Higher Total Cholesterol in APOE4 Carriers Contributes to Alzheimer’s Disease Risk: Findings from the Alzheimer’s Disease Neuroimaging Initiative

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INTRODUCTION

• APOE is the greatest genetic risk factor for Alzheimer’s disease (AD),1 with highest risk observed in ε4 allele carriers.2
• APOE contributes to blood cholesterol metabolism, and literature suggests associations between high total blood cholesterol, APOE ε4 allele, and AD.3-10
• However, mechanisms underlying APOE’s conferral of AD risk are poorly understood.2
• AIMS: 1) To examine whether total cholesterol levels differed between APOE genotypes.
  2) To determine whether total cholesterol levels differed between cognitively normal individuals and those with mild cognitive impairment or AD.
  3) To investigate potential causality between total cholesterol levels and AD using Mendelian randomization, with APOE as a genetic instrumental variable.

METHODS

Participants

• N = 1,534 participants from the Alzheimer’s Disease Neuroimaging Initiative (ADNI)
• Data collected 2004-2017 from 55 sites across US and Canada11-13

Materials

• Measurement of total blood cholesterol levels
• Baseline diagnosis of cognitively normal (CN), mild cognitive impairment (MCI) due to Alzheimer’s disease, or Alzheimer’s disease (AD)
• APOE genotyping and classification:
  APOE Groups | APOE Genotypes
  APOE2+ | ε2ε2, ε2ε3
  APOE3+ | ε3ε3, ε3ε4
  APOE4+ | ε4ε3, ε4ε4

Sample Characteristics

<table>
<thead>
<tr>
<th>APOE Genotype</th>
<th>Diagnostic Group</th>
<th>CN (N=404)</th>
<th>MCI (N=833)</th>
<th>AD (N=297)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>74.79 ± 5.73</td>
<td>72.97 ± 7.55</td>
<td>75.01 ± 7.71</td>
<td></td>
</tr>
<tr>
<td>Sex, % male</td>
<td>203</td>
<td>50.25</td>
<td>165.00</td>
<td>55.56</td>
</tr>
<tr>
<td>Education, years</td>
<td>16.30 ± 2.73</td>
<td>15.91 ± 2.85</td>
<td>15.08 ± 3.01</td>
<td></td>
</tr>
<tr>
<td>APOE Genotype (% N)</td>
<td>54</td>
<td>13.37</td>
<td>51</td>
<td>6.12</td>
</tr>
<tr>
<td>APOE3</td>
<td>241</td>
<td>59.65</td>
<td>373</td>
<td>44.78</td>
</tr>
<tr>
<td>APOE4</td>
<td>109</td>
<td>26.89</td>
<td>409</td>
<td>49.10</td>
</tr>
</tbody>
</table>

Statistical Analysis

• Generalized linear modeling of 1) total cholesterol across APOE groups and 2) total cholesterol across diagnostic groups
• Mendelian randomization (Wald Ratio Method):14
  1) Linear regression of lipids on APOE (bx)
  2) Logistic regression of diagnosis on APOE (by)
  3) Ratio of by/bx for each APOE group comparison

RESULTS

Total Cholesterol Across APOE and Diagnostic Groups

<table>
<thead>
<tr>
<th>APOE Groups</th>
<th>CN</th>
<th>MCI</th>
<th>AD</th>
</tr>
</thead>
<tbody>
<tr>
<td>APOE4+</td>
<td>200</td>
<td>200</td>
<td>200</td>
</tr>
<tr>
<td>APOE3+</td>
<td>200</td>
<td>200</td>
<td>200</td>
</tr>
<tr>
<td>APOE2+</td>
<td>200</td>
<td>200</td>
<td>200</td>
</tr>
</tbody>
</table>

Regression models were adjusted for sex, age, and use of cholesterol-lowering medication.

Mendelian Randomization: Investigating Causality

Alzheimer’s Disease

APOE

Total Cholesterol

Diagnosis

AD | 0.19* (0.09 to 0.39) | 0.77* (0.59 to 0.95) |
MCI | 0.10* (0.04 to 0.19) | 0.47 to -0.20, 0.13 to =
CD | 0.12* (0.06 to 0.245) | 0.54* (-0.14 to 0.99) |

Log Odds Ratio (95% CI) in APOE4 Carriers per mg/dL Increase in Total Cholesterol

OR = odds ratio, CI = confidence interval

*Statistically significant coefficients (p < 0.05) for regression of both total cholesterol on APOE and diagnosis on AD, as well as F-statistic > 10

REFERENCES


DISCUSSION

• APOE+ carriers had higher total cholesterol levels than both APOE2+ and APOE3 carriers.
• Total cholesterol levels were higher in AD and MCI groups compared to CN.
• Higher total cholesterol was associated with higher log odds ratios for MCI and AD in APOE4 compared to APOE3 carriers.
• These findings suggest that dyslipidemia may be involved in APOE4’s conferral of Alzheimer’s risk.
• Maintenance of healthy total cholesterol levels may help reduce AD risk, particularly for APOE4 carriers.

ACKNOWLEDGMENTS

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