Title

Lipoprotein (a) and the risk of elevated depressive symptoms: The Multi-Ethnic Study of Atherosclerosis.

Authors

Hui, Nicholas

Morris, Margaret

Allison, Matthew

et al.

Publication Date

2021

DOI

10.1016/j.jpsychires.2020.12.022

Peer reviewed

Published in final edited form as:

J Psychiatr Res. 2021 January ; 133: 119–124. doi:10.1016/j.jpsychires.2020.12.022.

Lipoprotein (a) and the risk of elevated depressive symptoms: The Multi-Ethnic Study of Atherosclerosis

Nicholas Hui[a], **Margaret J. Morris**[b], **Matthew A. Allison**[c], **Michael Y. Tsai**[d], **Kerry-Anne Rye**[a], **Fatiha Tabet**[a], **Kwok Leung Ong**[a,*]

[a]Lipid Research Group, School of Medical Sciences, University of New South Wales, Sydney, NSW, Australia

[b]Department of Pharmacology, School of Medical Sciences, University of New South Wales, Sydney, NSW, Australia

[c]Department of Family and Preventive Medicine, University of California San Diego, La Jolla, CA, United States

[d]Department of Laboratory Medicine and Pathology, University of Minnesota, Minneapolis, MN, United States

Abstract

Previous studies suggested a potential relationship between plasma lipoprotein (a) [Lp(a)] and elevated depressive symptoms. We aimed to investigate any such relationship in the Multi-Ethnic Study of Atherosclerosis participants who were free of cardiovascular events. Analysis included 4938 participants without elevated depressive symptoms and with Lp(a) levels measured at baseline. Participants were examined at four clinic visits over a 10-year period. Elevated depressive symptoms were assessed by the Center for Epidemiologic Studies Depression Scale (CES-D) and were defined as a CES-D score ≥16 or use of anti-depressants. Lp(a) level was measured with a latex-enhanced turbidimetric immunoassay. After adjusting for demographics, socioeconomic factors and other confounding factors in Cox regression analyses, a higher ln-transformed Lp(a) level was associated with new elevated depressive symptoms since baseline (hazard ratio [95% CI] = 1.09 [1.02–1.16] per SD increment in ln-transformed level, $P = 0.01$). However, no association was found when elevated Lp(a) levels were assessed using clinical cut-off point (≥30 or 50 mg/dL), nor in sensitivity analyses using alternative definitions of elevated depressive symptoms. No significant interaction with race/ethnicity was found for all the above analyses. Also, no significant association was found between baseline Lp(a) levels and absolute

*Corresponding author. School of Medical Sciences, University of New South Wales, Sydney, NSW, 2052, Australia. oklws@yahoo.com.hk (K.L. Ong).

Declaration of competing interest

None.

CRediT authorship contribution statement

Nicholas Hui: Conceptualization, Formal analysis, Investigation, Writing - original draft. **Margaret J. Morris:** Writing - review & editing. **Matthew A. Allison:** Writing - review & editing. **Michael Y. Tsai:** Writing - review & editing, Resources, Investigation. **Kerry-Anne Rye:** Writing - review & editing. **Fatiha Tabet:** Writing - review & editing. **Kwok Leung Ong:** Conceptualization, Formal analysis, Methodology, Supervision, Writing - review & editing.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jpsychires.2020.12.022.

or relative changes in CES-D score between baseline and last follow-up visits. Our study suggests a potential association between Lp(a) level and new elevated depressive symptoms, but such association was not robust in the sensitivity analyses. Future studies are warranted to investigate the role of Lp(a) in depressive symptoms in other cohorts.

Keywords

Biomarker; Depression; lipoprotein(a); Multi-ethnic study of atherosclerosis; Predictive model

1. Introduction

Multiple studies have shown that depression is a risk factor for the development and progression of coronary heart disease (CHD), but the exact mechanisms are not known (Lett et al., 2004). Furthermore, elevated plasma levels of lipoprotein (a) [Lp(a)] are associated with the progression of atherosclerosis and CHD (Emerging Risk Factors Collaboration et al., 2009). Previous cross-sectional studies reported that plasma Lp(a) levels from participants with major depressive disorder (MDD) without any past history of atherothrombotic events were significantly higher than those of healthy controls (Emanuele et al., 2006; Hamidifard et al., 2009; Paslakis et al., 2011). The severity of MDD, measured by the Beck Depression Inventory, was also positively correlated with Lp(a) levels (Hamidifard et al., 2009). While no association between Lp(a) levels and MDD was reported in another study (Sarandol et al., 2006), these results may have been confounded by participants with a past history of atherothrombotic events. Moreover, all these previous studies were also limited by small sample size and cross-sectional study design.

As Lp(a) levels have been shown to vary among different racial/ethnic groups (Banerjee et al., 2011), it is not known whether race/ethnicity influences the association between Lp(a) levels and elevated depressive symptoms. Given the positive association between Lp(a) levels and MDD in some cross-sectional studies, we therefore investigated the association between plasma Lp(a) levels at baseline and development of elevated depressive symptoms in the Multi-Ethnic Study of Atherosclerosis (MESA), and whether race/ethnicity could modify such a relationship.

2. Methods

2.1. Study participants

MESA is a prospective cohort study with the aim to investigate the epidemiology, risk factors, and progression of subclinical cardiovascular disease (Bild et al., 2002). A total of 6814 men and women of the four major racial/ethnic groups (Caucasian, African American, Hispanic American and Chinese American) were recruited from six U.S. communities (Bild et al., 2002). They were aged 45–84 years and free of clinical cardiovascular disease at baseline. The initial examination was conducted from July 2000 to August 2002. A total of 6233, 5947, 5818, and 4716 participants were followed up in the visits 2, 3, 4, and 5, respectively over a 10-year period. Details of study design and methodology were described previously (Radloff, 1977). Approval of study was obtained from the institutional review

boards of all participating institutions and informed consent was obtained from all subjects. The study was conducted in accordance with the Declaration of Helsinki.

Among 6814 subjects at baseline, 6705 subjects had valid data on plasma Lp(a) level, of whom 6027 had valid data on elevated depressive symptoms at baseline and follow-up visits 2 to 5. After excluding 1089 participants with elevated depressive symptoms at baseline, a total of 4938 participants were included in this analysis.

2.2. Assessment of depressive symptoms

Depressive symptomatology was assessed by the Center for Epidemiologic Studies Depression Scale (CES-D), a 20-item, self-reported questionnaire (Radloff, 1977), in visits 1, 3, 4 and 5. Although the CES-D is not an assessment of clinical depression and its cut-off points for elevated depressive symptoms varied among studies, in this analysis we used the cut-off point of CES-D score ≥16 which is the most widely accepted value for at least mild-to-moderate depression or dysthymia (Beekman et al., 1997). In visits 1, 3, 4 and 5, elevated depressive symptoms were defined as either the CES-D score ≥16, or self-reported use of anti-depressant medications (tricyclic anti-depressants, monoamine oxidase inhibitors, selective serotonin reuptake inhibitors, serotonin-norepinephrine reuptake inhibitors, and atypical anti-depressants) as described previously in other MESA studies (Golden et al., 2008; Ong et al., 2016; Remigio-Baker et al., 2014). In visit 2, given the unavailability of data on the CES-D score, elevated depressive symptoms were defined as self-reported use of anti-depressant medications. A meta-analysis has reported that the sensitivity and specificity of CES-D at the cut-off of 16 in detecting MDD was 87% and 70% respectively (Vilagut et al., 2016). Increasing the cut-off points to 20 increased the specificity to 78%, in exchange of a reduction in sensitivity to 83%. Therefore, in a sensitivity analysis, elevated depressive symptoms were defined as a CES-D score ≥20 or self-reported use of anti-depressant medications. We also performed a sensitivity analysis using an alternative definition using CES-D score ≥16 only, without using data on the use of anti-depressants. Moreover, since a CES-D score of ≥21 has been suggested as the cut-off of MDD, a sensitivity analysis using an alternative definition of elevated depressive symptoms (CES-D score of ≥21) was adopted (Zich et al., 1990).

2.3. Measurement of lipoprotein(a) level

Venous blood samples were collected after 12 h of overnight fasting in EDTA-anticoagulant tubes. Lp(a) level was measured with a latex-enhanced turbidimetric immunoassay (Denka Seiken, Tokyo, Japan) in the Health Diagnostics Laboratory (Richmond, Virginia) (Marcovina et al., 2000), with the inter-assay and intra-assay of <5% and <4% respectively (Abe et al., 1994; Puri et al., 2017). The active reagent (R2) contained a suspension of latex particles coated with anti-Lp(a) antibodies. Following incubation with serum, agglutination was detected by a change in absorbance at a wavelength of 700 nm, which was proportional to the mass, based on a five-level calibration.

2.4. Other variables of interest

Baseline assessment was conducted in visit 1. Information on demographics, socio-economic status and social history, including age, race/ethnicity, education level, marital

status, cigarette use, alcohol use, physical activity, and total gross family income, was collated via self-administered, standardized questionnaires. Physical activity was determined as the total number of hours of moderate and vigorous activity per week, multiplied by metabolic equivalent level. Medical history, including history of cancer, was collected through structured interviews. Participants were asked to bring to the clinic containers for all medications used in the past two weeks prior to the visit. The interviewer then transcribed the name of each medication, its strength, and for prescription medications, frequency of administration from the containers onto the data collection form.

For body mass index (BMI) measurement, participants were asked to wear light clothing and remove their shoes. Blood pressure was measured 3 times at a 2-min interval using a Dinamap model Pro 100 automated oscillometric sphygmomanometer (Critikon, Tampa, FL, USA) in a seated position after a 5 min rest period. The average of the last two blood pressure readings was used in the analysis. Hypertension was defined as blood pressure ≥140/90 mm Hg or use of antihypertensive medications. Diabetes was defined as fasting glucose ≥126 mg/dL or use of glucose-lowering medications. C-reactive protein (CRP) was measured by immunonephelometry using a BNII nephelometer (N High Sensitivity CRP; Dade Behring, Deerfield, IL, USA). Fibrinogen antigen was measured using the BNII nephelometer (N Antiserum to Human Fibrinogen; Dade Behring). Interleukin-6 (IL-6) was measured using ultrasensitive enzyme-linked immunosorbent assay (Quantikine HS Human IL-6 Immunoassay; R&D Systems, Minneapolis, MN, USA). Glomerular filtration rate was estimated using the creatinine-based Chronic Kidney Disease Epidemiology Collaboration equation (Levey et al., 2009). Serum creatinine was measured by rate reflectance spectrophotometry using thin film adaptation of the creatine amidinohydrolase method on the Vitros analyzer (Johnson & Johnson Clinical Diagnostics, Rochester, NY, USA).

2.5. Statistical analysis

Data analysis was performed using SPSS 25 (IBM, Armonk, NY, USA) and STATA 16.0 (StataCorp, College Station, TX, USA). Data were expressed as mean (standard deviation [SD]) or percentage (number). For variables with a skewed distribution, data were expressed as median (interquartile range) and ln-transformed before analysis.

Cox proportional hazard regression analysis was used to assess the association between baseline Lp(a) and new elevated depressive symptoms since baseline, after adjustment of confounding variables. For each participant who had new elevated depressive symptoms, the time to event (experienced elevated depressive symptoms) was defined as the time interval between the exact date of first baseline visit and the exact date of follow-up exam on which elevated depressive symptoms were ascertained (Ong et al., 2016). For participants who did not develop elevated depressive symptoms, the last follow-up time point would be censored at their last available visit (Ong et al., 2016). The proportional hazards assumption was checked using Schoenfeld residuals; we found violations for age, gender, BMI and ln-transformed CRP in the main analysis. Subsequent exploratory analysis led to inclusion of age-squared in the model, and treating the gender, BMI and ln-transformed CRP associations as time-dependent variables (i.e. their hazards ratio [HR] change as a function

of time). Results from meta-analyses of prospective, population-based studies showed Lp(a) levels >30 mg/dL to be associated with increased risk of CHD and myocardial infarction (MI) and Lp (a) levels >50 mg/dL associated with increased risk of ischemic stroke (Craig et al., 1998; Danesh et al., 2000; Emerging Risk Factors Collaboration et al., 2009; Nave et al., 2015). Therefore, a categorical variable using these cut-offs was also modeled in separate analyses.

Multivariable linear regression analysis using robust standard error estimation was used to assess the association of plasma Lp(a) levels at baseline with change in CES-D score between visits 1 and 5. Participants with elevated depressive symptoms at baseline or self-reported use of anti-depressant medications at both visits 1 and 5 were excluded from the analysis. Data were adjusted for the same confounding variables, except that the use of lipid-lowering medication at visit 1 was replaced by the history of lipid-lowering medication usage at visits 1 and 5. Data were also further adjusted for baseline CES-D score and the number of days between these two visits. No multi-collinearity was detected (variance inflation factors <3.5 in all the analyses).

In the above analyses, the association of ln-transformed Lp(a) levels with new elevated depressive symptoms or change in CES-D score were assessed for nonlinearity using regression splines to model potentially nonlinear relationships. The relationship of ln-transformed Lp(a) levels with measures of interest was allowed to be nonlinear with the assumption of a linear relationship of other confounding variables with the measures of interest. When nonlinearity was detected, the approximate knot position was used to fit regression analyses within strata defined by these thresholds. P for interaction with race/ethnicity was estimated by including the interaction term in the regression models in the full sample after adjustment for the main effects of the covariates. Participants with missing data were excluded from the analysis. A two-tailed $P < 0.05$ was considered statistically significant in all analyses.

3. Results

Among 4938 participants without elevated depressive symptoms at baseline, 1178 participants (23.9%) developed new elevated depressive symptoms since baseline. Compared to participants without new elevated depressive symptoms at follow-up, participants who developed new elevated depressive symptoms were more likely to be younger, female, less educated, current smokers, and not married. Participants with new elevated depressive symptoms were also more likely to have more pack-years of smoking, higher BMI and lower eGFR, but higher HDL cholesterol and lower LDL cholesterol (Table 1).

As shown in Table 1, there were no significant differences in Lp(a) levels and percentage of participants with Lp(a) ≥30 or ≥50 mg/dL between participants with and without new elevated depressive symptoms. As shown in Table 2, the association of higher ln-transformed Lp (a) levels with new elevated depressive symptoms was borderline not significant after adjusting for demographics ($P = 0.06$, model 1), and became significant after adjusting for more confounding factors in the full adjustment model ($P = 0.01$, model 3). When assessing elevated Lp (a) levels as a binary variable (≥30 mg/dL or ≥50 mg/dL),

no significant association with new elevated depressive symptoms was found. No significant interaction with race/ethnicity was found for all the above analyses.

In a separate analysis, we assessed the non-linear association of baseline continuous Lp(a) levels with new elevated depressive symptoms by regression spline. This analysis suggested that the association may be somewhat steeper at lower Lp(a) levels (HR [95% CI] = 1.31 [0.95–1.82] per SD increase in ln-transformed Lp(a) levels, $P = 0.10$), and flatter at higher Lp(a) cholesterol levels (HR [95% CI] = 0.97 [0.87–1.08], $P = 0.57$), with a threshold at approximately 7.6 mg/dL.

As only data on use of anti-depressant medications, but not CES-D score, was available in visit 2, a sensitivity analysis was performed in which data from visit 2 were not used in the definition of new elevated depressive symptoms. In such sensitivity analysis, similar results were obtained in which higher ln-transformed Lp(a) levels, but not elevated Lp(a) levels (≥30 mg/dL or ≥50 mg/dL), were associated significantly with new elevated depressive symptoms. However, when defining elevated depressive symptoms as a CES-D score ≥16 regardless of the use of anti-depressant medications at all visits, baseline Lp(a) levels were not associated with new elevated depressive symptoms (Supplementary Table 2). Similarly, in another sensitivity analysis, where elevated depressive symptoms were defined using alternative cut-off points of CES-D score ≥20 and ≥ 21, no significant associations between baseline Lp(a) levels and new elevated depressive symptoms were found (Supplementary Tables 3 and 4). No significant interaction with race/ethnicity was found for the above analyses.

Of the 4938 MESA participants included in the main analysis, valid data on the difference in CES-D score between visits 1 and 5 were available on 3485 participants without elevated depressive symptoms at baseline and without self-reported use of anti-depressant medications at both visits 1 and 5. Their mean CES-D score increased from 5.1 (SD 4.1) at visit 1 to 6.8 (SD 6.4) at visit 5 with a mean absolute difference of 1.66 (SD 6.32) and a mean relative change of 75.7% (SD 244.0%). As shown in Table 3, baseline ln-transformed Lp(a) levels were not associated with absolute or relative change in CES-D score between visits 1 and 5. No non-linear relationship and race/ethnicity interaction was found. Similar results were found when assessing elevated Lp(a) levels (≥30 or ≥50 mg/dL). As shown in Table 4, a significant interaction was found with race/ethnicity, in which elevated Lp(a) levels tended to be associated with a larger absolute decrease in CES-D score in Chinese Americans although such race/ethnicity interaction was not found when assessing the relative change in CES-D score.

4. Discussion

This is the first prospective study that examined the association between Lp(a) and new elevated depressive symptoms since baseline. We found a significant association of higher ln-transformed Lp(a) levels with new elevated depressive symptoms. However, analysis of change in CES-D score and sensitivity analyses using alternative definitions of elevated depressive symptoms did not find a robust association between baseline Lp(a) and new elevated depressive symptoms.

In addition to psychological factors, biological factors, especially inflammation, are now considered as contributing factors to the development of elevated depressive symptoms. In subjects with hepatitis C infection, injection of the pro-inflammatory cytokine, tumor necrosis factor-α (TNF-α), increased the concentration of neuroactive metabolites in cerebrospinal fluid (CSF), and stimulated depressive symptoms after 12 weeks (Raison et al., 2010). Moreover, a meta-analysis shows that the pro-inflammatory cytokines such as TNF-α significantly higher in individuals with MDD (Dowlati et al., 2010). Besides inflammation, in a depression model which exposed male Wistar rats to mild stress for 7 weeks, there were significant structural changes in plasma phospholipid and plasma peak cholesterol to phospholipid ratio (Depciuch et al., 2017). Further supporting the role of lipid in depression, an animal study demonstrated that LDL receptor knockout mice exhibited depressive symptoms, accompanied by increased activity of monoamine oxidase A, an enzyme involved in the metabolism of serotonin (Engel et al., 2016). These findings suggest that inflammation and dyslipidemia may be implicated in the pathogenesis of depression. Since Lp(a) is known to be pro-atherogenic (Kamstrup et al., 2012), Lp(a) may be a biological agent that mediates the development of depressive symptoms.

Although Lp(a) cannot cross an intact blood brain barrier, it has been found in 30–40% of CSF samples from patients with inflammatory or non-inflammatory causes of blood brain barrier dysfunction (Pepe et al., 2006). In fact, 37.5% of patients with affective disorders, including MDD, demonstrate blood brain barrier dysfunction (Bechter et al., 2010). Moreover, protein expression of the LDL receptor gene family member glycoprotein 330, which can mediate the metabolism of Lp(a) *in vitro*, is found in brain tissues from Lewis rats (Niemeier et al., 1999; Zheng et al., 1994). Besides, α-synuclein, a protein readily found in neurons, is present in Lp(a) plasma fraction in healthy subjects (Emamzadeh and Allsop, 2017). In an animal study using adult female Sprague–Dawley rats, injections of a recombinant virus vector expressing human α-synuclein into the brains provoked depressive behaviour after 3 weeks (Caudal et al., 2015). However, a definitive association between α-synuclein and depression in human studies is lacking. Together, the above results suggest that Lp(a) may cross the blood brain barrier in selected patients with MDD and may interact with neuronal tissues.

Despite the indirect evidence suggesting an association between Lp (a) and MDD, the evidence is limited. Incubation of platelets with physiological levels of Lp(a) *in vitro* significantly reduced release of serotonin (Gries et al., 1996), one of the neurotransmitters implicated in the development of depression. In MDD patients, Lp(a) levels were significantly decreased after 4-weeks of treatment with the selective serotonin reuptake inhibitor, paroxetine, compared to baseline (Paslakis et al., 2011). Nonetheless, depressive symptoms, as assessed by Hamilton Depression Rating Scale, did not show significant changes at 4 weeks post-treatment, and were not associated with plasma Lp(a) levels. However, the results of this study were limited by the short duration of treatment, with improvement in depressive symptoms taking up to 6 weeks (Santarsieri and Schwartz, 2015).

Although a significant association of higher ln-transformed Lp(a) levels with new elevated depressive symptoms was found in the full regression model in our study, sensitivity

analyses using alternative definitions of elevated depressive symptoms did not find an association between baseline Lp(a) and new elevated depressive symptoms. There are several potential explanations for the lack of association. First, Lp(a) is highly heterogeneous in structure with >30 isoforms and controversies remain in standardizing its measurement (van der Hoek et al., 1993). It is possible that the Lp(a) isoform size may be more important than the Lp(a) levels in the development of MDD. Proteomic analysis of Lp(a) has also revealed >35 different proteins involved in different processes of coagulation, complement activation and inflammatory response (von Zychlinski et al., 2011). This suggests different protein composition and dynamics of some Lp(a)-associated proteins may influence the function of Lp(a) and the measurement of Lp(a)-associated protein may be needed to elucidate the associations of different Lp(a) sub-population with MDD. Similar to our study, consistent negative findings have been reported in other cross-sectional studies. For example, there is no difference in plasma Lp(a) levels between participants with depressive symptoms for <3 years and ≥3 years (Peng and Li, 2017), and between participants with and without elevated depressive symptoms among young patients with diabetes (Hood et al., 2012) and healthy young people (Doulalas et al., 2006). Compared to these previous studies, our study has further extended the results in an ethnically diverse population aged 45–84 years, free of apparent cardiovascular disease at baseline. The present study has the advantages of using data from a longitudinal study with good quality control, and a large cohort of well-characterized participants. The long follow-up period and a large sample size are other strengths of our study.

However, the present study has a few limitations. First, since blood brain barrier is dysfunctional only in some MDD patients, CSF samples may be superior to plasma samples in predicting new elevated depressive symptoms. Second, as MDD can be a self-limiting disease, the infrequent measurement of depressive symptoms in the MESA study might not have captured participants who had recovered from a major depressive episode. Also, it is unclear whether plasma Lp(a) levels can predict the development of MDD. The lack of data on psychiatric history of the MESA participants is another study limitation. Since CES-D is a subjective self-reported screening tool of depression, the use of the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, which is the gold standard for assessing and diagnosing mental health disorders, in future studies to diagnose MDD will be of clinical importance and relevance, with less bias (American Psychiatric Association, 2013). However, CES-D is a widely validated and easily administered instrument for screening MDD (Vilagut et al., 2016). Moreover, all MESA participants were aged 45–84 years at baseline, which is a limitation because MDD is more prevalent in younger adults (Hasin et al., 2018). Lastly, in our analysis, participants who reported the use of anti-depressant medications were defined as having elevated depressive symptoms. However, it is possible that participants took anti-depressant medications for non-mental health purposes, leading to the apparently higher rate of new elevated depressive symptoms. Moreover, some medications such as neuroleptics and sleeping pills may also affect depressive symptoms.

5. Conclusion

In conclusion, our study suggested a potential association between Lp(a) level and elevated depressive symptoms since baseline, but such association was not robust in different

sensitivity analyses. Although the literature suggests a potential relationship between baseline Lp(a) levels and development of depression, further studies are warranted to investigate the role of Lp(a) in depressive symptoms.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

Kwok Leung Ong was supported by the Australian National Health and Medical Research Council Career Development Fellowship (1122854). The MESA study was supported by contracts 75N92020D00001, HHSN268201500003I, N01-HC-95159, 75N92020D00005, N01-HC-95160, 75N92020D00002, N01-HC-95161, 75N92020D00003, N01-HC-95162, 75N92020D00006, N01-HC-95163, 75N92020D00004, N01-HC-95164, 75N92020D00007, N01-HC-95165, N01-HC-95166, N01-HC-95167, N01-HC-95168 and N01-HC-95169 from the National Heart, Lung, and Blood Institute, and by grants UL1-TR-000040, UL1-TR-001079, and UL1-TR-001420 from the National Center for Advancing Translational Sciences (NCATS).

The authors thank the other investigators, the staff, and the participants of the MESA study for their valuable contributions. A full list of participating MESA investigators and institutions can be found at http://www.mesa-nhlbi.org.

References

Abe A, Yoshimura Y, Sekine T, Maeda S, Yamashita S, Noma A, 1994. Fully mechanized latex immunoassay for serum lipoprotein (a). Clin. Chim. Acta 225 (2), 105–113. [PubMed: 8088000]

American Psychiatric Association, 2013. Diagnostic and Statistical Manual of Mental Disorders (DSM-5®), fifth ed. American Psychiatric Association, Arlington, Virginia.

Banerjee D, Wong EC, Shin J, Fortmann SP, Palaniappan L, 2011. Racial and ethnic variation in lipoprotein (a) levels among asian Indian and Chinese patients. J. Lipids 2011, 291954. [PubMed: 21660301]

Bechter K, Reiber H, Herzog S, Fuchs D, Tumani H, Maxeiner HG, 2010. Cerebrospinal fluid analysis in affective and schizophrenic spectrum disorders: identification of subgroups with immune responses and blood–CSF barrier dysfunction. J. Psychiatr. Res 44 (5), 321–330. [PubMed: 19796773]

Beekman AT, Deeg DJ, Van Limbeek J, Braam AW, De Vries MZ, Van Tilburg W, 1997. Criterion validity of the Center for Epidemiologic Studies Depression scale (CES-D): results from a community-based sample of older subjects in The Netherlands. Psychol. Med 27 (1), 231–235. [PubMed: 9122304]

Bild DE, Bluemke DA, Burke GL, Detrano R, Diez Roux AV, Folsom AR, Greenland P, JacobsJr DR, Kronmal R, Liu K, Nelson JC, O'Leary D, Saad MF, Shea S, Szklo M, Tracy RP, 2002. Multi-ethnic study of atherosclerosis: objectives and design. Am. J. Epidemiol 156 (9), 871–881. [PubMed: 12397006]

Caudal D, Alvarsson A, Björklund A, Svenningsson P, 2015. Depressive-like phenotype induced by AAV-mediated overexpression of human α-synuclein in midbrain dopaminergic neurons. Exp. Neurol 273, 243–252. [PubMed: 26363495]

Craig WY, Neveux LM, Palomaki GE, Cleveland MM, Haddow JE, 1998. Lipoprotein (a) as a risk factor for ischemic heart disease: metaanalysis of prospective studies. Clin. Chem 44 (11), 2301–2306. [PubMed: 9799757]

Danesh J, Collins R, Peto R, 2000. Lipoprotein (a) and coronary heart disease: meta-analysis of prospective studies. Circulation 102 (10), 1082–1085. [PubMed: 10973834]

Depciuch J, Sowa-Kucma M, Nowak G, Papp M, Gruca P, Misztak P, Parlinska-Wojtan M, 2017. Qualitative and quantitative changes in phospholipids and proteins investigated by spectroscopic techniques in animal depression model. Spectrochim. Acta Mol. Biomol. Spectrosc 176, 30–37.

Doulalas AD, Rallidis LS, Gialernios T, Moschonas DN, Kougioulis MN, Rizos I, Tselegaridis TS, Kremastinos DT, 2006. Association of depressive symptoms with coagulation factors in young healthy individuals. Atherosclerosis 186 (1), 121–125. [PubMed: 16076469]

Dowlati Y, Herrmann N, Swardfager W, Liu H, Sham L, Reim EK, Lanctôt KL, 2010. A meta-analysis of cytokines in major depression. Biol. Psychiatr 67 (5), 446–457.

Emamzadeh FN, Allsop D, 2017. α-Synuclein interacts with lipoproteins in plasma. J. Mol. Neurosci 63 (2), 165–172. [PubMed: 28887769]

Emanuele E, Carlin MV, D'Angelo A, Peros E, Barale F, Geroldi D, Politi P, 2006. Elevated plasma levels of lipoprotein (a) in psychiatric patients: a possible contribution to increased vascular risk. Eur. Psychiatr 21 (2), 129–133.

Emerging Risk Factors Collaboration, Erqou S, Kaptoge S, Perry PL, Di Angelantonio E, Thompson A, White IR, Marcovina SM, Collins R, Thompson SG, Danesh J, 2009. Lipoprotein (a) concentration and the risk of coronary heart disease, stroke, and nonvascular mortality. J. Am. Med. Assoc 302 (4), 412–423.

Engel DF, de Oliveira J, Lopes JB, Santos DB, Moreira ELG, Farina M, Rodrigues ALS, de Souza Brocardo P, de Bem AF, 2016. Is there an association between hypercholesterolemia and depression? Behavioral evidence from the LDLr −/− mouse experimental model. Behav. Brain Res 311, 31–38. [PubMed: 27185735]

Golden SH, Lazo M, Carnethon M, Bertoni AG, Schreiner PJ, Roux AV, Lee HB, Lyketsos C, 2008. Examining a bidirectional association between depressive symptoms and diabetes. J. Am. Med. Assoc 299 (23), 2751–2759.

Gries A, Gries M, Wurm H, Kenner T, Ijsseldijk M, Sixma JJ, Kostner GM, 1996. Lipoprotein (a) inhibits collagen-induced aggregation of thrombocytes. Arterioscler. Thromb. Vasc. Biol 16 (5), 648–655. [PubMed: 8963722]

Hamidifard S, Fakhari A, Mahboob S, Gargari BP, 2009. Plasma levels of lipoprotein (a) in patients with major depressive disorders. Psychiatr. Res 169 (3), 253–256.

Hasin DS, Sarvet AL, Meyers JL, Saha TD, Ruan WJ, Stohl M, Grant BF, 2018. Epidemiology of adult DSM-5 major depressive disorder and its specifiers in the United States. JAMA Psychiatry 75 (4), 336–346. [PubMed: 29450462]

Hood KK, Lawrence JM, Anderson A, Bell R, Dabelea D, Daniels S, Rodriguez B, Dolan LM, Search for Diabetes in Youth Study Group, 2012. Metabolic and inflammatory links to depression in youth with diabetes. Diabetes Care 35 (12), 2443–2446. [PubMed: 23033243]

Kamstrup PR, Tybjærg-Hansen A, Nordestgaard BG, 2012. Genetic evidence that lipoprotein (a) associates with atherosclerotic stenosis rather than venous thrombosis. Arterioscler. Thromb. Vasc. Biol 32 (7), 1732–1741. [PubMed: 22516069]

Lett HS, Blumenthal JA, Babyak MA, Sherwood A, Strauman T, Robins C, Newman MF, 2004. Depression as a risk factor for coronary artery disease: evidence, mechanisms, and treatment. Psychosom. Med 66 (3), 305–315. [PubMed: 15184688]

Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro AF, Feldman HI, Kusek JW, Eggers P, Van Lente F, Greene T, Coresh J, Ckd-Epi (Chronic Kidney Disease Epidemiology Collaboration), 2009. A new equation to estimate glomerular filtration rate. Ann. Intern. Med 150 (9), 604–612. [PubMed: 19414839]

Marcovina SM, Albers JJ, Scanu AM, Kennedy H, Giaculli F, Berg K, Couderc R, Dati F, Rifai N, Sakurabayashi I, Tate JR, Steinmetz A, 2000. Use of a reference material proposed by the International Federation of Clinical Chemistry and Laboratory Medicine to evaluate analytical methods for the determination of plasma lipoprotein (a). Clin. Chem 46 (12), 1956–1967. [PubMed: 11106328]

Nave AH, Lange KS, Leonards CO, Siegerink B, Doehner W, Landmesser U, Steinhagen-Thiessen E, Endres M, Ebinger M, 2015. Lipoprotein (a) as a risk factor for ischemic stroke: a meta-analysis. Atherosclerosis 242 (2), 496–503. [PubMed: 26298741]

Niemeier A, Willnow T, Dieplinger H, Jacobsen C, Meyer N, Hilpert J, Beisiegel U, 1999. Identification of megalin/gp330 as a receptor for lipoprotein (a) in vitro. Arterioscler. Thromb. Vasc. Biol 19 (3), 552–561. [PubMed: 10073957]

Ong KL, Morris MJ, McClelland RL, Maniam J, Allison MA, Rye KA, 2016. Lipids, lipoprotein distribution and depressive symptoms: the multi-ethnic study of atherosclerosis. Transl. Psychiatry 6 (11), e962. [PubMed: 27898070]

Paslakis G, Kopf D, Westphal S, Gilles M, Lederbogen F, Hamann B, Heuser I, Deuschle M, 2011. Treatment with paroxetine, but not amitriptyline, lowers levels of lipoprotein (a) in patients with major depression. J. Psychopharmacol 25 (10), 1344–1346. [PubMed: 20952454]

Peng R, Li Y, 2017. Low serum thyroid-stimulating hormone levels are associated with lipid profile in depressive patients with long symptom duration. J. Affect. Disord 217, 99–104. [PubMed: 28395210]

Pepe G, Chimienti G, Liuzzi GM, Lamanuzzi BL, Nardulli M, Lolli F, Angĺés-Cano E, Mata S, 2006. Lipoprotein (a) in the cerebrospinal fluid of neurological patients with blood–cerebrospinal fluid barrier dysfunction. Clin. Chem 52 (11), 2043–2048. [PubMed: 16990412]

Puri R, Ballantyne CM, Hoogeveen RC, Shao M, Barter P, Libby P, Chapman MJ, Erbel R, Arsenault BJ, Raichlen JS, Nissen SE, Nicholls SJ, 2017. Lipoprotein (a) and coronary atheroma progression rates during long-term high-intensity statin therapy: insights from SATURN. Atherosclerosis 263, 137–144. [PubMed: 28641153]

Radloff LS, 1977. The CES-D scale: a self-report depression scale for research in the general population. Appl. Psychol. Meas 1 (3), 385–401.

Raison CL, Dantzer R, Kelley KW, Lawson MA, Woolwine BJ, Vogt G, Spivey JR, Saito K, Miller AH, 2010. CSF concentrations of brain tryptophan and kynurenines during immune stimulation with IFN-α: relationship to CNS immune responses and depression. Mol. Psychiatr 15 (4), 393–403.

Remigio-Baker RA, Allison MA, Schreiner PJ, Szklo M, Crum RM, Leoutsakos JM, Franco M, Carnethon MR, Nettleton JA, Mujahid MS, Diez Roux AV, Jensky N, Golden SH, 2014. Difference by sex but not by race/ethnicity in the visceral adipose tissue-depressive symptoms association: the Multi-Ethnic Study of Atherosclerosis. Psychoneuroendocrinology 47, 78–87. [PubMed: 25001957]

Santarsieri D, Schwartz TL, 2015. Antidepressant efficacy and side-effect burden: a quick guide for clinicians. Drugs Context 4, 212290. [PubMed: 26576188]

Sarandol A, Sarandol E, Eker SS, Karaagac EU, Hizli BZ, Dirican M, Kirli S, 2006. Oxidation of apolipoprotein B-containing lipoproteins and serum paraoxonase/arylesterase activities in major depressive disorder. Prog. Neuro-Psychopharmacol. Biol. Psychiatry 30 (6), 1103–1108.

van der Hoek YY, Wittekoek ME, Beisiegel U, Kastelein JJ, Koschinsky M, 1993. The apolipoprotein (a) kringle IV repeats which differ from the major repeat kringle are present in variably-sized isoforms. Hum. Mol. Genet 2 (4), 361–366. [PubMed: 8389224]

Vilagut G, Forero CG, Barbaglia G, Alonso J, 2016. Screening for depression in the general population with the Center for Epidemiologic Studies Depression (CES-D): a systematic review with meta-analysis. PloS One 11 (5), e0155431. [PubMed: 27182821]

von Zychlinski A, Kleffmann T, Williams MJ, McCormick SP, 2011. Proteomics of Lipoprotein (a) identifies a protein complement associated with response to wounding. J. Proteomics 74 (12), 2881–2891. [PubMed: 21802535]

Zheng G, Bachinsky D, Stamenkovic I, Strickland D, Brown D, Andres G, McCluskey R, 1994. Organ distribution in rats of two members of the low-density lipoprotein receptor gene family, gp330 and LRP/alpha 2MR, and the receptor-associated protein (RAP). J. Histochem. Cytochem 42 (4), 531–542. [PubMed: 7510321]

Zich JM, Attkisson CC, Greenfield TK, 1990. Screening for depression in primary care clinics: the CES-D and the BDI. Int. J. Psychiatr. Med 20 (3), 259–277.

Table 1

Baseline clinical characteristics of participants with and without new elevated depressive symptoms developed during follow-up.

Characteristics	n	Non-case	Case	*P*
n	4938	3760	1178	
Age, years	4938	62.2 (10.0)	61.2 (10.3)	0.003
Women, %	4938	46.3 (1739)	58.2 (686)	<0.001
Race/ethnicity, %	4938			<0.001
Caucasian	1927	38.3 (1440)	41.3 (487)	
African American	1380	29.1 (1094)	24.3 (286)	
Hispanic American	993	18.9 (711)	23.9 (282)	
Chinese American	638	13.7 (515)	10.4 (123)	
Education, %	4933			<0.001
<High school	768	14.4 (540)	19.4 (228)	
High school	2056	41.0 (1541)	43.8 (515)	
>High school	2109	44.6 (1675)	36.9 (434)	
Smoking, %	4887			<0.001
Never	2514	51.8 (1946)	48.3 (568)	
Former	1831	37.3 (1400)	36.6 (431)	
Current	589	10.9 (411)	15.1 (178)	
Pack-years of smoking	4934	10.3 (19.5)	12.2 (23.1)	0.010
Current alcohol use, %	4915	57.5 (2150)	57.4 (674)	0.97
Total gross family income	4767			<0.001
<$30 000	1599	31.9 (1155)	38.9 (444)	
$30 000- $74 999	1948	41.1 (1491)	40.1 (457)	
≥$75 000	1220	27.0 (980)	21.0 (240)	
Marital status, %	4898			<0.001
Married	3169	66.1 (2469)	60.1 (700)	
Widowed/divorced/separated	1346	26.6 (993)	30.3 (353)	
Single	383	7.3 (271)	9.6 (112)	
Physical activity, MET-hours/weeks	3946	98.4 (98.9)	97.3 (95.9)	0.74
BMI, kg/m^2	4938	28.1 (5.19)	28.5 (5.61)	0.017
Heart rate, beats per minute	4903	62.7 (9.4)	63.2 (9.6)	0.08
Diabetes, %	4934	11.0 (413)	12.0 (141)	0.36
Hypertension, %	4938	42.9 (1612)	44.8 (52.8)	0.24
Self-reported cancer, %	4930	8.0 (299)	6.9 (81)	0.23
Any lipid-lowering medication, %	4938	15.8 (594)	16.1 (190)	0.79
CRP, mg/L[a]	4919	1.83 (1.76–1.90)	1.87 (1.75–2.00)	0.57
Fibrinogen, mg/dL	4925	344 (72)	344 (73)	0.90
IL-6, pg/mL[a]	4828	1.20 (1.18.–1.23)	1.16 (1.12–1.21)	0.14
eGFR, mL/min/1.73 m^2	4934	77.4 (15.8)	79.0 (16.0)	0.002
Total cholesterol, mg/dL	4934	193.8 (34.6)	193.6 (36.9)	0.89

Characteristics	n	Non-case	Case	*P*
LDL cholesterol, mg/dL	4875	118.2 (30.9)	115.7 (30.7)	0.016
HDL cholesterol, mg/dL	4931	50.3 (14.6)	51.6 (14.9)	0.005
Triglycerides, mg/dL[a]	4934	111 (109–113)	113 (110–117)	0.33
Lp(a), mg/dL[a]	4938	16.7 (16.1–17.3)	17.3 (16.2–18.4)	0.35
Lp(a) ≥30 mg/dL	4938	33.2 (1249)	32.4 (382)	0.61
Lp(a) ≥50 mg/dL	4938	20.1 (755)	19.7 (232)	0.77

Data are expressed as mean (SD), percent (n), or geometric mean (95% confidence interval), where appropriate. *P* values were estimated by *t*-test for continuous variables and chi-square test for categorical variables respectively.

[a]Data were ln-transformed before analysis.

Table 2

Cox regression analysis on the associations of baseline Lp(a) levels with new elevated depressive symptoms (n = 4938).

Lp(a)	Case, % (n)	Model 1		Model 2		Model 3	
		HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*
ln Lp(a) (per SD increase)	23.9 (1178)	1.06 (1.00–1.13)	0.061	1.07 (1.00–1.14)	0.041	1.09 (1.02–1.16)	0.013
Lp(a) ≥30 mg/dL							
No	24.1 (796)	1.00 (referent)	–	1.00 (referent)	–	1.00 (referent)	–
Yes	23.4 (382)	1.01 (0.89–1.15)	0.91	1.00 (0.87–1.14)	0.95	1.02 (0.89–1.17)	0.80
Lp(a) ≥50 mg/dL							
No	23.9 (946)	1.00 (referent)	–	1.00 (referent)	–	1.00 (referent)	–
Yes	23.5 (232)	1.02 (0.88–1.18)	0.82	1.02 (0.87–1.20)	0.78	1.06 (0.90–1.24)	0.51

For continuous Lp(a) levels, data was expressed in terms of per SD (1.136) increase in ln-transformed mg/dL unit.

Model 1: Adjusted for age, age squared, sex (as both time-independent and -dependent variables), and race/ethnicity.

Model 2: Further adjusted for education, marital status, smoking, pack-years of smoking, current alcohol use, total gross family income, physical activity, use of any lipid-lowering medication (yes or no), BMI (as both time-independent and -dependent variables), heart rate, diabetes, hypertension, cancer, eGFR, ln-transformed CRP (as both time-independent and -dependent variables), fibrinogen, and ln-transformed IL-6.

Model 3: Further adjusted for HDL cholesterol, LDL cholesterol and ln-transformed triglycerides.

Table 3

Multivariable linear regression analysis on the associations of baseline ln-transformed Lp(a) levels with absolute change in CES-D score between visits 1 and 5 (n = 3485).

Model	ln Lp(a) (per SD increase)		Lp(a) ≥30 mg/dL		Lp(a) ≥50 mg/dL	
	B (95% CI)	*P*	B (95% CI)	*P*	B (95% CI)	*P*
Absolute change (n = 3485)						
1	−0.022 (−0.246, 0.203)	0.85	−0.175 (−0.654, 0.304)	0.47	−0.372 (−0.913, 0.169)	0.18
2	−0.024 (−0.262, 0.215)	0.85	−0.185 (−0.697, 0.326)	0.48	−0.318 (−0.896, 0.260)	0.28
3	0.106 (−0.137, 0.348)	0.39	−0.016 (−0.537, 0.506)	0.95	−0.105 (−0.688, 0.477)	0.72
4	0.145 (−0.084, 0.373)	0.21	0.042 (−0.457, 0.541)	0.87	−0.100 (−0.656, 0.455)	0.72
Relative % change (n = 3019)[a]						
1	−2.6 (−12.8, 7.5)	0.61	−12.9 (−31.5, 5.7)	0.17	−7.0 (−29.6, 15.5)	0.54
2	−2.1 (−13.0, 8.7)	0.70	−12.7 (−32.9, 7.5)	0.22	−5.2 (−30.2, 19.7)	0.68
3	3.2 (−6.8, 13.2)	0.53	−6.5 (−26.6, 13.5)	0.52	1.3 (−23.9, 26.5)	0.92
4	3.7 (−5.6, 13.1)	0.43	−5.6 (−24.4, 13.2)	0.56	3.7 (−20.0, 27.5)	0.76

Regression coefficient (B) were expressed as change in CES-D score per one SD (1.135 for absolute change analysis and 1.128 or relative percentage change analysis) increase in ln-transformed Lp(a) levels (mg/dL) in multivariable linear regression with absolute change in CES-D score as the dependent variable.

Model 1: Adjusted for age, sex, and race/ethnicity.

Model 2: Further adjusted for education, marital status, smoking, pack-years of smoking, current alcohol use, total gross family income, physical activity, history of lipid-lowering medication usage at visits 1 and 5 (“no use at both visits”, “use at visit 1, but no use at visit 5”, “no use at visit 1, but use at visit 5” and “use at both visits”), BMI, heart rate, diabetes, hypertension, cancer, eGFR, ln-transformed CRP, fibrinogen, and ln-transformed IL-6.

Model 3: Further adjusted for HDL cholesterol, LDL cholesterol and ln-transformed triglycerides.

Model 4: Further adjusted for baseline CES-D score and the number of days between these two visits.

[a]466 participants with a CES-D score of zero at baseline were excluded from the analysis of relative change.

Table 4

Linear regression analysis on the associations of elevated Lp(a) levels at baseline with absolute change in CES-D score between visits 1 and 5 by race/ethnicity (n = 3485).

Race/ethnicity	n	Lp(a) ≥30 mg/dL		Lp(a) ≥50 mg/dL	
		B (95% CI)	*P*	B (95% CI)	*P*
Caucasian	1347	0.774 (0.024, 1.524)	0.043	0.408 (−0.464, 1.281)	0.359
African American	974	−0.487 (−1.331, 0.358)	0.259	−0.474 (−1.334, 0.386)	0.280
Hispanic American	699	0.362 (−0.961, 1.685)	0.591	0.696 (−0.993, 2.385)	0.419
Chinese American	465	−1.392 (−2.821, 0.036)	0.056	−2.091 (−3.744, −0.438)	0.013
P for interaction			0.0095		0.032

All data were adjusted for age, sex, race/ethnicity, education, marital status, smoking, pack-years of smoking, current alcohol use, total gross family income, physical activity, BMI, heart rate, diabetes, hypertension, cancer, eGFR, ln-transformed CRP, fibrinogen, ln-transformed IL-6, HDL cholesterol, LDL cholesterol, ln-transformed triglycerides, and CES-D score at baseline, history of lipid-lowering medication usage at visits 1 and 5 (“no use at both visits”, “use at visit 1, but no use at visit 5”, “no use at visit 1, but use at visit 5” and “use at both visits”), and the number of days between these two visits.