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Association between APOE genotypes and metabolic syndrome in a middle aged and elderly Urban South Indian population

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ABSTRACT

Background: This study examines the association between apolipoprotein E (APOE) genotypes and metabolic syndrome (MetS) in an older urban population in South India, as part of the Tata Longitudinal Study on Aging.
Methods: A total of 618 participants aged 45 and above were analyzed cross-sectionally for the association between APOE carrier status and MetS (based on both NCEP ATP III and Consensus criteria).
Results: Despite the high prevalence of MetS observed in this cohort (51.62 % by NCEP-ATP III and 61.33 % by Consensus criteria), multivariable logistic regression revealed no significant association between APOE genotypes and MetS under both criteria. However, specific associations were noted in age and sex-stratified analyses; notably, E2 carriers under 60 showed 0.42-fold decreased odds (95%CI:0.20,0.89, p-value-0.023) for an increased waist circumference, and E4 carriers above 60 were at 1.85 times increased odds (95 % CI:1.04,3.28, p-value$<$0.05) for decreased HDL.
Conclusion: These findings suggest that while APOE genotypes influence certain metabolic parameters, their impact on MetS may be limited in this urban setting, possibly overshadowed by environmental factors and lifestyle influences, which was highlighted by the differences seen in its sister rural cohort.

1. Introduction

Metabolic syndrome (MetS) is the concurrent presence of elevated blood pressure, hyperglycemia, dyslipidemia, and abdominal obesity [1]. It is associated with a two-fold increased risk for cardiovascular disease (CVD) and a 1.5-fold increased risk of all-cause mortality [2].

The APOE gene plays a crucial role in managing various blood lipids, affecting the levels of triglycerides (TG), and lipoprotein particles in the plasma [3]. It has three common alleles—ε2, ε3, and ε4—which produce three major isoforms: E2, E3, and E4. These alleles result in three homozygous genotypes (E2/2, E3/3, E4/4) and three heterozygous genotypes (E2/3, E2/4, E3/4). Each allele has a distinct binding affinity for lipoprotein receptors, which significantly impacts lipid transport, thus contributing to differing risks for MetS [4]. Studies in diverse populations have noted associations between the APOE E4 allele and metabolic syndrome [1,5,6]. However, data from the Indian populations on this relationship are scarce.

Our study examines the link between APOE genotypes and metabolic syndrome (MetS) and its components in middle-aged and older adults from urban South India. We then compare these findings with those from a harmonized rural sister-cohort [7]. Considering previous findings that show the effects of the APOE gene vary by age and sex, particularly in factors like hypertension [8,9], we will employ an age and sex-stratified approach. Our hypothesis is that APOE carrier status is associated with metabolic syndrome.

2. Methods

This is a cross-sectional analysis of data from an ongoing aging cohort study in urban southern India named the Tata Longitudinal Study

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on Aging (TLSA), which recruits participants aged 45+ years from the city of Bangalore, India.

The analytical sample for this study (n = 618) includes participants who had undergone their baseline clinical and biochemical assessments between 2015, June, and 2023, December and had complete data on the variables included in this study, as seen in Supplementary Fig. 1. Individuals diagnosed with dementia, severe medical or psychiatric illnesses, and sensory or motor impairments that could affect the study evaluations were excluded. Further, participants with APOE ε2/ε4 genotype were excluded due to the potentially contrasting effects of ε2 and ε4 alleles on lipid levels.

Demographic characteristics, clinical history of comorbidities, data on physical inactivity, tobacco, and alcohol consumption were collected using a structured questionnaire. Anthropometric data, including waist circumference (WC) and blood pressure, were measured by trained nurses. Biochemical investigations involved fasting peripheral venous blood samples analyzed by an accredited lab for glucose, triglycerides, LDL, and HDL more details are available in **supplementary section 2**.

Metabolic syndrome (MetS) was defined according to the NCEP ATP III [10] and Consensus criteria [11]. APOE genotyping methods are detailed elsewhere [12] and in **supplementary section 2**. Participants were classified into E2 carriers (with either ε2/ε2 or ε2/ε3 genotype), E4 carriers (with either ε4/ε4 or ε3/ε4 genotype), and E3 homozygous (ε3/ε3 genotype) individuals, who served as the reference group in the logistic regression model.

Participant characteristics were summarized as frequencies and percentages for categorical variables and means with standard deviations for continuous ones. We tested differences in variables between healthy (no MetS) and metabolic syndrome (MetS), defined by NCEP ATP III criteria, using independent two-sample t-tests for continuous variables and chi-square tests for categorical variables. Multivariable binary logistic regression assessed the association between APOE genotypes and MetS and its components, adjusting for covariates. A p-value of <0.05 was deemed statistically significant. All analyses were conducted using Stata version 18.0.

3. Results

Out of the 618 study participants, 319 (51.62 %) were diagnosed with MetS (as per the NCEP ATP-III criteria). There were significant differences in the distribution of age, sex, education, diabetes mellitus, hypertension, cardiac illness, high blood pressure, hyperglycemia, hypertriglyceridemia, low HDL-C, body mass index, and high waist circumference between the MetS and no MetS group (Table 1). There was no statistically significant difference in the distribution of APOE genotypes by MetS in both criteria (Table 1 & Supplementary Table 1).

Multivariable logistic regression models showed no significant association between APOE genotypes and metabolic syndrome as per the NCEP ATP III or the Consensus criteria. Among the individual components of MetS, we only found that E2 carriers exhibited 0.42-fold decreased odds for high waist circumferences (95 % CI: 0.20,0.89, p-value- 0.023) according to the consensus criteria. **(Supplementary Table 2 and Fig. 1).**

On stratifying the population by sex, we again found no significant association between APOE and MetS for either criterion or its components in both sexes (Supplementary Table 3).

Upon age stratification (<60 and ≥60) there was no association seen between MetS and APOE in either group. In the group <60 years we found that E2 carriers had decreased odds for high WC (OR: 0.18, 95 % CI: 0.04,0.88, p-value <0.05). In the age group of ≥60 years for E4 carriers, we found that they had 1.85 times increased odds (95 % CI: 1.04,3.28, p-value <0.05) for decreased HDL (Supplementary Table 4).

4. Discussion

Our study of urban Indians aged 45 and older, found a high prevalence of metabolic syndrome: 51.62 % by NCEP-ATP III criteria and 61.33 % by Consensus criteria. Whereas the prevalence in the rural sister cohort was 38.5 % and 46.5 % respectively. This compares to a national prevalence of 41–50 % for a similar age group reported in a recent meta-analysis [13]. Even among the participants who did not meet the criteria for metabolic syndrome, there was a high prevalence of its components, ranging from 16 % to 54 %.

However, we found no significant association between APOE and MetS. Prior studies from various populations have revealed conflicting findings, reporting a significant association [5,6,14], while others from India [15] and Thailand [1] have reported a lack of association. Such variations in the findings could be attributed to the differences in the

Table 1
Demographic, anthropometric, and plasma biochemical characteristics of the participants of urban cohort (MetS defined by NCEP ATP-III criteria).

Characteristics	MetS (n = 319) (%)	No MetS (n = 299) (%)	P-value
Age, mean (SD)	60.81 (8.61)	62.71 (10.13)	0.012
Sex			<0.001
Male	134 (42.01)	172 (57.53)	
Female	185 (57.99)	127 (42.47)	
Education			0.002
Illiterate	14 (4.39)	7 (2.34)	
Primary/Middle school	17 (5.33)	7 (2.34)	
High school/Diploma	78 (24.45)	48 (16.05)	
Graduate/Postgraduate	210 (65.83)	237 (79.26)	
Marital status			0.326
Living without a partner	47 (14.73)	36 (12.04)	
Living with a partner	272 (85.27)	263 (87.96)	
Tobacco usage			0.368
No	304 (95.30)	280 (93.65)	
Yes	15 (4.70)	19 (6.35)	
Alcohol usage			0.108
No	262 (82.13)	230 (76.92)	
Yes	57 (17.87)	69 (23.08)	
Diabetes mellitus			<0.001
Yes	147 (46.08)	55 (18.39)	
No	172 (53.92)	244 (81.61)	
Hypertension			<0.001
Yes	252 (79.00)	157 (52.51)	
No	67 (21.00)	142 (47.49)	
Cardiac illness			<0.001
Yes	23 (7.21)	24 (8.03)	
No	296 (92.76)	275 (91.97)	
Hypertriglyceridemia			<0.001
Yes	202 (63.32)	50 (16.72)	
No	117 (36.68)	249 (83.28)	
Low HDL-C			<0.001
Yes	236 (73.98)	74 (24.75)	
No	83 (26.02)	225 (75.25)	
Asian body mass index			<0.001
Underweight	0 (0.00)	4 (1.35)	
Normal	28 (8.89)	73 (24.66)	
Overweight	29 (9.21)	63 (21.28)	
Obesity	258 (81.90)	156 (52.70)	
High waist circumference (NCEP ATP-III criteria)			<0.001
Yes	247 (77.43)	86 (28.76)	
No	72 (22.57)	213 (71.24)	
High waist circumference (Consensus criteria)			<0.001
Yes	297 (93.10)	227 (75.92)	
No	22 (6.90)	72 (24.08)	
APOE genotype			0.376
ε2/ε2	1 (0.31)	0 (0.00)	
ε2/ε3	18 (5.64)	28 (9.36)	
ε3/ε3	246 (77.12)	218 (72.91)	
ε3/ε4	52 (16.30)	51 (17.06)	
ε4/ε4	2 (0.63)	2 (0.67)	
APOE carriers			0.249
E2 carriers	19 (5.96)	28 (9.36)	
E3 homozygous	246 (77.12)	218 (72.91)	
E4 carriers	54 (16.93)	53 (17.73)	

Note. MetS Metabolic Syndrome; HDL-C High Density Lipoprotein Cholesterol; APOE Apolipoprotein E.

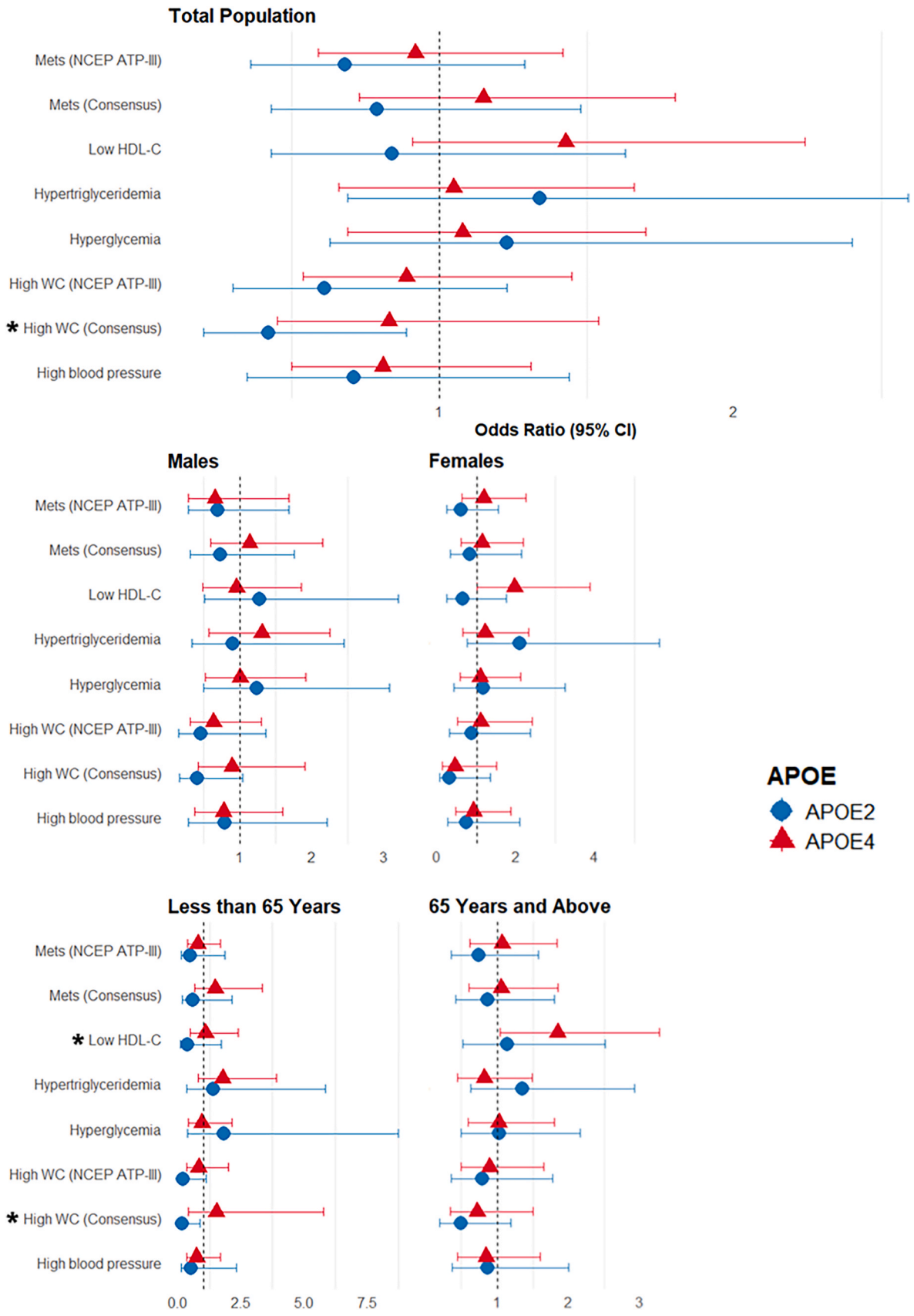

Fig. 1. Association between ApoE genotype and individual component of MetS for total population and when stratified by sex and age group. MetS Metabolic Syndrome; HDL-C High Density Lipoprotein, WC Waist Circumference, NCEP ATP-III National Cholesterol Education Program Adult Treatment Panel III.

demographics of the populations examined, different inclusion and exclusion criteria, and the use of different criteria for diagnosis of MetS.

Recent findings from the SANSCOG study revealed a sex-specific association between APOE and MetS, wherein the rural females had increased odds for MetS, hypertriglyceridemia, and low HDL [12]. In contrast, this study found no significant association with most of the MetS components, which is also contrary to the existing literature where APOE is significantly associated with lipid, glycemic [16], and blood pressure parameters [17]. However, when we age-stratified the sample, we saw that participants aged 60 years and above had increased odds of low HDL. Previous studies have indicated that the interaction of APOE with components of MetS changes with age [9]. Accordingly, we found a significant association between high WC (consensus criteria) and APOE genotype in the total population, which on age stratification was only present in the <60 age group.

The discordance of our results with our sister study and the overall contrasting evidence for APOE polymorphisms and MetS could be due to varying exposure to environmental risk factors, which, in turn, could have diminished the genetic influence of APOE on MetS. Further, differential healthcare access and treatment of the metabolic risk factors could potentially confound this association. Finally, since there is genetic diversity in the Indian population, it is possible that the lack of association between the APOE allele and MetS could be unique to our study population. Significant differences in APOE E4 allele frequency have been reported in the Indian population compared to other populations [18]. The role of APOE has been most widely studied as a risk factor for dementia and cognitive performance and differences in the association between APOE allele status and dementia/cognitive performance across ancestries and ethnicities have been reported [19]. Linkage disequilibrium, allele frequencies, and genetic architecture of a population could modulate the relationship between genetic effects and diseases [20].

The limitations of our study include its small sample size, which may hinder the generalizability of our findings. Additionally, the use of convenience sampling might not provide a sample that is representative of the broader urban Indian population. The cross-sectional design of the study also prevents us from establishing causality between APOE genotypes and MetS. Furthermore, we did not consider several other genetic factors that could influence the MetS burden.

To the best of our knowledge, this is the first and most comprehensive study from India to assess the association between APOE and MetS in the middle-aged and older urban population with an objective diagnosis of all MetS components. Also, this paper is the first of its kind to compare APOE polymorphisms between rural and urban populations from two harmonized studies, which are within a small geographical distance, thus making the comparison reliable. We also looked at sex-specific and age-specific associations and gathered important insights that align with the limited previous literature on the same.

In conclusion, environmental factors in the urban population could potentially outweigh the genetic predisposition in determining health risks, therefore, highlighting the requirement of lifestyle modification in managing cardio-metabolic diseases in this population.

5. Ethics approval statement

All participants provided written informed consent before their involvement in the study. The study protocol received approval from the Institutional Review Board at the Institute. All experiments conducted adhered to the appropriate guidelines and regulations. The Institutional Ethical Clearance number provided for this study is CBR/42/IEC/2022-23.

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CRediT authorship contribution statement

Shilna Azhuvalappil: Writing – review & editing, Writing – original draft, Formal analysis, Data curation, Conceptualization. **Raghav Prasad:** Writing – review & editing, Writing – original draft, Supervision, Methodology. **Pravin Sahadevan:** Formal analysis. **Priya Chatterjee:** Writing – review & editing, Writing – original draft. **Hitesh Pradhan:** Software, Formal analysis, Data curation. **Pooja Rai:** Supervision. **Anant Gupta:** Methodology, Investigation. **Reddy Peera Kommaddi:** Supervision, Methodology, Investigation. **Thomas G. Issac:** Supervision. **Jonas S. Sundarakumar:** Conceptualization.

Declaration of competing interest

All authors declare no conflicts of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.metop.2024.100301.

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