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# LDL Phenotype in Subjects with Mild Cognitive Impairment and Alzheimer's Disease

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## Abstract

**Background—**Centenarians with normal cognitive function have a "longevity phenotype" characterized by large low-density lipoproteins (LDL) and high-density lipoproteins (HDL) and low incidence of metabolic syndrome, hypertension, and cognitive impairment. Alzheimer's disease (AD) is associated with a number of cardiovascular risk factors, but it is not known if they have or lack the "longevity phenotype".

**Objective—**The study was designed to determine LDL size and body fat content and distribution in subjects with mild cognitive impairment (MCI) and AD.

**Results—**Fifty-eight persons with MCI or AD (cases) and 42 control subjects of similar age had measurement of LDL size and lipoprotein lipids after a 12 h fast and analysis of body composition by dual x-ray absorptiometry. Cases had small LDL size more often than controls (73% versus 66%) associated with significantly higher triglycerides, lower HDL cholesterol, and higher triglyceride/HDL cholesterol ratio ($p \leq 0.02$). Cases with large LDL had a better lipoprotein profile than those with small LDL. Cases and controls had similar percent body fat, fat index, and lean mass index. Forty-seven percent of cases and 39% of controls were obese.

**Conclusion—**The prevalence of small LDL phenotype in MCI and AD cases contrasts with the "longevity phenotype" reported for centenarians with preserved cognitive function. The small LDL phenotype is an atherogenic lipoprotein profile found in metabolic syndrome, type 2 diabetes, and insulin resistance. It is now also reported in persons with MCI and AD.

### Keywords

Atherogenic dyslipidemia; longevity phenotype; small LDL



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## INTRODUCTION

Alzheimer's disease (AD) is associated with risk factors for cardiovascular disease but it is unclear how these risk factors contribute to AD [1] and if they may be targets for therapeutic intervention. Mid-life risk factors for cardiovascular disease are also associated with the incidence of AD [2]. The CAIDE study, for example, showed that midlife obesity, high total cholesterol level, and high systolic blood pressure were all significant risk factors for dementia and that the risks were additive [3]. In recent years, there has also been an interest in the role of insulin resistance on cognition since some evidence suggests that type 2 diabetes is a risk factor for AD [4, 5]. All of these studies suggest that clustering of metabolic risk factors for cardiovascular disease may be causally related to AD. Many of these clusters start at mid-life and continue through late life.

Of interest, the center piece of cardiovascular disease risk is low density lipoprotein (LDL); high levels impart risk. However, large LDL and HDL, designated as "longevity phenotype", are frequently found in centenarians [6] who have a low risk. The phenotype is also associated with homozygozity for a genetic variant of cholesterol ester transfer protein (CETP) (VV homozygosity for 1405 V) and with preservation of cognitive function [7], e.g., Mini-Mental State Examination score ≤25 points. More recently it has been shown that the offspring of persons with exceptionally great longevity (age at death at age 85 or greater) have significantly lower incidence of AD than persons with shorter parental life spans (hazard ratio = 0.57, 95% CI = 0.35–0.93) after adjusting for several concomitant risk factors [8]. In contrast, small LDL is part of the "atherogenic dyslipidemia" that includes high triglycerides and reduced HDL C [9]. Small LDL also exhibit familial trends [10] and impart risk for cardiovascular disease and/or type 2 diabetes mellitus [11].

In this study we examine LDL size and metabolic concomitants for two reasons: 1) large LDL has been associated with a "longevity phenotype" and 2) small LDL has been associated with a "pro-atherogenic lipoprotein phenotype" frequently associated with insulin resistance and central obesity. Because of the epidemiologic data linking AD to dyslipidemia, we compared lipoprotein phenotypes and measures of body fat and its distribution in persons with mild cognitive impairment (MCI) and AD to age-matched control subjects to see if differences were detectable in MCI and early AD subjects. In the current study, we tested the hypotheses that the prevalence of large LDL would be lower in persons with MCI or early AD than in age-matched controls and that the proportion and distribution of body fat would differ in MCI and AD subjects from controls. We included persons with MCI because it is thought of as a transitional state to AD, which would be the ideal point for therapeutic intervention.

## MATERIALS AND METHODS

One hundred subjects were recruited from the UT Southwestern Alzheimer's Disease Center. "Cases" included both MCI and AD subjects, a total of 24 women and 34 men. Controls included 25 women and 17 men. Approximately one third of cases met criteria for mild, sporadic AD (Clinical Dementia Rating = 1.0), and the rest met criteria for MCI (CDR = 0.5). Controls were cognitively normal (CDR = 0).

AD subjects had a diagnosis of probable AD based on the criteria of McKhann et al. [12] and a Clinical Dementia Rating [13] score of 1 or greater. The diagnosis of mild cognitive impairment was made by consensus according to the criteria of Petersen et al. [14] and a Clinical Dementia Rating of 0.5. Subject demographics are summarized in Table 1.

The study had a cross-sectional design. Volunteers had fasting blood drawn for measurement of LDL size (Lipoprint from Quantimetrix) and plasma lipids and lipoprotein cholesterol [15]; they also had assessment of body composition by dual-x ray absorptiometry (DXA) using the Discovery W. Images were analyzed with Apex 3.3 software as previously detailed [16].

This study was approved by the Institutional Review Board of the University of Texas Southwestern Medical Center. All participants gave written informed consent to participate in the study.

### Statistical methods

Data are summarized as means ± standard deviation. Data transformation was made for skewed data as needed for comparisons of means by one-way analysis of variance using Bonferroni adjustments as needed. The primary end point of the study was the comparison of LDL size between cases and controls. Accordingly, sample size calculation was based on a 20% difference using a power of 0.87 and an alpha of 0.05.

## RESULTS

Cases and controls had similar ages, body mass index, and percent body fat (Table 1). They also had similar fat and lean mass indices and fat/lean mass ratio. However, there was a higher prevalence of obesity in the cases than in the controls but the prevalence of sarcopenia (low muscle mass) and sarcopenic obesity (low muscle mass associated with high fat mass) were similar between the two study groups. Cases also had a trend for higher truncal/lower extremity fat ratio (Table 1).

The relative distribution of LDL size for cases and controls is shown in Fig. 1. Cases had a higher frequency of smaller LDL compared to controls. The mean LDL size was significantly smaller in cases compared to controls (Fig. 2). Within cases, LDL size was significantly smaller in AD compared to controls (Fig. 2); MCI cases showed similar trends in having small LDL size than controls. There were no significant differences in LDL sizes between MCI and AD cases.

The characteristics of cases grouped by LDL size are summarized in Table 2. Cases with a large LDL had similar fat indices and lower lean indices than those with small LDL. They also had a better lipid profile than those with small LDL, i.e., the plasma triglycerides, non-HDL cholesterol, and the ratio of triglyceride/HDL C, were lower. The age of onset of the disease was not significantly different between cases with large and cases with small LDL.

Overall, 29.5% of all individuals had large LDL and 70.5% had small LDL (Table 3). The group characteristics for “large LDL” and “small LDL” subjects were examined together. Accordingly, subjects with small LDL pattern had a typical “dyslipidemia phenotype”. That

is, they had small LDL, higher plasma triglycerides, lower HDL cholesterol, and higher triglyceride/HDL cholesterol ratio than those with a large LDL and “normolipidemia” phenotype (Table 3). This metabolic pattern was present despite similarities in the fat mass index. A trend toward a higher lean mass index was also noted in subjects with small LDL but the ratio of fat to lean index was similar between those with small or large LDL.

## DISCUSSION

The current study was designed to compare LDL size in subjects with incipient and mild AD to controls. We aimed to ascertain if cases had a lower prevalence of a “longevity” phenotype. Other secondary end points included determination of obesity prevalence and the relation between body composition and the prevalence of “longevity” lipoprotein phenotype. We found a lower prevalence of the longevity phenotype, a higher prevalence of obesity, and small LDL phenotype in cases than in controls. We also noted that cases with large LDL had a better lipid profile than those cases with a small LDL despite similarities in the fat indices.

In the current study, 26.9% of cases and 33.3% of controls had large LDL. There were no significant differences between these groups in plasma levels of triglyceride, non-HDL cholesterol, or HDL cholesterol. Cases and controls with large LDL had low levels of plasma triglycerides, high HDL cholesterol, low ratio of triglyceride to HDL cholesterol, and low levels of non-HDL cholesterol. This phenotype was present along with similarities in body habitus.

It is also important to note that cases in this study did not have differences in BMI, or body fat or lean mass content. These similarities made the study comparisons easier, i.e., we did not have to make adjustments in the comparisons for body habitus differences. We expected that cases would have lower BMIs, or abnormalities in body composition relative to controls as reported by others [17]. However, other reports indicate that appropriate nutritional management of AD patients leads to normal weight [18]. The cases in our study were not malnourished. Still, there is a need for more systematic study of body composition in AD given the inconsistencies in reports of body composition.

We show that subjects with MCI and AD have smaller LDL size than control subjects (Figs. 1 and 2). The prevalence of small LDL was 73% in cases and 67% in controls. In addition both cases and controls with small LDL had higher levels of plasma triglyceride, lower HDL cholesterol, and higher levels of non-HDL cholesterol than those with large LDL.

LDL size has been a subject of intensive research. Small LDL arises from defective metabolism of VLDL. Small LDL is a poor ligand for hepatic LDL receptors and these lipoproteins are prone to oxidation and uptake by scavenger receptors located on the surface of macrophages. The size of the lipoprotein correlates positively with plasma HDL cholesterol levels and inversely with plasma triglyceride concentrations. That is, small LDL is generally associated with low HDL cholesterol and increased plasma triglycerides levels. This lipoprotein phenotype has been designated as “atherogenic” [19, 20]. Both familial and environmental factors underlie the LDL phenotype [21, 22]. In recent years, it has also been

shown that the atherogenic lipoprotein phenotype occurs in subjects with metabolic syndrome [9] and type 2 diabetes mellitus [23]. Reaven et al. [24] also have described the atherogenic lipoprotein phenotype in persons with insulin resistance. They have higher levels of plasma glucose, insulin, and triglyceride, and lower HDL cholesterol and higher blood pressures than persons with larger LDL.

How might the atherogenic lipoprotein phenotype contribute to the development of AD? LDL does not traverse the blood-brain barrier; but some recent studies suggest that dyslipidemia alters blood-brain barrier function in AD, particularly in subjects with elevated plasma triglycerides and low HDL cholesterol [25] and could conceivably set the stage for the entry of inflammatory lipids from the blood, as suggested by Zlokovic [26]. In summary, this study shows that small LDL phenotype is more prevalent in subjects with MCI and AD than controls. The LDL phenotype is associated with mild atherogenic dyslipidemia and may be influenced by obesity. The differences between cases and controls appear modest, but fit the possibility that there may be one or multiple atherogenic triggers for the pathology of AD.

The current observations need to be repeated in a large scale study taking into consideration that therapeutic modulation of LDL and HDL sizes may reduce risk imparted by cardiovascular risk factors. Since small LDL is linked to defective triglyceride metabolism, therapies targeted to triglyceride may be worth considering. Alternatively, since the longevity phenotype is seemingly linked to large LDL and HDL, it is of interest to determine whether the combination of statins and CETP inhibitors have an effect not only on cardiovascular risk but also on MCI/AD. The current drug trials using statins in combination with CETP inhibitors (ClinicalTrials.gov NCT00688896, NCT0125953, NCT1105975) may be instructive not only in cardiovascular risk management but also in risk for AD.

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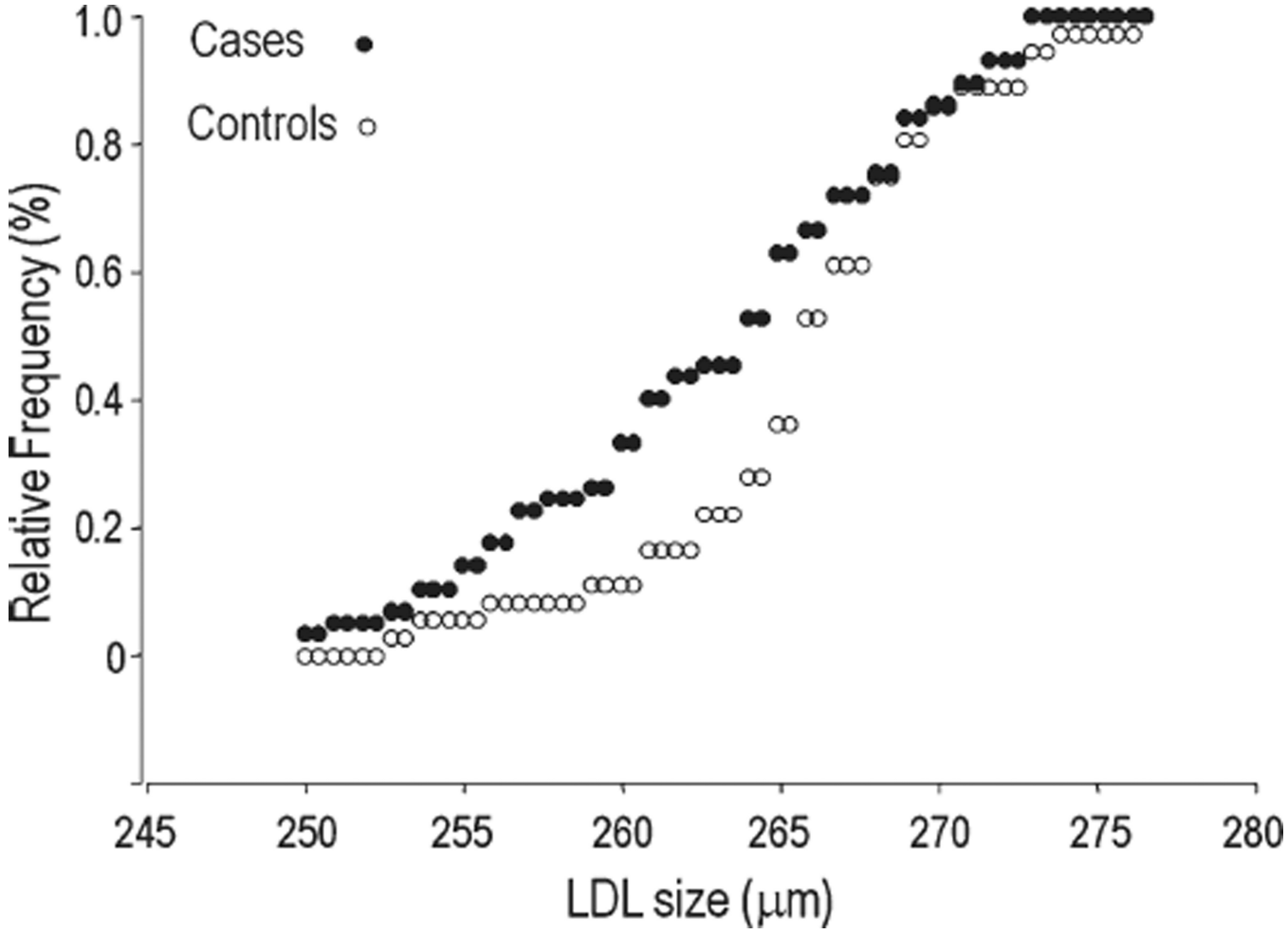


**Fig. 1.**

Relative frequency distribution of LDL size (nm) in cases (closed circles) and controls (open circles). Cases had a significantly higher prevalence of small LDL and a significantly smaller LDL size as shown by the mean sizes and standard deviation (SD) per group. The comparison was made by ANOVA with Bonferroni adjustment.

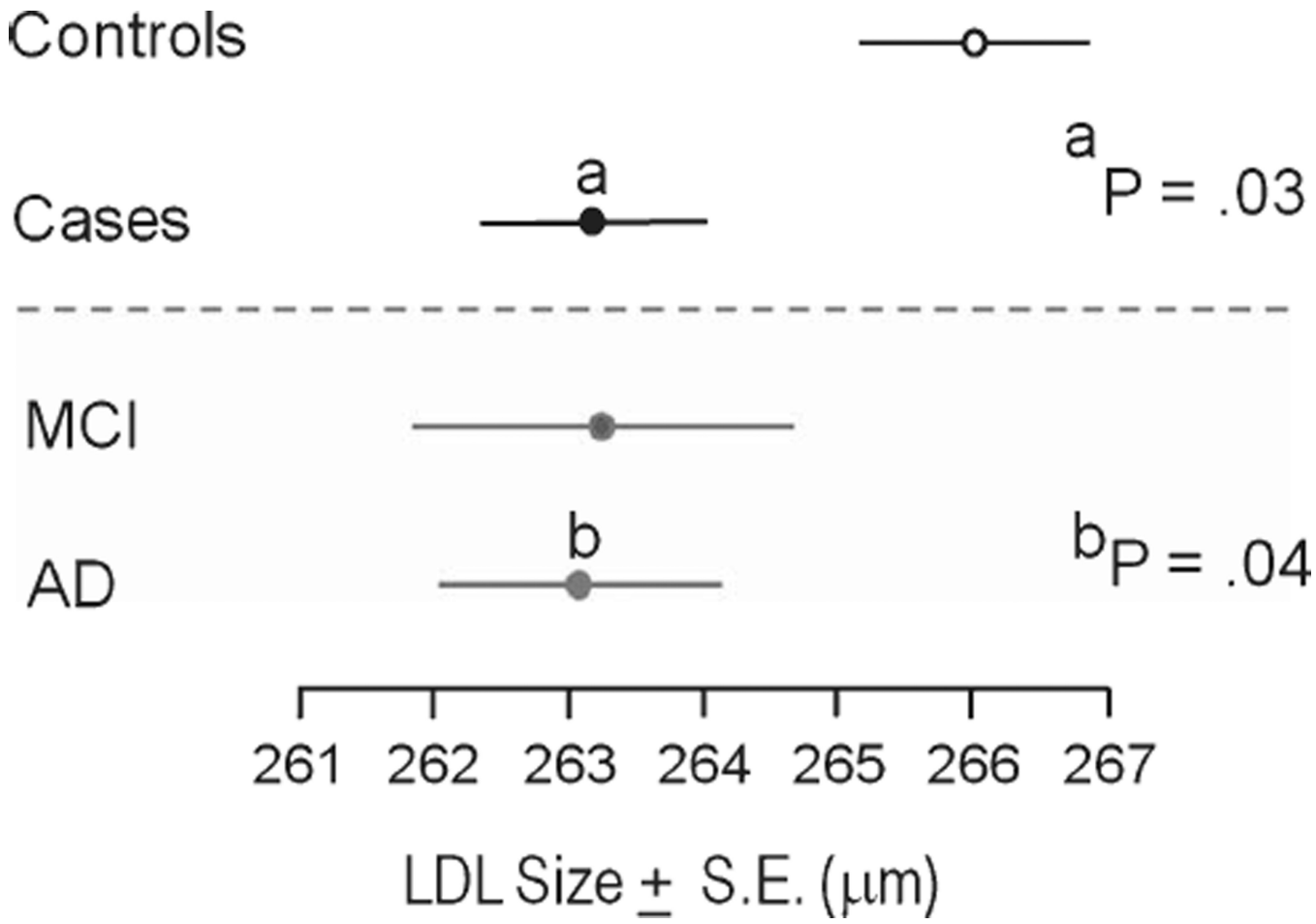


**Fig. 2.**

Comparison of LDL size between cases and controls. Cases had significantly smaller LDL size compared to controls. Also, AD had significantly smaller LDL than controls and the same trend was seen in MCI patients. However, there were no significant differences in LDL size between AD and MCI patients.

**Table 1**

Anthropometric characteristics of subjects

| | Cases | Controls |
|---|---|---|
| | Mean ± S.D. | |
| Number (% Men) | 58 (58.6) | 42 (40.5) |
| Age (years) | 72.3 ± 8.1 | 72.4 ± 7.2 |
| Age of onset of AD (years) | 69.3 ± 7.7 | Not applicable |
| Body Mass Index (kg/m$^2$) | 27.5 ± 5.4 | 28.1 ± 8.2 |
| % Body Fat | 33.2 ± 8.1 | 35.0 ± 8.1 |
| Fat Index (kg/m$^2$) | 9.4 ± 4.5 | 9.4 ± 3.6 |
| Lean Index (kg/m$^2$) | 18.0 ± 6.3 | 16.6 ± 3.0 |
| Fat/Lean Index ratio | 0.53 ± 0.20 | 0.58 ± 0.20 |
| Truncal/Lower extremity fat ratio | 1.85 ± 0.6 | 1.58 ± 0.6 |
| Obese* (%) | 46.9 | 38.8 |
| Sarcopenia (%) | 11.3 | 11.2 |
| Sarcopenic Obesity (%) | 11.2 | 15.3 |

* Obese: % Body fat >30% for women and >25% for men. Sarcopenia: Skeletal muscle mass index in men <7.26 kg/m$^2$ and in women <5.45 kg/m$^2$. Sarcopenic Obesity: sarcopenia plus body fat percentage >27% in men and 38% in women.

## Table 2

Characteristics of cases with large versus small LDL size

| | Large LDL | Small LDL |
|---|---|---|
| Cases (% of total) | 26.9 | 73.1 |
| LDL size (μm) | 271 ± 2[a] | 260 ± 5 |
| Age of Onset of disease (years) | 70 ± 10[b] | 69 ± 7 |
| Plasma Triglyceride (mg/dl) | 95 ± 29[a] | 132 ± 63 |
| HDL cholesterol (mg/dl) | 79 ± 19[b] | 54 ± 13 |
| Triglyceride/HDL Cholesterol ratio | 1.27 ± 0.49[a] | 2.69 ± 1.62 |
| Non-HDL cholesterol (mg/dl) | 110 ± 27[a] | 135 ± 49 |
| Fat Index ($kg/m^2$) | 8.4 ± 3.4 | 9.7 ± 4.8 |
| Lean Index ($kg/m^2$) | 15.0 ± 2.1[a] | 17.8 ± 6.8 |
| Fat/Lean Index ratio | 0.57 ± 0.51 | 0.49 ± 0.51 |

[a] Significantly different from cases with small LDL size; unpaired *t*-test, $p \leq 0.01$.

[b] Trend for differences: $p \geq 0.05$.

## Table 3

Prevalence of small LDL, higher triglycerides, and lower HDL in cases (MCI and Alzheimer's disease) and controls grouped by LDL size

| | Large LDL | Small LDL |
|---|---|---|
| | Mean ± S.D. | |
| Percent of total number of subjects | 29.5 | 70.5 |
| Controls (% of total controls) | 33.3 | 66.7 |
| LDL size (nm) | 271 ± 2 | 261 ± 5[a] |
| Plasma Triglyceride (mg/dl) | 91 ± 26 | 130 ± 71[a] |
| HDL cholesterol (mg/dl) | 74 ± 18 | 57 ± 15[a] |
| Triglyceride/HDL Cholesterol ratio | 1.30 ± 0.50 | 2.60 ± 2.10[a] |
| Non-HDL cholesterol (mg/dl) | 115 ± 27 | 136 ± 41[a] |
| Fat Index (kg/m$^2$) | 8.9 ± 3.9 | 9.7 ± 4.4 |
| Lean Index (kg/m$^2$) | 15.9 ± 2.7 | 18.3 ± 6.0[b] |
| Fat/Lean Index ratio | 0.56 ± 0.2 | 0.54 ± 0.19 |

[a] Significantly different between cases and controls; $p < 0.001$ or

[b] $p < 0.02$ by ANOVA.