Effects of Apolipoprotein E Gene and Sex On Serum Lipid Profiles in Alzheimer's Disease

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Abstract

Background: The ε2, ε3 and ε4 alleles of apolipoprotein (*APO*) *E* gene constitute a common polymorphism in most populations, among which the *APOEε4* allele is known to increase both the susceptibility and severity of Alzheimer's Disease (AD), and it is also associated with lipid profiles. High serum total cholesterol (TC) level in middle age has been proven to be a risk factor for AD and its related pathology. In addition, sex may alter the risk associated with the *APOEε4* allele, and gender-specific *APOE* gene interactions can alter the response to anticholinesterase therapy. Therefore, sex is an important factor in studying the relationship between the *APOE* gene, lipid profiles and AD, and the underlying mechanism. However, there are few studies on whether there are differences in the effects of *APOEε2* and *APOEε4* on AD patients and healthy people of different genders, respectively.

Material and methods: A total of 549 participants, including 298 AD patients and 251 body mass index (BMI)-matched health controls (HCs), were enrolled. Lipid profiles and *APOE* genes in both AD patients and matched controls were determined. The cognitive functions of the AD patients were evaluated using the Mini-mental State Examination (MMSE) and the Montreal Cognitive Assessment (MoCA).

Results:

(1) The levels of TC and LDL in the AD group were higher than those in HCs. Subgroup analysis found that the AD patients with the *APOEε4* allele had higher levels of TC and LDL than HCs carrying the *APOEε4* allele, while in individuals without the *APOEε4* allele. There was no significant difference in TG and HDL levels between the AD group and HCs. (2) The levels of TC and LDL in the *APOEε4* carriers were higher than those in non-*APOEε4* carriers. Subgroup analysis found that the increase of TC and LDL in the *APOEε4* carriers was found in the AD and female populations, but not in HCs and male populations. (3) The levels of TC and LDL in the *APOEε2* carriers were lower than those in non-*APOEε2* carriers. Subgroup analysis found that the TC of *APOEε2* carriers was lower than that of non-carriers in the male AD population, but not in the female AD population, female HCs, and male HCs. (4) The levels of TC, HDL and LDL in the female population were higher than the male population. (5) The increased LDL level may increase the risk of AD in female people carrying *APOEε4*.

Conclusion: AD patients had higher TC and LDL levels than HCs, especially in the population with the *APOEε4* allele. The levels of TC and LDL in the *APOEε4* carriers were higher than those in non-*APOEε4* carriers, especially in the female AD populations. The TC of *APOEε2* carriers was lower than that of non-carriers, especially in male AD populations.

Introduction

Alzheimer's disease (AD) is the most common neurodegenerative dementia disease which is characterized by insidious onset, progressive memory failure, cognitive impairment, and behavioral and psychological manifestations. The etiology and pathogenesis of AD are still unclear, and the development of AD could be the result of interaction between multiple genetic and environmental risk

factors [1]. Most AD is sporadic cases [2][3]. The most specific genetic risk factor for late-onset AD is the Apolipoprotein (*APO*) *E* gene [4]. The ε2, ε3 and ε4 alleles of the *APOE* gene, located on chromosome 19q13.2, constitute a common polymorphism in most populations[5][6]. The *APOEε4* allele is shown to be associated with a higher risk of AD and greater disease severity, whereas the *APOEε2* allele has an opposite role [4][7][8][9]. Patients with AD have a higher frequency of *APOEε4* allele than control participants [10][11][12][13]. An epidemiology study showed that the frequency of the *APOEε4* allele varied drastically among different populations; it occurs in about 25% African Americans, 15% Caucasians, and 7% Chinese [14].

There are plenty of studies focusing on the correlation between dyslipidemia and AD, but most of them are trying to explore the effect of cholesterol (TC) on AD. A previous study has shown that high serum TC level in middle age is a risk factor for AD and AD-related pathology [15]. Cerebrovascular risk factors, such as high cholesterol, had a mild combined effect on the earlier onset of AD [16]. High TC level in the brain was proven to play an important role in the process of amyloid-β (Aβ)-induced AD [17][18]. TC and low-density lipoprotein (LDL) were shown to be involved in the pathogenesis of AD by increasing amyloid accumulation and disrupting the cell cycle [19][20], but late-life hypercholesterolemia might also slow cognitive decline, particularly when in combination with other cerebrovascular risk factors, possibly due to enhanced cerebral perfusion [21]. However, a longitudinal study did not show significant associations of high cholesterol with cognitive or functional changes in AD [22]. High-density lipoprotein (HDL) was also indicated to play a key role in AD [23][24]. Some studies have found that plasma HDL levels were lower in AD patients [25][26][27], and were inversely associated with cognitive impairment, but opposite reports also existed [28][29].

The lipid profiles were also found to be associated with the *APOE*, but the results were inconsistent [10][30]. Previous studies found that the levels of LDL and TC in *APOEε4* carriers were increased or tended to be increased when compared with non-carriers [11][13][31]. However, Isbir et al. showed a decreasing trend, and Hall et al. found no statistical differences [10][32]. It was also reported that AD patients carrying the *APOEε2* allele had lower TC and LDL levels, and higher HDL levels than AD patients carrying the *APOEε4* allele[13][33], but other studies did not find statistical significance [10][11]. De Oliveira et al. considered that *APOEε4 non*-carriers might enhance lipid availability to protect neuronal membranes, thus overcoming their supposed dysfunction in cholesterol metabolism, while *APOEε4* carriers have inefficient neural repair mechanisms [34].

In addition, sex can affect *APOEε4* allele-associated cognitive impairment. The risk of AD or MCI conversion was higher in female *APOEε4* allele carriers than that in male *APOEε4* allele carriers [35][36][37]. There was a stronger correlation between *APOEε4* and CSF Tau levels in women than in men [38][39]. The gender-specific *APOE* haplotype interactions can alter the response to anticholinesterase therapy [40]. Among the females treated with anticholinesterase, the individuals carrying the *APOEε4* allele presented a poor response to treatment than those carrying other *APOE* alleles, and the anticholinesterase reactivity in the males was superior to that in the females [40]. Some studies found that TC was significantly higher in women with AD [41]. However, there are few studies on whether there

are differences in the effects of *APOEε2* and *APOEε4* on AD patients and healthy people of different genders, respectively.

Therefore, sex is an important factor affecting the interaction between the *APOE* gene and lipid profiles in AD. The sex-related difference is also crucial for precision therapy. Few studies have clearly elucidated the effect of different *APOE* alleles on the relationship between lipid profiles and AD in different genders. In order to explore the relationship between lipid profiles, *APOE* gene, and sex in AD, we examined the lipid profiles in AD patients and healthy controls (HCs) with different *APOE* alleles and analyzed the effect of *APOE* gene and sex on lipid profiles in both AD patients and HCs.

Materials And Methods

Participants

AD patients admitted to West China Hospital of Sichuan University from January 2020 to January 2021 were recruited, and the diagnosis of AD was made by trained doctors according to the NINCDS-ADRDA [42] and DSM V [43]. Detailed medical history-taking and physical examination were performed. Individuals without any disease in the central nervous system and normal cognitive function were recruited as healthy controls (HCs) during the same period, and they were matched for body mass index (BMI) to the AD group. The patients received the standardized assessments, including the Mini-mental State Examination (MMSE), the Montreal Cognitive Assessment (MoCA), and magnetic resonance imaging (MRI). AD patients with MMSE scores higher than 25 were excluded. Since MMSE has shown not to be adequate in detecting MCI and clinical signs of dementia, and MoCA is superior to MMSE in the identification of MCI [44], HCs with MoCA sore higher than 22 were included in the present study. All participants with vascular dementia (VaD), cardiopathy, hypertension, diabetes mellitus, demyelinating diseases, white matter lesions, obesity, fatty liver and other diseases closely related to blood lipids were excluded. The study was approved by the ethics committee of West China Hospital of Sichuan University. All AD patients and control participants gave their written informed consent to participate in the investigation.

Measurements

All blood samples were routinely collected in the early morning when patients were fasting. The lipid profiles, including TC, triglycerides (TG), LDL, and HDL, were measured by homogeneous enzyme colorimetry on Roche/Hitachi Cobas C analyzer. DNA was isolated from blood cells. Samples were amplified by polymerase chain reaction (ABI 7500 FAST, Applied Biosystem, Thermofisher, Waltham, USA). *APOE* haplotypes were determined according to the manufacturer's instruction using an *APOE* haplotype determinating kit (Memorigen, Xiamen, China).

Statistical Analyses

SPSS software 26.0 version (IBM, Armonk, USA) was used for data analysis. The χ^2 test was used to compare allele frequencies among groups. An independent t-test was used to compare lipid profiles in patients with different *APOE* haplotypes or sex. For those groups with significant age differences, age was adjusted by covariance analysis. For non-normal distribution data, non-parametric ANOVA (Kruskal-Wallis) and a non-parametric Mann-Whitney U test were used. Logistic regression was used to analyze the influences of various variables on the risk of disease. Two-tailed $p<0.05$ was considered statistically significant. Table data are expressed as the means ± standard deviation (SD), and image values are expressed as the mean (standard error).

Results

A total of 549 participants (298 AD patients, 251 HCs) were included in the study. The mean (SD) age of AD patients was 76.07 (7.12) years old, and the HCs were 65.85 (11.33) years old, so the age factor was adjusted in the subsequent lipid analysis. There were 113 male people in AD and 103 male people in HCs. In AD patients, the mean (SD) course of the disease was 2.5 (2.52) years, the mean (SD) of MMSE score was 18 (5.21), the mean (SD) of MOCA was 12.48 (3.56) (Table 1).

Table 1
APOE gene and sex distribution in AD group and HCs group (mean±standard deviation)

		AD (n=298)	HCs (n=251)	t/χ^2	p-value
Age and examination, yr		76.07±7.12	65.85±11.33	12.38	<0.001
Course of the disease, yr		2.54±2.52			
MoCA		12.48±5.21	24.00±1.48	21.428	<0.001
MMSE		18±3.56			
APOEε4	*APOE4* +, n (%)	149(50.00%)	38(20.30%)	73.719	<0.001
APOEε2	*APOE2* +, n (%)	18(6.00%)	53(21.10%)	27.498	<0.001
sex	Male, n (%)	113(37.90%)	103(41.00%)	0.554	0.457
subtypes				79.39	<0.001
	e2/e2, e2/e3, e3/e3, n (%)	149(41.20%)	213(58.80%)	73.719	<0.001
	e2/e4, e3/e4, n (%)	131(44.00%)	35(13.90%)	58.19	<0.001
	e4/e4, n (%)	18(6.00%)	3(1.20%)	8.694	0.003
APOE haplotypes				99.458	<0.001
	e2/e2, n (%)	0	5(0.90%)	5.991	0.02
	e2/e3, n (%)	18(6.00%)	41(16.30%)	15.053	<0.001
	e3/e3, n (%)	131(44.00%)	167(66.50%)	27.977	<0.001
	e2/e4, n (%)	0	7(2.80%)	8.461	0.004
	e3/e4, n (%)	131(44.00%)	28(11.20%)	71.263	<0.001
	e4/e4, n (%)	18(6.00%)	3(1.20%)	8.694	0.003

APOE **Gene analysis in AD patients and HCs**

There were significant differences in the haplotype frequency of *APOEε4* and *APOEε2* between the AD and HCs (Table 1). A significantly higher proportion of *APOEε4* carriers and a lower proportion of *APOEε2* carriers were found in the AD group than those in the HCs (Table 1).

Comparison of lipid profiles between AD patients and HCs

The levels of TC and LDL in the AD group were higher than those in the HCs group. In the subgroup analysis based on *APOE* alleles, AD patients carrying *APOEε4* had higher levels of TC and LDL than HCs

with *APOEε4* allele; AD patients without *APOEε2* allele had increased TC and LDL levels than HCs without *APOEε2* allele. In subgroup analysis based on sex, TC and LDL levels in the AD group were significantly higher than in the HCs group in both sexes. A subgroup analysis combined sex and *APOE* haplotypes showed that increased levels of TC and LDL in female *APOEε4* carriers than female non-*APOEε4* carriers and in male non-*APOEε2* carriers than male *APOEε2* carriers (Figure 1). In addition, serum HDL level in the AD group was higher than those in the HCs group. Subgroup analysis showed that the change of HDL level was found in AD patients with *APOEε4* allele and without *APOEε2* allele, as well as in male non-*APOEε2* carriers and male *APOEε4* carriers (Figure 1).

Comparison of lipid profiles between *APOEε4* allele-carriers and non-*APOEε4* allele-carriers

The levels of TC and LDL in the *APOEε4* carriers were higher than those in non-*APOEε4* carriers. In the subgroup analysis based on disease, we found that AD patients with *APOEε4* had significantly higher levels of TC and LDL than AD patients without *APOEε4*. No differences in the levels of TC and LDL between HCs with and without *APOEε4*. Furthermore, In the subgroup analysis based on sex, significantly higher levels of TC and LDL were only found in female AD patients with *APOEε4* than without *APOEε4* female AD patients. However, no differences were found between male AD patients with and without *APOEε4* (Figure 2).

Comparison of lipid profiles between *APOEε2* allele-carriers and non-*APOEε2* allele-carriers

The levels of TC and LDL in the *APOEε2* carriers were lower than those in non-*APOEε2* carriers. In the subgroup analysis based on sex and disease, similar changes in LDL levels were found in almost all subgroups except the female control population. The TC levels were lower in AD patients with the *APOEε2* allele than in AD patients without the *APOEε2* allele, but no such change was observed in the HCs. In addition, the TC of *APOEε2* carriers was lower than that of non-carriers in the male AD population, but there was no such change in the female AD population, female HCs, and male HCs (Figure 3).

Comparison of lipid profiles between the male and the female

The TC, HDL, and LDL levels in the female population were higher than the male population. In order to exclude the effect of disease and *APOE* gene, subgroup analyses were performed, and the results showed that sex had similar effects on TC and LDL in AD patients, *APOEε4* carriers, and *APOEε2* non-carriers. In the control participants and *APOEε4* non-carriers, TC and HDL in the female population were higher than the male population (Figure 4).

Complex interactions exist between AD, *APOE* haplotypes, lipid profiles and sex

Age, gender, course of the AD disease, *APOEε4,* and blood lipids level were considered influencing factors for Logistics regression analysis, and we found that age and APOE4 were important risk factors, while the blood lipids were not significantly related with AD. When TG, TC, HDL, and LDL were taken as targets to study the relationship with AD, no correlation was found between lipid profiles and AD through logistics regression analysis. However, in the subgroup analysis, adjusted APOE and sex, we found that LDL

increased the risk of AD in females with the *APOEε4* allele, that is, for every 1 unit increase in LDL, the risk of AD increased 898.46 times in the female population with *APOEε4* (P = 0.04). Therefore the increased LDL level may increase the risk of AD in female people carrying *APOEε4*.

Discussion

This study found that LDL and TC plasma levels in AD patients were higher than those in HCs, consistent with previous studies [13][45]. In addition, we found higher HDL levels in AD patients compared to controls. Similar to our study, Wang et al. [46] found that HDL level was higher in the AD group than in the control group. However, Raygani et al.[13] and Pedrini et al.[45] reported no differences in TG and HDL levels between AD patients and controls, while Li et al. [47] found that, in postmenopausal women, HDL level was lower in the AD patients than in the controls. A prospective study with approximately 7,000 French people found that HDL was not associated with AD [48]. A meta-analysis that combined all relevant studies before 2017 showed that HDL was not associated with AD in later life [49]. However, a prospective study published in 2021 reported very high plasma HDL cholesterol levels as an independent risk factor for either dementia or AD, and suggested that elevated HDL may serve as a plasma biomarker for assessing the risk of dementia [50]. Chan et al. studied and analyzed HDL's chemical properties and functions and found that the levels of H5 subcomponent and apo CIII in Ad-HDL were increased compared with those in the control group [51]. Marsillach et al. point out that functional HDL, rather than HDL cholesterol levels, is more important in disease [52]. Therefore, more attention should be paid to the interaction between HDL functional subtypes and AD.

In the AD population, the TC and LDL levels were increased in the *APOEε4* carriers compared to the non-*APOEε4* carriers, and this alteration was not found in the control population. In *APOEε4* allele carriers, the TC and LDL levels in the AD patients were found to be higher than those in control participants, but these differences in TC and LDL were not found in non-*APOEε4* carriers. These findings indicated that the involvement of *APOEε4* in AD could be associated with lipid profiles. Similarly, Wang et al. [46] found that the levels of TC in the AD population carrying *APOEε4* were higher than those without *APOEε4*, while no such change was observed in healthy controls. However, Raygani et al. [13] found these lipid changes between *APOEε4* carriers and non-*APOEε4* carriers in both AD and controls. In addition, we also found that LDL may increase the risk of AD in females with the *APOEε4* allele. A previous study showed that the association of elevated midlife TC level with late-life AD was not altered after adjusting for the *APOEε4* allele [53], but another study showed decreasing TC after midlife may represent a risk marker for late-life cognitive impairment [54], and these studies did not take into account the role of sex. Therefore, further research and exploration are needed to verify if the effect of *APOEε4* on lipid profiles is gender-specific in AD.

In subgroup analyses based on sex showed that TC and LDL in the AD group were higher than those of the control group in both male and female populations. In the female population, TC and LDL were higher in *APOEε4* carriers than in non-*APOEε4* carriers, but no change was found in the male population. Several recent studies have shown that sex can alter the risk of the *APOEε4* allele, and female people with

APOEε4 have a higher risk of AD than male carriers [35][36][37]. Women aged 65 to 75 with *APOEε4* had a higher risk of AD than men [55] and had higher levels of tau in the cerebrospinal fluid (CSF) [39][56]. In Liu's study, a significant sex-specific association was found between CSF apolipoprotein E and AD biomarkers. In women, baseline CSF apolipoprotein E was significantly associated with longitudinal changes in baseline CSF Aβ and tau, but no longitudinal association was observed in men [56]. Therefore, the change of TC and LDL is specific in female *APOEε4* carriers.

The effect of the *APOEε4* allele on lipid profiles in women was greater than that in men, but the effect of the *APOEε2* allele on lipid profiles was different from the *APOEε4* allele. In this study, the individuals were stratified according to the presence of the *APOEε2* allele, and we found that the role of the *APOEε2* allele in lipid levels was affected by the disease of AD. In the AD population, the TC level in *APOEε2* carriers was lower than those in non-carriers, but these changes were not found in the HCs. Although the TC level of *APOEε2* carriers was lower than that of non-carriers in both male and female populations, such change was only found in the male AD population, but not in the male HCs, female HCs, and female AD population. Therefore, we hypothesized that the reduction of TC by *APOEε2* allele seems to be more biased in male AD populations. Human studies have shown that the *APOEε2* allele is associated with decreased Aβ deposition in the brain of non-dementia elderly individuals and AD patients [57][58][59][60][61], and protects against cognitive impairment in individuals over 90 years of age with high levels of Aβ in the brain [62][63]. In vitro and in vivo studies have shown that *APOEε2* provides protection independent of Aβ pathology through multiple potential pathways, including the regulatory role of *APOEε2* in lipid metabolism [64][65][66][67]. A meta-analysis found that the *APOE ε2/ε3* haplotype had a greater protective effect on AD risk in women than in men, but this study was a meta-analysis based on non-Hispanic white individuals [55]. The frequency and function of the *APOE* alleles are different in different races [68], so the effect of the *APOEε2* allele on lipid profiles in AD patients with different gender needs to be further explored in more studies.

The differences in lipid profiles between AD patients and healthy populations provide possible biomarkers for the diagnosis of AD, especially LDL and TC. However, whether lipid profiles could be biomarkers for AD diagnosis is controversial. A recent review [69] summarized the correlation between lipid profiles and AD, discussed the possibility of lipid profiles as biomarkers for early diagnosis of AD, but failed to reach an effective conclusion on whether changes in lipid profiles can be used as a diagnostic indicator for AD, but it did not consider the effect of *APOE* gene. In 2018, the National Institute on Aging and Alzheimer's Association recommended using biomarkers as indicators for the clinical diagnosis of AD [70]. Especially for the early stage of AD, biomarkers are almost the only reliable choice for diagnosis [71]. At present, only a few biomarkers available in peripheral blood, but the examination of these biomarkers require advanced techniques and are expensive, which are inaccessible for most hospitals and communities. The blood lipid profiles could be used as potential candidates for AD diagnosis, especially in the female population with an *APOEε4* allele.

Conclusions

The TC and LDL levels of *APOEε4* allele carriers were higher than those of non-carriers, and the effect was more significant in the AD and female population. High LDL levels may increase the risk of AD in female people with the *APOEε4* allele. The TC levels in *APOEε2* allele carriers were lower than those in non-carriers, and the effect was more significant in the male AD population. Further prospective studies focusing on the relationship between the *APOE* gene, sex, lipid profiles and AD are essential to confirm our findings, and special attention should be paid to female AD patients with the *APOEε4* allele and male AD patients carrying the *APOEε2* allele when regulating the blood lipids.

Limitations

This study has the following limitations. First, Due to the large difference in whether AD patients take medication, type of medication, and dose, there is no stratification according to medication. Second, this study did not analyze the relationship between lipid profiles and AD severity due to limited data. Thirdly, This study is cross-sectional and lacks the dynamic changes and correlation of lipid profiles with time and disease. Fourthly, this study is a single-center, small-sample study, which needs to be verified by a larger sample and multi-center study.

Declarations

Ethics approval and consent to participate

The study was approved by the ethics committee of West China Hospital of Sichuan University. All AD patients and control participants gave their written informed consent to participate in the investigation.

Consent for publication

All authors approved its publication.

Availability of data and material

Detailed data have been shown in the supplementary materials. Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

Competing interests

We declare that there is no actual or potential financial and other conflict of interest related to the submitted manuscript.

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Authors' contributions

Jiajia Fu contributed to the compilation of articles and data analysis. Yan Huang and Ting Bao contributed to the selection and data entry of healthy controls. Ruwei Ou, Qianqian Wei, Yongping Chen and Jing Yang contributed to the screening and data entry of AD patients. Xueping Chen and Huifang Shang contributed to the review, editing and scientific research thinking and methods. All authors have read and approved the manuscript.

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Figures

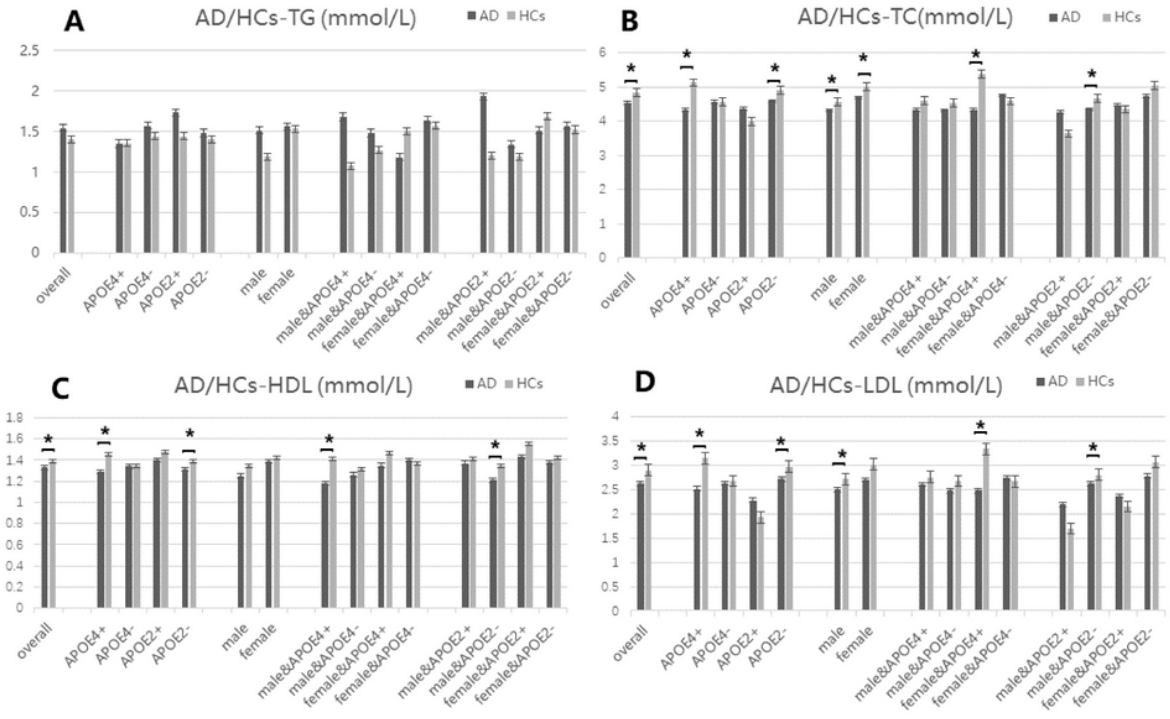

Figure 1: Comparison of lipid profiles between AD patients and CHs based on different populations; *: P < 0.05 Values are expressed as mean (standard error). A: TG; B: TC; C: HDL; D: LDL

Figure 1

See image above for figure legend

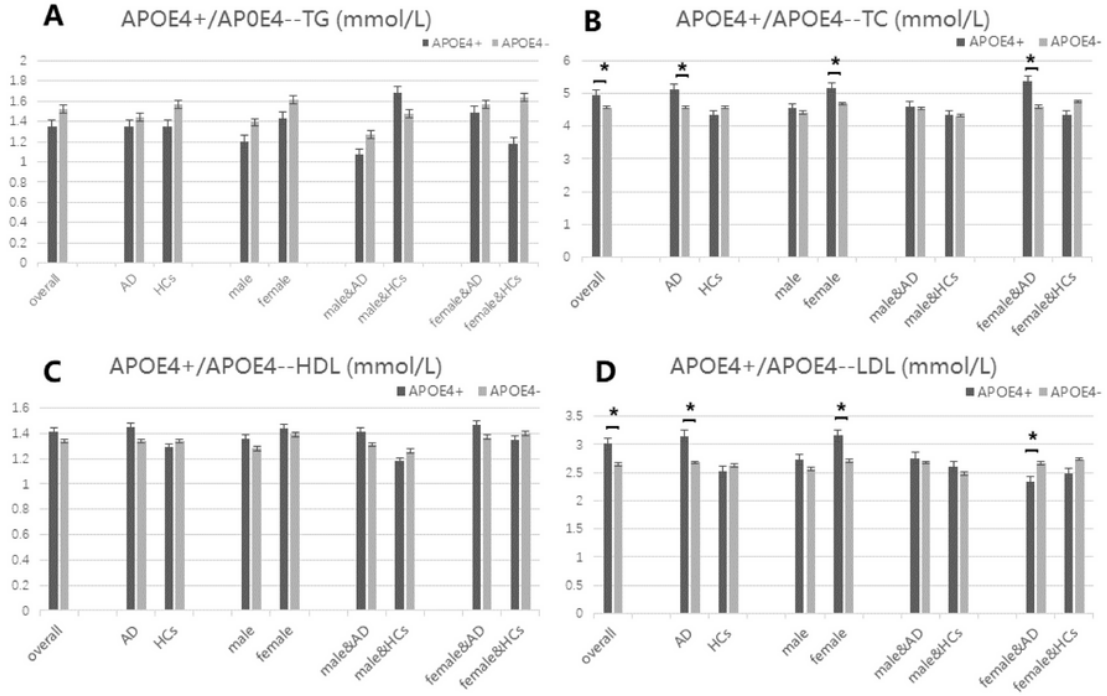

Figure 2: Comparison of lipid profiles between APOEε4 allele-carriers and non-APOEε4 allele-carriers based on different populations; *: P < 0.05; Values are expressed as mean (standard error). A: TG; B: TC; C: HDL; D: LDL

Figure 2

See image above for figure legend

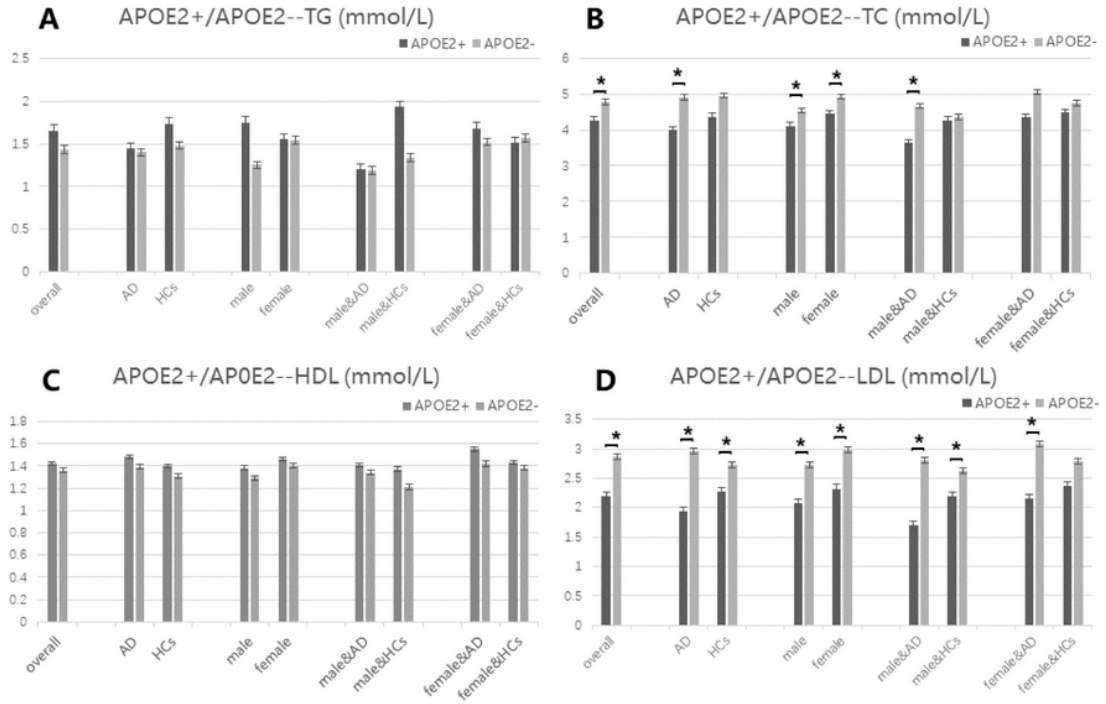

Figure 3: Comparison of lipid profiles between APOEε2 allele-carriers and non-APOEε2 allele-carriers based on different populations; *: $P < 0.05$; Values are expressed as mean (standard error). A: TG; B: TC; C: HDL; D: LDL

Figure 3

See image above for figure legend

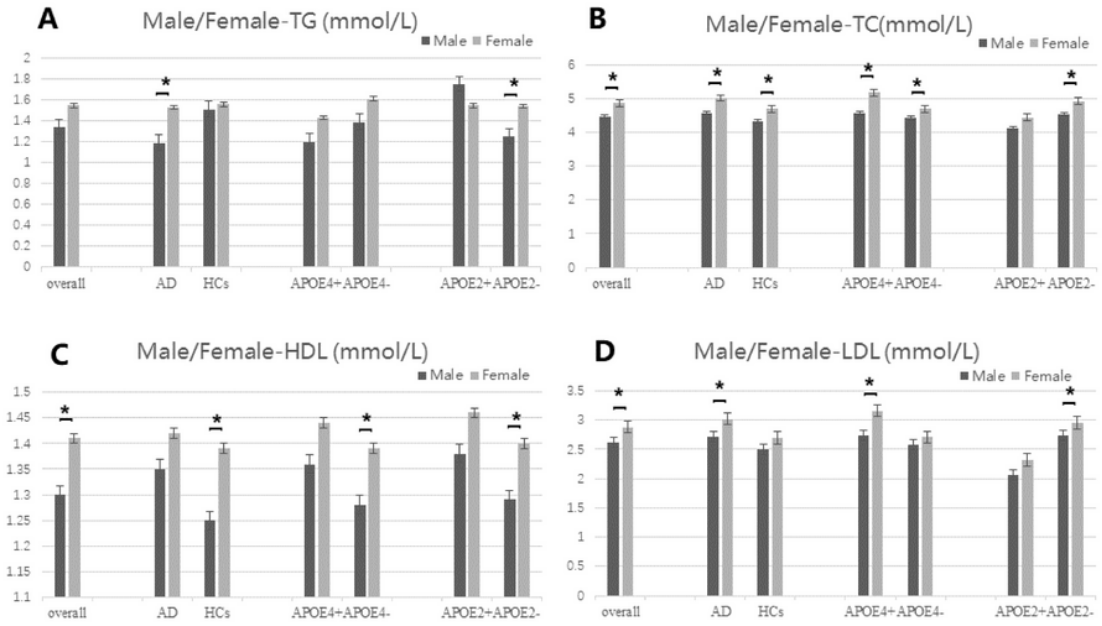

Figure 4: Comparison of lipid profiles between the male and the female based on different populations; *: P < 0.05 Values are expressed as mean (standard error). A: TG; B: TC; C: HDL; D: LDL

Figure 4

See image above for figure legend

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