Serum lipids and memory in a population based cohort of middle age women

V W Henderson, J R Guthrie, L Dennerstein

Human Research Ethics Committee of the University of Melbourne, and participants provided written informed consent.

Memory and mood assessment
Memory and mood were assessed during the year eight annual visit. Of 387 women in the MWMHP cohort at that time, 326 participated in memory testing; 42 were ineligible because of surgical menopause, 16 had moved from the metropolitan area, 2 were too busy, and 1 was ill. Memory was assessed using a 10 item supraspan word list recall task. One or two syllable nouns were read aloud to participants for three immediate recall trials. An unannounced delayed recall trial took place five minutes later, after an intervening task. In the absence of an a priori prediction that lipid concentrations would affect immediate and delayed recall differently, analyses were based on a total memory score representing the sum of the four recall trials. Positive and negative mood were assessed as previously described. Participants were presented with 10 positive and 10 negative adjectives and asked to rate whether they felt that way during the last week on a four point scale ranging from 0 (hardly ever) to 3 (most of the time).

Lipid concentrations
During each annual assessment, fasting morning blood samples were taken for lipid measurements. TC, HDL-C, and triglycerides were measured using standard enzymatic methods on routine automated chemistry systems. Lipid analyses were validated against serum reference materials supplied by the Center for Disease Control Lipid.
Lipids and memory

In the year 8 assessment, memory was significantly, negatively associated with negative mood ($r = -0.18$) and positively associated with education ($r = 0.28$), parity ($r = 0.12$) and alcohol use ($r = 0.14$). There were no associations with positive mood, age, paid employment, marital status, menopausal status (menopausal transition and postmenopausal among women not using hormone therapy), use of hormone therapy (ever never, or current past never), use of lipid lowering drugs, smoking, exercise, body mass index, or serum oestradiol concentration (all $p$ values $>0.1$).

Except where noted, subsequent analyses investigating the relation between lipids and memory adjusted for potentially confounding effects of education, parity, alcohol use, and negative mood. The absence of significant association with age presumably reflected the restricted age range of MWMHP participants; however, age was included as an additional control variable because of its known association with memory in other studies.

Current lipid concentrations and memory

In multiple regression analyses, year 7+8 LDL-C concentrations were significantly predictive of the memory score ($\beta = 0.714$, $p = 0.01$). The association with TC was of near significance ($\beta = 0.454$, $p = 0.08$), but there were no significant associations with levels of HDL-C ($\beta = 0.036$, $p = 1.0$) or triglycerides ($\beta = -0.377$, $p = 0.4$). In exploratory analyses using analysis of covariance, LDL-C concentration quartiles differed significantly with respect to memory scores $F = 2.92$, $p = 0.04$ (fig 1). In pairwise comparisons, the mean difference between first and fourth LDL-C quartiles on the memory task represented a difference of 0.44 standard deviations ($p = 0.005$).

Previous LDL-C concentrations and memory

To help determine whether observed cross sectional associations between memory and current LDL-C represented relatively short term effects of cholesterol concentrations or relatively long term effects, we examined the relation between memory and previous LDL-C concentrations. However, LDL-C from three years earlier did not predict memory scores ($\beta = 0.245$, $p = 0.4$).

Changes in lipid concentrations and memory

To assess whether longitudinal changes in lipid levels affected memory, we analysed the difference between current levels and those from previous years. In multiple regression analyses that included baseline TC levels as a control variable, an increase in TC between years 4+5 and years 7+8, but not between years 1+2 and years 7+8, was positively related to memory ($p = 0.01$) (table 3). In similar analyses, the change in serum LDL-C between years 4+5 and years 7+8 was negatively associated with memory, $r = -0.28$, $p = 0.04$ (fig 1). In pairwise comparisons, the mean difference between first and fourth LDL-C quartiles on the memory task represented a difference of 0.44 standard deviations ($p = 0.005$).
significantly predictive of the memory score (p = 0.003), whereas LDL-C differences between years 1+2 and years 7+8 were not (table 3). Compared with women whose LDL-C concentrations were unchanged or had increased between years 4+5 and years 7+8, the mean memory score was 0.39 standard deviations lower among LDL-C decliners (p = 0.002) (table 3). For TC concentrations, the 0.24 standard deviation difference in memory scores between decliners and non-decliners was also significant (p = 0.04) (table 3). In other analyses, there was no relation between memory and three-year changes in HDL-C or triglyceride concentrations (p values >0.1).

When memory was analysed in relation to three year changes in TC grouped by quartiles, there were significant differences in analysis of covariance that adjusted for baseline TC levels and other control variables (F = 4.50, p = 0.004). Adjusted mean memory scores for the first to the fourth quartiles were 28.1, 29.4, 29.0, and 30.7, respectively. Pairwise comparisons showed that women in the fourth quartile, the group with largest increases in TC, had significantly better mean memory scores than women in the first (p <0.0005) and third (p = 0.02) quartiles. For women in the fourth and first quartiles, there was a 0.59 standard deviation difference in mean memory score.

When memory was analysed in relation to quartiles of LDL-C change between years 4+5 and 7+8, there were also significant differences among quartiles in analysis of covariance that adjusted for baseline LDL-C levels and other variables (F = 3.24, p = 0.02) (fig 2). In post hoc comparisons, the mean difference of 2.1 points on the memory task between women in the fourth and first quartiles corresponded to a difference of 0.48 standard deviations (p = 0.006).

Immediate recall versus delayed recall
A word list memory task involves several cognitive domains, and immediate recall may involve different abilities from recall after a short delay. Post hoc analyses considered the relation between TC and LDL-C levels and memory performance summed over the three immediate recall trials and separately for the fourth (delayed recall) trial. In multiple

Table 1
Clinical features of Melbourne’s women midlife health project participants during the year 8 assessment∗

<table>
<thead>
<tr>
<th>N</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>56.7 (SD 2.5)</td>
<td>52–63</td>
</tr>
<tr>
<td>27.0 (SD 5.4)</td>
<td>16.2–57.1</td>
</tr>
</tbody>
</table>

Table 2
Serum lipid concentrations in cohort members∗

<table>
<thead>
<tr>
<th>Total cholesterol (SD)</th>
<th>LDL-C (SD)</th>
<th>HDL-C (SD)</th>
<th>Triglycerides (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Years 1+2</td>
<td>5.83 (0.91)</td>
<td>3.77 (0.89)</td>
<td>1.58 (0.41)</td>
</tr>
<tr>
<td>Years 4+5</td>
<td>5.83 (0.89)</td>
<td>3.64 (0.88)</td>
<td>1.62 (0.40)</td>
</tr>
<tr>
<td>Years 7+8</td>
<td>5.84 (0.91)</td>
<td>3.79 (0.87)</td>
<td>1.49 (0.39)</td>
</tr>
</tbody>
</table>

SD, standard deviation; LDL-C, low density lipoprotein cholesterol; HDL-C, high density lipoprotein cholesterol.

*Values in mmol/l were calculated from means of two annual samples. For total cholesterol, LDL-C, and HDL-C, to convert mmol/l to mg/dl, multiply by 38.6. For triglycerides, to convert mg/dl to mmol/l, multiply by 0.018. Years 1+2 samples were obtained in both years from 313 women, in years 4+5 from 309 women, and in years 7+8 from 300 women.
There were no significant or near significant associations with other control variables. In separate multiple regression analyses adjusting for effects of exercise and memory scores, current TC, LDL-C, HDL-C, or triglyceride levels were not predictive of positive mood or negative mood (all p values >0.1). Similarly, there were no significant associations between three year lipid changes and mood (all p values >0.1). Post hoc analyses that excluded the memory score as a control variable did not alter results.

**Statin use, memory, and mood: post hoc analyses**

Use of prescription lipid lowering agents was reported by 29 women during year 8; all agents were 3β-hydroxy-3β-methylglutaryl-coenzyme A reductase inhibitors (statins). Analyses of covariance compared statin users with other women. Statin use was not associated with memory, positive mood, or negative mood (all p values >0.1). Results did not change after further adjustment for TC levels.

**DISCUSSION**

Cholesterol, an integral component of cell membranes, modulates membrane protein function.40 The brain has a high lipid content, and dietary cholesterol directly influences brain cholesterol concentrations.41 For women in the MWMHP cohort, greater serum concentrations of LDL-C were positively associated with better memory performance. There was a non significant trend between current TC levels and the total memory score, but there was no association for HDL-C or triglyceride levels.

Research on the relation between serum cholesterol and cognition is inconsistent. Hypercholesterolaemia promotes atherosclerosis,6 and TC elevations are linked to vascular dementia.5 Higher TC and LDL-C levels were associated with lower scores on a global cognitive measure in an observational study of older women (mean age 71 years) with coronary heart disease.22 In a retirement community cohort, TC and LDL-C concentrations were higher among women (mean age 80 years) who performed poorly on a clock drawing task administered four years later.24 Although the association between TC and Alzheimer’s disease is inconsistent,5,7 experimental cholesterol reduction lowers production of β-amyloid,25 a key biochemical abnormality in this disorder.26

Statin use is linked to reduced risk of dementia.11–13 It is not certain, however, that lowered cholesterol is causative, as the association is stronger for less potent statins5 and may occur in other classes of lipid lowering agents.27 Because confounding by indication or cessation bias was not always confidently excluded in reported studies,28 in the MWMHP cohort, we observed no association between statin use and memory independent of lipid concentrations; speculatively, anti-inflammatory and antioxidant actions of statins are more relevant to dementia than lipid lowering effects.35

The relation between cholesterol and memory in the elderly may differ from that in younger or middle age adults, where prevalences of atherosclerosis and dementia are lower. Present results thus support previous reports that higher concentrations of TC or LDL-C are associated with better cognition, particularly for tasks dependent on mental manipulation or rapid mental processing.12 In university students, choice reaction times were worse in women with lower TC.10 In healthy volunteers (mean age 44 years), higher TC and LDL-C concentrations were associated with better performance on a timed visuconstructive task (block design test) but not on tasks that depend primarily on previously acquired knowledge (information and vocabulary).2 In a small five year longitudinal study of monogynotic twin pairs (mean age 55 years) discordant for decline on a digit symbol...
substitution task, TC levels were significantly lower among decliners.8

In the MWMHP cohort, the magnitude of memory score variance attributed to LDL-C concentration was small (2%) but not negligible. Education accounted for over 6% of the variance and negative mood for 2.5%; other identified control variables were less important than LDL-C. On the memory task, women in the lowest LDL-C quartile scored more than two fifths of a standard deviation below those in the highest quartile (fig 1). By way of comparison, in the Heart and Estrogen/progestin Replacement Study of older women with known cardiovascular disease, women in the lowest LDL-C quartile compared with those in the highest quartile scored about one fourth standard deviation higher on a global cognitive measure.27

The association between LDL-C and memory was stronger for serum concentrations measured close to the time of memory testing than for levels obtained three years before. Putative effects of LDL-C on memory therefore reflect more recent levels. However, three year changes in TC and LDL-C concentrations were also significantly related to memory (table 3), accounting for about 2% (TC) or 3% (LDL-C) of memory score variance. Memory scores of women whose LDL-C levels declined during this three year interval were 0.39 SD lower than scores of women whose levels had remained the same or increased (table 3). Results were similar in post hoc analyses comparing LDL-C changes between women in the first and fourth quartiles (fig 2). Not all studies agree,28 but low TC is associated with suicide risk and depression.29 30 We were unable to detect a link between serum lipids and mood in women without diagnosed depression. Similarly, interventions that reduce cholesterol do not affect mood.27 31

In post hoc analyses, effects of TC and LDL-C concentrations on memory—as well as effects of three year changes in concentrations of these lipids—were more pronounced for immediate recall than delayed recall. Both tasks involve long term episodic memory. For immediate recall from a supra-span word list, cognitive demands might also include attentional and organisational skills involved in working memory and executive functions. It is unknown why TC and LDL-C effects were evident only for immediate recall, but this finding supports previous claims that cholesterol elevation is linked to better performance on tasks where information processing demands are greater.2

Clinical trial data also provide partially consistent findings. In a 12 week randomised trial involving hypercholesterolaemic adults (mean age 53 years), participants receiving dietary interventions performed significantly worse than controls on a sustained attention task (but not on several other tasks)27: decrements in sustained attention correlated with declines in serum TC.28 In another randomised trial, hypercholesterolaemic patients (mean age 46 years) treated with statins for six months showed small but significant performance decrements on tests of attention and psychomotor speed; memory was unaffected in this study.29 In older women with heart disease, statin use is linked to better cognition, but interestingly this association is unrelated to lipid levels.29

LDL-C is routinely calculated from TC,30 and TC and LDL-C are therefore not independent determinations. Our findings from LDL-C were generally more robust than those from TC, and LDL-C is probably the critical lipid variable influencing memory scores. Whether this association is causal, however, cannot be determined from our data.

It is unlikely that our findings were influenced by inclusion of women with early dementia. MWMHP participants were not old enough to face a substantial risk of dementia (table 1), and the significant association between LDL-C and memory was unaltered in post hoc analyses excluding women who scored poorly on delayed recall or on the total memory score. Although pathological changes of Alzheimer’s disease may begin years before the onset of frank dementia,31 our findings indicate that higher LDL-C levels in women may protect memory at midlife.

Our results are derived from a well characterised population based cohort where blood samples and a portion of the clinical data were collected prospectively. Limitations of our findings include their observational nature, the absence of additional cognitive measures, and the absence of male participants. The e4 allele of apolipoprotein E influences serum lipid concentrations44 and Alzheimer’s disease risk,32 but apolipoprotein E genotyping was not performed. Public health implications of our results are uncertain, given the well documented vascular risks in later life associated with TC and LDL-C elevations.3 However, medications that reduce serum cholesterol are widely prescribed,41 and long term consequences of TC and LDL-C reductions on cognitive functioning are unknown. Future trials that evaluate cholesterol lowering interventions in healthy adults should consider possible effects on cognition.

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Portions of this research were conducted while the first author was Portion of this research was conducted while the first author was a Visiting Professor, Department of Psychiatry, University of Melbourne, and the Kearney Visiting Professor at the Mental Health Research Institute of Victoria

Competing interest: LD has received a grant in aid from Pfizer Pharmaceuticals. VWH and JRG have no competing interests to declare

REFERENCES


The apolipoprotein E phenotype is not a visual loss susceptibility gene in Leber hereditary optic neuropathy.

The apolipoprotein E phenotype (APOE) is known to be strongly associated with several neurodegenerative conditions including Alzheimer disease and dementia with Lewy bodies. Since APOE is produced by Muller cells within the retina and rapidly transported to the optic nerve, researchers from Newcastle upon Tyne (UK) and Milan (Italy) postulated that the genotype might modulate the expression of the primary mtDNA mutations in Leber Hereditary Optic Neuropathy (LHON).

Sixteen pedigrees from the UK and 44 from Italy were ascertained and investigated with family controls who were unaffected carriers. The authors found no effect of the specific APOE type upon disease penetrance. The age of onset of blindness was no different in those with the e4/- genotype than in those with the non-e4/- genotypes.

It remains possible the genotype may have a subtle effect, for example by affecting the chance of visual recovery after the acute phase.

**Figure 1** Effect of APOE e4 allele on age of onset of visual failure in LHON pedigrees from the north east of England (Y axis indicates probability of remaining unaffected).
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