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Depression and Serum Low-Density Lipoprotein: A Systematic Review and Meta-analysis

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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.

Keywords

Depression; Low-density lipoprotein; Meta-analysis; Lipids; Cholesterol

Introduction

In Hyman 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

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(Engelberg 1992). 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. 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 (Freemantle, Chen et al. 2013). Similarly, Beasley et al. 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 (Beasley, Honer et al. 2005). Similarly, Pucadyil and Chattopadhyay found evidence that cholesterol depletion impairs the ligand-binding function of the 5-HT_{1A} receptor (Pucadyil and Chattopadhyay 2005), 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} (Dreja, Voldstedlund et al. 2002, Sommer, Montano et al. 2009) and 5-HT_7 (Sjogren and Svenningsson 2007, Sjogren and Svenningsson 2007). 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 (Lindberg, Larsson et al. 1994, Olusi and Fido 1996, Rutledge, Reis et al. 2001, Sevincok, Buyukozturk et al. 2001, Aijanseppa, Kivinen et al. 2002, Pozzi, Troisi et al. 2003, Ergun, Uguz et al. 2004, Huang and Chen 2004, Karlovic, Buljan et al. 2004, Elovainio, 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, Suls 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.

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 (Moher, 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 Figure 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.

Results

The 42 studies identified as eligible for inclusion in this systematic review and meta-analysis employed a variety of reporting methods; for this reason, a series of meta-analyses were conducted, dividing between studies that modeled serum LDL as a continuous measure and those that modeled serum LDL as a categorical measure.

Meta-analysis of Studies Modeling Serum LDL as a Continuous Measure

A total of 36 eligible studies modeled serum LDL as a continuous measure. Of these, 32 studies reported the mean and standard deviation by depression status. An additional three studies reported the mean and 95% confidence interval and one study reported the mean and standard error, from which standard deviations were hand-calculated. Meta-analysis for these 36 studies reporting mean and standard deviation by depression status can be seen in Figure 2. Meta-analysis of studies modeling serum LDL as a continuous measure demonstrates overall significantly lower serum LDL in depression (Mean difference=−4.29 mg/dL, 95% CI=−8.19, −0.40, p=0.03).

Heterogeneity—High heterogeneity was found with respect to studies modeling serum LDL as a continuous measure (I^2 = 95%). To address the possibility that high heterogeneity might be explained by variations in study design, sub-analyses were conducted to distinguish between case-control and cohort studies, and between prevalent and incident depression. The results of these analyses can be seen in Figures 3–6.

Sub-analyses to Address Moderation by Study Design: Sub-analyses were conducted to examine whether heterogeneity might be explained by variations in study design, participant characteristics, or depression assessment method and whether these variations may also influence the overall effect estimate for the association between LDL and depression. The first such analysis distinguishes between case-control studies and cohort studies (Figures 3 & 4). While case-control studies continued to demonstrate high heterogeneity (I^2=96%), a marked decrease in heterogeneity was seen in meta-analysis of cohort studies (I^2=69%). Both cohort studies (Mean difference=−3.15 mg/dL, 95% CI=−6.05, −0.24, p<0.001) and case-control studies (Mean difference=−9.39 mg/dL, 95% CI=−16.41, −2.37, p<0.001) continued to demonstrate an overall significantly lower mean LDL in depression, with case-control studies demonstrating a more marked overall difference.

The next analysis distiniguishes between studies reporting prevalent depression and studies reporting incident depression (Figures 5 & 6). Heterogeneity showed a marked decrease for both studies reporting prevalent depression (I^2=66%) and studies reporting incident depression (I^2=77%). Both prevalent depression studies (Mean difference: −1.69 mg/dL, 95% CI=−5.28, 1.90, p<0.001) and incident depression studies (Mean difference=−7.21

mg/dL, 95% CI=−14.20, −0.21, p<0.001) continued to demonstrate an overall significantly lower mean LDL in depression, with incident depression studies demonstrating a more marked overall difference.

The next analysis distinguishes between studies reporting clinical diagnosis of depression and those that utilized self-assessment instruments (Figures 7 & 8). Heterogeneity remained high for studies that assessed depression via clinical diagnosis (I^2=96%) and for studies that assessed depression via self-assessment instrument (I^2=91%). Studies that measured depression via clinical diagnosis continued to demonstrate an overall significantly lower mean LDL in depression (Mean difference= −10.98 mg/dL, 95% CI=−18.20, −3.76, p=0.003), but this effect was not seen in studies that measured depression via self-assessment instrument (Mean difference= 0.84 mg/dL, 95% CI=−4.46, 6.14, p=0.76).

The next set of analyses stratifies by gender, reporting meta-analytic results for men (Figure 9) and women (Figure 10) for studies in which data was presented separately by sex. Heterogeneity showed a marked decrease for both the men-only (I^2=30%) and the women-only strata (I^2=31%). The men-only studies continued to demonstrate an overall significantly lower mean LDL in depression (Mean difference= −9.65 mg/dL, 95% CI=−13.81, −5.50, p<0.001), but this effect was not seen in the women-only studies (Mean difference= 1.30 mg/dL, 95% CI=−4.04, 6.64, p=0.63).

Together, these sub-analyses suggest that heterogeneity may be in part explained by variations in study design, participant characteristics, and assessment of depression status and that these may be important considerations in deriving and interpreting effect estimates.

Meta-analysis of Studies Modeling Serum LDL as a Categorical Measure

A total of seven eligible studies modeled serum LDL as a categorical measure, reporting study findings as an odds ratio and 95% confidence interval. Meta-analysis of studies modeling serum LDL as a categorical measure was conducted using high serum LDL as the reference group. For studies reporting low serum LDL as the reference group (Katon, Lin et al. 2004, Almeida, Flicker et al. 2007, Tedders, Fokong et al. 2011), the inverse of the odds ratio and 95% confidence interval was calculated to reflect high serum LDL as the reference group. The threshold used to define low LDL varied by study, including cutpoints of 89 mg/dL (men) and 92 mg/dL (women) (Tedders, Fokong et al. 2011), 116 mg/dL (Lehto, Hintikka et al. 2008, Lehto, Niskanen et al. 2010, Lehto, Ruusunen et al. 2010), 118 mg/dL (men) and 120 mg/dL (women) (Ancelin, Carriere et al. 2010), 130 mg/dL (Katon, Lin et al. 2004, Ji-Rong, Bi-Rong et al. 2009), 131 mg/dL (Almeida, Flicker et al. 2007), and 158 mg/dL (Liang, Yan et al. 2014), with cutpoints differing between studies by as much as 69 mg/dL.

Meta-analysis of studies modeling serum LDL as a categorical measure can be seen in Figure 11. Meta-analysis for these seven studies 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).

The studies by Ancelin et al. (Ancelin, Carriere et al. 2010) and Tedders et al. (Tedders, Fokong et al. 2011) both used an intermediate LDL category (120.26 mg/dL – 165.51 mg/dL and 92 mg/dL – 137 mg/dL, respectively) as the reference group, which may not be comparable to studies that compared low serum LDL relative to high serum LDL. To account for this possibility, a subsequent analysis was conducted following the exclusion of the aforementioned studies. This analysis demonstrates a statistically significant lower odds of depression in the presence of low serum LDL relative to high serum LDL (OR=0.85, 95% CI=0.73, 0.99, p=0.04).

Publication Bias

The potential for publication bias to influence study findings was assessed visually via funnel plot and quantitatively via Egger's test. Funnel plots indicate moderate asymmetry, which suggests that publication bias cannot be entirely ruled out as an influential factor. Separate funnel plots for studies modeling serum LDL as a continuous measure and studies modeling serum LDL as a categorical measure can be seen in Figures 12 and 13.

Egger's test was used for quantitative analysis of the potential for publication bias for studies modeling serum LDL as a continuous measure. Egger's test is a linear regression analysis that tests for a linear association between each included study's standard normal deviate (mean/standard error) and precision (1/standard error), weighted by the inverse of its variance (Egger, Davey Smith et al. 1997, Rothstein, Sutton et al. 2005). This test was selected because it is the preferred method recommended by the Cochrane Group for assessment of funnel plot asymmetry for meta-analyses with continuous outcomes and an effect measured as mean difference (Higgins and Green 2006). Analysis was conducted using SAS 9.3 using the PUB_BIAS macro developed by Rendina-Gobioff and Kromrey (Rendina-Gobioff 2006). The Egger's test detected publication bias within this study sample (t=−7.168, p<0.0001).

Quantitative analysis of the potential for publication bias for studies modeling serum LDL as a categorical variable was not undertaken due to the small number of studies included in the analysis; generally, meta-analyses including fewer than ten studies are considered to be underpowered to detect funnel plot asymmetry and as such performing quantitative tests of funnel plot asymmetry on is not advised (Higgins and Green 2006).

Discussion

Overall, this systematic review and meta-analysis echoes the earlier work of Shin et al. in the detection of lower mean serum LDL in depression. Interestingly, meta-analysis of studies modeling serum LDL as a categorical measure suggests a reduced odds of depression in the presence of low serum LDL relative to high serum LDL, in contrast to the findings suggested by analysis of serum LDL modeled as a continuous measure. One explanation for these contradictory findings may lie in the lack of consensus in the selection of the cut-off point by which to distinguish between low and high serum LDL in modeling serum LDL as a categorical measure, suggesting that more work must be done toward identifying an appropriate cutpoint by which to distinguish low LDL from LDL that is within normal limits or high.

The seemingly discordant findings observed between the meta-analysis of those studies which used cholesterol as a continuous measure and those which used cholesterol as a categorical measure may also suggest the presence of a U-shaped relationship between serum LDL and depression, with both high and low levels of serum LDL associated with an increased risk of depression. The cross-sectional association between depression and high serum LDL may be the product of a different mechanism than that underlying the cross-sectional association between depression and low serum LDL. It may be simultaneously true that low LDL heralds the onset of depression and that chronic depression, over the course of decades, leads to weight gain and, consequently, metabolic syndrome and high serum LDL, underscoring the importance of prospective analyses that can untangle the temporal association between depression and serum LDL levels.

Limitations

A limitation of this study is the high heterogeneity noted across sampled studies, which may be a function of variations in study design, participants sampled, or other factors. This meta-analysis is also limited in that it does not include data from unpublished studies and only a small number of authors provided supplemental data. The detection of publication bias suggests that additional unaccounted for data may exist.

Conclusions

This meta-analysis demonstrates a cross-sectional link between depression and low serum LDL for studies modeling serum LDL as a continuous measure. Findings in the opposite direction, however, were noted for studies modeling serum LDL as a categorical measure, underscoring the importance of prospective analyses to assess temporality and the need for more work must be done to arrive at a commonly agreed-upon threshold by which to distinguish low LDL within a psychiatric context.

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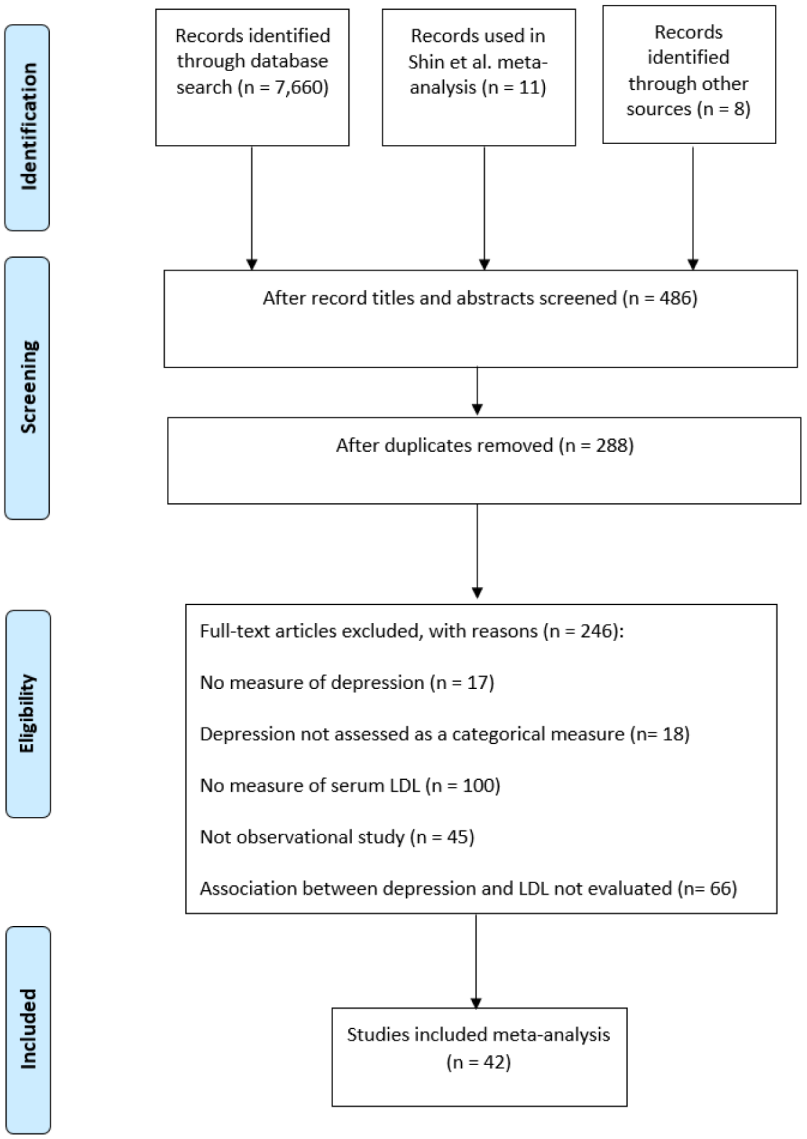

Figure 1.
Systematic Literature Search

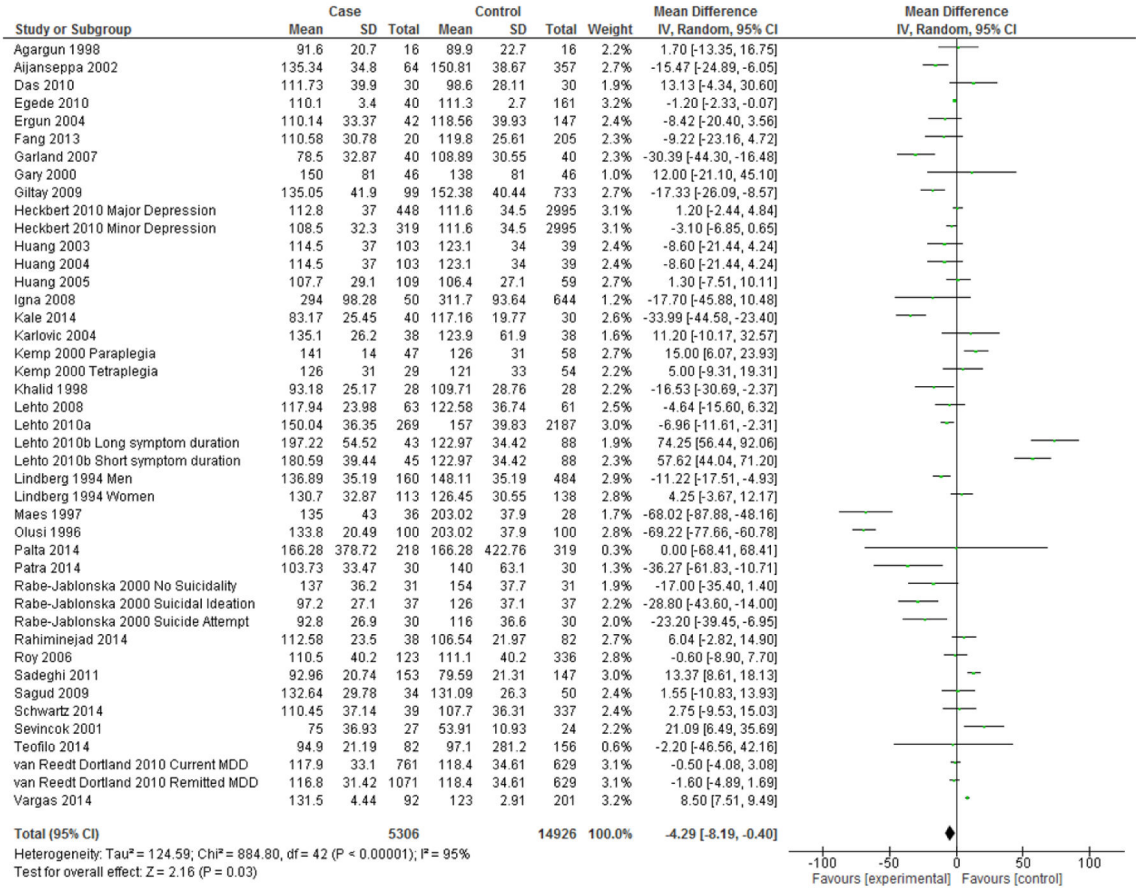

Figure 2.
Forest Plot of Studies Modeling Continuous LDL

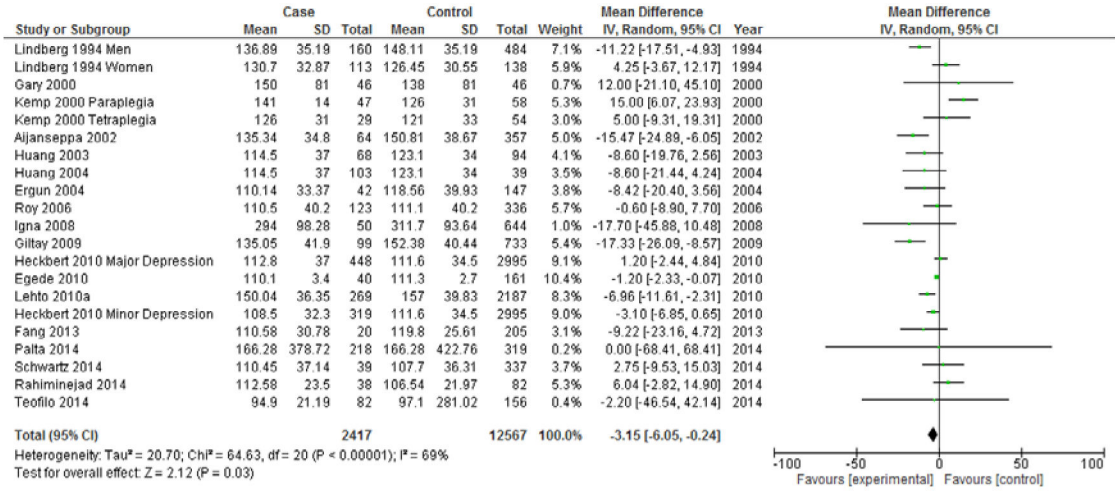

Figure 3.
Forest Plot of Cohort Studies Modeling Continuous LDL

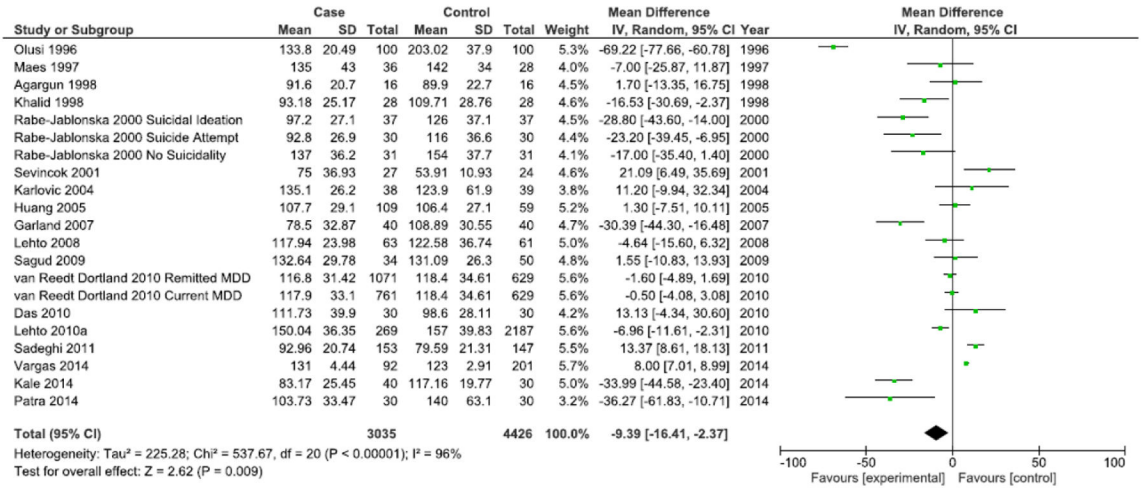

Figure 4.
Forest Plot of Case-control Studies Modeling Continuous LDL

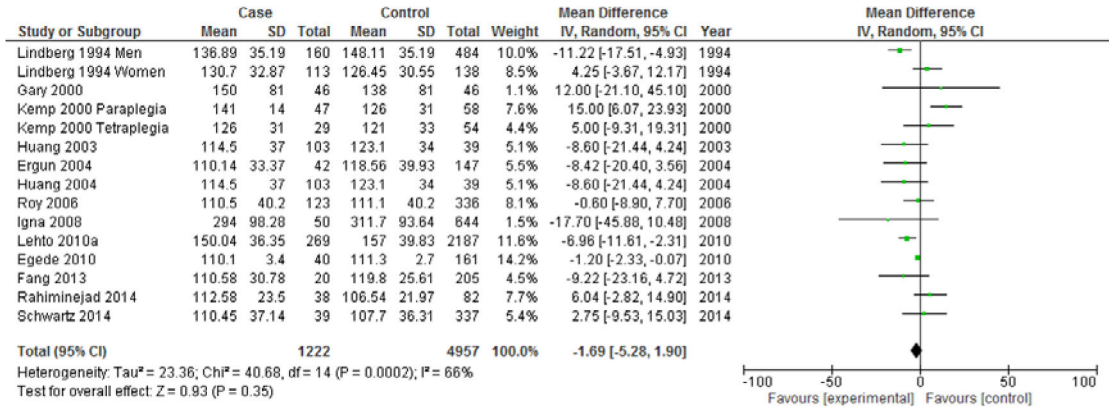

Figure 5.
Forest Plot of Prevalent Depression Studies Modeling Continuous LDL

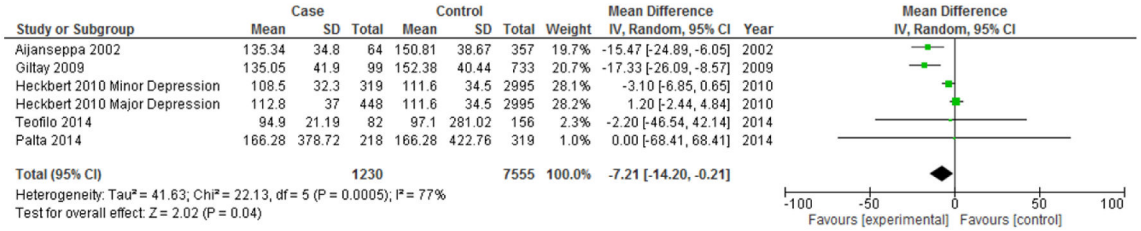

Figure 6.

Forest Plot of Incident Depression Studies Modeling Continuous LDL

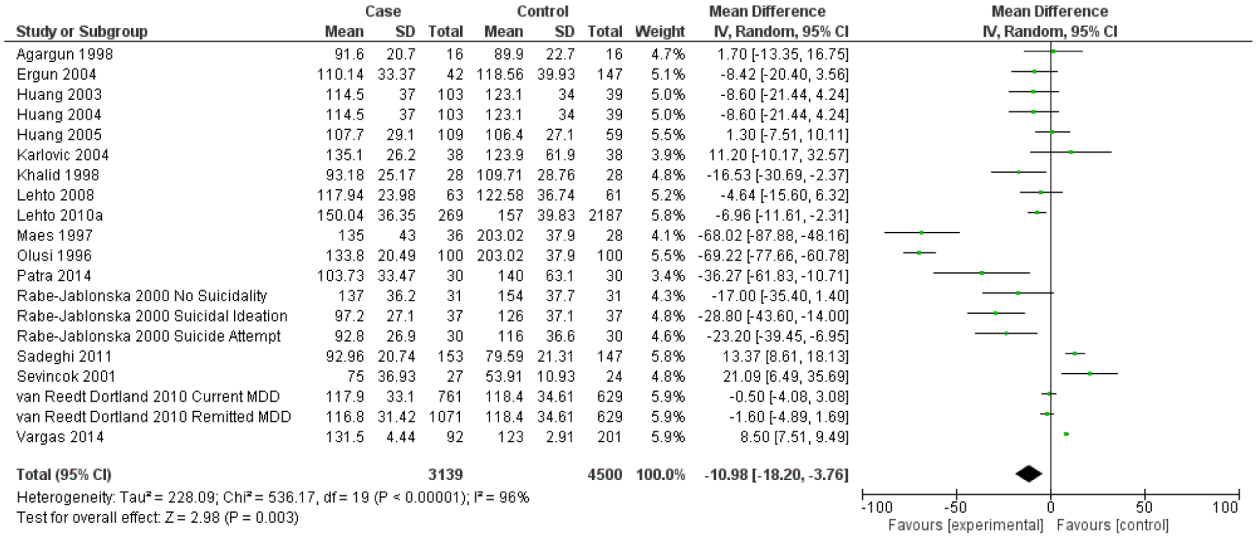

Figure 7.
Forest Plot of Studies Using Clinical Depression Diagnosis

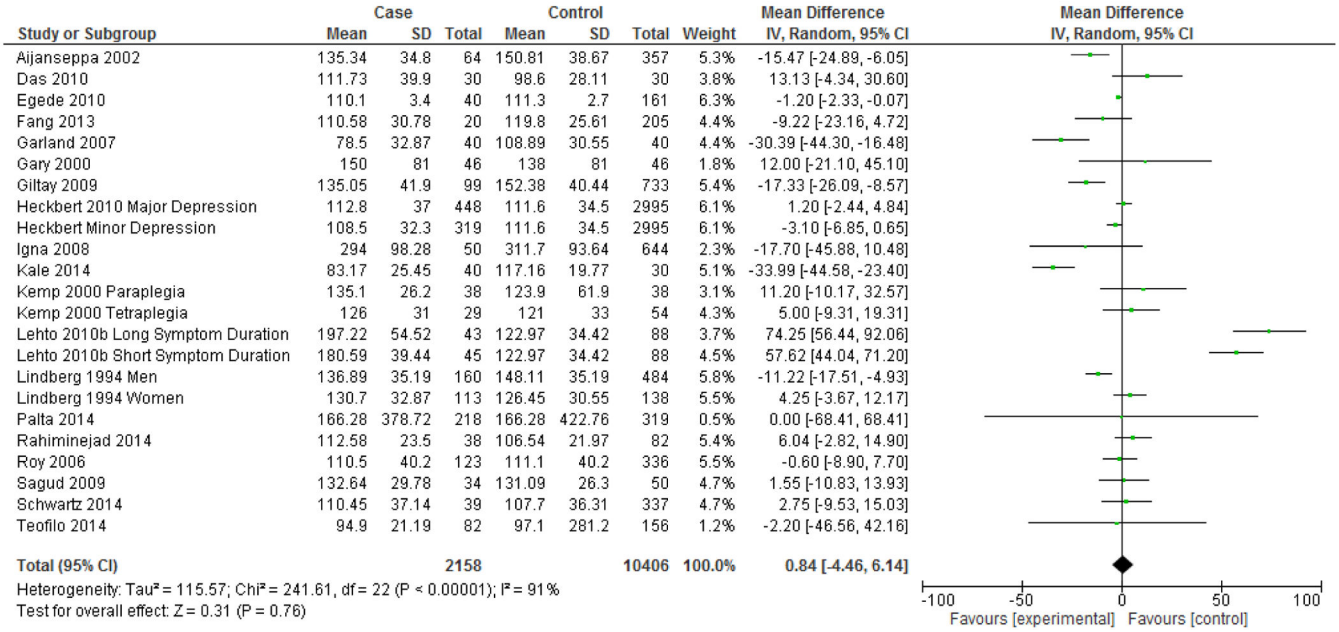

Figure 8.

Forest Plot of Studies Using Depression Self-Assessment Instruments

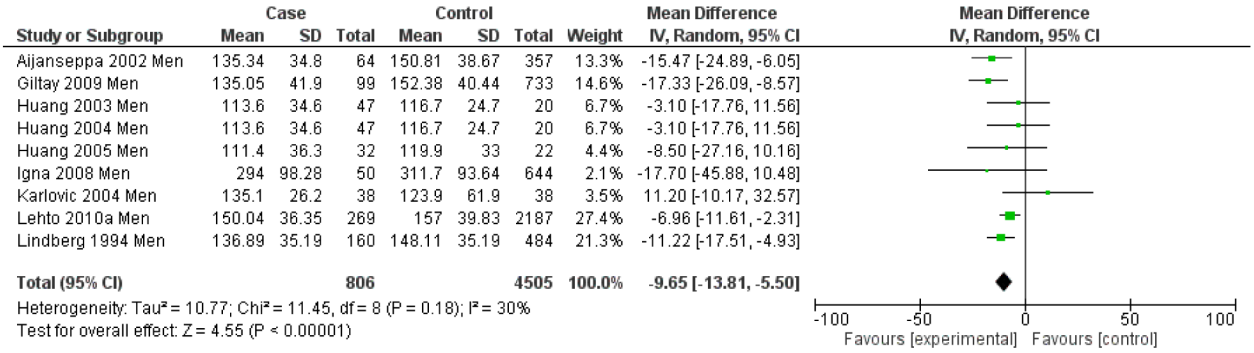

Figure 9.
Forest Plot of Men-only Studies

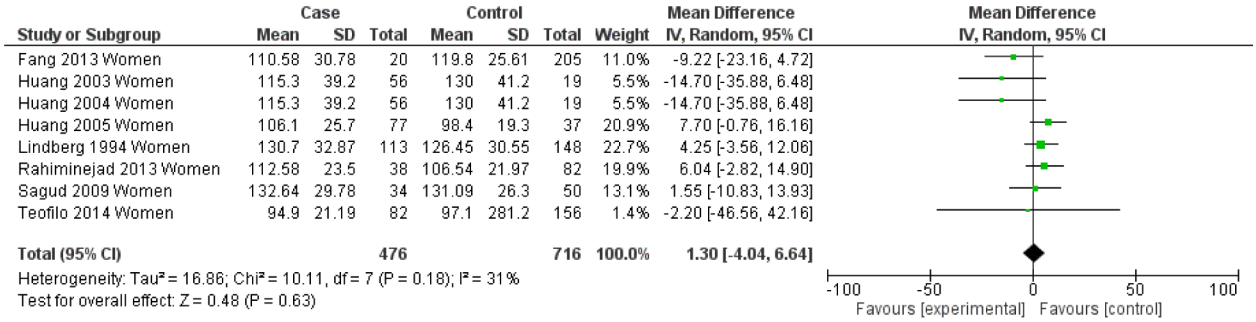

Figure 10.
Forest Plot for Women-only Studies

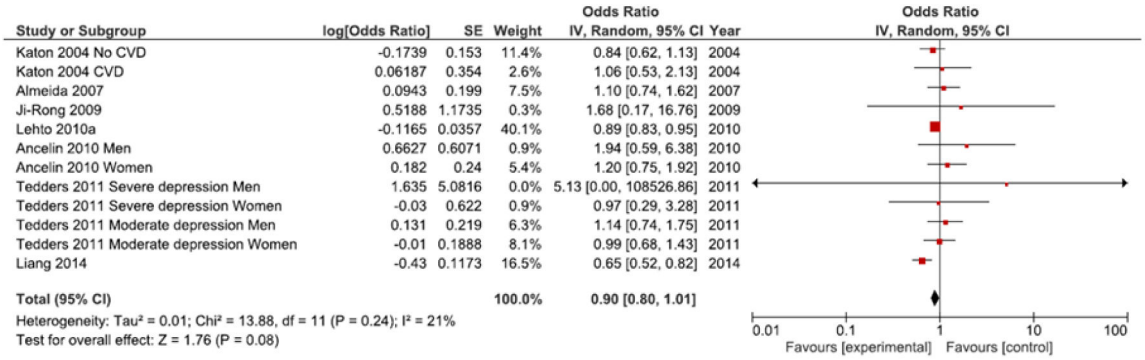

Figure 11.
Forest Plot of Studies Reporting Odds Ratios

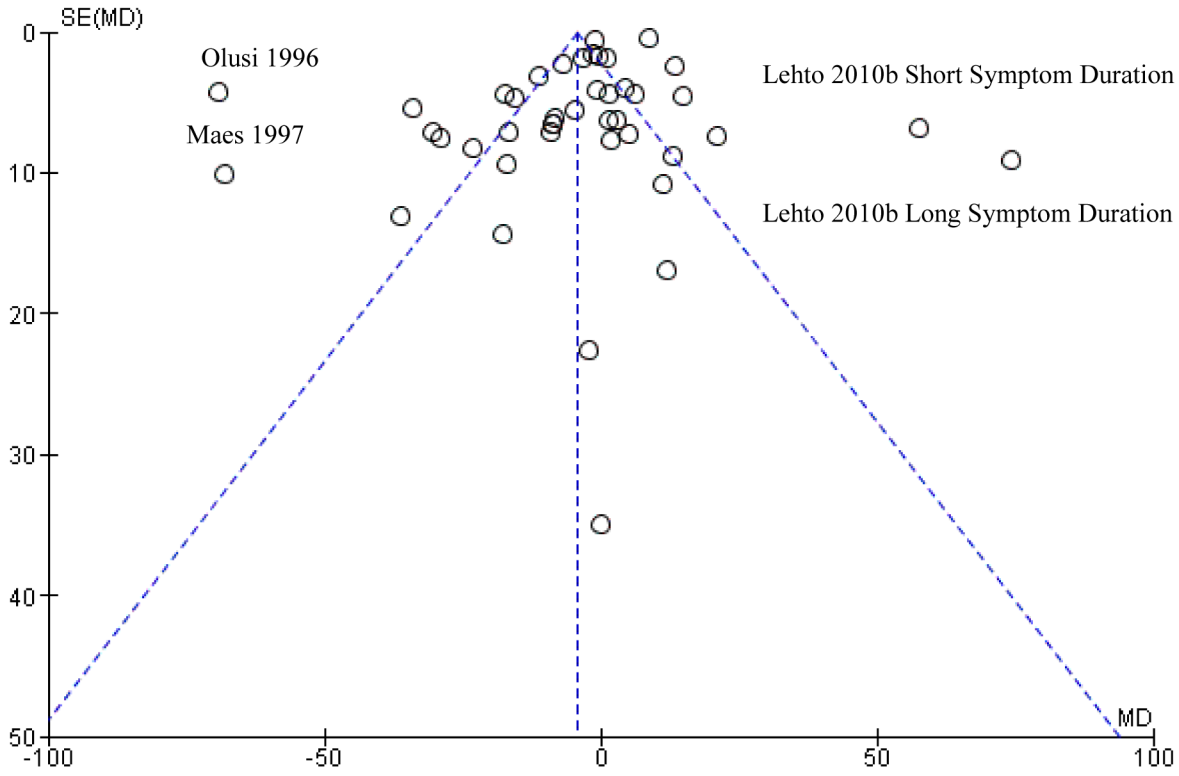

Figure 12.
Funnel Plot for Studies Modeling Serum LDL as a Continuous Measure

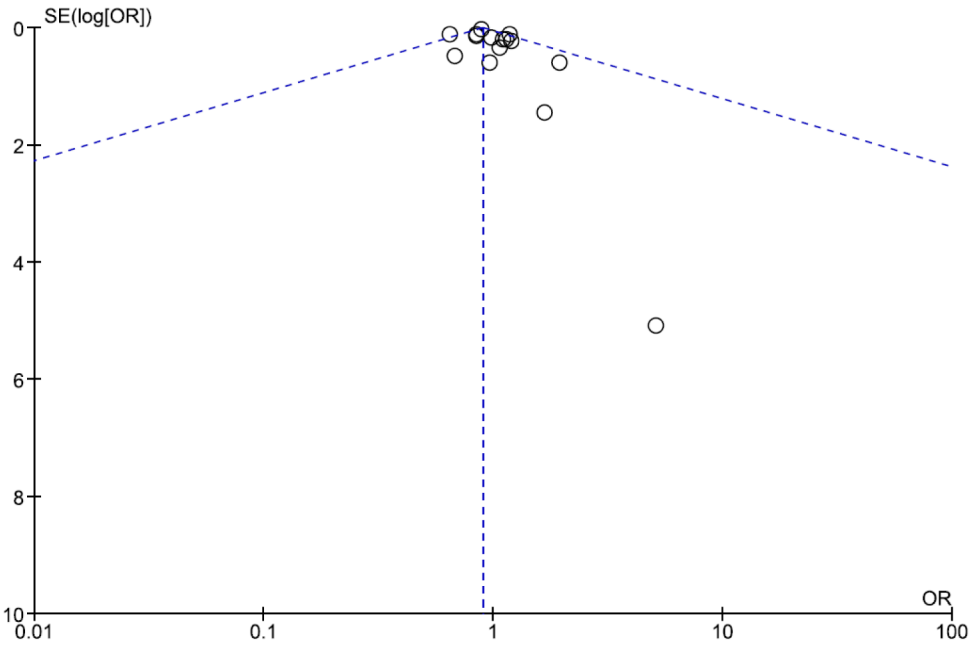

Figure 13.
Funnel Plot for Studies Modeling Serum LDL as a Categorical Measure

Table 1

Characteristics of Studies Included in Meta-analysis

Author and date	Study design	Sample size	LDL measure	Depression measure
(Lindberg, Larsson et al. 1994)	cross-sectional	905 (28.8% women)	Estimated : (total cholesterol - HDL cholesterol - 0.45) * triglyceride Fasting mmol/L Continuous	Single-item response: How often during the past month have you experienced low mood or glumness? Cases defined as responses of “sometimes”, “often”, or “very often” 273 participants (30.2%) met case criteria; of these, 160 men and 113 women met case criteria
(Olusi and Fido 1996)	1:1 sex- and age-matched case-control	200 (36% women)	Friedewald formula Fasting mmol/L Continuous	Chart review using ICD-10 criteria for MDD
(Maes, Smith et al. 1997)	case-control	64 (84.4% women) 36 with depression 28 controls	Friedewald formula Fasting mg/dL Continuous	Semi-structured interview using DSM-III-R criteria for MDD Hamilton Depression Rating Scale (HAM-D)
(Agargun, Algun et al. 1998)	1:1 age-, sex-, and weight-matched case-control	52 (40% women) 16 with depression and panic disorder 16 with panic disorder 16 controls	Friedewald formula Fasting mg/dL Continuous	Structured clinical interview for DSM III-R (SCID)
(Khalid, Lal et al. 1998)	1:1 age- and sex-matched case-control	56 (46.4% women) 28 with depression 28 controls	Friedewald formula Fasting mg/dL Continuous	Semi-structured interview using DSM-III-R criteria for major depression single episode or recurrent depression
(Gary, Crum et al. 2000)	cross-sectional	183 (76% women)	Direct measure Fasting mg/dL Continuous	Center for Epidemiologic Studies Depression scale (CES-D) Data-driven quartiles
(Kemp, Spungen et al. 2000)	cross-sectional	188 (19% women)	Direct measure Fasting mg/dL Continuous	Older Adult Health and Mood Questionnaire (OAHMQ) Cases were defined as OAHMQ scores ≥ 6 76 participants (40%) met case criteria
(Rabe-Jablonska and Poprawska 2000)	case-crossover	102 (69.6% women)	Direct measure Fasting mg/dL Continuous	Semi-structured interview using DSM-IV criteria for MDD HAM-D Acute phase was defined as a HAM-D score above 20 Remission was defined as no longer meeting DSM-IV criteria for major depression and achieving a score of 0 in HAM-D item 1
(Sevincok, Buyukozturk et al. 2001)	age-, sex-, and BMI-matched case-control	117 (72.6% women) 40 with GAD and MDD 27 with MDD 26 with GAD 24 controls	Friedewald formula Fasting mg/dL Continuous	SCID for DSM-III-R Beck Depression Inventory (BDI)
(Aijanseppa, Kivinen et al. 2002)	prospective cohort	421 (0% women)	Friedewald formula Fasting mmol/l Continuous	Zung Self-Rating Depression Scale Cases were defined as scores ≥ 48/80 64 participants (15.2%) met case criteria
(Huang, Wu et al. 2003)	cross-sectional	162 (53.7% women)	Direct measure Fasting mg/dL Continuous	Screened with the Chinese Health Questionnaire and the Taiwanese Depression Questionnaire Semi-structured clinical interview using DSM-IV criteria for MDD 68 participants (42%) met case criteria

Author and date	Study design	Sample size	LDL measure	Depression measure
(Ergun, Uguz et al. 2004)	cross-sectional	189 (56.6% women)	Direct measure Fasting mg/dL Continuous	SCID for DSM-IV 42 participants (22.2%) met case criteria
(Huang and Chen 2004)	cross-sectional	142 (52.8% women)	Direct measure Fasting mg/dL Continuous	Screened with the Chinese Health Questionnaire and the Taiwanese Depression Questionnaire Semi-structured clinical interview using DSM-IV criteria 35 participants (24.6%) met criteria for dysthymia 22 participants (15.5%) met criteria for MDD with melancholic features 46 participants (32.4%0 met criteria for MDD with atypical features
(Karlovic, Buljan et al. 2004)	case-control	157 (0% women) 43 with PTSD 37 with PTSD and MDD 38 with MDD 39 controls	Friedewald formula Fasting mg/dL Continuous	SCID for DSM-IV Montgomery-Asberg Depression Rating Scale (MADRS)
(Katon, Lin et al. 2004)	cross-sectional	4,225 (48.7% women) Stratified by CVD: 2,017 without CVD 991 with CVD	Not reported mg/dL Categorical	Patient Health Questionnaire(PHQ-9) 493 participants (11.7%) met case criteria 320 participants without CVD (10.6%) met case criteria 173 participants with CVD (14.2%) met case criteria
(Huang 2005)	case-control	168 (67.8% women) 109 with depression 59 normal controls	Direct measure Fasting mg/dL Continuous	SCID for DSM-IV
(Roy and Roy 2006)	cross-sectional	459 (58.7% women)	Not reported mg/dL Continuous	BDI Cases were defined as BDI ≥ 14 123 participants (26.8%) met case criteria
(Almeida, Flicker et al. 2007)	cross-sectional	4,204 (0% women)	Friedewald formula Fasting mmol/L Categorical	15-item Geriatric Depression Scale (GDS-15) Cases were defined as GDS-15 ≥ 7 212 participants (5.0%) met case criteria
(Garland, Hallahan et al. 2007)	1:1 age- and sex-matched case-control	80 (67.5% women) 40 with self-harm 40 controls	Not reported Fasting mmol/L Continuous	BDI
(Igna, Julkunen et al. 2008)	cross-sectional	694 (0% women)	Friedewald formula Fasting mmol/L Continuous	BDI Cases were defined as BDI ≥ 19 50 participants (7.20%) met case criteria* *Supplemental data provided by corresponding author
(Lehto, Hintikka et al. 2008)	nested case-control	124 (71% women) 63 with depression 61 controls	Friedewald formula Fasting mmol/L Categorical	BDI Cases were defined as BDI ≥ 10 Controls were defined as BDI <10 Diagnoses verified via SCID for DSM-IV Severity assessed using HAM-D-21
(Giltay, van Reedt Dortland et al. 2009)	prospective cohort	832 (0% women)	Friedewald formula Fasting (Finland cohort) Non-fasting (Italy and the Netherlands cohorts) mmol/L Continuous	Zung Self-rating Depression Scale Cases were defined as Zung Self-rating Depression Scale score ≥ 60 99 participants (11.90%) met case criteria* *Supplemental data provided by corresponding author

Author and date	Study design	Sample size	LDL measure	Depression measure
(Ji-Rong, Bi-Rong et al. 2009)	cross-sectional	678 (67.8% women)	Direct measure Fasting mmol/L Categorical	Geriatric Depression Scale – Chinese edition (GDS-CD) Cases were defined as GDS-CD ≥ 10 226 participants (33.3%) met case criteria
(Sagud, Mihaljevic-Peles et al. 2009)	case-control	125 (100% women) 41 with bipolar 1 (22 in manic episode and 19 in depressive episode) 34 with major depression 50 controls	Direct measure Fasting mmol/L Continuous	SCID for DSM-IV HAMD-17 Young Mania Rating Scale (YMRS) MDD and bipolar depression cases were defined as HAMD-17 ≥ 18 and YMRS ≤ 5
(Ancelin, Carriere et al. 2010)	prospective cohort	1792 (58.0% women)	Friedewald formula Fasting mmol/L Categorical	Mini International Neuropsychiatric Interview (MINI) to confirm diagnosis of MDD CES-D Cases were defined as CES-D ≥ 16 536 participants (29.9%) met case criteria, which included 159 men and 377 women
(Das, Malhotra et al. 2010)	case-control	60 (sex not reported) 30 with depression 30 controls	Direct measure Fasting mg/dL Continuous	Semi-structured interview using DSM-IV criteria HAM-D Cases were defined as HAM-D > 7
(Egede and Ellis 2010)	cross-sectional	201 (72.6% women)	Not reported Abstracted from electronic medical records mg/dL Continuous	CES-D Cases were defined as CES-D ≥ 16 40 participants (20%) met case criteria
(Heckbert, Rutter et al. 2010)	prospective cohort	3,762 (47.9% women)	Not reported Abstracted from electronic medical records mg/dL Continuous	PHQ-9 Case definition criteria not reported 319 participants (8.5%) met case criteria for minor depression 448 participants (11.9%) met case criteria for major depression
(Lehto, Ruusunen et al. 2010)	cross-sectional	2456 (0% women)	Direct measure Fasting mmol/L Continuous and categorical	18-item Human Population Laboratory Depression Scale (HPL-D) Cases were defined as HPL-D ≥ 5 269 participants (10.9%) met case criteria
(Lehto, Niskanen et al. 2010)	1:1 age- and sex-matched case-control	176 (55.7% women) 88 with depression (43 with long duration of symptoms and 45 with short duration of symptoms) 88 controls	Friedewald formula Fasting mmol/L Categorical	SCID for DSM-IV BDI
(van Reedt Dortland, Giltay et al. 2010)	case-control	2,461 (66.9% women) 761 with current MDD 1,071 with remitted MDD 629 controls	Direct measure Fasting mg/dL Continuous	Composite International Diagnostic Interview using DSM-IV criteria for MDD 30-item Inventory of Depressive Symptoms – Self-Report
(Sadeghi, Roohafza et al. 2011)	case-control	300 (63.3% women) 153 with depression 147 controls	Friedewald formula Fasting mg/dL Continuous	SCID for DSM-IV HAM-D was used to quantify depression severity
(Tedders, Fokong et al. 2011)	cross-sectional	8,390 (50.9% women)	Friedewald formula Fasting Categorical	PHQ-9 Mild-to-moderate depression was defined as a PHQ-9 of 10-19 Severe depression was defined as PHQ-9 ≥ 20 226 participants (2.7%) met case criteria for severe depression; of these, 71 were men and 155 were women

Author and date	Study design	Sample size	LDL measure	Depression measure
				1683 participants (20.0%) met case criteria for mild-to-moderate depression; of these, 676 were men and 1,007 were women
(Fang, Egleston et al. 2013)	cross-sectional	225 (100% women)	Friedewald formula Fasting mg/dL Continuous	CES-D Cases defined as CES-D ≥ 16 20 participants (8.89%) met case criteria* *Supplemental data provided by corresponding author
(Kale, Kale et al. 2014)	case-control	70 (58.6% women) 40 with depression 30 controls	Direct measure Fasting mg/dL Continuous	BDI
(Liang, Yan et al. 2014)	cross-sectional	1,839 (59.2% women)	Direct measure Fasting mmol/L Categorical	GDS-15 Continuous and categorical Case definition not reported 311 participants (16.9%) met case criteria
(Palta, Golden et al. 2014)	prospective cohort	613 (69.5% women)	Friedewald formula Fasting mmol/L Continuous	Brief Comprehensive Assessment and Referral Evaluation (SHORT-CARE) Cases were defined as SHORT-CARE score ≥ 7 218 participants (35.6%) met case criteria
(Patra, Khandelwal et al. 2014)	1:1 age- and sex-matched case-control	60 (36.6% women) 30 with depression 30 controls	Friedewald formula Fasting mg/dL Continuous	ICD-10-DCR HAM-D
(Rahiminejad, Moaddab et al. 2014)	cross-sectional	120 (100% women)	Not reported mg/dL Continuous	BDI Semi-structured interview using DSM-IV criteria Cases were defined as BDI > 15 38 participants (31.7%) met case criteria
(Schwartz, Rowland et al. 2014)	twin study	376 (55.4% women)	Friedewald formula Fasting mmol/L Continuous	CES-D Cases were defined as CES-D ≥ 16 39 participants (10.37%) met case criteria
(Teofilo, Farias et al. 2014)	prospective cohort	238 (100% women)	Friedewald formula Fasting mg/dL Continuous	Edinburgh Postnatal Depression Scale (EDPS) Cases were defined as EDPS ≥ 11 82 participants (34.5%) met case criteria
(Vargas, Nunes et al. 2014)	case-control	342 (66.1% women) 92 with depression 49 with bipolar disorder 201 controls	Friedewald formula Fasting mg/dL Continuous	semi-structured interview for DSM-IV HAM-D