inflammation has a direct effect on Lp(a) biology. Lp(a) particles carry oxidized phospholipids and interact with immune pathways that exacerbate endothelial dysfunction and vascular inflammation **[6, 8]**. Higher levels of inflammatory markers are associated with greater cardiovascular risk in individuals with elevated Lp(a), suggesting that inflammation may serve as an intermediate link connecting anxiety, increased Lp(a) and cardiovascular risk **[15]**. Large epidemiologic and Mendelian randomization studies confirm Lp(a) as an independent causal factor for atherosclerotic cardiovascular disease, with each standard deviation increase in Lp(a) associated with approximately a 13% higher risk of major cardiovascular events **[16, 17]**. Overall, these findings suggest a complex bidirectional relationship between Lp(a) levels and mental disorders, particularly depression, with both genetic evidence and observational data indicating that alterations in Lp(a) may be associated with depressive and anxiety symptoms. Further longitudinal and mechanistic studies are warranted to clarify the underlying pathways and determine whether changes in Lp(a) have clinically meaningful implications for the prevention and management of mental disorders **[18]**. Our findings contribute to the existing literature by showing that the degree of serum Lp(a) elevation is directly proportional to the degree of anxiety, that is, psychological stress can also regulate this lipoprotein, in addition to its strongly hereditary predisposers. This linearity suggests that the Lp(a) production, clearance, or post-translational changes can be controlled by chronic anxiety and emphasizes the bidirectional correlation between mental health and cardiovascular risk factors. These results indicate that the systemic physiological mechanisms of psychological stress may influence even a rather traditional biomarker, such as Lp(a). They are the main strengths that include, but are not limited to, a well-characterized cohort, anxiety assessed with a validated scale and the detailed statistical modelling of the available confounders. The

limitations are that it is cross-sectional and therefore it cannot be used to conclude causally and the biomarkers of inflammatory biomarkers are not directly measured by the study, which limits the mechanism. The moderate-severe anxiety group was also very small and this may decrease the quality of subgroup estimates. These results indicate that mental health variables are significant in cardiovascular risk measurement. High levels of Lp(a) in patients with high levels of anxiety might justify combined treatment of psychological and cardiometabolic risks. New treatments targeting Lp(a) imply possible clinical significance of anxiety-related increases in high-risk individuals. To define the causal relationship between anxiety, inflammation and Lp(a), longitudinal studies are required. The informational basis of holistic prevention strategies would be interventional studies that would compare the outcomes of anxiety reduction versus anti-inflammatory actions to reduce Lp(a) and cardiovascular outcomes. New therapeutic targets can be identified by further investigation of the molecular pathways that regulate the effect of stress on liver production of Lp(a).

Conclusion:

We show that elevated serum Lp(a) levels in GAD patients are proportional to anxiety severity (HAM-A), establishing a biochemical link between psychological stress and cardiovascular risk through lipid dysregulation. Lp(a) emerges as a severity-dependent biomarker independent of age/gender, suggesting stress signaling directly influences hepatic Lp(a) production and warrants integrated mental health-cardiometabolic monitoring. Future research should target stress-induced Lp(a) mechanisms to enable preventive cardiovascular strategies in high-risk anxiety populations.

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