Associations Between Serum Lipids and Major Depressive Disorder: Results From the Netherlands Study of Depression and Anxiety (NESDA)

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Background: Several studies have suggested an association between lipids or lipoproteins and depression, but findings are contradictory. However, previous studies did not always take into consideration potentially mediating factors or heterogeneity of symptoms, which may clarify contradicting findings.

Method: We compared levels of serum total, low-density lipoprotein (LDL), and high-density lipoprotein (HDL) cholesterol and triglyceride between 761 subjects with current major depressive disorder (MDD) (Composite International Diagnostic Interview, based on the *DSM-IV*), 1,071 subjects with remitted MDD, and 629 controls, aged 18 to 65 years. Subjects participated in the baseline assessment of the Netherlands Study of Depression and Anxiety, which lasted from September 2004 to February 2007. We studied the impact of adjustment for sociodemographics, lifestyle-related covariates, and antidepressant use and examined the association between specific psychopathological characteristics and lipid/lipoprotein levels.

Results: HDL cholesterol level was lower ($P = .007$) and triglyceride level was higher ($P = .001$) in current MDD versus remitted MDD and controls. After adjustment for level of education, body mass index (BMI), smoking status, and alcohol use, dissimilarities lost statistical significance. Depression severity, comorbid dysthymia, and melancholic and atypical features were all associated with lipids/lipoproteins, but most associations attenuated after adjustment for covariates, especially BMI. The association between melancholic features and lower HDL cholesterol ($P = .038$) and between atypical depression and higher total and LDL cholesterol ($P = .004$ and $P = .002$, respectively) persisted after full adjustment.

Conclusions: Adverse lipoprotein patterns were found in patients with MDD. The fact that these associations diminished after adjustment for lifestyle-related factors, especially BMI, suggests that the unfavorable lipid/lipoprotein pattern among depressed subjects is mainly secondary to lifestyle-related factors. However, melancholic features were independently associated with lower HDL cholesterol, and atypical depression was independently associated with higher total and LDL cholesterol.

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Serum lipids and lipoproteins are argued to be associated with depression, but findings regarding this link have been inconsistent. Most studies have found lower total cholesterol in subjects with depressive symptoms versus controls.[1–7] Other studies have reported higher total cholesterol[8] or found no differences.[9–12] Levels of low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, and triglyceride were assessed in relation to depression or depressive complaints as well,[2,3,6,7,11–13] but less extensively. Again, contradictory results were obtained.

Several possible explanations exist for these mixed findings. First, study designs differed widely. For example, various depression assessment scales were used, and the universal gold standard to identify clinical depression, the *Diagnostic and Statistical Manual of Mental Disorders* (*DSM*), was infrequently applied.[2,3,8,11,12] Furthermore, some samples were small[3]; contained a small proportion of depressed subjects[8]; covered a restricted age range, such as elderly[1,6,7,9,11] or adolescents[4]; or included either men[1,5–8] or women.[4] This reduces comparability of studies and generalizability of results to clinical practice.

Second, the inconsistencies in previous research might be due to the fact that major depressive disorder (MDD) is often approached as a homogeneous disorder. Therefore, its range of psychopathological characteristics has been ignored. Depressed subjects differ concerning depression severity and often display comorbid anxiety disorders or dysthymia. Also, suicidality regularly accompanies depression, which might also be associated with lipid/lipoprotein deviations.[14] Furthermore, some depressed subjects exhibit atypical or melancholic features, which may be more strongly associated with lipid/lipoprotein alterations.

A third explanation for the contradictory results is the potential mediation of lifestyle in the association between depression and lipids/lipoproteins. In previous studies, body mass index,[4,5,7,11,12] smoking behavior,[7] and alcohol use[5,7] were seldom taken into account, whereas depressed subjects on average have a higher body mass index,[15] are more likely to smoke,[16,17] and use either less[18] or more alcohol[19] compared to nondepressed subjects. Moreover, obesity,[20] smoking,[21] and alcohol use[22] modify lipid/lipoprotein metabolism and are important anchor points in the management of an unhealthy lipid profile.[23] Another possible confounder might be antidepressant use, as some are known to induce antihistaminergic side effects: for example, weight gain.[24,25]

To our knowledge, this is the largest sample in which the association between lipids/lipoproteins and *DSM*-diagnosed MDD is studied. Our sample includes men and women over

a broad age range. We distinguish between controls, those with a remitted MDD, and those with a current MDD, since residual symptoms in persons with a remitted depression are commonly found,[26] and, therefore, we expect the associations in our study to be graded over the control, remitted depression, and current depression groups. By investigating the role of psychopathological characteristics, lifestyle, and antidepressant use, we aim to elucidate aspects that mainly influence the association between lipids/lipoproteins and depression.

METHOD

Subjects

Subjects participated in the baseline assessment of the Netherlands Study of Depression and Anxiety (NESDA), which lasted from September 2004 to February 2007 and included 2,981 persons aged 18 to 65 years. Subjects were recruited from community, primary care, and mental health care in 5 Dutch regions (Amsterdam, Emmen, Groningen, Heerenveen, Leiden). The baseline assessment comprised a face-to-face interview, written questionnaires, and biologic measurements. The detailed study design is described elsewhere.[27] The study protocol was approved by the Ethical Review Board of each participating center, and all subjects signed informed consent at baseline assessment.

For the current analyses, 3 groups were included, ie, subjects with an MDD diagnosis in the past month (ie, "current MDD," n = 802), subjects with an MDD diagnosis before the last month (ie, "remitted MDD," n = 1,123), and those who never had a depressive or anxiety disorder (ie, "controls," n = 652), resulting in a preliminary sample size of 2,577. Excluding cases with 1 or more missing values on total, HDL, or LDL cholesterol, triglyceride, or depression severity (see below) resulted in a sample of 2,461 subjects (ie, 761 with current MDD, 1,071 with remitted MDD, and 629 controls).

Measures

Major depressive disorder. Major depressive disorder was diagnosed according to the *Diagnostic and Statistical Manual for Mental Disorders,* Fourth Edition (*DSM-IV*) criteria using the Composite International Diagnostic Interview (CIDI).[28]

Psychopathological characteristics. For subjects with current MDD, various psychopathological characteristics were assessed. Depression severity was assessed by the 30-item Inventory of Depressive Symptoms–Self-Report (IDS-SR),[29] with scores ranging from 0 to 84. Atypical depression was coded as "absent/present," as done before,[30] based on the following IDS-SR items: a score of 0, 1, or 2 on item 8 for mood reactivity as well as 2 or more of the following: a score of 3 on item 28 for leaden paralysis; a score of 2 or 3 on item 12 or item 14 for weight gain; a score of 2 or 3 on item 4 for hypersomnia; a score of 3 on item 27 for interpersonal sensitivity. Similarly, the presence of melancholic features was coded as "absent/present," with the following criteria: a score of 2 or 3 on item 19 for capacity for pleasure, or 3 on item 8 for mood responsiveness, and 3 or more of the following: a score of 2 or 3 on item 10 for quality of mood; a score of 0 on item 9a for morning mood; a score of 3 on item 3 for early awakening; a score of 2 or 3 on item 23 or 24 for psychomotor changes; a score of 2 or 3 on item 11 or 13 for anorexia; a score of 2 or 3 on item 16 for feelings of guilt. The presence of comorbid current (past month) anxiety disorder (social phobia, agoraphobia with or without panic disorder, or generalized anxiety disorder) and comorbid current dysthymia was identified by the CIDI. Suicide attempt in history (absent/present) was determined by a single question.[31]

Lipids/lipoproteins. Blood samples were taken around 8:47 AM (SD = 20 min) after a mean 11 hours 15 minutes (SD = 111 min) overnight fasting period. The samples were transported to a laboratory within 1 hour. Levels of total, LDL, and HDL serum cholesterol as well as triglyceride were determined according to routine laboratory methods in all 5 participating laboratories. All methods were standardized through periodical external quality assessments by the Dutch Foundation for Quality Assessment in Clinical Laboratories. The maximum intra-assay variation coefficients of the methods were 0.8% for total cholesterol, 0.8% for LDL cholesterol, 1.0% for HDL cholesterol, and 1.5% for triglycerides. The maximum interassay variation coefficients were 1.7% for total cholesterol, 1.2% for LDL cholesterol, 1.3% for HDL cholesterol, and 1.8% for triglycerides.

Covariates. Sociodemographic variables (age, sex, level of education), smoking status (non, former, or current), alcohol use (mean of 0, 1–2, or >2 glasses per day), presence of cardiovascular disease (CVD) or diabetes, and use of oral anticonceptives were assessed by standardized questionnaires. Level of education was classified as basic (ie, elementary education or less), intermediate (ie, lower or intermediate vocational education), or high (ie, higher vocational, college, or university education). Cardiovascular disease was defined as the self-reported cardiac infarct, angina pectoris, heart failure, heart rhythm disorders, or cardiac surgery. Diabetes diagnosis was identified through self-report and/or the present use of antidiabetics. Use of antidiabetics, lipid-lowering medication (ATC code[32] C10) and antidepressants (tricyclic antidepressant [TCA]/selective serotonin reuptake inhibitor [SSRI]/other) in the past month was registered by observation of drug containers brought in. Antidepressants were subdivided into SSRI (ATC code N06AB), TCA (ATC code N06AA), and other antidepressants (monoamine oxidase inhibitors N06AG, nonselective N06AF, and antidepressants classified as N06AX). Height and weight were measured to calculate body mass index (BMI). Because a nonlinear association between depressive symptoms and BMI is conceivable, BMI was divided into 4 categories (< 18.5, 18.5–24.99, 25–29.99, and ≥ 30 kg/m^2).[33]

Statistical analyses. Differences between study groups were analyzed by analysis of variance for quantitative variables or χ^2 linear-by-linear test for categorical variables. Lipid and lipoprotein data were naturally log transformed because of their positively skewed distribution, and geometric mean values are presented. Potential

Table 1. Characteristics According to Study Group for 2,461 Subjects

Characteristic	Current MDD (n = 761)	Remitted MDD (n = 1,071)	Controls (n = 629)	Overall *P* Value[a]
Age, mean (95% CI), y	41.7 (40.9–42.6)	42.4 (41.6–43.1)	41.2 (40.1–42.4)	.18
Sex (% men)	33.6	29.5	38.6	.08
Level of education, %				< .001
Basic	10.1	5.2	3.5	
Intermediate	64.9	56.6	52.8	
High	25.0	38.2	43.7	
Body mass index, %				< .001
< 18.5	3.0	1.8	2.2	
18.5–24.99	43.6	52.0	54.4	
25.0–29.99	30.9	30.8	29.9	
≥ 30.0	22.5	15.4	13.5	
Smoking status, %				.97
Nonsmoker	27.1	23.7	36.4	
Former smoker	27.7	35.6	36.2	
Current smoker	45.2	40.7	27.3	
Alcohol use, %				.012
< 1 glass/d	66.5	61.3	57.9	
1–2 glasses/d	16.8	23.8	23.7	
> 2 glasses/d	16.7	14.9	18.4	
Use of oral anticonceptives, %	17.6	17.6	18.9	.54
Antidepressant medication use, %				
Selective serotonin reuptake inhibitors	30.6	19.8	0.6	< .001
Tricyclic antidepressants	3.9	3.5	0.2	< .001
Other antidepressants	10.8	6.3	0.2	< .001
Diabetes, %	8.5	6.9	6.2	.09
Cardiovascular disease, %	6.2	6.2	5.6	.65
Use of lipid-lowering medication, %	8.5	6.5	6.0	.06
Depression severity score (IDS-SR), mean (95% CI)[b]	35.9 (35.1–36.7)*	19.8 (19.1–20.4)**	8.6 (8.0–9.2)***	< .001
Melancholic features, %	17.3	1.5	0.0	< .001
Atypical features, %	27.2	6.8	1.4	< .001
Comorbid anxiety disorder, %	62.9	33.1	0.0	< .001
Comorbid dysthymia, %	28.5	2.3	0.0	< .001
History of suicide attempt, %	23.1	12.0	1.4	< .001

[a] *P* value by analysis of variance for quantitative variables or χ^2 linear-by-linear test for categorical variables. [b] Asterisks that are dissimilar between groups indicate that the post hoc *P* values of corresponding groups differ significantly ($P < .05$ after Bonferroni correction).
Abbreviations: IDS-SR = Inventory of Depressive Symptoms–Self-Report, MDD = major depressive disorder.

nonlinear (ie, curved) associations between depression and lipids/lipoproteins were explored by plotting mean IDS-SR total score and the prevalence of diagnoses (current MDD, lifetime MDD, controls) by lipid/lipoprotein quintiles. Correlations between overall lipid/lipoprotein levels were calculated by Pearson correlation coefficient. Geometric mean values (and 95% confidence intervals [CIs]) were calculated by analysis of covariance to compare lipid/lipoprotein levels (dependent variables) between study groups (factor variable), adjusting for basic sociodemographic and health covariates (ie, age, sex, level of education, use of lipid-lowering medication, use of oral anticonceptives [yes/no], CVD, and diabetes) in model 1, adjusting for additional lifestyle-related covariates (ie, basic covariates and smoking status, alcohol use, and BMI categories) in model 2, and additionally adjusting for use of antidepressants in model 3. Cohen's *d* (the difference in group geometric means, divided by their pooled standard deviation) was calculated as a measure of effect size. Linear regression analyses were used to assess associations between IDS-SR total score and other psychopathological characteristics (as separate independent variables) and lipid/lipoprotein levels (as continuous dependent variables) after basic (model 1) and additional (model 2 and model 3) adjustment in subjects with current MDD. In additional analyses, we excluded subjects using lipid-lowering medication and subjects with CVD or diabetes, and we additionally adjusted for laboratory site. Statistical significance was inferred at $P < .05$. All statistical analyses were undertaken with SPSS 14.0 (SPSS Inc, Chicago, Illinois).

RESULTS

Table 1 shows the characteristics of the study groups. The mean age of the sample was 41.9 (SD = 12.9) years and 33.1% were male. Subjects with current or remitted depression were less educated than controls but did not differ statistically in age, sex, or diabetes and CVD prevalence. Subjects with a current MDD had a higher BMI and tended to use less alcohol than the other 2 groups. Subjects with a remitted MDD demonstrated a higher depression severity score (IDS-SR) as compared to controls but a lower score than subjects with a current MDD.

Because the plotted distribution pattern of mean IDS-SR total score and of depression diagnoses across quintiles of lipid/lipoprotein levels did not indicate curved associations (data not shown), all subsequent analyses were based on linear models. Correlations between lipid/lipoprotein levels ranged from –.14 (for LDL and HDL cholesterol) through .88 (for total and LDL cholesterol). Table 2 presents lipid/lipoprotein levels across study groups. In crude analyses,

Table 2. Serum Lipid and Lipoprotein Levels in Controls and Subjects With a Remitted or Current MDD[a]

	Current MDD (n = 761)		Remitted MDD (n = 1,071)		Controls (n = 629)		
Variable[b]	Mean	95% CI	Mean	95% CI	Mean	95% CI	Overall *P* Value
Total cholesterol, mg/dL							
Crude	193.3	190.5–196.1	193.7	191.3–196.1	191.4	188.4–194.5	.51
Model 1[c]	193.8	191.3–196.4	193.0	190.9–195.1	191.9	189.2–194.7	.61
Model 2[d]	193.3	190.9–195.9	192.9	190.8–195.0	192.6	189.9–195.4	.93
Model 3[e]	192.2	189.7–194.7	192.7	190.6–194.8	194.4	191.5–197.3	.53
LDL cholesterol, mg/dL							
Crude	119.7	117.0–122.3	117.2	114.9–119.5	115.6	112.9–118.4	.12
Model 1[c]	119.6	117.2–122.1	117.0	115.0–119.0	116.0	113.4–118.6	.11
Model 2[d]	118.9	116.5–121.3	117.0	115.0–119.0	116.9	114.3–119.5	.42
Model 3[e]	117.9	115.6–120.4	116.8	114.8–118.7	118.4	115.7–121.2	.57
HDL cholesterol, mg/dL[f]							
Crude	59.2*	58.0–60.3	61.4**	60.4–62.4	61.4**	60.1–62.7	.007
Model 1[c]	59.8	58.8–60.9	60.7	59.8–61.6	61.7	60.5–62.9	.08
Model 2[d]	60.7	59.7–61.7	60.7	59.8–61.5	60.7	59.7–61.8	.99
Model 3[e]	60.6	59.6–61.6	60.7	59.8–61.5	60.8	59.7–62.0	.97
Triglycerides, mg/dL[f]							
Crude	104.8*	101.1–108.5	97.1**	94.1–100.1	95.7**	91.9–99.7	.001
Model 1[c]	103.3*	99.9–106.9	97.9**	95.2–100.7	95.8**	92.3–99.4	.008
Model 2[d]	101.0	97.8–104.3	98.3	95.7–100.9	97.9	94.6–101.4	.34
Model 3[e]	100.1	96.9–103.4	98.1	95.5–100.7	99.3	95.7–102.9	.62

[a]Geometric means are presented, based on estimated marginal means, calculated by analysis of covariance. [b]To convert total, LDL, or HDL cholesterol values from mg/dL to mmol/L, divide by 38.7. To convert triglyceride values from mg/dL to mmol/L, divide by 88.6. [c]Adjusted for age, sex (male/female), level of education (basic/intermediate/high), use of lipid-lowering medication (yes/no), use of oral anticonceptives (yes/no), cardiovascular disease (yes/no), and diabetes (yes/no). [d]Additionally adjusted for smoking status (current/former/none), alcohol use (0/1–2/> 2 glasses/d), and body mass index categories (< 18.5/18.5–24.99/25–29.99/> 30). [e]Additionally adjusted for antidepressant use (selective serotonin reuptake inhibitor/tricyclic antidepressant/other). [f]Asterisks that are dissimilar between groups indicate that, in post hoc analyses, groups differed significantly ($P < .05$ after Bonferroni correction).

Abbreviations: HDL = high-density lipoprotein, LDL = low-density lipoprotein, MDD = major depressive disorder.

total and LDL cholesterol levels did not differ significantly between groups. Lower HDL cholesterol level was found in the current MDD versus the remitted MDD and control groups (post hoc *P* values after Bonferroni correction were .01 and .03, respectively), with a small effect size for current MDD versus controls ($d = –0.137$). Furthermore, higher triglyceride levels in the current MDD group versus the remitted MDD and control groups were found (post hoc *P* values after Bonferroni correction were .005 and .003, respectively), with a small effect size for current MDD versus controls ($d = 0.178$). Subjects with remitted MDD and controls did not differ significantly with regard to HDL cholesterol or triglyceride levels. Adjustment for covariates in model 1 reduced HDL cholesterol differences between groups to statistically nonsignificant. Both education level and BMI as the only covariate already reduced these differences to statistically nonsignificant. Differences in triglyceride levels between study groups in crude analyses ($P = .001$) and in model 1 ($P = .008$) were not found after additional adjustment in model 2 ($P = .34$). BMI largely explained the differences in triglyceride levels between groups. Additional adjustment for antidepressant use in model 3 did not change associations importantly.

Associations between psychopathological characteristics (ie, independent variables) and lipids/lipoproteins (ie, continuous dependent variables) were assessed in currently depressed subjects (Table 3). Crude associations are not shown because associations did not change importantly after adjustment for covariates in model 1. In model 1, statistically significant, positive associations were found between IDS-SR total score and total cholesterol ($\beta = .073$, $P = .025$), LDL cholesterol ($\beta = .082$, $P = .015$), and triglyceride levels ($\beta = .102$, $P = .003$), and an inverse association was seen with HDL cholesterol ($\beta = –.118$, $P = .001$). However, associations were no longer statistically significant after additional adjustment in model 2. Again, BMI as the only covariate already resulted in statistically nonsignificant associations. The presence of atypical depression (n = 207; 27.2% of the currently depressed) was associated with higher levels of total and LDL cholesterol as well as triglyceride and lower HDL cholesterol levels. The associations between atypical features and total ($\beta = .096$, $P = .004$) and LDL cholesterol ($\beta = .102$, $P = .002$) remained statistically significant after full adjustment in model 3. Corresponding effect sizes for current MDD with versus without atypical features were small to modest ($d = 0.234$ and $d = 0.253$, respectively). Associations between melancholic features (n = 131; 17.2% of the currently depressed) and triglycerides and inverse HDL cholesterol found in model 1 were somewhat attenuated in model 2 and model 3. The association between melancholic features and HDL cholesterol remained statistically significant ($\beta = –.066$, $P = .038$), with a small to modest effect size for current MDD with versus without melancholic features ($d = –0.203$). Other psychopathological characteristics (comorbidity of dysthymia or anxiety or suicide attempt in history) were not associated with lipid/lipoprotein levels after additional adjustment (model 2 and model 3).

Figure 1 shows that geometric mean total and LDL cholesterol as well as triglyceride levels were higher and HDL cholesterol levels were lower in MDD with atypical features versus MDD without atypical features or controls. Also, geometric mean LDL cholesterol and triglyceride levels were

Table 3. Associations Between Lipids/Lipoproteins and Psychopathological Characteristics in 761 Subjects With a Current Major Depressive Disorder

		Total Cholesterol		LDL Cholesterol		HDL Cholesterol		Triglycerides	
Psychopathological Characteristic	n[a]	β[b]	*P* Value	β[b]	*P* Value	β[b]	*P* Value	β[b]	*P* Value
Model 1[c]									
Depression severity score (IDS-SR)		.073	.025	.082	.015	–.118	.001	.102	.003
Atypical features	207	.110	.001	.122	< .001	–.075	.031	.067	.05
Melancholic features	131	.047	.15	.052	.13	–.092	.008	.074	.03
Comorbid anxiety disorder	479	.006	.84	–.018	.60	–.008	.82	.002	.99
Comorbid dysthymia	217	.019	.55	.006	.86	–.062	.07	.083	.014
Suicide attempt in history	176	.053	.11	.039	.24	.014	.69	.027	.44
Model 2[d]									
Depression severity score (IDS-SR)		.063	.06	.056	.10	–.034	.28	.045	.17
Atypical features	207	.107	.001	.116	.001	–.038	.24	.031	.34
Melancholic features	131	.048	.14	.051	.13	–.069	.029	.060	.07
Comorbid anxiety disorder	479	–.002	.95	–.028	.40	.017	.58	–.020	.54
Comorbid dysthymia	217	.014	.66	.002	.94	–.035	.27	.057	.08
Suicide attempt in history	176	.050	.13	.033	.33	.040	.21	.007	.84
Model 3[e]									
Depression severity score (IDS-SR)		.047	.16	.036	.29	–.031	.34	.036	.29
Atypical features	207	.096	.004	.102	.002	–.035	.28	.023	.48
Melancholic features	131	.035	.29	.034	.31	–.066	.038	.050	.13
Comorbid anxiety disorder	479	–.007	.83	–.034	.30	.019	.54	–.023	.47
Comorbid dysthymia	217	.007	.83	–.007	.84	–.033	.30	.053	.10
Suicide attempt in history	176	.045	.17	.027	.41	.040	.20	.004	.90

[a]Number of the 761 currently depressed subjects with the concerning psychopathological characteristic. [b]β Coefficients indicate the standardized β by linear regression analyses. [c]Adjusted for age, sex (male/female), use of lipid lowering medication (yes/no), use of oral anticonceptives (yes/no), education level (basic/intermediate/high), cardiovascular disease (yes/no), and diabetes (yes/no). [d]Additionally adjusted for smoking status (none/former/current), alcohol use (0/1–2/> 2 glasses per day), and body mass index categories (< 18.5/18.5–24.99/25–29.99/> 30). [e]Additionally adjusted for antidepressant use (selective serotonin reuptake inhibitor/tricyclic antidepressant/other).
Abbreviations: HDL = high-density lipoprotein, IDS-SR = Inventory of Depressive Symptoms–Self-Report, LDL = low-density lipoprotein.

higher and HDL cholesterol levels were lower in MDD with melancholic features compared to MDD without melancholic features or controls. Additional analyses that excluded subjects using lipid-lowering medication or those suffering from CVD or diabetes and analyses that were additionally adjusted for laboratory site showed largely similar results (data not shown).

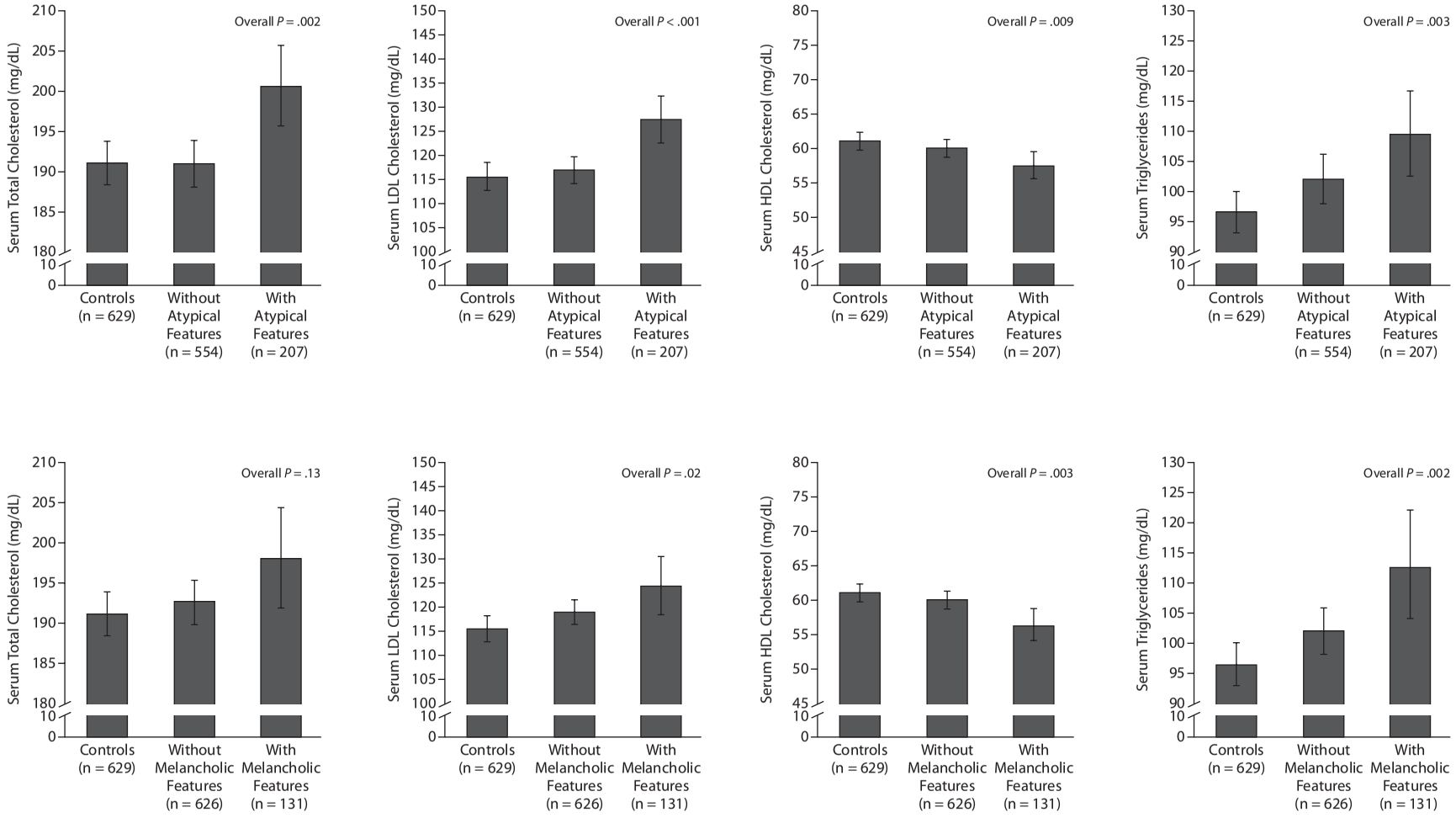
DISCUSSION

This large-scale study showed that currently depressed subjects had significantly lower mean HDL cholesterol and higher triglyceride levels compared to subjects with a remitted depression and healthy controls. No differences were found for total and LDL cholesterol levels. Although control subjects and those with remitted and current depression displayed a graded increase in depression severity scores, we did not find graded differences in lipid levels among study groups. Among currently depressed subjects, lipids/lipoproteins were especially unfavorable among those with high depression severity and atypical and melancholic features. Differences in lipids/lipoproteins between study groups and most associations with psychopathology characteristics attenuated after adjustment for smoking status, alcohol use and, especially, BMI. Yet, atypical features remained associated with higher levels of total and LDL cholesterol, and melancholic features remained associated with lower HDL cholesterol levels, even after additional adjustment for antidepressant use.

Equality of total cholesterol among study groups is in line with some previous studies[9–12] but contradicts others.[1–8] However, we found high levels of total cholesterol in atypical depression only, and insufficient attention for depression heterogeneity in previous research possibly accounts for these discrepant results. Also, variability in study design might have contributed to these varying results. Our finding of lower HDL cholesterol level in depression is in line with previous findings.[3,13] However, one study[12] found higher instead of lower HDL cholesterol levels and lower instead of higher triglyceride levels in major depressed subjects compared to controls. The fact that their depressed participants visited a general health screening unit, and consequently might have been preoccupied with health, might explain these findings. Furthermore, their sample size was small (n = 107), and participants were of Taiwanese origin, which might account for cultural and other differences (eg, in genetic background and diet) compared to our study. In line with our findings, depression severity has previously been associated with higher total cholesterol level.[34]

Only few studies investigating lipids/lipoproteins in depression adjusted analyses for factors like smoking,[7] alcohol use,[5,7] and BMI.[4,5,7,11,12] One study[11] that adjusted for BMI found no differences in lipids/lipoproteins between depressed and nondepressed elderly. Likewise, an association between low total cholesterol level and more severe depressive complaints was attenuated after adjustment for lifestyle-related factors.[9] Combined with the attenuation in our study of associations between lipids/lipoproteins and depression after adjustment for smoking, alcohol use, and BMI, these findings suggest that this association is not direct but rather secondary to health-related factors. Depressed persons have less healthy eating habits,[16] are more likely

Figure 1. Lipid/Lipoprotein Levels in Subjects With Atypical or Melancholic Features[a]



[a]In the upper 4 graphs, adjusted geometric mean lipid/lipoprotein levels in controls and current MDD without or with atypical features are presented. In the lower 4 graphs, adjusted geometric mean lipid/lipoprotein levels in controls and current MDD without or with melancholic features are presented. Bars indicate geometric means adjusted for age, sex (male/female), use of lipid-lowering medication (yes/no), use of oral anticonceptives (yes/no), education level (basic/intermediate/high), cardiovascular disease (yes/no), and diabetes (yes/no) in analysis of covariance; error bars indicate 95% CIs.
Abbreviations: HDL = high-density lipoprotein, LDL = low-density lipoprotein.

to be obese,[15] more often smoke,[10,17] and use either less[18] or more alcohol[19] compared to nondepressed persons. In the present study, these tendencies were also found regarding obesity and decreased alcohol use. As a consequence, obesity,[20] smoking,[21] and alcohol use[22] might have affected lipid/lipoprotein metabolism. The hypothesis of an indirect relationship between depression and lipids/lipoproteins is supported by statin trials in which no effect[35,36] or even a protective effect[37] of total cholesterol reduction on depression or suicide risk has been found. Our finding of a lower BMI and current smoking status in subjects with a remitted depression compared to subjects with a current depression and the remitted subjects' lipid profiles being comparable to controls also supports this hypothesis. Alternatively, increased BMI might partly be the result of an adverse lipoprotein pattern in depression through an as yet unknown mechanism. Still, other (biologic) mechanisms may be involved, for example, hypothalamic-pituitary-adrenal axis dysregulation,[38] or a low-grade inflammatory process as observed in depression may result in altered lipid metabolism (possibly through an increase in lipid peroxidation through oxidative stress).[39] Otherwise, obesity might lead to depression through increased bodily pain or psychosocial factors, such as a negative self-body image.[40] Another possible confounder in the association between depression and lipids/lipoproteins is the use of antidepressants. Despite its known antihistaminergic side effects, such as weight gain, especially of the tricyclic class,[24,25] use of antidepressants was not taken into account in previous studies. However, the use of antidepressants did not explain the associations between depression and lipids/lipoproteins in the present study.

The fact that study groups displayed a graded increase in depression severity score yet we did not find graded differences in lipid levels among study groups suggests that alterations in lipid levels are dependent on a current depressive state rather than on a history of lifetime depression. This is in line with a study by Olusi and Fido,[2] in which lipid levels tended to normalize after clinical recovery from MDD.

Persistent dyslipidemia in atypical depression could be explained by 2 of its diagnostic criteria that might increase total and LDL cholesterol levels[41]: an increased appetite and/or weight and leaden paralysis, which might reduce physical activity. The continual association between melancholic features and lower HDL cholesterol level might be explained by the metabolic syndrome,[38] which comprises reduced HDL cholesterol[23] and is thought to be associated with depression[42] through shared underlying biologic pathways, such as hypercortisolism.[43]

Finally, although previous research suggests that both CVD and diabetes more often occur in depressed subjects as compared to controls,[44,45] we did not find a significant difference in CVD or diabetes prevalence between controls and subjects with a current or remitted depression. This may reflect the rather young age of our sample in which these somatic conditions are not yet highly prevalent.

Our study has some limitations. Because of our cross-sectional analyses, no causal inferences can be made. Furthermore, nutritional data, which were not available, could have helped to study underlying mechanisms of our results. A strength of our study is the large sample size, which provides enough subjects with depression to reliably differentiate the association between lipids/lipoproteins and several psychopathological characteristics. Importantly, depression was diagnosed according to the gold standard, *DSM-IV*, and important potential confounders were taken into account.

In conclusion, we found that current depression was associated with an unfavorable lipid and lipoprotein profile, especially in patients with melancholic and atypical features but that this association is to a large extent due to underlying lifestyle-related factors, especially obesity. Unfavorable lipid/lipoprotein patterns are associated with an increased CVD morbidity and mortality risk[23] and could therefore contribute to the increased CVD risk among the depressed.[46] Consequently, it could be advisable for care providers to promote a healthy lifestyle, especially obesity prevention/reduction, within psycho-education for their depressed patients.

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