Association between APOE polymorphism and metabolic syndrome in Uyghur ethnic men

YuPing Sun,1 Rong Wei,2 DanDan Yan,3 FeiLi Xu,2 XiaoJin Zhang,4 Bei Zhang,1 Delixiati Yimiti,1 Hui Li,5 HongYan Sun,6 Cheng Hu,3 Li Luo,4 Hua Yao4

ABSTRACT

Objectives: This study aimed to examine the association between apolipoprotein E (APOE) polymorphism and metabolic syndrome (MetS) among Uyghur ethnic men in Xinjiang, China.

Participants: A total of 482 patients with MetS and 510 healthy sex-matched and age-matched controls were recruited from the Xinjiang Uyghur Autonomous Region of China. The participants were subjected to routine physical and blood biochemical tests, and APOE genotyping was performed.

Results: The APOE ε3/3 was the predominant type, with a frequency of 71.8%, while ε2/2 was less common than ε4/4 in Uyghur males. The frequencies of the APOEε2, E3 and E4 alleles in Uyghur males were 8.5%, 80.0% and 11.5%, respectively. However, the distribution of APOE genotypes was significantly different between the MetS and control groups (p<0.001). In the MetS group, the frequencies of the ε2 and ε4 alleles and the frequencies of the ε2/2, ε2/3 and ε2/4 genotypes were significantly lower than those of the control group. Those individuals without the ε2 and ε4 alleles had higher MetS prevalence than the other gene carriers, and the ORs of these individuals developing MetS were 1.5 and 1.27 compared to the gene carriers. Triglyceride, serum total cholesterol and low-density lipoprotein cholesterol levels were lower and serum high-density lipoprotein was higher in the ε2 carriers than the ε3 carriers, and the prevalence of MetS, central obesity, high blood pressure, hypercholesterolaemia and hypertriglyceridaemia was lower in the APOE2 group than in the APOE4 group. The risks of these individuals with ε4 allele carriers getting these changes were 1.327, 1.780, 1.888, 1.428 and 2.571 times greater than those of ε2 allele carriers.

Conclusions: APOE4 is associated with many individual components of MetS, whereas APOE2 was associated with a reduced risk of MetS at the univariate level in Uyghur ethnic men.

INTRODUCTION

Metabolic syndrome (MetS) is characterised by a cluster of disorders that promotes atherosclerosis and increases the risk of cardiovascular diseases and diabetes mellitus, for example: atherogenic dyslipidemia, insulin resistance and diabetes, hypertension, or abdominal obesity and other diseases.

The apolipoprotein E (APOE) gene, containing four exons and three introns, is mapped on the long arm of chromosome 19 (19q13.2). There are three common alleles (ε2, ε3 and ε4); the ε3 allele is the most common and can be found in more than 80% of the general population, followed by ε4 and ε2.

APOE is a multifunctional protein found in all lipoproteins except for low-density lipoprotein cholesterol (LDL-C); it plays a critical role in lipoprotein metabolism. Therefore, it is biologically possible for APOE to influence an individual’s susceptibility to MetS, especially in terms of both triglyceride and cholesterol levels, which are major complications of MetS. The altered expression or genetic polymorphism of APOE is considered as a risk factor for MetS. Although the possible association of APOE with the risk of MetS has been widely investigated in different populations, MetS still remains under-represented in the Xinjiang population, especially in the Uyghur ethnic group. Our previous study found that in the Uyghur ethnic population, there is a tendency of higher frequency of the clustering of MetS. Thus, this is the first study in terms of the

CrossMark

For numbered affiliations see end of article.

Correspondence to
Dr Hua Yao
yaohua01@sina.com

Strengths and limitations of this study

- This is the first study of Uyghur ethnic men to explore the association between apolipoprotein E (APOE) polymorphism and metabolic syndrome (MetS).
- The study was limited by lack of independent replication.
- The study lacks more detailed in-depth studies to confirm the link between APOE polymorphisms and MetS risk.


Received 22 September 2015
Revised 14 November 2015
Accepted 17 November 2015

BMJ Open: first published as 10.1136/bmjopen-2015-010049 on 6 January 2016. Downloaded from http://bmjopen.bmj.com/ on December 27, 2023 by guest. Protected by copyright.
distribution of \textit{APOE} genetic polymorphisms and their association with metabolic profiles in patients with MetS, aimed at identifying possible genetic markers for this disease in this special population.

\section*{METHODS AND MATERIALS}

\subsection*{Participants and study design}

This case control study recruited 992 participants who were selected from the Affiliated Hospitals of Xinjiang Medical University Urumqi China. These participants were all Uyghur men who resided in the Xinjiang area, 482 with MetS, whereas the age-matched healthy control subjects had no history of MetS. All of the participants were fully informed of the purpose of this study, and every participant provided written informed consent before enrolment in the study.

\subsection*{Data collection and blood tests}

A questionnaire was used to collect data on the demographic, lifestyle and disease histories from all of the participants. A physical examination was also performed on every participant, including taking measurements of height (measured in centimetres with an error of <0.5 cm), body weight (measured in kilograms with an error of <0.1 kg), body mass index (BMI), waist circumference (WC) and hip circumference (calibrated weekly to within 1 mm using a plastic tape). The WC was measured at the end of a gentle expiration midway between the lowest rib and the iliac crest with the study participant standing, while the hip circumference was measured at the greater trochanter. The waist-to-hip ratio was determined as the WC (cm) divided by the hip circumference (cm). Blood pressure was measured using an automatic clinical blood pressure monitor three times in the sitting position following a standard protocol. All of the participants were at rest for at least 10 min before the physical examination.

All of the participants were also asked to fast for at least 12 h and to not consume any alcohol or high-fat foods the night before blood withdrawal. Two millilitres of venous blood was collected from each participant to assess the serum triglyceride and cholesterol, high-density lipoprotein cholesterol (HDL-C), LDL-C and fasting plasma glucose levels as measured using the 7060 Automatic Biochemical Analyzer (Hitachi, Ltd, Tokyo, Japan). All of the laboratory analyses were performed in the same certified laboratory. Quality control measures were followed for the estimation of all the variables.

\section*{Standard of diagnosis}

The participants were divided into two groups based on affiliation with MetS. The diagnostic criteria for MetS were according to the 2005 National Cholesterol Education Program Adult Treatment Panel III,\textsuperscript{25} the 2005 International Diabetes Federation,\textsuperscript{27} the 2004 Chinese Diabetes Society\textsuperscript{28} and the 2007 Joint Committee for Developing Chinese Guidelines for the

\begin{table}[h!]
\centering
\caption{Comparison of the quantitative variables between the MetS and non-MetS groups}
\begin{tabular}{lccc}
\hline
Variable(s) & Non-MetS group (510) & MetS group (482) & p Value \\
\hline
Age (years) & 46.77±13.27 & 47.54±11.83 & 0.0680 \\
BMI (kg/m\textsuperscript{2}) & 26.52±4.11 & 28.16±3.15 & <0.0001 \\
Waistline (cm) & 92.79±10.65 & 98.43±9.08 & <0.0001 \\
SBP (mm Hg) & 120.61±12.26 & 126.92±14.64 & <0.0001 \\
DBP (mm Hg) & 85.33±13.78 & 96.62±12.10 & <0.0001 \\
FGP (mmol/L) & 5.01±1.13 & 5.59±1.77 & <0.0001 \\
Triglyceride (mmol/L) & 1.97±1.45 & 3.26±1.65 & <0.0001 \\
TC (mmol/L) & 4.37±1.27 & 4.06±1.60 & 0.0010 \\
HDL-C (mmol/L) & 1.23±0.53 & 1.10±0.51 & <0.0001 \\
LDL-C (mmol/L) & 2.67±0.86 & 2.74±0.78 & 0.1920 \\
\hline
\end{tabular}
\end{table}

Data are shown as mean±SD. The Mann-Whitney U test was used to analyse the differences in the quantitative variables between the MetS and non-MetS groups. BMI, body mass index; DBP, diastolic blood pressure; FPG, fasting plasma glucose; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; MetS, metabolic syndrome; SBP, systolic blood pressure; TC, total cholesterol.

\begin{table}[h!]
\centering
\caption{Genotype and allele distributions of the \textit{APOE} in the MetS and non-MetS groups}
\begin{tabular}{lccc}
\hline
Genotype & Total (992) & Non-MetS group (510) & MetS group (482) \\
\hline
\varepsilon\textsuperscript{2}/\varepsilon\textsuperscript{2} & 25 (2.5%) & 20 (3.9%) & 5 (1.0%) \\
\varepsilon\textsuperscript{2}/\varepsilon\textsuperscript{3} & 105 (10.6%) & 66 (12.9%) & 39 (8.1%) \\
\varepsilon\textsuperscript{2}/\varepsilon\textsuperscript{4} & 14 (1.4%) & 11 (2.2%) & 3 (0.6%) \\
\varepsilon\textsuperscript{3}/\varepsilon\textsuperscript{3} & 712 (71.8%) & 332 (65.1%) & 380 (78.8%) \\
\varepsilon\textsuperscript{3}/\varepsilon\textsuperscript{4} & 59 (5.9%) & 32 (6.3%) & 27 (5.6%) \\
\varepsilon\textsuperscript{4}/\varepsilon\textsuperscript{4} & 77 (7.8%) & 49 (9.6%) & 28 (5.8%) \\
\chi\textsuperscript{2} Value & – & 29.1 & \textless 0.0001 \\
p Value & – & <0.0001 & \textless 0.0001 \\
\hline
Allele & & & \\
\varepsilon\textsuperscript{2} & 169 (8.5%) & 117 (11.5%) & 52 (5.4%) \\
\varepsilon\textsuperscript{3} & 1588 (80.0%) & 762 (74.9%) & 826 (85.5%) \\
\varepsilon\textsuperscript{4} & 227 (11.5%) & 139 (13.7%) & 88 (9.1%) \\
\chi\textsuperscript{2} Value & – & 37.7 & \textless 0.0001 \\
p Value & – & <0.0001 & \textless 0.0001 \\
\hline
\end{tabular}
\end{table}

Data are shown as n (%). Pearson’s \chi\textsuperscript{2} test was used to analyse the differences of \textit{APOE} (genotype or allele) between the MetS and non-MetS groups. MetS, metabolic syndrome.
RESULTS

Characterisation of the study population

Table 3: Comparison of the anthropometric, biochemical and clinical parameters among different APOE genotypes in the two groups (mean±SD)

<table>
<thead>
<tr>
<th></th>
<th>Non-MetS group</th>
<th>MetS group</th>
<th>p&lt;sub&gt;a&lt;/sub&gt;</th>
<th>p&lt;sub&gt;b&lt;/sub&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total 499</td>
<td>APOE2 86</td>
<td>APOE3 332</td>
<td>APOE4 81</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>26.48±4.09</td>
<td>25.52±3.36</td>
<td>26.76±4.44</td>
<td>26.37±3.02</td>
</tr>
<tr>
<td>Waistline (cm)</td>
<td>92.71±10.55</td>
<td>90.59±10.90</td>
<td>93.12±10.79</td>
<td>92.38±8.92</td>
</tr>
<tr>
<td>SBP (mm Hg)</td>
<td>120.81±12.27</td>
<td>118.66±14.02</td>
<td>120.65±11.46</td>
<td>123.70±13.05</td>
</tr>
<tr>
<td>DBP (mm Hg)</td>
<td>85.52±13.82</td>
<td>82.44±13.51</td>
<td>85.81±13.78</td>
<td>87.56±13.40</td>
</tr>
<tr>
<td>FPG (mmol/L)</td>
<td>5.00±1.14</td>
<td>5.16±1.79</td>
<td>4.96±0.81</td>
<td>5.00±1.38</td>
</tr>
<tr>
<td>Triglyceride (mmol/L)</td>
<td>1.94±1.39</td>
<td>1.71±1.00</td>
<td>2.02±1.49</td>
<td>1.85±1.32</td>
</tr>
<tr>
<td>TC (mmol/L)</td>
<td>4.43±1.25</td>
<td>4.19±1.18</td>
<td>4.31±1.26</td>
<td>4.61±1.25</td>
</tr>
<tr>
<td>HDL-C (mmol/L)</td>
<td>1.23±0.52</td>
<td>1.17±0.43</td>
<td>1.23±0.53</td>
<td>1.25±0.57</td>
</tr>
<tr>
<td>LDL-C (mmol/L)</td>
<td>2.68±0.86</td>
<td>2.29±0.82</td>
<td>2.74±0.85</td>
<td>2.86±0.81</td>
</tr>
</tbody>
</table>

A t test was used to analyse the differences in parameters among different APOE genotypes.

P<sub>a</sub>: p values that were obtained when comparing APOE2 participants with APOE3 participant.

P<sub>b</sub>: p values that were obtained when comparing APOE3 participants with APOE4 participants.

1. APOE3 group: participants carrying the ε3/ε3 genotype; (2) APOE2 group: participants carrying the ε2/ε2 or ε2/ε3 genotype; (3) APOE4 group: participants carrying the ε4/ε4 or ε3/ε4 genotype. Participants with the ε2/ε4 genotype (n=14) were excluded from the extra analyses because of the opposite effects of the ε2 and ε4 alleles on the lipid levels.

*The mean difference was significant at the 0.05 level.

BMI, body mass index; DBP, diastolic blood pressure; FPG, fasting plasma glucose; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; MetS: metabolic syndrome; SBP, systolic blood pressure; TC, total cholesterol.

Statistical analysis

The data were summarised as numbers, percentages or means±SDs. Inferential statistics were calculated using the SPSS, Chicago, Illinois, USA. Simple descriptive statistics were used to describe the variables among the participants. The differences in the measurements among the different groups were compared with Student t test and a one-way analysis of variance. The APOE alleles were lower, and the frequencies of the ε2/2, ε3/3 and ε4/4 genotypes were presented in table 2. There was no evidence of significant deviation from the Hardy-Weinberg equilibrium in any of the distributions. The frequencies of the APOE ε2 and ε4 alleles were lower, and the frequencies of the APOE ε3 alleles were higher than those in the non-MetS group (table 1). The allele and genotype distributions of the APOE genotypes met the Hardy-Weinberg equilibrium. The frequencies of the APOE alleles and genotypes were compared with Student t test and a one-way analysis of variance. The APOE alleles were lower, and the frequencies of the ε2/2, ε3/3 and ε4/4 genotypes were presented in table 2. There was no evidence of significant deviation from the Hardy-Weinberg equilibrium in any of the distributions. The frequencies of the APOE ε2 and ε4 alleles were lower, and the frequencies of the APOE ε3 alleles were higher than those in the non-MetS group (table 1). The allele and genotype distributions of the APOE genotypes met the Hardy-Weinberg equilibrium. The frequencies of the APOE alleles and genotypes were compared with Student t test and a one-way analysis of variance. The APOE alleles were lower, and the frequencies of the ε2/2, ε3/3 and ε4/4 genotypes were presented in table 2. There was no evidence of significant deviation from the Hardy-Weinberg equilibrium in any of the distributions. The frequencies of the APOE ε2 and ε4 alleles were lower, and the frequencies of the APOE ε3 alleles were higher than those in the non-MetS group (table 1).
Comparison of the means of anthropometric, biochemical and clinical parameters between different APOE genotypes in the two groups

To evaluate the effect of the APOE genotype and the anthropometric, biochemical and clinical parameters, the participants in our study were subdivided into three groups: (1) $e3/e3$ participants (APOE3 group), (2) participants carrying $e2/e2$ or $e2/e3$ genotypes ($e2$ carriers, APOE2 group) and (3) participants carrying $e4/e4$ or $e3/e4$ ($e4$ carriers, APOE4 group). The participants with the $e2/e4$ genotype (n=14) were excluded from this analysis because of the opposite effects of the $e2$ and $e4$ alleles on the lipid levels.

In the MetS groups, none of the parameters had significant associations when comparing $e3$ allele carriers with $e4$ allele carriers, in contrast to the comparison of $e2$ allele carriers with $e3$ allele carriers. In the non-MetS group, the BMI, waistline, DBP and LDL-C in the $e2$ allele carriers were lower ($p<0.05$) than those in the $e3$ allele carriers). In contrast, the $e4$ allele carriers had significantly higher means of these parameters than the $e2$ allele carriers (table 3).

The prevalence of MetS and the individual components of dyslipidemia between the APOE2 and APOE4 groups

By evaluating the effects of MetS and the individual components of dyslipidemia between the APOE2 and APOE4 groups, we found that the prevalence of MetS, abdominal obesity, high blood pressure, hypertriglyceridaemia and hypercholesterolaemia were lower in the APOE2 group ($p<0.05$); the prevalence of hyperglycaemia and low HDL-C was higher in the APOE2 group but had no significant association ($p>0.05$) (table 4).

DISCUSSION

The APOE genotypes and allele distributions vary among different races and geographic areas. In this study, we found that the general distribution of APOE allele E3 in Uyghur men was 80.0%, which is between the distributions reported in the Han Chinese and Caucasian populations. Our data indicated that the Uyghurs had a different allele distribution from the Han Chinese and Caucasians, prompting a different genetic background of the Uyghur. Indeed, an earlier study which was aimed at identifying the origin of human species applying DNA sequencing technology to have analysed a Uyghur mummy that was unearthed 3000 years ago from a dry desert in the Tarim basin of Xinjiang, China, has demonstrated that the Uyghur ethnic group currently living in Xinjiang, China originated from Europe. Our current data of the APOE polymorphism may provide additional evidence for this finding. However, after approximately 3000 years of evolution, one may expect that the APOE3 allele may have changed. We previously demonstrated that the MetS prevalence was higher in the Uyghur ethnic group.

Our study found that the frequencies of the APOE alleles $e2$, $e3$ and $e4$ in Uyghur men were 8.5%, 80.0% and 11.5%, respectively; that the frequencies of the APOE $e2$ and $e4$ alleles were lower in the MetS group than in the non-MetS group; and that the $e2/2$, $e2/3$ and $e2/4$ genotype frequencies were clearly lower in the MetS group than in the non-MetS group ($p<0.05$). The frequency of the $e2/2$ genotype was higher in the MetS group than the frequency of the $e4/4$ genotype in the control subjects, but in patients with MetS, the $e2/2$ carrier frequency was lower than that of $e4/4$. Variations in the genetic structures in different populations are possible, but differences in testing methods should also be considered. The frequency of APOE2 was lower in the MetS group than in the non-MetS group. The APOE2 genotype carriers had the lowest HDL-C and LDL-C levels. The mechanism of this effect is most likely due to decreased conversion of the very low-density lipoprotein (VLDL) into LDL-C as observed in $e2$ carriers. Thus, a high frequency of the $e2$ allele would appear to predict a favourable lipid profile, indicating that APOE2 may be a protective factor against MetS.

Many studies have suggested that variation in the APOE gene is associated with the lipid levels. We

<table>
<thead>
<tr>
<th>Table 4</th>
<th>The prevalence of MetS and the individual components of dyslipidemia between the APOE2 and APOE4 groups</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>APOE2</td>
</tr>
<tr>
<td>n</td>
<td>130</td>
</tr>
<tr>
<td>MetS (no/yes)</td>
<td>86/44 (33.8%)</td>
</tr>
<tr>
<td>Abdominal obesity (no/yes)*</td>
<td>46/84 (64.6%)</td>
</tr>
<tr>
<td>Hypertension (no/yes)</td>
<td>67/63 (48.5%)</td>
</tr>
<tr>
<td>Hypertriglyceridaemia (no/yes)</td>
<td>61/69 (53.1%)</td>
</tr>
<tr>
<td>Hypercholesterolaemia (no/yes)*</td>
<td>120/10 (7.7%)</td>
</tr>
<tr>
<td>Hyperglycaemia (no/yes)</td>
<td>114/16 (12.3%)</td>
</tr>
<tr>
<td>Low HDL-C (no/yes)</td>
<td>103/27 (13.6%)</td>
</tr>
</tbody>
</table>

Pearson’s $\chi^2$ test was used to analyse the differences.

Power by YOZOSOFT.

*The mean difference was significant at the 0.05 level.

HDL-C, high-density lipoprotein cholesterol; MetS, metabolic syndrome.
found that the triglyceride and LDL-C levels were lower in the ε2 allele carriers than in the ε3 allele carriers. In contrast, the ε4 allele carriers had significantly higher means of these plasma lipid levels than did the ε2 and ε3 allele carriers. The prevalence of abdominal obesity, high blood pressure, hypertriglyceridaemia and hypercholesterolaemia was lower in the APOE2 group than in the APOE4 group. The risks of these individuals with ε4 allele gene carriers for getting these changes were 1.327, 1.780, 1.888, 1.428 and 2.571 times greater than the risks of those with ε2 allele gene carriers.

Some limitations of this study should be considered. Since we only genotyped the APOE gene of the participants, and could not do population stratification analyses, we could not ensure whether there were biases due to confounding by ancestry or not. However, since all the participants were recruited from the same geographic region and reported to be Uyghur, the issue of population stratification should be limited in the current study. Besides, although we found that APOE alleles were associated with MetS risk for Uyghur men residing in the Xinjiang area, studies in a larger sample or other population to replicate this result are urged.

In conclusion, the distribution of the APOE alleles and genotype frequencies in Uyghur men is unique and is associated with MetS risk. APOE2 is associated with hypertriglyceridaemia, with a slightly increased risk for MetS, but APOE2 is associated with protection against MetS in Uyghur males in China. However, this study is an initial step in understanding the relationship between APOE gene polymorphisms and MetS in Uyghur men, and more detailed in-depth studies in the future are needed to confirm the link between APOE polymorphisms and MetS risk.

Author affiliations

College of Basic Medical Science, Xinjiang Medical University, Xinjiang, China
2The Fourth Affiliated Hospital, Xinjiang Medical University, Xinjiang, China
3Shanghai Key Laboratory of Diabetes Mellitus, Shanghai Diabetes Institute, Shanghai Clinical Center for Diabetes, Shanghai Jiao Tong University Affiliated Sixth People’s Hospital, Shanghai, China
4The Key Laboratory of Metabolic Diseases, The First Affiliated Hospital, Xinjiang Medical University, Urumqi, China
5The Second Affiliated Hospital, Xinjiang Medical University, Urumqi, China
6Department of Science and Technology, Xinjiang Medical University, Urumqi, China

Acknowledgements

The authors would like to thank all of the participants, individuals and institutions which supported this study.

Contributors

HY and YPS designed the study. BZ performed DNA extraction and APOE genotyping. RW, FLX and LL collected blood samples. All the authors approved the final version of the manuscript.

Funding

This study was supported in part by grants from the Natural Science Foundation of China (#81160115 and #81460153); The Natural Science Foundation of the Xinjiang Uyghur Autonomous Region (#2015211014); The State Key Laboratory Incubation Base of Xinjiang Major Diseases Research (#2010DS890294) and The Key Laboratory of Metabolic Diseases, Department of Education, Xinjiang, China.

Competing interests

None declared.

REFERENCES


Patient consent

Obtained.

Ethics approval

The Ethics Committee of the First Affiliated Hospital of Xinjiang Medical University and was conducted according to the standards of the Declaration of Helsinki.

Provenance and peer review

Not commissioned; externally peer reviewed.

Data sharing statement

No additional data are available.

Open Access

This is an Open Access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: http://creativecommons.org/licenses/by-nc/4.0/


