Learning Objectives

1. Explain the clinical presentations, pathophysiology, and diagnostic criteria for depression
2. Review the physiological roles of lipoproteins
3. Discuss the disorders of lipoproteins including the inherited causes of low-density lipoprotein cholesterol (LDL-C)
4. Evaluate current literature to determine the effects and safety of low LDL-C on the risks of depression
Major Depressive Disorder

I. Epidemiology
   A. Incidence and prevalence
      i. Leading cause of disability in the U.S. for ages 15-44
      ii. May first appear at any age, but the likelihood of onset increases significantly with puberty
      iii. Prevalence in the U.S.
         a. Annual: ~6.7%
         b. Lifetime: ~16.4%
      iv. Females experience 1.5-3 fold higher rates than males beginning in early adolescence
   B. Risk factors
      i. Female
      ii. Native American
      iii. Middle-aged
      iv. Widowed, separated, divorced
      v. Low income
      vi. Concomitant psychiatric disorder (e.g., substance dependence, panic disorder, generalized anxiety disorder)
      vii. Personality disorders (e.g., avoidance, dependent, paranoid, schizoid)
      viii. General medical conditions (e.g., diabetes, stroke, cancer)
      ix. First-degree relative with depression
      x. Stressful or traumatic life events

II. Diagnosis of MDD

<table>
<thead>
<tr>
<th>Table 1. Diagnostic Criteria Per Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-V)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. Five (or more) of the following symptoms have been present during the same 2-week period and represent a change from previous functioning; at least one of the symptoms is either (1) depressed mood or (2) loss of interest or pleasure</td>
</tr>
<tr>
<td>1. Depressed mood most of the day, nearly every day</td>
</tr>
<tr>
<td>2. Markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day</td>
</tr>
<tr>
<td>3. Significant weight loss or weight gain</td>
</tr>
<tr>
<td>4. Insomnia or hypersomnia nearly every day</td>
</tr>
<tr>
<td>5. Psychomotor agitation or retardation nearly every day</td>
</tr>
<tr>
<td>6. Fatigue or loss of energy nearly every day</td>
</tr>
<tr>
<td>7. Feelings of worthlessness or excessive or inappropriate guilt</td>
</tr>
<tr>
<td>8. Diminished ability to think or concentrate or indecisiveness nearly every day</td>
</tr>
<tr>
<td>9. Recurrent thoughts of death (not just fear of dying) recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide</td>
</tr>
<tr>
<td>B. The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning</td>
</tr>
<tr>
<td>C. The episode is not attributable to the physiological effects of a substance or to another medical condition</td>
</tr>
</tbody>
</table>
III. Pharmacotherapy *(See Appendix A)*

IV. Symptoms: “SIGECAPS” mnemonic

A. Sleep changes
B. Interest (loss of)
C. Guilt (feelings of worthlessness or guilt)
D. Energy (lack of)
E. Concentration/cognition (reduced and/or difficulties)
F. Appetite (increase or decrease)
G. Psychomotor activity (agitation or retardation)
H. Suicidal thoughts/ideations

V. Etiology and pathogenesis

A. Precise etiology unclear – generally characterized as a complex relationship between genetics and environment exposures.

B. Twin and family

i. Twin studies suggest a heritability of 40-50%
ii. Family studies show a 2-3 fold increase in lifetime risk among first-degree relatives

C. Genes

i. Susceptibility genes have suggested several regions in the genome
ii. No universal gene for MDD
iii. Several genes have been implicated in MDD
   a. Serotonin transporter gene (5-HTTLPR/SLC6A4)
   b. Serotonin receptor 2A (HTR2A)
   c. Brain-derived neurotrophic factor (BDNF) gene
   d. Tryptophan hydroxylase (TPH2) gene

<table>
<thead>
<tr>
<th>Table 2. Possible Mechanisms of Depression</th>
</tr>
</thead>
<tbody>
<tr>
<td>Theory</td>
</tr>
<tr>
<td>------------------------</td>
</tr>
<tr>
<td>Monoamine-deficiency hypothesis</td>
</tr>
<tr>
<td>Dysfunctions of the hypothalamic-pituitary-adrenal axis (HPA)</td>
</tr>
<tr>
<td>Neurotrophic hypothesis</td>
</tr>
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<tr>
<td>Altered glutamatergic neurotransmission</td>
</tr>
<tr>
<td>Thyroxe abnormalities</td>
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<tr>
<td></td>
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<tr>
<td>Deficient neurosteroid Synthesis</td>
</tr>
</tbody>
</table>
Emergence of a Link Between Low LDL-C and Depression

I. Initial findings
   A. Relationship between cholesterol and depression first noted in the early 1990s
   B. Patients with depression
      i. Lower total cholesterol
      ii. Lower LDL-C
      iii. Total cholesterol improved following antidepressant therapy

II. Hypotheses of mechanisms
   A. Affected serotonin function
      i. Reduction in cholesterol may cause a decrease in serotonergic functioning
      ii. Cholesterol depletion may impair the function of serotonin receptors and serotonin transporter activities
   B. Genes
      i. Association between depression and short allele polymorphism (s/s) for serotonin transporter gene
      ii. Association between MDD and apolipoprotein E (apoE)

Plasma Lipids

I. Lipids
   A. A class of organic macromolecules
   B. Biologically important lipids
      i. Triglycerides (TG)
      ii. Sterols
      iii. Fatty acids and their derivatives
      iv. Phospholipids and related compounds
   C. Biological functions of lipids
      i. Energy storage
      ii. Structural components of cell membranes
      iii. Signaling of chemical and biological activities

II. Lipoproteins (LP)
   A. Major lipids that are relatively insoluble in aqueous solutions and do not circulate in the free form
   B. Function: facilitate transport of lipids around cells in the extracellular fluids
   C. Components
      i. LP core
         a. TG
         b. Cholesterol esters
      ii. LP single layer membrane
         a. Phospholipids
         b. Apolipoproteins (also known as apoproteins)
         c. Cholesterol
I. Classification of LP

A. Five major subtypes
   i. Chylomicrons
   ii. Very low-density lipoprotein cholesterol (VLDL-C)
   iii. Intermediate-density lipoprotein cholesterol (IDL-C)
   iv. Low-density lipoprotein cholesterol (LDL-C)
   v. High-density lipoprotein cholesterol (HDL-C)

B. Characteristically defined by particle density
   i. Protein component increases the relative density of a given particle compared to the lipid component
   ii. Denser lipoprotein have an increased protein:lipid ratio
   iii. Highest to lowest density: HDL-C > LDL-C > IDL-C > VLDL-C > chylomicron
Table 3. Major Functions of Specific LP

<table>
<thead>
<tr>
<th>Classification</th>
<th>Primary Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chylomicrons</td>
<td>Transport exogenous TG from the intestine to the liver, skeletal muscle, and adipose tissue</td>
</tr>
<tr>
<td>VDL-C</td>
<td>Transport endogenous TG from the liver to the skeletal muscles and adipose tissue</td>
</tr>
<tr>
<td>IDL-C</td>
<td>Transport endogenous cholesterol for conversion to LDL-C or receptor-mediated endocytosis by liver</td>
</tr>
<tr>
<td>LDL-C</td>
<td>Transport endogenous cholesterol for receptor-mediated endocytosis by the liver or by extrahepatic tissues</td>
</tr>
<tr>
<td>HDL-C</td>
<td>Removal of cholesterol from extrahepatic tissues via transfer of cholesterol to IDL-C and LDL-C</td>
</tr>
</tbody>
</table>

II. Apolipoproteins

A. Apolipoproteins are polypeptides found in various types of LP

B. Functions of apolipoproteins
   i. Provide structural stability to the LP
   ii. Function as ligands in LP receptor interactions
   iii. Function as cofactors in enzymatic processes that regulate lipoprotein metabolism
   iv. Assist in the transport of LP

C. Apolipoproteins are divided into class and sub-class
   i. Class: A, B, C, D, E, H
   ii. Sub-class: AIV, AIII, Av, B48, B100, CIII, CIV

III. Components and measurement of a lipid panel

A. Total cholesterol (TC)
B. HDL-C
C. TG
D. LDL-C
   i. LDL-C may be measured directly or calculated using Friedewald formula
   ii. Friedewald formula: LDL-C = TC − (HDL-C + TG/5)
   iii. Calculation not valid if TG > 400 mg/dL

IV. Lipid transport system

A. LDL-C is the main carrier of circulating cholesterol
B. LDL-C particles are taken up by LDL-C receptors in the liver
C. Free cholesterol is released and accumulates within the cells as LDL-C is taken up by receptors

Disorders of Lipoproteins

I. Occur as a result of ≥ 1 genetic abnormalities or secondary to underlying diseases

II. Fredrickson, Levy, and Lees first classified hyperlipoproteinemias

   A. Classification according to the type of LP particle that accumulates in the blood
   B. Provides insights into the critical roles of apolipoproteins, enzymes, and receptors in lipid metabolism
   C. Not a diagnostic classification
Table 4. Fredrickson Classification

<table>
<thead>
<tr>
<th>Phenotype</th>
<th>LP Elevated</th>
<th>Cholesterol Level</th>
<th>TG Level</th>
<th>Atherogenicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Chylomicrons</td>
<td>Normal to mild ↑</td>
<td>Very severely ↑</td>
<td>None</td>
</tr>
<tr>
<td>IIa</td>
<td>LDL-C</td>
<td>Moderately ↑</td>
<td>Normal</td>
<td>Severe</td>
</tr>
<tr>
<td>IIb</td>
<td>LDL-C and VLDL-C</td>
<td>Moderately ↑</td>
<td>Moderately ↑</td>
<td>Severe</td>
</tr>
<tr>
<td>III</td>
<td>IDL-C</td>
<td>Moderately ↑</td>
<td>Severely ↑</td>
<td>Severe</td>
</tr>
<tr>
<td>IV</td>
<td>VLDL-C</td>
<td>Normal to mild ↑</td>
<td>Moderately ↑</td>
<td>Mild to Moderate</td>
</tr>
<tr>
<td>V</td>
<td>VLDL-C and chylomicrons</td>
<td>Normal to mild ↑</td>
<td>Very severely ↑</td>
<td>Mild to moderate</td>
</tr>
</tbody>
</table>

A Focus on the 2013 Cholesterol Guidelines

I. Prior classification of LDL-C levels per the National Cholesterol Education Program (NCEP) Third Adult Treatment Panel (ATP III) \(^2^9\)
   A. < 100 mg/dL: optimal
   B. 100-129 mg/dL: above optimal
   C. 130-159 mg/dL: borderline high
   D. 160-189 mg/dL: high
   E. ≥ 190 mg/dL: very high

II. Per the 2013 American College of Cardiology/American Heart Association (ACC/AHA) cholesterol guidelines \(^3^0\)
   A. “The Expert Panel was unable to find RCT evidence to support continued use of specific LDL-C and/or non-HDL-C treatment targets”
   B. Therapy no longer modified to target specific LDL-C or non-HDL-C goals
   C. Definition of ASCVD
      i. Acute coronary syndromes (ACS)
      ii. History of myocardial infarction (MI)
      iii. Stable or unstable angina
      iv. Coronary or other arterial revascularization
      v. Stroke
      vi. Transient ischemic disease (TIA)
      vii. Peripheral arterial disease (PAD) presumed to be of atherosclerotic origin
   D. New treatment approach
      i. Goal: treat the level of ASCVD risk
      ii. Patients stratified into 4 statin benefit groups (See Appendices B and C)
         a. Clinical ASCVD
         b. LDL-C ≥ 190 mg/dL
         c. Diabetes mellitus (DM) age 40-75 years with an LDL-C 70-189 mg/dL and without ASCVD
         d. LDL-C 70-189 mg/dL and an estimated 10-year ASCVD risk ≥ 7.5% without DM or ASCVD
III. Pharmacological therapy: initiation of statin therapy

<table>
<thead>
<tr>
<th>Patient Group Characteristics</th>
<th>Target Reduction of LDL-C</th>
<th>Recommended Statin Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical ASCVD</td>
<td>By ≥ 50%</td>
<td>High intensity</td>
</tr>
<tr>
<td>LDL-C ≥ 190 mg/dL</td>
<td>By ≥ 50%</td>
<td>High intensity</td>
</tr>
<tr>
<td>DM age 40-75 years with an LDL-C of 70-189 mg/dL and without ASCVD</td>
<td>By 30-49%</td>
<td>Moderate intensity</td>
</tr>
<tr>
<td>LDL-C of 70-189 mg/dL and an estimated 10-year ASCVD risk ≥ 7.5% without DM or ASCVD</td>
<td>By 30-49%</td>
<td>Moderate to high intensity</td>
</tr>
</tbody>
</table>

IV. Other approaches to treatment of blood cholesterol have been advocated

A. Treat to target
   i. No understanding on magnitude of additional ASCVD risk reduction between one target LDL-C to another
   ii. No data on potential adverse drug events from multidrug therapy that may be needed to achieve LDL-C goal

B. Lowest is best: no consideration of potential adverse effects of multidrug therapy with unknown magnitude of ASCVD event reduction

V. Impact of new cholesterol guidelines in statin use *(See Appendix D)*

A. Statin use increase
   i. From 43.2 million to 56.0 million U.S. adults
   ii. Adults without cardiovascular disease and with lower LDL-C
   iii. Adults with DM increase from 4.5 million to 6.7 million
   iv. Largest increase in adults with an indication for primary prevention and ASCVD ≥ 7.5% (15.1 million versus 6.9 million adults)

B. LDL-C < 100 mg/dL not eligible according to ATP III would be eligible per 2013 guidelines: 2.4 million adults

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**Insights from Populations with Inherited Causes of Low LDL-C**

I. TC and LDL-C change as humans age
II. TC and LDL-C levels reach approximately 55 and 30 mg/dL during late gestation in utero
III. Abetalipoproteinemia (ABL)
   A. Etiology and pathogenesis
      i. Rare autosomal recessive disorder
      ii. Mutations in the processing of apoB or secretion of apoB-containing LP
         a. Heterozygous for mutation: no abnormalities of LP or clinical signs
         b. Homozygous for mutation: all forms of apoB are absent
      iii. LP abnormalities
         a. LDL-C: undetectable
         b. TG: < 10-20 mg/dL and fail to rise after a fat load
         c. TC : < 90 mg/dL
B. Clinical features
   i. Paucity of adipose tissue
   ii. Retinal degeneration
   iii. Fat soluble vitamin deficiencies
   iv. Steatorrhea
   v. Impaired growth in infancy
   vi. Acanthocytosis
   vii. Ataxia
   viii. Sensory neuropathy
   ix. Cardiomyopathy with arrhythmia has been reported

IV. Familial hypobetalipoproteinemia (FHBL) 28
   A. Autosomal dominant disorder
   B. Defects at the apoB locus
   C. Heterozygous for mutation
      i. No clinical features
      ii. TC: < 120 mg/dL
      iii. LDL-C: < 80 mg/dL
      iv. TG: normal
   D. Homozygous for mutation
      i. TC: < 80 mg/dL
      ii. LDL-C levels: < 20 mg/dL
      iii. Clinical and biochemical features may be indistinguishable from ABL
   E. Clinical features
      i. Intestinal fat malabsorption
      ii. Hepatic steatosis
      iii. Fat soluble vitamin deficiencies

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**Effects of Low LDL-C**

I. Hypolipidemia is defined as a TC < 120 mg/dL or LDL-Cholesterol < 50 mg/dL 33

II. Scant data are available on the safety of “very low” LDL-C levels despite expanded indications for high-intensity statin

III. What do we know?
   A. LDL-C is the major carrier of cholesterol
   B. Strategies aimed at lowering LDL-C remain a primary approach to reduce cardiovascular risk
   C. Patients with ABL and FHBL exhibit negative clinical features
   D. 12.8 million more adults are on statin therapy

IV. Per ACC/AHA cholesterol guidelines: “Decreasing the statin dose may be considered when 2 consecutive values of LDL-C are < 40 mg/dL”

V. Current evidence on very-low LDL-C
   A. Increase risk of cancer *(See Appendix E)* 34-37
   B. Increase risk of intracranial hemorrhage *(See Appendix F)* 38-41
   C. Increase risk of depression 42-44

<table>
<thead>
<tr>
<th>Objective</th>
<th>Investigate the association between serum lipids and depressive symptoms in a population of elderly men</th>
</tr>
</thead>
<tbody>
<tr>
<td>Design</td>
<td>Retrospective chart review</td>
</tr>
<tr>
<td>Population</td>
<td>Finnish cohort (N_total=421) of men ages 70-89 years born between 1900 and 1919</td>
</tr>
<tr>
<td>Outcomes</td>
<td>Prevalence of depression</td>
</tr>
<tr>
<td>Methods</td>
<td>• 30 year follow-up from 1989 &lt;br&gt;• Scales Assessments &lt;br&gt;  o Zung Self-Rating Depression Scale (ZSDS): used to assess depressive symptoms &lt;br&gt;  • Scoring ≥ 48/80 was defined as depressed &lt;br&gt;  o Mini-Mental State Examination (MMSE): used to assess cognitive status &lt;br&gt;  o Activities of Daily Living (ADL) &lt;br&gt;  o Presence of concomitant chronic conditions (e.g., heart disease, cerebrovascular disease, lung disease, heart disease, arthritis, ulcer, cancer, disease of the gall bladder, diabetes) &lt;br&gt;  o Lipid panel from 1984 and 1989</td>
</tr>
<tr>
<td>Statistics</td>
<td>• Mantel-Haenszel test used to assess relationship between categorical depression and cholesterol quartiles</td>
</tr>
<tr>
<td>Results</td>
<td>• Prevalence of depression &lt;br&gt;  o Depressed: 15.2% (n=64) &lt;br&gt;  o Not depressed: 14.8% &lt;br&gt;• Psychotropic medication use (5 of which were antidepressants) &lt;br&gt;  o Depressed: 35.9% &lt;br&gt;  o Not depressed: 14.8% &lt;br&gt;• None were on lipid-lowering medications</td>
</tr>
</tbody>
</table>

Table 6-1. Characteristics of the Study Population by Depressive Status

<table>
<thead>
<tr>
<th>Variable</th>
<th>Not depressed ZSDS &lt; 48 (n=357)</th>
<th>Depressed ZSDS &gt; 48 (n=64)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>TC in 1989 (mg/dL)</td>
<td>224.28 ± 42.5</td>
<td>204.9 ± 38.7</td>
<td>0.001</td>
</tr>
<tr>
<td>TC in 1984 (mg/dL)</td>
<td>243.6 ± 46.4</td>
<td>224.3 ± 42.5</td>
<td>0.002</td>
</tr>
<tr>
<td>Cholesterol Change 1984-1989 (mg/dL)</td>
<td>-20.1 ± 34.8</td>
<td>-20.1 ± 30.9</td>
<td>0.986</td>
</tr>
<tr>
<td>HDL-C (mg/dL)</td>
<td>46.4 ± 11.6</td>
<td>38.7 ± 11.6</td>
<td>0.004</td>
</tr>
<tr>
<td>LDL-C (mg/dL)</td>
<td>150.8 ± 38.7</td>
<td>135.34 ± 34.8</td>
<td>0.005</td>
</tr>
<tr>
<td>TG (mg/dL)</td>
<td>58 ± 27.07</td>
<td>58 ± 27.07</td>
<td>0.686</td>
</tr>
</tbody>
</table>

Table 6-2. Determinants of Depression

<table>
<thead>
<tr>
<th>Variable</th>
<th>OR</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>TC</td>
<td>0.67</td>
<td>0.48-0.94</td>
<td>0.022</td>
</tr>
<tr>
<td>LDL-C</td>
<td>0.67</td>
<td>0.46-0.98</td>
<td>0.041</td>
</tr>
<tr>
<td>HDL-C</td>
<td>0.45</td>
<td>0.11-1.76</td>
<td>0.249</td>
</tr>
</tbody>
</table>

Authors’ conclusions <br>• Low TC and LDL-C are associated with heightened depressive symptomatology in elderly men <br>• This association is independent of the effect of chronic disease, change in weight and other health related factors
Critique

<table>
<thead>
<tr>
<th>Strengths</th>
<th>Limitations</th>
</tr>
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<tbody>
<tr>
<td>• Long follow-up time</td>
<td>• Limited external validity</td>
</tr>
<tr>
<td>• High response rate</td>
<td>• Retrospective study</td>
</tr>
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<td></td>
<td>• Potentially ↓ participation by depressed patients</td>
</tr>
<tr>
<td></td>
<td>• Higher ZSDS score cut-off has been recommended</td>
</tr>
</tbody>
</table>


**Objective**
Determine the association between lipid levels and depressive symptoms, in coordination with gender

**Design**
Prospective, cross-sectional analysis

**Population**
- Participants drawn at random from the Montpellier district between March 1999 and February 2001
- ≥ 65 years of age and non-institutionalized (N_{total}=1792)

**Outcomes**
Prevalence of depression

**Methods**
- Scales, assessments, and exams
  - Mini-International Neuropsychiatric Interview (MINI) and DSM-IV
    - Diagnose lifetime depression or anxiety disorders
  - Center for Epidemiologic Studies-Depression Scale (CES-D)
    - Assess levels of depressive symptomatology
  - Mini Mental State Examination (MMSE)
    - Assess cognitive function
  - Standardized interview
    - Included questions about socio-demographic characteristics, height, weight, mobility, recent loss of appetite, smoking, alcohol consumption
  - Detailed medical questionnaires
    - Included information on history of vascular disease, drugs used during the preceding month
  - Genotyping of ApoE and 5-HTTLPR
- Classification of depression
  - Clinical level of depression (DEP) defined as MINI diagnosis of MDD or CES-D ≥ 16
  - MINI diagnosis showing absent of MDD or CES-D ≤ 15: referred to as low symptom group
- Three models for analysis
  - Model 0: Adjusted for age and education level
  - Model 1: Model 0 adjusted for marital status, body mass index, mobility, cognitive impairment, ischemic pathologies, hypertension, diabetes, tobacco and alcohol intake, loss of appetite, and apolipoprotein E
  - Model 2: Model 1 adjusted for antidepressant and anxiolytic use, lifetime anxiety disorder, and past major depression

**Statistics**
- Un adjusted analyses were carried out using chi-square tests or analysis of variance for qualitative and quantitative data
- Associations between lipid classes and DEP were assessed using logistic regression models

**Results**
- Baseline characteristics
  - 29.9% had DEP
  - Women had increased levels of depression, TC, HDL-C, LDL-C, but decreased TG
  - Males and females found to be different on all levels except for age, use of lipid agent use, and genotype 5-HTTLPR
Table 7.1: Adjusted Models for Associations Between LDL-C and Depression

<table>
<thead>
<tr>
<th></th>
<th>Model 0</th>
<th></th>
<th>Model 1</th>
<th></th>
<th>Model 2</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR</td>
<td>95% CI</td>
<td>p</td>
<td>OR</td>
<td>95% CI</td>
<td>p</td>
</tr>
<tr>
<td>Men</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HDL-C</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 21.4</td>
<td>1.28</td>
<td>0.84-1.97</td>
<td>0.25</td>
<td>1.06</td>
<td>0.67-1.67</td>
<td>0.82</td>
</tr>
<tr>
<td>≥ 29.2</td>
<td>1.12</td>
<td>0.73-1.34</td>
<td>0.61</td>
<td>1.13</td>
<td>0.71-1.79</td>
<td>0.61</td>
</tr>
<tr>
<td>LDL-C</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 117.9</td>
<td>1.90</td>
<td>1.25-2.89</td>
<td>0.003</td>
<td>1.75</td>
<td>1.11-2.74</td>
<td>0.2</td>
</tr>
<tr>
<td>≥ 158.9</td>
<td>0.97</td>
<td>0.61-1.54</td>
<td>0.91</td>
<td>1.10</td>
<td>0.68-1.78</td>
<td>0.70</td>
</tr>
<tr>
<td>Women</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>HDL-C</td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 26.1</td>
<td>1.42</td>
<td>1.04-1.94</td>
<td>0.03</td>
<td>1.37</td>
<td>0.98-1.91</td>
<td>0.06</td>
</tr>
<tr>
<td>≥ 36.0</td>
<td>1.09</td>
<td>0.79-1.49</td>
<td>0.61</td>
<td>1.04</td>
<td>0.75-1.44</td>
<td>0.83</td>
</tr>
<tr>
<td>LDL-C</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 120.3</td>
<td>1.17</td>
<td>0.85-1.59</td>
<td>0.34</td>
<td>1.14</td>
<td>0.82-1.57</td>
<td>0.44</td>
</tr>
<tr>
<td>≥ 165.5</td>
<td>0.88</td>
<td>0.64-1.22</td>
<td>0.45</td>
<td>0.87</td>
<td>0.6-1.22</td>
<td>0.42</td>
</tr>
</tbody>
</table>

- **LDL-C**
  - Men: < 117.9 mg/dL statistically significantly associated with depression
  - Women: not statistically significant with depression
- **HDL-C**
  - Men: not statistically significantly associated with depression
  - Women: < 26.1 mg/dL statistically significantly associated with depression
- **Lipid-lowering agent use and DEP**
  - Men (OR 0.90, 95% CI 0.60-1.36, p=0.63)
  - Women (OR 1.18, 95% CI 0.89-1.58, p=0.26)
- **LDL-C and DEP by 5-HTTLPR polymorphism**
  - Men
    - LDL-C < 117.9 mg/dL with s/s alleles were at high risk (OR 6.00, 95% CI 1.40-25.63, p=0.02) compared with middle-quartiles LDL-C
    - LDL-C < 117.9 mg/dL with s/l alleles were at high risk (OR 2.69, 95% CI 1.15-6.29, p=0.02) compared with middle-quartiles LDL-C
    - No significant interactions between LDL-C levels and l/l genotype (OR 0.71, 95% CI 0.20-2.56, p=0.60)
  - Women
    - No significant interaction between low HDL-C levels and other covariates including 5-HTTLPR

**Authors’ conclusions**
- There is an increased prevalence of DEP among men with a low LDL-C level and in women with low HDL-C levels
- Lower 5-HTTLPR activity may ↑ depression in men
- Low HDL-C were associated with an ↑ risk in women

**Critique**
- **Strengths**
  - MDD measured by various scales, including diagnostic interviews
  - Controlled for a large number of covariates
- **Limitations**
  - Covariates were self-reported
<table>
<thead>
<tr>
<th>Objective</th>
<th>Assess the impact on cardiovascular and adverse events of attaining LDL-C levels &lt; 50 mg/dL with rosuvastatin in apparently healthy adults</th>
</tr>
</thead>
<tbody>
<tr>
<td>Design</td>
<td>Multicenter, double-blind, parallel-group, randomized, placebo-controlled trial</td>
</tr>
<tr>
<td>Population</td>
<td>(N&lt;sub&gt;total&lt;/sub&gt;=16,304)</td>
</tr>
</tbody>
</table>

**Inclusion**
- Men ≥ 50 years, women ≥ 60 years
- LDL-C < 130 mg/dL
- C-Reactive Protein (CRP) > 2.0 mg/L
- TG < 500 mg/dL

**Exclusion**
- Use of lipid-lowering therapy in the past
- History of cardiovascular or cerebrovascular events
- Active liver disease
- DM
- Uncontrolled hypertension or hypothyroidism
- History of certain malignancies
- Chronic inflammatory conditions
- History of alcohol or drug abuse

**Outcomes**
**Primary**
- A composite of myocardial infarction (MI), stroke, arterial revascularization, unstable angina, or confirmed death from cardiovascular causes

**Safety**
- Any adverse event, musculoskeletal/connective tissue disorders, gastrointestinal disorders, respiratory, thoracic, mediastinal disorders, nervous system disorders, nervous system disorders, renal and urinary disorders, eye disorders, cancer, psychiatric disorders, DM, hepatobiliary disorders

**Methods**

- **Follow-up**
  - Median follow-up was 2 years
  - Lipid profiles at baseline, annually thereafter, and at the final visit

**Statistics**
- Post-hoc analysis which includes all randomized JUPITER participants with at least 1 post-randomization lipid profile
- Multivariable logistic regression used to identify predictors of attaining LDL-C < 50 mg/dL
- Cox proportional hazard model used to calculate hazard ratio and 95% confidence interval

**Results**
- Baseline and 1-year LDL-C
  - Placebo: 109 and 110 mg/dL
  - Rosuvastatin, LDL-C ≥ 50 mg/dL: 113 and 70 mg/dL
  - Rosuvastatin, LDL-C < 50 mg/dL: 103 and 44 mg/dL

---

**Table 8.** Hsia J, MacFadyen JG, Monyak J, Risker PM. Cardiovascular event reduction and adverse events among subjects attaining low-density lipoprotein cholesterol < 50 mg/dL with rosuvastatin. The JUPITER trial (Justification for the Use of Statins in Prevention: An Intervention Trial Evaluating Rosuvastatin). *J Am Coll Cardiol.* 2011;57:1666–1675. 44

**Figure 8-1. Stratification of Patients**

- LDL-C < 50 mg/dL
- LDL-C ≥ 50 mg/dL
- LDL-C < 50 mg/dL
- LDL-C ≥ 50 mg/dL

---

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Table 8-1. Independent Predictors of Attaining LDL-C < 50 mg/dL Among Rosuvastatin Arm

<table>
<thead>
<tr>
<th>Variable</th>
<th>Odds Ratio</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>1.023</td>
<td>1.017-1.030</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Men</td>
<td>1.190</td>
<td>1.069-1.324</td>
<td>0.002</td>
</tr>
<tr>
<td>Impaired fasting glucose</td>
<td>1.251</td>
<td>1.129-1.385</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Adherence to study medication</td>
<td>1.025</td>
<td>1.022-1.029</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Body mass index</td>
<td>1.027</td>
<td>1.018-1.036</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Baseline LDL-C</td>
<td>0.968</td>
<td>0.965-0.971</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Baseline HDL-C</td>
<td>0.996</td>
<td>0.993-1.000</td>
<td>0.023</td>
</tr>
<tr>
<td>Baseline CRP</td>
<td>0.990</td>
<td>0.985-0.996</td>
<td>0.001</td>
</tr>
</tbody>
</table>

- Primary end point
  - Placebo vs. rosuvastatin, no LDL-C < 50 mg/dL compared to placebo vs. LDL-C < 50 mg/dL
    - NO LDL-C < 50 mg/dL (HR 0.76 vs. placebo, 95% CI 0.57-1.00) compared with LDL-C < 50 mg/dL (HR 0.35, 95% CI 0.25-0.49, p < 0.0001)
  - LDL-C < 50 mg/dL vs. NO LDL-C < 50 mg/dL patients: HR 0.39, 95% CI 0.26-0.59, p = 0.0001)
- All-cause mortality
  - HR 1.15, 95% CI 0.83-1.58 vs. HR 0.54, 95% CI 0.37-0.78 for patients without and with LDL-C 50 mg/dL, respectively; p < 0.004
- Adverse events (focus on Psychiatric Disorders)

Table 8-2. Numbers and Rates (Per 100 Person-Years) of Treatment Emergent Adverse Events

<table>
<thead>
<tr>
<th></th>
<th>Placebo (n=8,150)</th>
<th>LDL-C ≥ 50 mg/dL (n=4,000)</th>
<th>LDL-C &lt; 50 mg/dL (n=4,154)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>N</td>
<td>p-value vs. placebo</td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td>619</td>
<td>307</td>
<td>0.67</td>
</tr>
<tr>
<td>Insomnia</td>
<td>205</td>
<td>104</td>
<td>0.79</td>
</tr>
<tr>
<td>Depression</td>
<td>217</td>
<td>103</td>
<td>0.83</td>
</tr>
<tr>
<td>Anxiety</td>
<td>158</td>
<td>66</td>
<td>0.29</td>
</tr>
<tr>
<td>Anger</td>
<td>4</td>
<td>0</td>
<td>-</td>
</tr>
</tbody>
</table>

Authors’ conclusions
- Psychiatric disorders among the arms did not differ; however rate of depression was statistically significant when comparing rosuvastatin, LDL-C < 50 mg/dL vs. placebo

Critique
- Strengths
  - Randomized, placebo control trial
  - Large sample size
  - Systematic adverse event ascertainment
- Limitations
  - Shortened follow-up time of 2 years
**Additional Considerations**

<table>
<thead>
<tr>
<th>Table 9. Evidence Table with Studies that Failed to Find an Association Between LDL-C and Depression</th>
<th>45,46</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Study</strong></td>
<td><strong>Study Design</strong></td>
</tr>
</tbody>
</table>
| Ergun UG, et al. | • Prospective, cross-sectional study | • N=189 females and males  
• Inclusion  
  o ≥ 65 years old  
• Exclusion  
  o Stroke, brain hemorrhage, cancer, broken hip, depression due to general medical conditions or medications, current treatment with lipid lowering or antidepressant medications | • Depressed: N=42 (22%)  
• No relationship between TC, TG, HDL-C, LDL-C levels and depression (p > 0.05) |
| Deisenhammer EA, et al. | • Retrospective chart review  
• Treatment: inpatient antidepressants  
  o Tricyclics (14%), SSRIs (46%), other antidepressants (46%), mood stabilizers (14%), antipsychotics (58%), BZD (74%)  
• Follow-up: 4 weeks | • N=92 females and males admitted into the Department of Psychiatry Innsbruck University Hospital inpatient ward  
• Inclusion  
  o MDD per DSM-IV, 19-65 years old  
• Exclusion  
  o Not suffering from somatic disease, Axis 1 diagnosis other than mood disorders, borderline personality disorders, current treatment with lipid lowering medications | • Drop out  
  o Week 1: N=86  
  o Week 4: N=50  
• No significant changes for LDL-C and TG between weeks 1 and 4  
• Serum cholesterol levels did not change significantly during antidepressant treatment |

*SSRI: selective serotonin reuptake inhibitor; BZD: benzodiazepine*

**Conclusions and Recommendations**

I. Depression is a complex and multifactorial trait with important genetic and nongenetic contributory factors

II. Monitoring of LDL-C in patients with depression
   A. The evidence is weak to suggest there is a correlation between LDL-C and depression
   B. There is a lack of evidence to recommend the consideration of establishing threshold for LDL-C to minimize the risk of depression
   C. Causality between depression and low LDL-C remains unclear

III. In accordance with FDA specialists’ opinion, level of risk for death from coronary heart disease should be the most important factor and that prescribers should not be discouraged from prescribing cholesterol lowering drugs in cases in which they are indicated


44. Hsia J, MacFadyen JG, Monyak J, Risker PM. Cardiovascular event reduction and adverse events among subjects achieving low-density lipoprotein cholesterol <50 mg/dl with rosuvastatin. The JUPITER trial (Justification for the Use of Statins in Prevention: An Intervention Trial Evaluating Rosuvastatin). J Am Coll Cardiol. 2011;57:1666–1675.


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### Appendix A. Pharmacotherapy for MDD

<table>
<thead>
<tr>
<th>Agent</th>
<th>Starting Dose</th>
<th>Standard Dose</th>
<th>Target Receptors</th>
<th>Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Selective Serotonin Reuptake Inhibitors (SSRI)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>20 mg daily</td>
<td>20-40 mg daily</td>
<td>NE and DA</td>
<td>Activating effect</td>
</tr>
<tr>
<td>Paroxetine</td>
<td>20 mg daily</td>
<td>20-40 mg daily</td>
<td>Anticholinergic (M1), weak NE</td>
<td>Sedating; anticholinergic</td>
</tr>
<tr>
<td>Sertraline</td>
<td>50 mg daily</td>
<td>50-150 mg daily</td>
<td>Weak DA</td>
<td>Sedating; antihistamine</td>
</tr>
<tr>
<td>Citalopram</td>
<td>20 mg daily</td>
<td>20-40 mg daily</td>
<td>Antihistamine</td>
<td>Slightly sedating; QT prolongation potential associated with &gt; 40 mg daily*</td>
</tr>
<tr>
<td>Escitalopram</td>
<td>10 mg daily</td>
<td>10-20 mg daily</td>
<td>--</td>
<td>May be twice as potent as citalopram</td>
</tr>
<tr>
<td>Fluvoxamine</td>
<td>50 mg daily</td>
<td>100-250 mg daily</td>
<td>Weak NE</td>
<td>Activating effect</td>
</tr>
<tr>
<td><strong>Serotonin and Norepinephrine Reuptake Inhibitors (SNRI)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Venlafaxine</td>
<td>37.5 mg daily (IR)</td>
<td>150-375 mg daily</td>
<td>Higher doses: adds NRI (~225 mg)</td>
<td>Slight inhibition of DA reuptake (high dosages)</td>
</tr>
<tr>
<td></td>
<td>75 mg daily (ER)</td>
<td>150-225 mg daily</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Dopamine and Norepinephrine Reuptake Inhibitors (DNRI)</strong></td>
<td></td>
<td></td>
<td></td>
<td>Low incidence of sexual ADR; seizures at high doses (&gt; 450 mg daily or &gt; 150 mg/dose)</td>
</tr>
<tr>
<td>Bupropion</td>
<td>150 mg daily</td>
<td>150-300 mg daily</td>
<td>--</td>
<td></td>
</tr>
<tr>
<td><strong>Other</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mirtazapine</td>
<td>30 mg daily</td>
<td>30-60 mg daily</td>
<td>Antihistamine, alpha 1-adrenergic antagonist</td>
<td>Weight gain; antihistamine</td>
</tr>
</tbody>
</table>

*Citalopram maximum of 20 mg daily recommended for patients with: hepatic failure, age > 60 years old, CYP 2C19 poor metabolizers; ADR: adverse drug reactions; DA: dopamine; NE: norepinephrine; 5-HT: serotonin
Appendix B. Summary of Statin Initiation Recommendations for the Treatment of Blood Cholesterol to Reduce ASCVD Risk in Adults per 2013 AHA/ACC Guidelines

Appendix C. High-, Moderate-, and Low-Intensity Statin Therapy

<table>
<thead>
<tr>
<th>High-Intensity</th>
<th>Moderate-Intensity</th>
<th>Lower-Intensity</th>
</tr>
</thead>
<tbody>
<tr>
<td>When taken daily, will lower LDL-C an average of ≥ 50%</td>
<td>When taken daily, will lower LDL-C an average of 30% to &lt; 50%</td>
<td>When taken daily, will lower LDL-C an average of &lt; 30%</td>
</tr>
<tr>
<td>Atorvastatin 40–80 mg</td>
<td>Atorvastatin 10–20 mg</td>
<td>Simvastatin 10 mg</td>
</tr>
<tr>
<td>Rosuvastatin 20–40 mg</td>
<td>Rosuvastatin 5–10 mg</td>
<td>Pravastatin 10–20 mg</td>
</tr>
<tr>
<td></td>
<td>Simvastatin 20–40 mg</td>
<td>Lovastatin 20 mg</td>
</tr>
<tr>
<td></td>
<td>Pravastatin 40–80 mg</td>
<td>Fluvastatin 20–40 mg</td>
</tr>
<tr>
<td></td>
<td>Lovastatin 40 mg</td>
<td>Pitavastatin 1 mg</td>
</tr>
<tr>
<td></td>
<td>Fluvastatin XL 80 mg</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Fluvastatin 40 mg</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pitavastatin 2–4 mg</td>
<td></td>
</tr>
</tbody>
</table>
Appendix D. Changes in Statin Use and Statin Recommendations

A ATP-III Guidelines

Adults 40-75 Yr of Age 115.4 million

- Have clinical cardiovascular disease?
  - Yes: Currently Receiving Statin
    - Statin Newly Recommended: 3.6 million
    - Statin Not Recommended: LDL >100 mg/dl: 2.4 million
  - No: Receiving statin for primary prevention?
    - Yes: Currently Receiving Statin: 19.4 million
    - No: Have LDL-cholesterol >190 mg/dl?
      - Yes: Statin Recommended: 3.0 million
      - No: Have diabetes?
        - Yes: Statin Recommended: LDL >100 mg/dl: 4.5 million
        - No: Eligible according to 10 yr coronary disease risk + LDL cholesterol level?
          - Yes: Statin Recommended: 6.9 million
          - No: Statin Not Recommended: 66.9 million

B 2013 ACC-AHA Guidelines

Adults 40-75 Yr of Age 115.4 million

- Have clinical cardiovascular disease?
  - Yes: Currently Receiving Statin: 5.8 million
  - No: Receiving statin for primary prevention?
    - Yes: Currently Receiving Statin: 19.4 million
    - No: Have LDL-cholesterol >130 mg/dl?
      - Yes: Statin Recommended: 3.0 million
      - No: Have diabetes?
        - Yes: Statin Recommended: LDL >70 mg/dl: 6.7 million
        - No: Statin Not Recommended: LDL <70 mg/dl: 0.7 million
        - Eligible because 10 yr cardiovascular disease risk >7.5%?
          - Yes: Statin Recommended: 15.1 million
          - No: Statin Not Recommended: 58.7 million
### Appendix E. Evidence Table for Low LDL-C and Cancer

<table>
<thead>
<tr>
<th>Clinical Trial</th>
<th>Intervention</th>
<th>Absolute LDL-C reduction</th>
<th>Achieved LDL-C (mg/dL)</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>PROSPER</td>
<td>Pravastatin 40 mg vs placebo (N\textsubscript{total}=5,804)</td>
<td>50</td>
<td>97</td>
<td>• Pravastatin vs placebo: HR 1.25, 95% CI 1.04-1.51, p=0.020</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• Type of cancer: gastrointestinal (N=65), genitourinary (N=58), respiratory (N=46), breast (N=18), other (N=58)</td>
</tr>
<tr>
<td>Alsheikh-Ali AA, et al.</td>
<td>Meta-analysis of 15 statin treatment arms (N\textsubscript{total}=75,317)</td>
<td>--</td>
<td>62-142</td>
<td>• Significant inverse association between cancer incidence and achieved LDL-C levels ($R^2$=0.43, p=0.009)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• Results do not indicate causality</td>
</tr>
<tr>
<td>ALLHAT-LLT</td>
<td>Pravastatin 40 mg vs usual care (N\textsubscript{total}=10,355)</td>
<td>25</td>
<td>104</td>
<td>• 6-year incident cancer rates were similar in the two groups (378 vs. 369, RR 1.03, 95% CI 0.89-1.19, p=0.66)</td>
</tr>
<tr>
<td>Cholesterol Treatment</td>
<td>Meta-analysis of 27 clinical trials (N\textsubscript{total}=175,000)</td>
<td>--</td>
<td>--</td>
<td>• Reducing LDL-C with a statin for ~5 years had no effect on newly diagnosed cancer or on death from cancers</td>
</tr>
<tr>
<td>Trialists' (CTT)</td>
<td></td>
<td></td>
<td></td>
<td>• No indication was found that a ↓ of LDL-C in patients with a lower baseline LDL-C level ↑ their cancer risk</td>
</tr>
</tbody>
</table>

\(HR=\)hazard ratio; \(CI=\)confidence interval
## Appendix F. Evidence Table for Low LDL and Intracerebral Hemorrhage (ICH) 38-41

<table>
<thead>
<tr>
<th>Clinical Trial</th>
<th>Population</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Noda H, et al.</td>
<td>N_{total} = 30,802 men and 60,417 women</td>
<td>• Death due to intraparenchymal hemorrhage compared to LDL-C &lt; 80 mg/dL</td>
</tr>
</tbody>
</table>
|                | 40 to 79 years of age with no history of stroke or CHD | o LDL-C 80-99 (HR 0.65, 95% CI 0.44-0.96)  
|                |                      | o LDL-C 100-119 (HR 0.48, 95% CI 0.32-0.71)  
|                |                      | o LDL-C 120-139 (HR 0.50, 95% CI 0.33-0.75)  
|                |                      | o LDL-C > 140 (HR 0.45, 95% CI 0.30-0.69) |
| Bang OY, et al. | N_{total} = 104 patients | • LDL-C with or without statin treatment were independently related to a ↑ risk of symptomatic hemorrhagic transformation after recanalization therapy |
|                | Mean age = 70 years | • Low LDL-C (OR 0.968, 95% CI, 0.941-0.995, p=0.020) |
| SPARCL | N_{total} = 4,731 in patients with recent cerebrovascular accident or TIA and no known CHD, TIA or stroke 1 to 6 months before randomization, with a Rankin score ≤ 3 and a LDL-C level of 100-190 mg/dL | • Mean LDL-C achieved  
|                |                      | o Atorvastatin: 73 mg/dL  
|                |                      | o Placebo: 123 mg/dL  
|                |                      | • 16% ↓ in fatal and nonfatal stroke  
|                |                      | • Post hoc analysis  
|                |                      | o 22% ↓ in ischemic stroke  
|                |                      | o 45% ↓ in unclassified stroke  
|                |                      | o 66% ↑ in hemorrhagic stroke |
| Ramírez-Moreno JM, et al. | N_{total} = 88 presenting with ICH | • Low LDL-C levels were independently associated with death after intracranial hemorrhage (HR=3.07, 95% CI:1.04-9.02, p=0.042) |

*HR: hazard ratio; CI: confidence interval; TI: transient ischemic attack; CHD: coronary heart disease*