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HIGHER SERUM TOTAL CHOLESTEROL LEVELS IN LATE MIDDLE AGE ARE ASSOCIATED WITH GLUCOSE HYPOMETABOLISM IN BRAIN REGIONS AFFECTED BY ALZHEIMER'S DISEASE AND NORMAL AGING

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Abstract

Epidemiological studies suggest that higher midlife serum total cholesterol levels are associated with an increased risk of Alzheimer's disease (AD). Using fluorodeoxyglucose positron emission tomography (PET) in the study of cognitively normal late-middle-aged people, we demonstrated an association between apolipoprotein E (APOE) $\epsilon 4$ gene dose, the major genetic risk factor for late-onset AD, and lower measurements of the cerebral metabolic rate for glucose (CMRgl) in AD-affected brain regions, we proposed using PET as a presymptomatic endophenotype to evaluate other putative AD risk modifiers, and we then used it to support an aggregate cholesterol-related genetic risk score in the risk of AD. In the present study, we used PET to investigate the association between serum total cholesterol levels and cerebral metabolic rate for glucose metabolism (CMRgl) in 117 cognitively normal late middle-aged APOE $\epsilon 4$ homozygotes, heterozygotes and noncarriers. Higher serum total cholesterol levels were associated with lower CMRgl bilaterally in precuneus, parietotemporal and prefrontal regions previously found to be preferentially affected by AD, and in additional frontal regions previously found to be preferentially affected by normal aging. The associations were greater in APOE $\epsilon 4$ carriers than non-carriers in some of the AD-affected brain regions. We postulate the higher midlife serum total cholesterol levels accelerate brain processes associated with normal aging and conspire with other risk factors in the predisposition to AD. We

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propose using PET in proof-of-concept randomized controlled trials to rapidly evaluate the effects of midlife cholesterol-lowering treatments on the brain changes associated with normal aging and AD.

Keywords

Alzheimer's disease; aging; cholesterol; positron emission tomography

INTRODUCTION

Time-consuming prospective cohort studies have raised the possibility that higher serum total cholesterol levels in midlife increases a person's risk for developing late-onset Alzheimer's disease (AD) (Kivipelto et al., 2001; Klag et al., 1993; Martin et al., 1986; Solomon et al., 2007). However, studies in older adults have not confirmed this association (Li et al., 2005; Mielke et al., 2005), perhaps due to an accelerated rates of age-related decline in total cholesterol levels in those individuals who go on to develop AD (Stewart et al., 2007). As a complement to traditional epidemiological studies, we have proposed using brain-imaging measurements as a pre-symptomatic quantitative endophenotype of AD, a feature more closely related to disease predisposition than the clinical syndrome itself (Gottesman and Gould, 2003), to evaluate putative modifiers of AD risk (Reiman et al., 2005). By evaluating the relationship between total cholesterol levels and brain-imaging measurements in late middle-aged people in the present study, this strategy could help overcome the time-consuming nature of prospective cohort studies, as well as the potentially confounding effect of accelerated age-related declines in total cholesterol levels in those individuals who go on to develop AD in retrospective case-control studies. By characterizing and comparing this relationship in people with no copies, one copy and two copies of the apolipoprotein E (APOE) $\epsilon 4$ allele, this strategy could also consider how higher total cholesterol levels interact with this well-established genetic risk factor in the predisposition to AD.

Analyzing FDG PET images from cognitively normal, late-middle-aged persons, we previously demonstrated a significant association between APOE $\epsilon 4$ gene dose (the number of $\epsilon 4$ alleles in a person's APOE genotype) and lower CMRgl in the brain regions known to be preferentially affected by AD (Reiman et al., 2005). Since APOE $\epsilon 4$ gene dose reflects three levels of genetic risk for late-onset AD, we suggested that FDG PET could be used as a quantitative pre-symptomatic endophenotype to help assess the individual and aggregate effects of putative modifiers of AD risk.

In addition to its other biological properties, APOE is the major transporter of cholesterol in the blood and central nervous system (Mahley, 1988), and the APOE E4 isoform is associated with a higher risk of AD (Corder et al., 1993; Farrer et al., 1997) and amyloid- β neuropathology (Ohm et al., 1995; Reiman et al., 2009). Although less well-established, other cholesterol-related genes may be associated with AD risk and neuropathology as well. In one study, a cluster of nine cholesterol- and lipid-related single nucleotide polymorphisms (SNPs) from seven genes, including the APOE $\epsilon 4$ allele, was implicated in the predisposition to AD and an aggregate cholesterol-related genetic risk score (CREGS) was found to distinguish between 74% of the AD cases and controls (Papassotiropoulos et al., 2005). Using PET images from our late-middle-aged cognitively normal subjects, we demonstrated a significant association between CREGS and lower CMRgl in AD-affected brain regions, even when controlling for the effects of APOE $\epsilon 4$ gene dose (Reiman et al., 2008).

In the present study, we used our proposed PET endophenotype to test the hypothesis that higher serum total cholesterol levels in cognitively normal, late middle-aged persons are

associated with lower CMRgl in brain regions known to be preferentially affected by AD (Alexander et al., 2002; Langbaum et al., 2009), to explore the possibility that higher levels are also associated with lower CMRgl in frontal regions known to be preferentially affected by normal aging (Kuhl et al., 1982; Loessner et al., 1995; Reiman et al., 2004; Salmon et al., 1991), and to compare these associations in our APOE $\epsilon 4$ carrier and non-carrier groups.

METHODS

Participants

To enroll subjects into our ongoing longitudinal study, newspaper advertisements were used previously to recruit cognitively normal volunteers 47 to 68 years of age who reported a family history of probable Alzheimer's disease in at least one first-degree relative, understood that they would not receive any information about their APOE genotype, provided their informed consent, and were studied under guidelines approved by the human subjects committees at Banner Good Samaritan Medical Center and the Mayo Clinic (Reiman et al., 1996). Venous blood samples were drawn and APOE genotypes characterized as previously described (Crook et al., 1994; Reiman et al., 1996). Originally, one APOE $\epsilon 4$ heterozygote (with the $\epsilon 3\epsilon 4$ genotype) and two $\epsilon 4$ non-carriers were matched to a different $\epsilon 4$ homozygote for their gender, age (within 3 years), and educational level (within 2 years). They denied having an impairment in memory or other cognitive skills, had scores of at least 28 on the Mini-Mental State Examination (MMSE) (Folstein et al., 1975) and less than 10 on the Hamilton Depression Rating Scale (HAM-D) (Hamilton, 1960), did not satisfy criteria for a current psychiatric disorder using a structured psychiatric interview, and had a normal neurological exam. Study subjects have been assessed every two years using a medical examination, clinical ratings, neuropsychological tests, volumetric MRI and fluorodeoxyglucose PET as previously described (Reiman et al., 1996; Reiman et al., 2001). On the day of the returning subject's most recent PET scan (an average of four years following their initial enrollment), venous samples were acquired, stored at -70°C , and serum lipid profiles characterized to permit the analyses reported here. Serum total cholesterol levels were determined enzymatically (Haubenwallner et al., 1995). Serum lipoprotein cholesterol profiles and distribution among lipoproteins were determined by high performance gel filtration chromatography (Kuo et al., 1998).

For the current cross-sectional report, we compared clinical ratings, neuropsychological test scores, FDG PET measurements and serum lipid levels from 117 returning, cognitively normal subjects. There were 60 ± 6 years of age and included 24 APOE $\epsilon 4$ homozygotes (HM), 38 heterozygotes (HT), and 55 non-carriers (NC). 25% of the subjects reported use of cholesterol-lowering medications.

Brain Imaging

Volumetric T_1 -weighted MRI and PET were performed as previously described (Reiman et al., 1996; Reiman et al., 2005). PET was performed using the HR+ scanner (Siemens, Knoxville, TN) in the 3D mode, a transmission scan, the intravenous injection of 5–8 mCi of $[^{18}\text{F}]$ fluorodeoxyglucose, and a 60-minute dynamic sequence of emission scans as the participants, who had fasted for at least 4 hours, lay quietly with eyes closed in a darkened room. The reconstructed images consisted of 63 horizontal slices with a center-to-center slice separation of 2.46 mm, an axial field of view of 15.5 cm, an in-plane resolution of 4.2–5.1 mm full width at half-maximum (FWHM), and an axial resolution of 4.6–6.0 mm FWHM. Voxel-based analyses were performed using the PET images (counts relative to the whole brain uptake) acquired during the last 30 minutes.

An automated algorithm (SPM99, Wellcome Department of Cognitive Neurology, London, U.K.) was used to deform each person's PET image linearly and non-linearly into the coordinates of a standard brain atlas, normalize the data for the variation in absolute whole-brain measurements using proportionate scaling, smooth the images using a three-dimensional Gaussian filter to a spatial resolution of 12 mm full-width-at-half-maximum, and generate statistical parametric maps of the correlations between higher serum total cholesterol and lower regional CMRgl ($p < 0.005$, uncorrected for multiple comparisons). The statistical maps were superimposed onto a map of CMRgl reductions in previously studied probable AD patients (Alexander et al., 2002) and a spatially standardized, volume-rendered MRI. Significance levels were then adjusted for the number of resolution elements in the AD-affected posterior cingulate, precuneus, parietotemporal, and frontal brain regions postulated to be preferentially affected in cognitively normal persons at genetic risk for AD using the small-volume correction procedure in SPM ($p < 0.05$, corrected for multiple comparisons) (Reiman et al., 2005; Reiman et al., 2008). Findings in other brain regions, including frontal regions preferentially affected by normal aging, were not corrected for multiple comparisons and are considered exploratory. Following the correlational analysis in the overall group, we characterized correlations within each of the APOE $\epsilon 4$ HM, HT and NC groups and compared the regression slopes of cholesterol levels against CMRgl in each of the two $\epsilon 4$ carrier groups to that in the $\epsilon 4$ non-carrier group.

RESULTS

Participant characteristics, clinical ratings, neuropsychological scores, and serum lipid panel measurements are shown in Table 1. The APOE $\epsilon 4$ subgroups did not statistically differ in their age, years of education, gender, demographic features, lipid profile measurements (HDL, LDL, serum total cholesterol), use of statins, or baseline cognitive functioning, with the exception that on average the APOE $\epsilon 4$ HT group performed better than the NC group on the WAIS-R Digit Span ($p = 0.04$).

Statistical parametric maps are displayed in Figure 1A and the location and magnitude of the most significant correlations between higher total serum cholesterol and lower CMRgl are shown in Table 2. Higher serum total cholesterol levels were significantly correlated with lower CMRgl in bilaterally in the precuneus, parietotemporal and prefrontal regions previously found to be preferentially affected by AD, and in additional frontal regions previously found to be preferentially affected by normal aging. A post-hoc analysis controlling for participants' use of cholesterol-lowering medications did not significantly alter the results (data not shown).

Correlations between higher serum total cholesterol and lower CMRgl were observed in AD-affected parietotemporal areas bilaterally for the HM and in the left hemisphere for the HT group (Figures 1B and 1C). Significant correlations were also observed in AD-affected parietal areas for the NC group (Figure 1C). Additional correlations were observed in frontal regions affected by AD and normal aging in the HM group (Figure 1B). Slopes of the association between higher serum total cholesterol levels and lower CMRgl were significantly greater in the AD-affected temporal cortex for each of the APOE $\epsilon 4$ carrier groups compared to the NC group (Table 3, Figure 2).

Figure 3 shows relationships between individual serum total cholesterol levels and CMRgl measurements from a) the AD-affected parietal cortex voxel with the most significant Pearson correlation coefficient in the overall group, b) the AD-affected left temporal cortex voxel with the most significant difference in the regression line slopes in APOE $\epsilon 4$ homozygotes versus non-carriers and c) the AD-affected left temporal cortex voxel with the most significant difference in the regression line slopes in APOE $\epsilon 4$ heterozygotes versus non-carriers.

DISCUSSION

This study demonstrates associations between higher serum total cholesterol levels in late middle-aged people and lower CMRgl in extensive brain regions, including precuneus, parietotemporal and prefrontal brain regions known to be preferentially affected by AD (Alexander et al., 2002; Langbaum et al., 2009) and in additional frontal regions known to be preferentially affected by normal aging (Kuhl et al., 1982; Loessner et al., 1995; Reiman et al., 2004; Salmon et al., 1991). The associations were greater in each of the APOE $\epsilon 4$ carrier groups than the non-carrier group in the AD-affected temporal regions. Moreover, the correlations between higher total serum cholesterol levels and lower CMRgl were not solely attributable to the subjects' reported use of 3-hydroxy-3-methylglutaryl-coenzyme-A-reductase inhibitors (statins) or other cholesterol-lowering medications. Based on these findings, we postulate that higher serum total cholesterol levels accelerate the brain changes associated with normal aging and conspire with certain AD risk factors, such as the APOE $\epsilon 4$ allele, in the predisposition to AD.

Findings from the present study complement those from our previous study (Reiman et al., 2008), which found a significant association between an aggregate cholesterol-related genetic score and lower CMRgl in AD-affected brain regions in cognitively normal late middle-aged subjects. Both of these studies support the possibility that individual differences in cholesterol metabolism contribute to the predisposition to AD. Considering the correlational nature of our findings, however, we cannot exclude the possibility that other genetic or non-genetic factors contribute to higher cholesterol levels and AD risk through independent mechanisms.

Here, we briefly consider findings and uncertainties regarding the relationship between higher serum total cholesterol levels and the predisposition to AD. We also consider findings, uncertainties, and opportunities regarding the role of statins and other cholesterol-lowering drugs in the risk of AD, in the treatment of clinically affected patients, and in the possible pre-symptomatic treatment of AD. We raise the possibility that higher cholesterol levels might modify the risk of AD (and certain other age-related disorders) by slowing down some of the brain processes associated with normal aging. Finally, we propose using PET to rapidly evaluate the effects of cholesterol-lowering treatments on the brain changes associated with AD and aging in cognitively normal late-middle-aged APOE $\epsilon 4$ carriers and non-carriers.

Cholesterol and the risk of AD

Epidemiological studies suggest that elevated serum total cholesterol during midlife, but not late-life, is associated with increased risk of AD (Kivipelto et al., 2001; Klag et al., 1993; Martin et al., 1986; Mielke et al., 2005) and AD neuropathology (Launer et al., 2001; Pappolla et al., 2003). Based on studies which have tracked age-related changes in serum total cholesterol levels, it has been suggested that discordant findings from prospective cohort studies, which support the relationship between higher midlife cholesterol levels and AD risk, and case-control studies, which do not support a relationship between late-life cholesterol levels and AD risk (Bonarek et al., 2000), may be attributable to accelerated rates of age-related decline in these levels prior to the clinical onset of AD (Stewart et al., 2007).

Experimental studies suggest that cholesterol may promote the accumulation of amyloid- β peptide (A β) and amyloid plaques, cardinal features of AD (Frears et al., 1999; Refolo et al., 2000; Simons et al., 1998; Sparks et al., 1994). It remains unclear whether serum cholesterol levels increase AD risk directly via the transport of cholesterol into the brain or through indirect mechanisms, such as an increase in cholesterol metabolites which can then enter the brain and trigger A β production (Prasanthi et al., 2009), cholesterol-related cerebrovascular disease, or an increase in brain copper levels (Sparks and Schreurs, 2003). Since the intact blood-brain barrier is thought to prevent the movement of peripheral cholesterol into the brain, it has been

suggested that vascular injuries may mediate the relationship between cholesterol and A β metabolism (Shobab et al., 2005).

If, as we postulate, higher serum cholesterol levels increase AD risk through peripheral mechanisms, a non-lipophilic (i.e., hydrophilic) cholesterol-lowering drug that does not readily cross the blood-brain barrier (e.g., rosuvastatin, pravastatin) (Schachter, 2005) might be preferable in the pre-symptomatic treatment of AD. If, however, the association between higher serum cholesterol levels and increase AD risk by leading to or mirroring an increase in brain cholesterol levels, a lipophilic drug that readily crosses the blood-brain barrier (e.g., simvastatin) (Schachter, 2005) might be preferable in the pre-symptomatic treatment of AD.

While the causal nature of the relationship between serum total cholesterol and AD remains unclear, there is some evidence to suggest that the association is modified by vascular factors. For instance, a recent study found that a higher cardiovascular risk profile, including elevated serum total cholesterol, was associated with lower CMRgl in the left frontal lobe (Kuczynski et al., 2009). Predominately frontal findings from our study, as well as theirs, lead us to postulate that higher cholesterol levels and other cardiovascular disease risk factors increase the risk of AD by accelerating some of the brain changes associated with normal aging that, combined with APOE ϵ 4, increase a person's risk of AD.

Statins in the risk and presymptomatic treatment of AD

Several cross-sectional and case-control studies have suggested an association between the use of cholesterol-lowering drugs, particularly statins, and lower prevalence of AD (Dufouil et al., 2005; Green et al., 2005; Jick et al., 2000; Rockwood et al., 2002; Wolozin et al., 2000; Zamrini et al., 2004). However, the findings from prospective studies has been mixed, with the many studies failing to detect a protective effect of statin use on incident AD (Arvanitakis et al., 2008; Haag et al., 2009; Li et al., 2004; Rea et al., 2005; Zandi et al., 2005). The inconsistent findings may be due to several factors, including duration of treatment and age in which treatment was started, particularly because findings from some studies suggest that statin use may be most effective at reducing incident AD in persons younger than 80 years of age (Cramer et al., 2008; Li et al., 2006; Li et al., 2007; Li et al., 2008; Rockwood et al., 2002). Inconsistent findings may also be due to grouping all cholesterol-lowering medications together, as there is some evidence to suggest that only statins, and not other cholesterol-lowering medications, are associated with a reduced risk of AD (Green et al., 2005; Haag et al., 2009), and there is some debate as to whether hydrophilic compared to lipophilic statins are more effective at decreasing brain amyloid and reducing the risk of AD (Haag et al., 2009; Sparks et al., 2002; Wolozin et al., 2007). Findings from the study of animal model (Chauhan et al., 2004; Fassbender et al., 2001; Howland et al., 1998; Hutter-Paier et al., 2004; Refolo et al., 2001) and expired brain donors (Li et al., 2007) suggest that statins may protect against AD neuropathology. Statins may potentially exert protective effects by modulating the amyloid-precursor protein by promoting α -secretase activity (Chauhan et al., 2004; Parvathy et al., 2004), decreasing A β levels (Buxbaum et al., 2002; Chauhan et al., 2004; Fassbender et al., 2001) decreasing cerebral inflammation (Cordle and Landreth, 2005) but see (Chauhan et al., 2004)), or reducing the risk of cerebrovascular disease (Heart Protection Study Collaborative Group, 2002), which in itself is a risk factor for AD (Snowdon et al., 1997).

So far, the findings from randomized clinical trials of statin treatments in clinical affected AD patients have been inconsistent. While small proof-of-concept study found a trend for an atorvastatin-related reduction in cognitive decline in patients with probable AD (Sparks et al., 2005), particularly in those particularly in those individuals who have an APOE ϵ 4 allele or higher cholesterol levels (Sparks et al., 2006), preliminary findings from larger multi-center studies of atorvastatin (Jones et al., 2008) and simvastatin (Sano, 2008) suggest that statin treatment does not protect against cognitive decline in patients with probable AD. Whether or

not these treatments prove to be beneficial in clinically affected patients, findings from our study and others suggest the need to study their pre-symptomatic effects, perhaps starting in middle-age, before the onset of extensive AD neuropathology and perhaps before extensive brain aging effects.

Rigorous randomized controlled trials of statins in the pre-symptomatic treatment of AD are limited, partly due to the number of cognitively normal subjects and extensive time needed to evaluate their effects using clinical endpoints. In a small four-month randomized clinical trial of cognitively normal middle-aged adults who were at increased risk of AD, simvastatin was associated with improved cognition without changing cerebrospinal fluid (CSF) biomarkers of AD (Carlsson et al., 2008). Two larger trials in which cognitive and clinical endpoints were not the primary consideration in the design of these studies failed to find a secondary benefit of treatment on incident cognitive impairment or dementia, including a five-year study of simvastatin in 40–80 year-old subjects (Heart Protection Study Collaborative Group, 2002) and a three-year study of pravastatin in 70–82 year-old subjects (Shepherd et al., 2002). Thus, there remains a need to evaluate these and other cholesterol-lowering drugs in the pre-symptomatic treatment of AD, perhaps starting in middle to late-middle age.

As we previously proposed, FDG PET could provide a quantitative presymptomatic endophenotype – a measurable feature that is more closely related to disease susceptibility than the clinical syndrome itself – to help evaluate the individual and aggregate effects of putative genetic and non-genetic modifiers of AD risk (Reiman et al., 2005). More recently, we found an association between APOE $\epsilon 4$ gene dose and PET measurements of fibrillar amyloid- β burden, suggesting that this brain imaging measurement could also be used as a quantitative pre-symptomatic endophenotype for the assessment of putative AD risk modifiers (Reiman et al., 2009). As a complement to observational studies of older Alzheimer's dementia cases and controls, our proposed endophenotypes could help overcome potential confounds, such as differential survivor bias or an accelerated age-related decline in the cholesterol levels prior to the onset of AD. As a complement to prospective cohort studies, these endophenotypes could provide information about putative AD risk modifiers, such as higher cholesterol levels of mid-life statin treatment, without having to study thousands of people or wait many years to determine their rates of cognitive decline or clinical conversion.

Just as we have proposed the use of pre-symptomatic brain-imaging endophenotypes to assess the effects of putative AD risk modifiers, we have proposed using brain-imaging and other biomarker measurements to evaluate pre-symptomatic treatments without having to study thousands of cognitively normal volunteers or wait many years to characterize rates of cognitive decline or clinical conversion (Reiman and Langbaum, in press; Reiman et al., 2001). For instance, we have proposed how PET could be used in cognitively normal late-middle-aged APOE $\epsilon 4$ carriers to evaluate the effectiveness of promising pre-symptomatic treatments to slow down the progressive regional CMRgl declines (Reiman et al., 2001). We have also proposed a strategy to demonstrate that the effects of treatments on these biomarkers are reasonably likely to predict a clinical benefit in cognitively normal people at the highest risk for AD close to their estimated median age at dementia onset (Reiman and Langbaum, in press). This strategy is needed to give regulatory agencies the evidence needed to approve pre-symptomatic treatments solely on the basis of biomarker endpoints.

With the rising number of people living to older ages, the prevalence and cost of AD is projected to become overwhelming (Brookmeyer et al., 1998; Hebert et al., 2003). A treatment that delayed the onset of AD by only five years without also increasing lifespan would have the potential to reduce the number of AD cases by half. We propose using FDG PET and other biomarkers in proof-of-concept studies to rapidly evaluate the efficacy of cholesterol-lowering

treatments to slow down the brain changes associated with aging in cognitively normal late-middle-aged carriers and non-carriers of the APOE ϵ 4 allele.

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Figure 1.

Statistical brain maps showing the correlations between higher serum total cholesterol levels and lower CMRgl ($p < 0.005$, uncorrected for multiple comparisons) are shown in dark and light blue in (A) all 117 cognitively normal, late-middle-aged participants, (B) 24 APOE $\epsilon 4$ homozygotes, (C) 38 APOE $\epsilon 4$ heterozygotes, and (d) 55 APOE $\epsilon 4$ non-carriers. These statistical maps are projected onto the lateral and medial surfaces of the left and right cerebral hemispheres and shown in relationship to brain regions preferentially affected by AD (Alexander et al., 2002), which are shown in dark blue and purple. The dark blue areas thus reflect significant correlations between higher serum total cholesterol levels and lower CMRgl in the brain regions that are preferentially affected by AD. The light blue areas in frontal cortex are known to be preferentially affected by normal aging.

Figure 2.

Statistical brain maps showing greater associations between higher serum total cholesterol levels and lower CMRgl ($p < 0.005$, uncorrected for multiple comparisons and reflecting a comparison of slopes) are shown in dark and light blue in (A) APOE $\epsilon 4$ homozygotes compared to non-carriers, and (B) APOE $\epsilon 4$ heterozygotes compared to non-carriers. These statistical maps are projected onto the lateral and medial surfaces of the left and right cerebral hemispheres and shown in relationship to brain regions preferentially affected by AD (Alexander et al., 2002), which are shown in dark blue and purple. As indicated in dark blue, significantly greater associations between higher serum total cholesterol levels and lower CMRgl in each of the $\epsilon 4$ carrier groups are almost entirely confined to temporal cortex regions that are preferentially affected by AD.

Figure 3.

Scatterplots of the association between higher serum total cholesterol levels and lower CMRgl from A) the AD-affected parietal cortex voxel with the most significant inverse correlation in the overall group, B) the AD-affected left temporal cortex voxel with the most significant difference in the regression line slopes in APOE $\epsilon 4$ homozygotes versus non-carriers, and C) the AD-affected left temporal cortex voxel with the most significant difference in the regression line slopes in APOE $\epsilon 4$ heterozygotes versus non-carriers. Data were extracted from the atlas location shown in Tables 2 and 3. In figure 3B, the closed circles and solid regression lines correspond to data from the APOE $\epsilon 4$ homozygotes ($r=-0.56$, $p=0.004$), the open circles and dashed regression lines correspond to data from the APOE $\epsilon 4$ non-carriers ($r=0.08$, $p=0.59$). In figure 3C, the closed circles and solid regression lines correspond to data from the APOE $\epsilon 4$ heterozygotes ($r=-0.52$, $p=0.001$), the open circles and dashed regression lines correspond to data from the APOE $\epsilon 4$ non-carriers ($r=0.10$, $p=0.47$).

Table 1

Participant characteristics, clinical ratings, neuropsychological scores and lipid panel measurements

	ε4 Non-carriers n = 55 (mean ± SD)	ε4 Heterozygotes n = 38 (mean ± SD)	ε4 Homozygotes n = 24 (mean ± SD)	p-value[†]
Age (years)	59.8±6.5	60.5±43.9	58.7±6.3	0.56
Gender (F/M)	35/20	23/15	18/6	0.47
Years of Education	16.1±2.1	16.1±2.2	16.2±2.2	0.88
MMSE	29.6±0.7	29.8±0.6	29.8±0.5	0.37
Body Mass Index	26.7±4.5	28.3±12.9	28.3±4.0	0.29
Statin Use, %	18.5	26.3	37.5	0.20
HAM-D	2.5 ± 3.2	1.1 ± 1.4	1.9 ± 2.5	0.07
AVLT				
Total Learning	47.2 ± 9.6	50.7 ± 8.4	48.7 ± 10.3	0.27
Short Term Memory	9.3 ± 2.6	10.0 ± 2.7	9.5 ± 3.8	0.49
Long Term Memory	8.6 ± 3.0	9.8 ± 2.9	8.7 ± 4.6	0.27
Complex Figure Test				
Copy	34.5 ± 1.9	34.9 ± 1.9	34.5 ± 3.3	0.62
Recall	19.1 ± 7.1	20.9 ± 8.0	19.0 ± 8.7	0.50
Boston Naming Test	56.3 ± 4.2	55.8 ± 4.2	57.2 ± 2.2	0.88
WAIS-R				
Information	12.5 ± 2.3	11.9 ± 2.6	11.9 ± 1.9	0.33
Digit Span	10.9 ± 2.7	12.5 ± 2.7	11.8 ± 1.9	0.04
Block Design	12.6 ± 2.7	12.8 ± 3.1	12.4 ± 3.2	0.89
Arithmetic	12.2 ± 2.5	12.4 ± 2.9	11.9 ± 2.9	0.81
Similarities	12.8 ± 1.9	12.7 ± 2.4	13.0 ± 1.7	0.79
COWAT	43.8 ± 9.8	46.3 ± 11.5	45.6 ± 9.4	0.52
WMS-R Orientation	13.8± 0.4	13.9 ± 0.3	13.9 ± 0.4	0.63
Lipid Panel Measurements				
Serum total cholesterol (mg/dL)	195±36	195±38	205±46	0.31
LDL (mg/dL)	115±32	114±33	121±37	0.48
HDL (mg/dL)	59±18	62±18	62±20	0.39
Triglyceride (mg/dL)	128±77	115±64	131±68	0.20

Abbreviations: MMSE, Mini-Mental State Exam; HAM-D, Hamilton Depression Rating Scale; AVLT, Auditory Verbal Learning Test; WAIS-R, Wechsler Adult Intelligence Scale-Revised; COWAT, Controlled Oral Word Association Test; WMS-R, Wechsler Memory Scale-Revised; LDL, Low-density lipoprotein; HDL, High-density lipoprotein

[†]P-values were calculated using analysis of variance (ANOVA) and chi-square test, uncorrected for multiple comparisons

Table 2

Location and Magnitude of Most Significant Correlations Between Serum Total Cholesterol and Lower Regional-to-Whole Brain CMRgl^a

Brain region	Atlas coordinates (mm) ^b			Correlation coefficient	p-value ^c
	X	Y	Z		
<i>AD areas</i>					
Precuneus	Left -4	-40	80	-0.28	1.0×10^{-3}
Parietal	Left -34	-61	58	-0.35	$4.8 \times 10^{-5*}$
	Right 51	-29	42	-0.38	$1.5 \times 10^{-5*d}$
Temporal	Left -51	-46	13	-0.26	$2.6 \times 10^{-3*}$
	Right 51	-52	14	-0.30	$4.8 \times 10^{-4*}$
Prefrontal	Left -4	36	53	-0.35	$4.4 \times 10^{-5*}$
	Right 10	50	38	-0.34	$1.0 \times 10^{-4*}$
<i>Aging areas</i>					
Frontal	Left -26	31	46	-0.32	2.5×10^{-4}
	Right 30	48	31	-0.29	7.6×10^{-4}

^aThe data were extracted from voxels associated with the most significant correlations in each of the brain regions previously found to be associated with abnormally low CMRgl in patients with Alzheimer's dementia (Alexander et al., 2002).

^bThe coordinates were obtained from Talairach and Tournoux (1988). X is the distance to the right (+) or left (-) of the midline, Y is the distance anterior (+) or posterior (-) to the anterior commissure, and Z is the distance superior (+) or inferior (-) to a horizontal plane through the anterior and posterior commissures.

^cThe reported significance levels are one-tailed and uncorrected for multiple comparisons;

* each of these correlations remained significant ($p < 0.05$) after correcting for multiple comparisons in the relevant AD-related search regions.

^dData from this location were extracted from each subject and are shown in the scattergraph in Figure 3A.

Table 3

Location and Magnitude of the Most Significant Differences in the Higher Total Cholesterol-Lower CMRgl Regression Lines in the Respective APOE $\epsilon 4$ Carrier Versus Non-Carrier Groups.^a

Brain region	Atlas coordinates (mm) ^b			p-value ^c
	X	Y	Z	
<i>$\epsilon 4$ Homozygotes vs. Non-carriers</i>				
Temporal Left	-55	-21	1	0.002 ^d
Right	63	-58	10	7.9×10 ⁻⁴
<i>$\epsilon 4$ Heterozygotes vs. Non-carriers</i>				
Temporal Left	-48	-53	21	5.6×10 ⁻⁴ * ^d

^aThe data were extracted from voxels associated with the most significant correlations in each of the brain regions previously found to be associated with abnormally low CMRgl in patients with Alzheimer's dementia (Alexander et al., 2002).

^bThe coordinates were obtained from Talairach and Tournoux (1988). X is the distance to the right (+) or left (-) of the midline, Y is the distance anterior (+) or posterior (-) to the anterior commissure, and Z is the distance superior (+) or inferior (-) to a horizontal plane through the anterior and posterior commissures.

^cThe reported significance levels are one-tailed and uncorrected for multiple comparisons;

* each of these correlations remained significant ($p < 0.05$) after correcting for multiple comparisons in the relevant AD-related search regions.

^dData from these locations were extracted from each subject and are shown in the scattergraphs in Figures 3B and 3C.