Reduced cerebrospinal fluid concentration of apolipoprotein A-I in patients with Alzheimer's disease

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Abstract

Objective: Apolipoprotein E (ApoE) has been extensively studied in Alzheimer's disease (AD), but relatively little is known of apolipoprotein A-I (ApoA-I) in cerebrospinal fluid (CSF).

Material and methods. In a mono-center study, consecutive patients with AD (n = 29), stable MCI (SMCI, n = 13), other dementias (n = 14), and healthy controls (n = 18) were included. We measured ApoA-I and ApoE concentrations in plasma and CSF as well as plasma lipid concentrations.

Results. AD patients had higher plasma triglycerides and lower CSF ApoA-I concentration than controls (both $P < 0.05$). CSF ApoE concentration was reduced in other dementias ($P < 0.01$). In AD as well as other dementias, the ratios between CSF and plasma concentrations of both ApoA-I and ApoE were lower than those in the controls. Serum and CSF concentrations of ApoA-I and ApoE were not influenced by *APOE* ε4 allele distribution. In the total study population (n = 74), CSF ApoA-I correlated positively with mini mental state examination (MMSE) score (r = 0.26, $P < 0.05$) and negatively with CSF P-tau (r = -0.25, $P < 0.05$). CSF ApoE correlated positively with CSF concentrations of T-tau and P-tau in the total study population and in AD patients.

Conclusion: CSF ApoA-I was lower in AD patients compared with controls and associated with measures of cognitive function and AD disease status. The mechanisms underlying the decreased CSF:plasma ratios of ApoA-I and ApoE observed in AD and other dementias need to be explored in further studies.

Introduction

High-density lipoproteins (HDLs) eliminate excess cholesterol by transporting cholesterol from peripheral tissues to the liver [1]. Low-density lipoproteins (LDLs) carry the major part of plasma cholesterol and supply cholesterol to many cells [1]. Low levels of HDL and the associated apolipoprotein A-I (ApoA-I), and elevated LDL, are risk factors for atherosclerosis [1]. Although an impaired lipid pattern has been associated with increased dementia risk [2], it is controversial whether lipid-lowering statin treatment can affect the progression of Alzheimer's disease (AD) [2]. In contrast to plasma, most CSF lipoproteins are HDL-like in both density and size (HOLTZMAN, D. M., BALES, K. R., WU, S., BHAT, P., PARSADANIAN, M., FAGAN, A. M., CHANG, L. K., SUN, Y. & PAUL, S. M. 1999. Expression of human apolipoprotein E reduces amyloid-beta deposition in a mouse model of Alzheimer's disease. J Clin Invest, 103, R15-R21; BORGHINI, I., BARJA, F., POMETTA, D. & JAMES, R. W. 1995. Characterization of subpopulations of lipoprotein particles isolated from human cerebrospinal fluid. Biochim Biophys Acta, 1255, 192-200).

Apolipoprotein E (ApoE), produced by the liver and for example macrophages [3], is found in several types of lipoprotein particles [3]. In the central nervous system (CNS), ApoE is mainly produced by astrocytes and microglia [3]. ApoE transports cholesterol to neurons via ApoE receptors [3], thereby being involved in the mobilization of lipids in repair, growth and maintenance of myelin and axonal membranes [3,4]. The epsilon4 (ε4) allele of the *APOE* gene is a major genetic risk factor for AD [3,4], and meta-analyses demonstrate decreased blood and cerebrospinal fluid (CSF) ApoE concentrations in AD [5,6].

ApoA-I is mainly produced in the liver and the intestine [7,8]. Although experimental data suggest that ApoA-I can be secreted from cerebral microvascular endothelial porcine cells [9], there is no evidence of ApoA-I synthesis in the human CNS [8,10]. ApoA-I gains access to the CNS by crossing the blood-cerebrospinal fluid barrier via specific cellular mediated transport, and to a lesser extent by transport across the blood-brain barrier [11]. ApoA-I has been less well studied than ApoE, but experimental data suggest that Apo A-I might protect from amyloid toxic effects [12]. Overexpression of human ApoA-I in a mouse AD model (APP/PS1/AI mice) prevented learning and memory deficits [13], whereas lack of ApoA-I in mice aggravated memory deficits and increased cerebral amyloid angiopathy [14]. ApoA-I administration protected hippocampal neuronal cultures from β-amyloid (Aβ)-induced oxidative stress and neurodegeneration [15]. In the human brain, ApoA-I has been found in association with Aβ deposits [16], and complexes between ApoA-I and Aβ can be detected in CSF from AD patients [15].

In serum or plasma, several studies have shown decreased ApoA-I concentration in AD patients [17,18], although unchanged ApoA-I levels have also been observed [19]. In a longitudinal study, high serum ApoA-I was associated with reduced risk of dementia [20]. In terms of CSF, two *in vivo* studies showed normal ApoA-I concentration in AD [21,22], whereas in another small *in vivo* study, decreased CSF ApoA-I concentration was observed in seven AD patients compared to seven controls [23]. Furthermore, CSF ApoA-I concentration was reduced in two postmortem studies [24,25].

The apolipoproteins ApoA-I and ApoE may be involved in the pathogenesis of brain disorders leading to cognitive decline, but the nature of this involvement is still not fully clear. In a well characterized mono-center cohort of patients with cognitive impairment and matched healthy controls, we determined plasma lipids as well as plasma and CSF concentrations of ApoA-I and

ApoE. We also studied whether there were associations with MMSE score and CSF levels of AD biomarkers.

Materials and methods

Study participants

The study participants as well as AD CSF biomarkers have been reported previously [26]. The study consisted of consecutively recruited Caucasian patients admitted by their general practitioner for evaluation of cognitive impairment to a memory clinic in Falköping, Sweden. The participants were recruited by a single specialized physician (P.J.) 2000-2008. Inclusion criteria, besides being referred to Falköping Hospital for evaluation of suspected dementia, were age 65-80 years, body mass index (BMI) 20-26 kg/m², and waist: hip ratio 0.65-0.90 in women and 0.70-0.95 in men. Exclusion criteria were serum creatinine > 175 mmol/L, diabetes mellitus, previous myocardial infarction, malignancy including brain tumor, subdural hematoma and ongoing alcohol abuse.

Control subjects were recruited contemporaneously from the same geographical area among spouses of the included patients and by advertisements in local newspapers. The controls had no subjective symptoms of cognitive dysfunction but otherwise, inclusion and exclusion criteria were similar as those in the patients. Totally, 60 patients and 20 healthy controls were recruited. However, in this analysis, patients treated with lipid lowering agents were excluded. Therefore, 56 patients (29 men and 27 women) and 18 healthy controls (10 men and 8 women) were included in the present study.

The presence or absence of dementia was diagnosed according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV), criteria. Patients with dementia were classified as suffering of Alzheimer's disease (AD) [27], vascular dementia (VaD) according to the requirements by NINDS-AIREN [28] or the guidelines by Erkinjuntti et al. for the

subcortical type of VaD [29]. Dementia with Lewy bodies (DLB) and frontotemporal lobe dementia (FTD) were diagnosed as described previously [26].

Mild cognitive impairment (MCI) was diagnosed in patients with cognitive impairment that did not fulfil the criteria for dementia [30]. Patients with MCI were followed at least annually for a median of 3 (range 1-7) years to evaluate whether they later developed dementia. All diagnoses were assessed by an independent specialized physician [26]. During the follow-up visits, 13 MCI patients remained in stable cognitive function (SMCI). Others progressed, during the follow-up period, to dementia and were diagnosed with AD (n = 5), VaD (n = 3), or FTD (n = 1). MCI patients diagnosed with AD on follow-up visits did not differ in CSF levels of the AD biomarkers β-amyloid$_{1-42}$ (Aβ_{1-42}), total-tau (T-tau) or phosphorylated tau protein (P-tau) from patients with established AD at baseline (data not shown). Totally, the study population consisted of AD dementia or MCI diagnosed with AD dementia upon follow-up (n = 29), other dementias (n = 14), SMCI (n = 13), and healthy controls (n = 18). The distribution of diagnoses in the other dementia group was VaD or MCI diagnosed with VaD upon follow-up (n = 9), DLB (n = 4), and MCI diagnosed with FTD upon follow-up (n = 1).

Ethical considerations

The study was approved by the ethical committee of University of Gothenburg, and informed consent was obtained from all participants.

Cognitive and physical examination

Before the test day, a mini-mental state examination (MMSE) [31] was performed. On the test day morning with the patients in the fasted state, before lumbar puncture was performed, body weight was measured to the nearest 0.1 kg, body height was measured barefoot to the nearest 0.01 m, and body mass index (BMI) was calculated as the weight in kilograms divided by the

height in meters squared. Waist circumference and hip girth was measured as described previously [26].

CSF sampling

All CSF samples were collected by lumbar puncture in the L3/L4 or L4/L5 interspace at the standardized time point 8.30-9.00 am. The first 12 mL of CSF was collected in a polypropylene tube and immediately transported to the local laboratory for centrifugation at 2.000g at +4˚C for 10 minutes. The supernatant was pipetted off, gently mixed to avoid possible gradient effects, and aliquoted in polypropylene tubes that were stored at -80ºC pending biochemical analyses, without being thawed and re-frozen.

Blood samples

Blood samples were drawn in the morning in the fasted state. Plasma concentrations of total cholesterol, HDL-cholesterol, and triglycerides were analyzed in the routine clinical setting. Plasma samples for determination of ApoA-I and ApoE concentrations were stored at -80ºC pending biochemical analyses, without being thawed and re-frozen.

Biochemical procedures

Plasma concentrations of total cholesterol, HDL-cholesterol, and triglycerides were measured using clinical routine methods on Roche Hitachi (717 and 911) and Siemens Advia (1650 and 1800) instruments. Cross-calibration measurements showed similar values for the methods used and reference ranges were identical. CVs were < 7 %. LDL-cholesterol was calculated according to Friedewald's formula [32].

All biochemical analyses of ApoA-I and ApoE concentrations as well as CSF AD biomarkers were performed at the Clinical Neurochemistry Laboratory in Mölndal, Sweden, with the

analyst blinded to the clinical diagnoses and other clinical information. All analyses were done at one occasion, using the same batch of reagents. Saknas här: metodbeskrivning för ApoA-I och ApoE i plasma och CSF. (Verkar ha blivit analyserade med metod från Linco.)

CSF $A\beta_{1-42}$ levels were determined using the INNOTEST® ELISA assay technology (Innogenetics, Ghent, Belgium) [33]. The axonal damage marker CSF T-tau and CSF concentrations of tau phosphorylated at threonine 181 (P-tau181) were measured using INNOTEST® ELISA assays [34,35].

Apolipoprotein E (*APOE*) (gene map locus 19q13.2) genotyping was performed by minisequencing as described previously in detail [36]. Genotypes were obtained for the two SNPs, which are used to unambiguously define ε2, ε3, and ε4 alleles (rs7412 and rs429358).

Statistical analyses

The descriptive statistical results are given as the median (25th-75th percentile) if not otherwise stated. Between-group differences were assessed using the non-parametric Kruskal-Wallis test for multiple variables, followed by the Mann-Whitney U test for pair-wise comparisons. Correlations were sought using the Spearman rank order correlation test. Significance was obtained if the two-tailed *P*-value was ≤ 0.05.

Results

The patients and healthy controls were comparable in terms of age, gender, BMI, and waist: hip ratio (Table 1). AD biomarkers have been reported previously [26]. None of the investigated variables in plasma or CSF correlated with age or CSF/serum albumin ratio (data not shown).

Plasma concentrations of lipids and apoplioproteins

Plasma triglyceride concentration was increased in AD and SMCI patients compared to controls ($P < 0.05$ and $P < 0.01$, respectively) (Table 2). In addition, plasma triglyceride concentration was elevated in SMCI patients compared to patients with other dementias ($P < 0.05$). Plasma concentrations of total cholesterol, HDL-cholesterol, and LDL-cholesterol as well as plasma concentrations of ApoA-I and ApoE were similar in all groups (Table 2).

CSF concentrations of ApoA-I and ApoE

CSF ApoA-I concentration was decreased in AD patients compared to SMCI patients and healthy controls (both $P < 0.05$) (Fig. 1A). CSF ApoE was reduced in other dementias compared to AD and healthy controls ($P < 0.05$ and $P < 0.01$, respectively) (Fig. 1B). The ratio between CSF and plasma concentrations of ApoA-I (CSF: plasma ApoA-I ratio) was decreased in AD and other dementias compared to healthy controls ($P < 0.01$ and $P < 0.05$, respectively) (Fig. 1C). Furthermore, also the CSF: plasma ApoE ratio was decreased in AD and other dementias compared to the controls ($P < 0.05$ and $P < 0.01$, respectively) (Fig. 1D).

Lipids and apolipoproteins in relation to *APOE* ε4 allele distribution (Table 3)

In the total study population, plasma total cholesterol concentration was increased in study participants that were heterozygous or homozygous in terms of the *APOE* ε4 allele compared to participants lacking the APOE ε4 allele (both $P < 0.05$) (Table 3). Plasma HDL-cholesterol

concentration was increased in participants with heterozygous *APOE* ε4 allele distribution compared to no *APOE* ε4 allele ($P < 0.05$). Plasma and CSF concentrations of other lipids and apolipoproteins as well as CSF: plasma ratios of apolipoproteins were statistically similar in all groups (Table 3).

Correlation analysis

We evaluated whether concentrations of apolipoproteins correlated with MMSE score and CSF AD biomarkers. In the total study population (n = 74), CSF ApoA-I concentration correlated positively with MMSE score (r = 0.26, $P < 0.05$), and negatively with CSF P-tau concentration (r = -0.25, $P < 0.05$). CSF ApoE concentration correlated positively with CSF concentrations of $A\beta_{1-42}$ (r = 0.25, $P < 0.05$), T-tau (r = 0.27, $P < 0.05$) and P-tau (r = 0.39, $P < 0.001$). CSF: plasma ApoA-I ratio correlated positively with MMSE (r = 0.31, $P = 0.01$), but not with CSF AD biomarkers. CSF: plasma ApoE ratio did not correlate with MMSE or CSF AD biomarkers.

In AD patients (n = 29), CSF ApoE concentration correlated positively with CSF concentrations of T-tau (r = 0.44, $P < 0.05$) as well as P-Tau (r = 0.52, $P < 0.01$). CSF ApoA-I concentration or CSF: plasma ratios of ApoA-I and ApoE did not correlate with MMSE score or CSF AD biomarker concentrations in AD patients.

Discussion

In the present mono-center study, we included community-dwelling patients under primary evaluation for cognitive impairment and thus in the early phases of cognitive decline (median MMSE score in the AD group was 23). Strictly defined procedures were followed in terms of diagnostic procedures and clinical assessments including lumbar puncture [26], and ApoA-I and ApoE were analyzed using standardized methods in plasma and CSF samples that had previously not been thawed. Patients and controls were matched in terms of age, gender, BMI, and waist: hip ratio and none of the study participants had diabetes mellitus or received medical treatment with lipid lowering agents, glucocorticoids, or acetylcholine esterase inhibitors [26]. Thus, several factors that could influence lipids and apolipoproteins were highly standardized. However, a limitation is the cross-sectional design, and changes over time could therefore not be studied.

We found increased plasma triglyceride concentration in AD and SMCI patients compared to healthy controls whereas other lipids in plasma were similar between groups. In previous studies of AD, circulating HDL-cholesterol was reduced in some studies [37,38], total cholesterol and/or LDL-cholesterol were increased in part of the studies [38-40], and plasma triglyceride concentrations were increased [37] or normal [39,40]. Therefore, most studies including the present one show impaired circulating lipid pattern in AD although concentrations of cholesterol fractions and triglycerides have been relatively variable between studies.

Plasma ApoA-I concentration was similar in all study groups. Although most previous studies have shown decreased circulating ApoA-I in AD [17,18], unchanged plasma ApoA-I concentration has also been observed [19]. Furthermore, ApoA-I polymorphisms could influence the risk of AD [41]. The A allele of the APOA1 -75bp G/A polymorphism was associated with increased risk of early-onset nonfamiliar AD [41]. The natural variant of ApoA-I found in carriers of the ApoA-I Milano polymorphism provides protection from

atherosclerosis [42]. A recombinant ApoA-I Milano/phospholipid complex (ETC-216) reduced coronary atherosclerosis in patients with acute coronary syndromes [43], which has generated interest in using ApoA-I mimetics as therapeutic agents [44]. In a mouse AD model (APPSwe-PS1 Delta E9 mice), addition of an oral ApoA-I mimetic peptide to lipid-lowering statin treatment inhibited Aβ deposition and improved cognitive function [45].

In our study, CSF ApoA-I concentration was decreased in AD compared to SMCI and healthy controls. Two previous *in vivo* studies showed normal [21] or a non-significant trend to increased [22] CSF ApoA-I concentration in AD, whereas another study revealed decreased CSF ApoA-I in seven AD patients compared to seven controls [23]. In addition, two postmortem studies displayed reduced CSF ApoA-I in AD [24,25]. Furthermore, we observed reduced CSF: plasma ApoA-I ratio in AD patients compared to the controls. This ratio has previously not been studied in AD as earlier studies did not measure both circulating and CSF ApoA-I [21-25]. Experimental data suggest that ApoA-I can be transported into the CNS [11], while ApoA-I production has not been documented in the human CNS [8,10]. Therefore, the reduced CSF: plasma ApoA-I ratio in our AD patients could suggest reduced passage of ApoA-I through blood-cerebrospinal and/or the blood-brain barrier. However, it cannot be excluded that ApoA-I passes normally into the CNS and that Apo-I then is lowered due to aggregation/sequestration of ApoA-I around amyloid plaques in the AD brain.

In the present study, plasma as well as CSF ApoE concentration was similar in AD patients as that in the controls. After the first study showing a reduction in CSF ApoE levels in AD [REF], most studies have confirmed such a decrease [21,46-48], although some found either normal [49], or increased [21,50] CSF ApoE concentration in AD. A meta-analysis also revealed decreased ApoE both in blood and CSF from AD patients [5,6]. A recent study in which ApoE was quantified in plasma and CSF using mass spectrometry-based assays specific for the E3

and E4 isoforms, respectively, revealed an age-related increase in both isoforms (ref: Baker-Nigh AT, Mawuenyega KG, Bollinger JG, Ovod V, Kasten T, Franklin EE, Liao F, Jiang H, Holtzman D, Cairns NJ, Morris JC, Bateman RJ. J Biol Chem. 2016 Oct 28. pii: jbc.M116.721779. [Epub ahead of print]). Presence of amyloid pathology, determined by amyloid PET, was associated with increased CSF ApoE3 concentration, but unaltered ApoE4 concentration. Moreover, there was no correlation for total ApoE, ApoE3 and ApoE4 concentrations between plasma and CSF, suggesting that CNS and peripheral ApoE are separate pools and differentially regulated. In contrast to the unchanged CSF:plasma ApoE ratio in AD in a previous study [51], we observed–decreased CSF:plasma ApoE ratio in AD patients compared to the controls. An animal study [52], as well as a human study performed before and after liver transplantation [53], indicated that ApoE in CNS/CSF is predominantly synthesized locally. This suggests that the decreased CSF: plasma ApoE ratio in our study could be caused by increased reutilization of ApoE-lipid complexes as part of a generalized brain repair process in AD, or that ApoE might be aggregated /sequestered in senile plaques and neurofibrillary tangles.

We observed higher plasma total cholesterol in study participants carrying the APOE ε4 allele compared to non-carriers. Furthermore, plasma HDL-cholesterol concentration was increased, and LDL-cholesterol tended to be increased, in APOE ε4 allele carriers. However, plasma and CSF concentrations of ApoA-I or ApoE were not significantly affected by APOE ε4 allele distribution. Possession of the ε4 allele has, in the circulation, been related to a disturbed pattern of lipids, ApoA-I, and ApoE in some [17,54,55] but not all [56,57] previous studies. CSF ApoE concentration was not associated with ApoE ε4 genotype in several studies [46,47], whereas the relation between the ApoE ε4 genotype and CSF ApoA-I concentration has previously not been determined. In summary, although there has been mixed results, some studies including our study have found that the ApoE ε4 genotype influences the circulating pattern of

lipids/apolipoproteins but not CSF concentrations of apolipoproteins.

In the total population, CSF ApoA-I concentration as well as CSF: plasma ApoA-I ratio correlated positively with MMSE score. In addition, CSF ApoA-I correlated negatively with CSF P-Tau in the total study population but not in AD patients. Furthermore, CSF ApoE concentration correlated positively with CSF concentrations of T-tau and P-Tau both in the total population and in AD patients. Therefore, the results of the correlation analyses might suggest that CSF levels of apolipoproteins to some extent associate with cognitive decline and/or AD disease status.

We measured lipids and apolipoproteins also in SMCI and other dementias, conditions with different underlying pathogenesis and clinical presentation than AD. One *in vivo* study [22] and one postmortem study [25] showed unchanged CSF ApoA-I concentration in non-AD dementia. In our study, serum and CSF concentrations of ApoA-I were unchanged in SMCI and other dementias, whereas the CSF: plasma ApoA-I ratio was reduced in other dementias. In the line with the results of another study [47], we observed reduced CSF ApoE concentration in other dementias compared to the controls. Furthermore, plasma triglyceride concentration was increased in SMCI patients compared to the controls. However, there were relatively few patients in the other dementia and SMCI groups and the number of each specific diagnosis was comparatively low in the other dementia group. Therefore, the role of ApoA-I in dementing disorders other than AD needs to be explored in further studies.

In conclusion, in a homogenous, well-controlled study cohort, CSF ApoA-I concentration was decreased in AD patients and was associated with measures of cognitive function and AD disease status. The mechanisms underlying the decreased CSF: plasma ratios of ApoA-I and ApoE in AD could include increased sequestration of the apolipoproteins in the CNS or in case of the CSF: plasma ApoA-I ratio, decreased passage from the periphery into the CNS could

speculatively be of importance. Disturbances of lipids/apolipoproteins were seen also in patients with SMCI and other dementias, but these groups were small and the number of each specific diagnosis was relatively low in the other dementia group.

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Legend to Figures

Figure 1

A) CSF ApoA-I concentration, B) CSF ApoE concentration, C) CSF:serum ApoA-I ratio, and D) CSF:serum ApoE ratio in the study population of patients with AD (n=29), other dementias (n=14), SMCI (n=13), and healthy controls (n=18). Values in the box plots are given as medians (horizontal lines), 25th-75th percentiles (boxes), and ranges (whiskers). Between-group differences were assessed using the Kruskal-Wallis test for multiple variables, followed by the Mann-Whitney U test for pair-wise comparisons.

Table 1. Age, anthropometric measures, MMSE score, and CSF biomarkers in the total study population of 56 patients with cognitive impairment and 18 healthy matched controls.

	AD (n = 29)	**Other dementias (n = 14)**	**SMCI (n = 13)**	**Controls (n = 18)**	***P*-values**
Men/women	14/15	10/4	5/8	10/8	0.35
Age (years)	75 (71-77)	74 (72-76)	72 (69-74)	74 (70-78)	0.32
BMI (kg/m^2)	22.6 (21.7-25.0)	24.2 (20.9-25.6)	24.0 (23.1-26.0)	24.3 (23.3-25.2)	0.29
Waist/hip ratio	0.87 (0.77-0.90)	0.90 (0.87-0.93)	0.82 (0.78-0.88)	0.88 (0.83-0.91)	0.06
MMSE score	23 (19-25)[a,b]	24 (20-26)[c,d]	29 (27-29)	28 (27-29)	< 0.0001
Aβ$_{1-42}$ (ng/L)	430 (326-490)[a,d]	400 (338-801)[e]	671(528-851)[f]	990 (785-1031)	< 0.0001
T-tau (ng/L)	595 (413-729)[a,b,g]	312 (247-381)	270 (224-393)	324 (223-405)	< 0.0001
P-tau (ng/L)	97 (78-113)[c,d,g]	47 (32-63)	60 (38-76)	63 (47-79)	< 0.0001

Values are given as the median (25th-75th percentile). The *P*-values in the right column refers to differences between all four groups using the Kruskal-Wallis test for multiple variables. Comparisons between two separate groups were performed using the Mann-Whitney U test.

[a]$P < 0.0001$ *vs*. controls; [b]$P < 0.0001$ *vs*. SMCI; [c]$P < 0.001$ *vs.* controls; [d]$P < 0.001$ *vs*. SMCI; [e]$P < 0.01$ *vs.* controls; [f]$P < 0.05$ *vs.* controls; [g]$P < 0.0001$ *vs*. other dementias

Table 2. Plasma concentrations of lipids and apolipoproteins in the study population of 56 patients with cognitive impairment and 18 healthy matched controls.

	AD (n = 29)	**Other dementias (n = 14)**	**SMCI (n = 13)**	**Controls (n = 18)**	***P*-values**
Trigycerides (mmol/L)	1.40 (1.00-1.67)[a]	1.04 (0.81-1.30)	1.42 (1.07-2.33)[b,c]	0.98 (0.72-1.34)	0.01
Total cholesterol (mmol/L)	6.30 (5.50- 6.90)	5.50 (4.65-6.20)	6.40 (5.10-7.55)	5.95 (5.40-6.30)	0.19
HDL-cholesterol (mmol/L)	1.60 (1.44-1.80)	1.64 (1.48-1.99)	1.51 (1.21-1.59)	1.51 (1.23-1.70)	0.22
LDL-cholesterol (mmol/L)	3.82 (3.41-4.32)	3.29 (2.65-3.69)	3.60 (3.25-5.15)	3.84 (3.32-4.18)	0.13
ApoA-I (µg/mL)	3826 (2973-5013)	3710 (3377-4878)	3714 (3139-4796)	2686 (1993-3789)	0.055
ApoE (µg/mL)	160 (50 – 341)	148 (50-236)	175 (82-506)	80 (32-115)	0.13

Values are given as the median (25^{th}-75^{th} percentile). The *P*-values in the right column refers to differences between all four groups using the Kruskal-Wallis test for multiple variables. Comparisons between two separate groups were performed using the Mann-Whitney U test.

[a]$P < 0.05$ *vs.* controls; [b]$P < 0.01$ *vs*. controls; [c]$P < 0.05$ *vs.* other dementias

Table 3. Levels of lipids and apolipoproteins in relation to APOE ε4 allele distribution in the total study population (n = 74).

APOE ε4 allele	**None (n = 37, 55%)**	**Heterozygous (n = 20, 30%)**	**Homozygous (n = 10, 15%)**	***P*-values**
Plasma values				
Triglycerides (mmol/L)	1.00 (0.78-1.50)	1.18 (1.06-1.65)	1.40 (0.82-1.75)	0.12
Total cholesterol (mmol/L)	5.60 (5.20-6.30)	6.20 (5.85-6.83)[a]	6.75 (6.10-7.40)[a]	0.03
HDL-cholesterol (mmol/L)	1.46 (1.24-1.70)	1.64 (1.56-1.90)[a]	1.73 (1.44-2.13)	0.04
LDL-cholesterol (mmol/L)	3.47 (3.10-3.99)	3.89 (3.54-4.66)	3.97 (3.53-4.82)	0.21
ApoA-I (μg/mL)	3487 (2419-4459)	3589 (2800-4448)	3792 (3213-4864)	0.53
ApoE (μg/mL)	109 (68-238)	79 (43-294)	97 (33-335)	0.89
CSF values				
ApoA-I (μg/mL)	2.74 (2.12-3.94)	3.40 (2.63-3.90)	3.12 (2.85-3.48)	0.62
ApoE (μg/mL)	4.87 (4.07-7.52)	4.83 (3.65-6.09)	4.42 (3.15-6.39)	0.42
CSF/plasma ratios				
ApoA-I (%)	0.088 (0.057-0.175)	0.094 (0.069-0.116)	0.077 (0.051-0.112)	0.62
ApoE (%)	4.6 (2.3-12.0)	5.8 (1.7-14.3)	4.8 (1.9-14.7)	0.90

APOE genotyping was not performed in 7 of the study participants. Values are given as the median (25th-75th percentile). The *P*-values in the right column refers to differences between all three groups using the Kruskal-Wallis test for multiple variables. Comparisons between two separate groups were performed using the Mann-Whitney U test.

[a]$P < 0.05$ *vs.* no APOE ε4 allele