Journal of Affective Disorders 206 (2016) 55–67

Contents lists available at ScienceDirect

Journal of Affective Disorders

journal homepage: www.elsevier.com/locate/jad

Review article

Depression and serum low-density lipoprotein: A systematic review and meta-analysis

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ARTICLE INFO

Article history:
Received 30 March 2016
Received in revised form
26 June 2016
Accepted 16 July 2016
Available online 19 July 2016

Keywords:
Depression
Low-density lipoprotein
Meta-analysis
Lipids
Cholesterol

ABSTRACT

Background: A cross-sectional association between depression and serum low-density lipoprotein (LDL) has been noted in the literature. This study aims to employ meta-analytic techniques to clarify the relationship between depression and serum LDL.
Methods: Published articles through April 2015 were identified through systematic query of PubMed with follow-up manual searches. Data from 36 studies reporting mean difference and 7 studies reporting odds ratios were analyzed separately.
Results: Meta-analysis of studies modeling serum LDL as a continuous measure demonstrates overall significantly lower serum LDL in depression (Mean difference = −4.29, 95% CI = −8.19, −0.40, $p = 0.03$). Meta-analysis of studies modeling serum LDL as a categorical measure demonstrates a marginally significant lower odds of depression in the presence of low serum LDL relative to high serum LDL (OR = 0.90, 95% CI = 0.80, 1.01, $p = 0.08$).
Limitations: High heterogeneity was noted across sampled studies, which may be a function of variations in study design, participants sampled, or other factors. The potential for publication bias was also assessed.
Conclusions: This meta-analysis demonstrates a cross-sectional link between depression and low serum LDL.

Contents

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http://dx.doi.org/10.1016/j.jad.2016.07.033
0165-0327/

1. Introduction

In Engelberg's (1992) paper, "Low Serum Cholesterol and Suicide," it is posited that cholesterol depletion leads to suicidality by way of serotonin-mediated mood alterations. A cross-sectional association between depression and low serum low density lipoprotein (LDL) has been noted in the literature. It has been speculated that this interplay between depression and LDL in the peripheral body system may be reflective of this aforementioned cholesterol depletion within the central nervous system. The blood-brain barrier segregates brain and body cholesterol into two distinct pools; in the body, LDL transports cholesterol to the cell membrane, whereas in the brain cholesterol is synthesized on-site (Orth and Bellosta, 2012). As such, it may be the case that the relationship between depression and low LDL in the periphery is indicative of a link between cholesterol depletion in the brain by way of a common upstream process. A study by Freemantle et al. (2013) found evidence suggesting that psychopathology may occur subsequent to elevated cholesterol turnover in the brain, which in turn may be associated with cholesterol depletion at the cell membrane. Similarly, Beasley et al. (2005) found evidence suggesting that the mechanism guiding the relationship between low cholesterol and depression pathogenesis may, at least in part, involve cholesterol-mediated alterations in nerve terminal structure and function. Additionally, Pucadyil and Chattopadhyay (2005) found evidence that cholesterol depletion impairs the ligand-binding function of the 5-HT_{1A} receptor, which they later determined to be due to organizational changes in cholesterol-depleted membrane (Pucadyil and Chattopadhyay, 2007). The importance of membrane cholesterol in proper functioning has also been demonstrated in the serotonin receptor subclasses 5-HT_{2A} (Voldstedlund et al., 2002; Montano et al., 2009) and 5-HT_7 (Sjogren and Svenningsson, 2007a, 2007b). Together, these studies suggest that one potential mechanism guiding depression pathogenesis may involve cholesterol depletion-mediated alterations in central nerve terminal structure and function that in turn influence receptor responsiveness to serotonin.

While a number of cross-sectional studies present evidence suggesting an inverse association between serum LDL and depression, conflicting findings do exist. Meta-analytic studies are an indispensable tool for bringing clarity to a disparate body of literature; however, to date there has been only one meta-analysis conducted to examine the relationship between depression and serum LDL. In 2008, Shin et al. conducted a meta-analysis of 11 observational studies (Larsson et al., 1994; Olusi and Fido, 1996; Reis et al., 2001; Buyukozturk et al., 2001; Aijanseppa, Kivinen et al., 2002; Troisi et al., 2003; Uguz et al., 2004; Huang and Chen, 2004; Buljan et al., 2004; Keltikangas-Jarvinen et al., 2006; Roy and Roy, 2006) to evaluate the association between depression and serum LDL and determined there to be a non-significant inverse association (d $= -0.17$, 95% CI $= -0.44$, 0.10) (Shin et al., 2008). The meta-analysis conducted by Shin et al. included studies published through 2006; subsequent to 2006, there have been 23 additional studies conducted to examine the association between depression and serum LDL. This current study aimed to provide a more current meta-analysis on the relationship between depression and serum LDL in light of the growing body of literature.

2. Methods

Although this study aims to build upon the work of Shin et al. by providing a more recent meta-analysis on the association between LDL and depression, it is not intended to be an update of their 2008 manuscript and as such does not follow the selfsame meta-analytic approach. This study used PRISMA guidelines to conduct a systematic review and meta-analysis on the relationship between depression and serum LDL (Liberati et al., 2009). Papers meeting the following criteria were included:

1. Observational study using human subjects: Review articles, invited commentary, clinical trials, and animal studies were excluded from analysis.
2. Includes a standard measure of serum LDL: Serum LDL was included regardless of whether it was measured via direct assay or estimated via the Friedewald formula, and regardless of whether it was presented in milligrams per deciliter, grams per liter, or millimoles per liter. For the purpose of analysis, all serum LDL values reported in millimoles per liter were converted to milligrams per deciliter.
3. Includes a standard measure of depression: To maximize the number of eligible studies, depression was broadly defined to include the occurrence of depressive symptoms whether or not they occur as a component of major depressive disorder or another mood disorder, such as schizoaffective disorder or bipolar disorder. Depression assessment was not limited to one specific assessment instrument, and included self-assessment, clinician-administered scales, and clinical diagnosis.

Studies assessing depression scale scores as a continuous variable were not considered eligible for inclusion, as the purpose of this analysis was to evaluate the relationship between serum LDL levels and depression status, rather than depressive symptom burden or severity of depressive symptoms, as would be addressed by a continuous measure. For these studies, corresponding authors were contacted and requested to provide sufficient supplemental information to allow for calculation of mean serum LDL levels by depression status, dichotomizing continuous depression scale scores based on cutpoints previously established in the literature for the assessment instrument used in the study. Of the fourteen corresponding authors approached for additional data, three messages were returned as undeliverable due to outdated contact information, two authors declined participation, four accepted and responded with additional data, and no response was received from the remaining five. The four studies for which the additional requested data was provided were included in meta-analysis.

To identify studies, a systematic search of the literature was conducted through a database search of PubMed for articles published through April 2015, using the search terms 'LDL AND Depression,' 'LDL AND Mood,' 'Cholesterol AND Depression,' and 'Serum lipid AND Depression.' The database search was supplemented by hand-search of relevant papers for additional citations. Titles and abstracts of papers retrieved through this initial search were screened to identify potentially relevant studies. Of those identified as potentially-relevant, full text articles were next screened for inclusion in the meta-analysis. A summary of the study selection process can be seen in Fig. 1.

Through systematic review, 42 studies were identified for inclusion in the meta-analysis and data extraction was undertaken for these studies (Table 1). Meta-analysis was conducted using RevMan version 5.3. For studies modeling serum LDL as a continuous measure, a random effects model was used to calculate mean difference and 95% confidence interval. For studies modeling serum LDL as a categorical measure, a random effects model was used to combine study-specific odds ratios to calculate the pooled odds ratio and 95% confidence interval. Results are reported as text and presented visually via Forest plot.

3. Results

The 42 studies identified as eligible for inclusion in this