APOE Polymorphism Is Associated with C-reactive Protein Levels but Not with White Blood Cell Count: Dong-gu Study and Namwon Study

Yong-Woon Yun,1 Sun-Seog Kweon,2,3 Jin-Su Choi,2 Jung-Ae Rhee,4 Young-Hoon Lee,4 Hae-Sung Nam,5 Seul-Ki Jeong,6 Kyeong-Soo Park,7 So- Yeon Ryu,8 Seong-Woo Choi,9 Hee Nam Kim,9 Jane A. Cauley,10 and Min-Ho Shin2,9

1Gwangju-Jeonnam Regional Cardiocerebrovascular Center, Chonnam National University Hospital, Gwangju; 2Department of Preventive Medicine, Chonnam National University Medical School, Gwangju; 3Jeonnam Regional Cancer Center, Chonnam National University Hwasun Hospital, Hwasun; 4Department of Preventive Medicine & Institute of Wonkwang Medical Science, Wonkwang University College of Medicine, Iksan; 5Department of Preventive Medicine, Chungnam National University Medical School, Daejeon; 6Department of Neurology & Research Institute of Clinical Medicine, Chonbuk National University-Biomedical Institute of Chonbuk National University Hospital, Jeonju; 7Department of Preventive Medicine, Seonam University College of Medicine, Namwon; 8Department of Preventive Medicine, Chosun University Medical School, Gwangju; 9Center for Creative Biomedical Scientists, Chonnam National University, Gwangju; 10Department of Epidemiology, Graduate School of Public Health, University of Pittsburgh, Pittsburgh, USA

Received: 19 August 2014
Accepted: 17 February 2015

Address for Correspondence:
Min-Ho Shin, MD
Department of Preventive Medicine, Chonnam National University Medical School, 160 Baekseo-ro, Dong-gu, Gwangju 501-746, Korea
Tel: +82.62-220-4166, Fax: +82.62-233-0305
E-mail: mhshinx@paran.com

Funding: This study was supported by a grant (CRI11020-1) Chonnam National University Hospital Biomedical Research Institute.

We evaluated the association of the APOE polymorphism with serum C-reactive protein levels and white blood cell count in two large population-based studies in Korean. The datasets included the Dong-gu study (n = 8,893) and the Namwon study (n = 10,032). APOE genotypes were identified by polymerase chain reaction-restriction fragment length polymorphism. Multivariable linear regression analysis was performed to evaluate the relationship of APOE genotypes with C-reactive protein levels and white blood cell count with adjustments for age, sex, body mass index, smoking, diabetes, hypertension, and serum lipids. In the multivariate model, carriers of E3E4 or E4E4 genotype had significantly lower C-reactive protein levels compared with carriers of E3E3 genotype group (0.50 mg/L vs. 0.67 mg/L; 0.37 mg/L vs. 0.67 mg/L, respectively, for the Dong-gu Study and 0.47 mg/L vs. 0.66 mg/L; 0.45 mg/L vs. 0.66 mg/L, respectively, for the Namwon Study). However, there was no difference in white blood cell count among APOE genotypes. We found that the APOE E4 allele is associated with lower C-reactive protein levels, but not white blood cell count. Our results suggest that APOE genotype may influence C-reactive protein levels through non-inflammatory pathway.

Keywords: C-reactive Protein; Apolipoprotein E; Polymorphism, Genetic; Inflammation

INTRODUCTION

C-reactive protein (CRP) is a sensitive and nonspecific systemic marker of inflammation (1). Increased CRP levels are associated with mortality, coronary heart disease, and stroke (2, 3). Serum CRP levels are substantially influenced by genetic factors, with a heritability of 35% to 40% (4). White blood cell count (WBC) is also a marker of systemic inflammation and higher WBC count has been associated with cardiovascular disease incidence and mortality (5, 6). WBC count is also moderately influenced by heritable factors, with heritability estimates ranging from 14% to 40% across the WBC subtypes (7).

Apolipoprotein E (apoE = protein, APOE = gene) has a central role in the metabolism of cholesterol and triglycerides (8-10). APOE gene has three common alleles (E2, E3, and E4) arising from two single nucleotide polymorphisms (rs429358 and rs7412) in exon 4 that give six possible genotypes (E2E2, E2E3, E2E4, E3E3, E3E4, and E4E4) (11). APOE genotypes have been associated with ischemic cerebrovascular disease (12) and coronary heart disease (13). Differences among APOE genotypes in the risk of cardiovascular disease have traditionally been explained by lipid metabolism. In previous our study of the same data set, APOE genotypes was associated with carotid atherosclerosis and this association was partly mediated through blood lipid (14). However, APOE genotype may also affect the risk of cardiovascular disease through anti-inflammatory and antioxidant properties of apoE protein (15, 16).

Since Manttari and colleagues first described the association of APOE E4 allele with low CRP levels in 2001, many studies have investigated relationships between APOE genotype and CRP levels. Most studies have reported that E4 allele is associated with
low levels of CRP (17-26). However, there is little research on the relationship between other markers of inflammation and APOE genotype. In addition, most studies were carried out in Caucasians, and few studies have been carried out in Asians. Therefore, we evaluated the association of the APOE genotype with serum CRP levels and WBC in two large population-based studies in South Korea.

MATERIALS AND METHODS

Subjects
The Dong-gu Study and Namwon Study are ongoing prospective studies designed to investigate the prevalence, incidence, and risk factors for chronic disease in urban and rural populations, respectively. Details of the study subjects and measurements have been published previously (27).

In the Dong-gu Study, 9,260 subjects aged 50 yr and older were recruited in the baseline survey between April 2007 and June 2010 in the Dong-gu district of Gwangju Metropolitan City in South Korea. Of these, 101 subjects were excluded because of missing data on APOE genotype, CRP, WBC, blood lipids and medical history and smoking. Subjects with WBC counts of less than 2,000 cells/μL or more than 12,000 cells/μL and/or CRP ≥ 10 mg/L were excluded because of a high probability of acute inflammation and other medical disorders, which left 8,893 (3,525 men and 5,368 women) for analysis.

In the Namwon Study, 10,667 participants (4,201 men and 6,466 women) were recruited in the baseline survey between January 2004 and February 2007 in Namwon city of Jeollabuk-do province in South Korea. Of these, 225 subjects were excluded because of missing data on APOE genotype, CRP, WBC, blood lipids and medical history and smoking. Subjects with WBC counts of less than 2,000 cells/μL or more than 12,000 cells/μL and/or CRP ≥ 10 mg/L were excluded, which left 10,032 (3,909 men and 6,123 women) for analysis.

APOE genotyping
Genomic DNA was extracted from peripheral blood with an AccuPrep Genomic DNA Extraction Kit (Bioneer, Seoul, Korea) or a QIAamp DNA Mini Kit (Qiagen Inc., Chatsworth, CA, USA) according to the manufacturer’s protocol. APOE genotypes were determined as described by Hixson and Vernier, with slight modifications (28). Our APOE genotyping method has been reported previously (29). The genotyping method was validated by direct sequencing (ABI PRISM 3100 Genetic Analyzer, Applied Biosystems) of 96 subjects with 100% concordance.

Other clinical variables
Demographic characteristics, lifestyle and medical history were obtained by standardized questionnaires. Smoking status was classified into non-smoker and current smoker. Height was measured to the nearest 0.1 cm, and weight to the nearest 0.1 kg. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared.

Diabetes was defined by a fasting plasma glucose ≥ 126 mg/dL or use of antidiabetic medication. Blood pressure was measured in the right upper arm using a mercury sphygmomanometer (Baumanometer; WA Baum Co, Inc, Copiague, NY, USA) with an appropriately sized cuff after subjects rested at least 5 min while seated. Three consecutive measurements of systolic and diastolic blood pressures were performed at 1-min intervals, and the average was used in the analysis. Hypertension was defined by systolic blood pressure ≥ 140 or diastolic blood pressure ≥ 90 mmHg, or use of antihypertensive medication.

Blood samples were drawn from an antecubital vein in the morning after a 12-hr overnight fast. Serum was separated within 30 min and stored at -70°C until analyzed. Serum total cholesterol, high-density lipoprotein cholesterol (HDL), triglycerides, and fasting blood glucose levels were measured enzymatic methods. All samples were analyzed using an automatic analyzer (model 7600 chemical analyzer; Hitachi Ltd, Tokyo, Japan). CRP level was determined by means of particle-enhanced immunonephelometry using BN II nephelometer (Dade Behring, Marburg, Germany). The lower detection limit for CRP was 0.2 mg/L. White blood cell (WBC) count was determined using a cell counter (Micro 60, ABX, Montpellier, France).

Statistical analysis
Data are presented as mean ± standard deviation (SD) or percentage for categorical variables. Because the distribution of triglycerides and CRP levels was skewed, triglycerides and CRP values were logarithmically transformed, and geometric means with 95% confidence intervals are presented. The APOE genotypes were categorized into E2E2, E2E3, E2E4, E3E3, E3E4, and E4E4. The APOE genotype was also categorized into three groups for analytical purposes: APOE E2 (E2E2 and E2E3), APOE E3 (E3E3), and APOE E4 (E3E4 and E4E4). Subjects with the E2E4 genotype were excluded because of the opposing biological effects of the E2 and E4 alleles. Multivariable linear regression analysis was performed to evaluate the association between APOE genotypes and CRP levels and white blood cell count after adjusting for age, sex, BMI, smoking, diabetes and hypertension, total cholesterol, HDL cholesterol, and log-transformed triglycerides. The Bonferroni method was used to correct multiple comparisons. Hardy-Weinberg equilibrium was tested by use of a chi-square goodness of fit test. Statistical analyses were performed using the SPSS version 21.0 (SPSS, Inc., an IBM Company, Chicago, IL, USA).

Ethics statement
This study was conducted in accordance with the Declaration of Helsinki guidelines. The study protocol was approved by the
institutional review board of Chonnam National University Hospital (Dong-gu Study, IRB No. I-2008-05-056; Namwon Study, IRB No. I-2007-07-062), and informed consent was obtained from each subject.

RESULTS

The baseline characteristics of the study subjects are presented in Table 1. The mean age was 65.1 ± 8.2 yr in the Dong-gu Study, and 61.6 ± 8.0 yr in the Namwon Study. The APOE genotype frequencies were consistent with Hardy-Weinberg equilibrium (P = 0.86 for the Dong-gu Study, P = 0.91 for the Namwon Study) and not significantly different. The frequency of APOE genotypes for E2E2, E2E3, E2E4, E3E3, E3E4, and E4E4 was 0.4, 10.7, 1.3, 71.0, 15.6, and 1.0%, respectively in the Dong-gu Study and 0.4, 10.2, 1.1, 72.6, 14.9, and 0.9%, respectively, in the Namwon Study.

The associations of APOE genotypes and allele with CRP are shown in Table 2. There was significant difference in CRP across the APOE genotypes and alleles in both studies in all Models. Carriers of E3E4 or E4E4 genotype had significantly lower CRP levels compared with carriers of APOE E3E3 genotype group in both studies (0.51 mg/L vs. 0.67 mg/L; 0.37 mg/L vs. 0.67 mg/L, respectively, for the Dong-gu Study and 0.48 mg/L vs. 0.67 mg/L; 0.47 mg/L vs. 0.67 mg/L, respectively, for the Namwon Study). This association was not attenuated after adjustment for age, sex, BMI, smoking, diabetes and hypertension, total cholesterol, HDL cholesterol, and log-transformed triglycerides (0.50 mg/L vs. 0.67 mg/L; 0.37 mg/L vs. 0.67 mg/L, respectively, for the Dong-gu Study and 0.47 mg/L vs. 0.66 mg/L; 0.45 mg/L vs. 0.66 mg/L, respectively, for the Namwon Study).

Carriers of E4 allele had significantly lower CRP levels compared with carriers of APOE E3 allele in both studies (0.50 mg/L vs. 0.67 mg/L for the Dong-gu Study and 0.48 mg/L vs. 0.67 mg/L for the Namwon Study). This association was not attenuated after adjustment for potential confounders (0.49 mg/L vs. 0.67 mg/L for the Dong-gu Study and 0.47 mg/L vs. 0.66 mg/L for the Namwon Study). There was no difference in CRP levels between

Table 1. Baseline characteristics of the study subjects

| Parameters                  | Dong-gu study (n = 8,893) | Namwon study (n = 10,032) | P value |
|-----------------------------|---------------------------|---------------------------|---------|
| Age (yr)                    | 65.1 ± 8.2                | 61.6 ± 8.0                | < 0.001 |
| Men (%)                     | 5,252 (39.6)              | 3,909 (39.0)              | 0.344   |
| Body mass index (kg/m²)     | 24.4 ± 2.9                | 24.4 ± 3.1                | 0.617   |
| Current smoking (%)         | 962 (10.8)                | 1,512 (15.1)              | < 0.001 |
| Hypertension (%)            | 3,960 (44.5)              | 3,945 (39.3)              | < 0.001 |
| Diabetes mellitus (%)       | 1,662 (18.7)              | 1,205 (12.0)              | < 0.001 |
| Total cholesterol (mg/dL)   | 201.3 ± 39.9              | 189.3 ± 37.0              | < 0.001 |
| HDL cholesterol (mg/dL)     | 51.6 ± 11.9               | 47.6 ± 12.0               | < 0.001 |
| Triglycerides (mg/dL)       | 118.0 (84.0-172.0)        | 130.0 (89.0-193.0)        | < 0.001 |
| C-reactive protein (mg/L)   | 0.60 (0.30-1.20)          | 0.60 (0.30-1.30)          | 0.104   |
| White cell blood count (× 10⁹/µL) | 5.81 ± 1.53         | 6.20 ± 1.60               | < 0.001 |
| Myocardial infarction (%)   | 114 (13.3)                | 37 (4.0)                  | < 0.001 |
| Stroke (%)                  | 369 (4.1)                 | 352 (3.5)                 | 0.022   |

Data are means ± SD, medians (interquartile range) or n (%). HDL, high density lipoprotein.

Table 2. Adjusted geometric means and 95% confidence intervals for C-reactive protein (mg/L) in different APOE genotypes or alleles

| Genotypes       | No. (%) | Unadjusted mean (95% CI) | Adjusted mean (95% CI)* | No. (%) | Unadjusted mean (95% CI) | Adjusted mean (95% CI) |
|-----------------|---------|--------------------------|-------------------------|---------|--------------------------|------------------------|
| E2E2            | 40 (0.4) | 0.57 (0.43-0.77)         | 0.61 (0.46-0.81)        | 40 (0.4) | 0.62 (0.44-0.87)         | 0.67 (0.48-0.93)        |
| E2E3            | 954 (10.7)| 0.66 (0.62-0.70)         | 0.68 (0.64-0.72)        | 1,026 (10.2)| 0.67 (0.63-0.72)     | 0.71 (0.66-0.76)        |
| E2E4            | 115 (1.3) | 0.52 (0.44-0.62)         | 0.53 (0.45-0.63)        | 106 (1.1) | 0.62 (0.51-0.77)         | 0.65 (0.53-0.79)        |
| E3E3            | 6,312 (71.0)| 0.67 (0.65-0.68)         | 0.67 (0.65-0.68)        | 7,280 (72.6)| 0.67 (0.65-0.68)       | 0.66 (0.65-0.68)        |
| E3E4            | 1,386 (15.6)| 0.51 (0.49-0.54)         | 0.50 (0.48-0.53)        | 1,493 (14.9)| 0.48 (0.45-0.51)       | 0.47 (0.44-0.49)        |
| E4E4            | 86 (1.0)  | 0.37 (0.31-0.46)         | 0.37 (0.30-0.45)        | 87 (0.9)  | 0.47 (0.37-0.59)         | 0.45 (0.36-0.57)        |
| P < 0.001 P < 0.001 |        | 0.47 (0.37-0.59)         | 0.45 (0.36-0.57)        | 0.47 (0.37-0.59) | 0.45 (0.36-0.57) |
| Partial R² = 0.014 | Partial R² = 0.016 | Partial R² = 0.012 | Partial R² = 0.016 |
| E2              | 994 (11.2)| 0.66 (0.62-0.70)         | 0.66 (0.64-0.72)        | 1,066 (10.6)| 0.67 (0.63-0.72)       | 0.71 (0.66-0.75)        |
| E3              | 6,312 (71.0)| 0.67 (0.65-0.68)         | 0.67 (0.65-0.68)        | 7,280 (72.6)| 0.67 (0.65-0.68)       | 0.66 (0.65-0.68)        |
| E4              | 1,472 (16.6)| 0.50 (0.48-0.53)         | 0.49 (0.47-0.52)        | 1,580 (15.7)| 0.48 (0.45-0.51)       | 0.47 (0.44-0.49)        |
| P < 0.001 P < 0.001 |        | 0.47 (0.44-0.49)         | 0.47 (0.44-0.49)        | 0.47 (0.44-0.49) | 0.47 (0.44-0.49) |
| Partial R² = 0.012 | Partial R² = 0.015 | Partial R² = 0.012 | Partial R² = 0.016 |

Values are geometric mean (95% confidence interval). *Adjusted for age, sex, BMI, smoking, diabetes mellitus, total cholesterol, HDL cholesterol, and log triglycerides. †P < 0.05 compared with E3E3 or E3 with a Bonferroni multiple comparisons test; ‡Variance explained by APOE genotype after adjustment for covariates.
Table 3. Adjusted means and 95% confidence intervals for white blood cell count in different APOE genotypes or alleles

| Genotypes | Dong-gu study | Namwon study |
|-----------|---------------|--------------|
|           | No. (%)       | Unadjusted mean (95% CI) | Adjusted mean (95% CI)* | No. (%)       | Unadjusted mean (95% CI) | Adjusted mean (95% CI) |
| E2E2      | 40 (0.4)      | 5.56 (5.11-6.01) | 5.72 (5.44-6.00) | 40 (0.4)      | 5.70 (5.21-6.20) | 5.82 (5.25-6.28) |
| E2E3      | 954 (10.7)    | 5.52 (5.37-5.67) | 5.72 (5.44-6.00) | 1,026 (10.3) | 6.21 (6.11-6.31) | 6.22 (6.12-6.31) |
| E2E4      | 115 (1.3)     | 5.72 (5.46-5.93) | 7.22 (6.57-7.86) | 106 (1.1)     | 6.04 (5.73-6.34) | 6.07 (5.79-6.30) |
| E3E3      | 6,312 (71.0)  | 5.80 (5.77-5.84) | 5.87 (5.79-5.94) | 1,493 (14.9) | 6.16 (6.08-6.25) | 6.16 (6.08-6.23) |
| E3E4      | 1,386 (15.6)  | 5.80 (5.80-5.96) | 5.87 (5.79-5.94) | 1,580 (15.7) | 6.16 (6.09-6.24) | 6.16 (6.09-6.23) |
| E4E4      | 86 (1.0)      | 5.75 (5.43-6.03) | 5.73 (5.42-6.03) | 87 (0.9)      | 5.68 (5.44-5.91) | 5.68 (5.44-5.91) |
| E3        | 994 (11.2)    | 5.61 (5.72-5.91) | 5.72 (5.73-5.91) | 1,066 (10.6) | 6.19 (6.11-6.29) | 6.20 (6.11-6.29) |
| E4        | 1,472 (16.6)  | 5.68 (5.80-5.95) | 5.86 (5.78-5.95) | 1,580 (15.7) | 6.16 (6.09-6.24) | 6.16 (6.09-6.23) |

Values are arithmetic mean (95% confidence interval) for white blood cell count (×10^3/µL). *Adjusted for age, sex, BMI, smoking, hypertension, diabetes mellitus, total cholesterol, HDL cholesterol, and log triglycerides.

tween carriers of E2 allele and carriers of E3 alleles.

The variance of CRP explained by the APOE genotype after adjustment for covariates was 1.6% in both studies. However, there was no difference in WBC among APOE genotypes in both studies (Table 3).

**DISCUSSION**

In this population based study, we observed that the E3E4 and E4E4 genotypes were associated with lower C-reactive protein compared with the E3E3 genotype group, while WBC count was not associated with APOE genotype. To our knowledge, this is the largest population-based study on the association of the APOE genotype and CRP levels and WBC count.

Our results that E3E4 and E4E4 genotype are associated with lower CRP levels are in agreement with previous studies (17-26). In a few studies, there was no association between APOE E4 allele and low CRP levels (30, 31). The small sample size of these studies might have contributed to the negative findings. Recently, Hubacek et al. (25) observed the lowest CRP levels in carriers of the APOE E3E3 and E4E4 genotypes in a large general population sample of 6,230 aged 45-69 yr. In a meta-analysis in Asians including a Korean cohort and two Filipino cohorts, APOE E4 haplotype was significantly associated with decreased CRP levels compared to the APOE E3 haplotype (32).

There is still limited research on the association of APOE genotype with pro- and anti-inflammatory markers except for CRP in humans. In the present study, APOE genotype was not associated with WBC count. There was only one study that reported an association between APOE genotype and WBC count (18), which is in accordance with our study. This study showed that the APOE genotype is associated with CRP levels, but not white blood cells. However, a limitation of this study is the small sample number of participants who had undergone coronary angiography. Tziakas et al. (33) reported that E3E4 carriers were not only associated with lower levels of IL-10, an anti-inflammatory cytokine, but also with lower CRP levels, an inflammatory marker in patients with acute coronary syndrome and chronic stable angina. Tziakas et al. (33) speculated that in E4 carriers, the deleterious effects of low IL-10 levels may outweigh the protective effects of low CRP levels found in these patients, and that an imbalance between anti- and pro-inflammatory forces may be responsible for the increased CAD risk associated with the E4 allele. Drabe et al. (34) reported that the presence of the E4 allele is associated with increased release of IL-8 and TNF-alpha in 22 patients receiving standard coronary artery bypass grafting. Further studies are needed to clarify the association of APOE genotype and inflammation markers.

The underlying mechanisms by which APOE genotype affects CRP levels are poorly understood. This mechanism may not be related to inflammation for following reasons. First, the negative association between E4 allele and CRP levels is in contradiction to the observation that E4 allele is a risk factor for CVD and Alzheimer’s disease (13, 35) and has been associated with increased brain and macrophage inflammation (36). Second, in our study, there was no association between APOE genotype and WBC count, an important cellular marker of systemic inflammation. März et al. (18) postulated that the metabolism of CRP could be related to the activity of the mevalonate pathway in the liver, since in E4 carriers, the mevalonate pathway that produces cholesterol in vivo is downregulated, which could also lead to low production of CRP. This postulation can be supported by the findings that statins, the inhibitor of the mevalonate pathway, would modify the association between CRP and inflammation-related disease. Because of the two opposing effects of APOE E4 on inflammation, APOE E4 allele may influence atherosclerosis in a positive or negative way and using CRP as the biomarker in assessing CVD risk could underestimate the CVD risk in the car-

http://dx.doi.org/10.3346/jkms.2015.30.7.860
rriers of E4 allele (36).

The strengths of this study are its very large sample size and adequate statistical power to assess whether APOE genotype is associated with CRP levels. Our study has some limitations. First, we measured the CRP levels and WBC count only once in this study, which may have affected the results. However, the within-person biologic variation of CRP is low (38) and so there may be little bias. Second, we did not measure other inflammatory markers such as interleukin-6, tumor necrosis factor-α, and fibrinogen which might have helped us to better clarify the relationship between APOE genotype and inflammation.

In conclusion, our data demonstrated that the APOE E4 allele is associated with lower CRP levels, but not WBC count. Our results suggest that APOE genotype may influence CRP levels through a non-inflammatory pathway.

DISCLOSURE

The authors have no conflicts of interest to disclose.

AUTHOR CONTRIBUTION

Conception and design: Shin MH, Kweon SS. Acquisition of data: Yun YW, Kweon SS, Choi JS, Rhee JA, Lee YH, Nam HS, Jeong SK, Park KS, Ryu SY, Choi SW, Kim HN, Shin MH. Analysis and interpretation of data: Yun YW, Kweon SS, Choi JS, Rhee JA, Lee YH, Nam HS, Jeong SK, Park KS, Ryu SY, Choi SW, Kim HN, Shin MH. Preparation, critical revision and final approval of manuscript approval: all authors.

ORCID

Yong-Woon Yun http://orcid.org/0000-0001-6715-1768
Sun-Seog Kweon http://orcid.org/0000-0003-2378-8550
Jin-Su Choi http://orcid.org/0000-0001-9001-0365
Jung-Ae Rhee http://orcid.org/0000-0003-1610-1001
Young-Hoon Lee http://orcid.org/0000-0003-1367-025X
Hae-Sung Nam http://orcid.org/0000-0003-0911-4576
Seul-Ki Jeong http://orcid.org/0000-0002-9868-621X
Kyeong-Soo Park http://orcid.org/0000-0001-8838-4894
So-Yeon Ryu http://orcid.org/0000-0001-5006-1192
Seong-Woo Choi http://orcid.org/0000-0002-6150-3934
Hee Nam Kim http://orcid.org/0000-0002-6153-2612
Jane A. Cauley http://orcid.org/0000-0003-0752-4408
Min-Ho Shin http://orcid.org/0000-0002-2217-5624

REFERENCES

1. Pepys MB, Hirschfield GM. C-reactive protein: a critical update. J Clin Invest 2003; 111: 1805-12.
2. Kaptoge S, Di Angelantonio E, Lowe G, Pepys MB, Thompson SG, Collins R, Danesh J; Emerging Risk Factors Collaboration. C-reactive protein concentration and risk of coronary heart disease, stroke, and mortality: an individual participant meta-analysis. Lancet 2010; 375: 132-40.
3. Danesh J, Wheeler JG, Hirschfield GM, Eda S, Eiriksdottir G, Rumley A, Lowe GD, Pepys MB, Gudnason V. C-reactive protein and other circulating markers of inflammation in the prediction of coronary heart disease. N Engl J Med 2004; 350: 1387-97.
4. Pankow JS, Folsom AR, Cushman M, Borecki IB, Hopkins PN, Eckfeldt JH, Tracy RP. Familial and genetic determinants of systemic markers of inflammation: the NHLBI family heart study. Atherosclerosis 2001; 154: 681-9.
5. Kannel WB, Anderson K, Wilson PW. White blood cell count and cardiovascular disease. Insights from the Framingham Study. JAMA 1992; 267: 1253-6.
6. Lee CD, Folsom AR, Nieto FJ, Chambless LE, Shahar E, Wolfe DA. White blood cell count and incidence of coronary heart disease and ischemic stroke and mortality from cardiovascular disease in African-American and White men and women: atherosclerosis risk in communities study. Am J Epidemiol 2001; 154: 758-64.
7. Keller MF, Reiner AP, Okada Y, van Rooij FJ, Johnson AD, Chen MH, Smith AV, Morris AP, Tanaka T, Ferrucci L, et al.; CHARGE Hematology; COGENT; BioBank Japan Project (RIKEN) Working Groups. Trans-ethnic meta-analysis of white blood cell phenotypes. Hum Mol Genet 2014; 23: 6944-60.
8. Eichner JE, Dunn ST, Perveen G, Thompson DM, Stewart KE, Stroehla BC. Apolipoprotein E polymorphism and cardiovascular disease: a HuGE review. Am J Epidemiol 2002; 155: 487-95.
9. Mahley RW. Apolipoprotein E cholesterol transport protein with expanding role in cell biology. Science 1988; 240: 622-30.
10. Song Y, Stampler MJ, Liu S. Meta-analysis: apolipoprotein E genotypes and risk for coronary heart disease. Ann Intern Med 2004; 141: 137-47.
11. Davignon J, Gregg RE, Sing CF. Apolipoprotein E polymorphism and atherosclerosis. Arterioscler Thromb Vasc Biol 1998; 8: 1-21.
12. McCarron MO, Delong D, Alberts MJ. APOE genotype as a risk factor for ischemic cerebrovascular disease: a meta-analysis. Neurology 1999; 53: 1308-11.
13. Bennet AM, Di Angelantonio E, Ye Z, Wensley F, Dahlin A, Ahlbom A, Keavney B, Collins R, Wiman B, de Faire U, et al. Association of apolipoprotein E genotypes with lipid levels and coronary risk. JAMA 2007; 298: 1300-11.
14. Shin MH, Choi JS, Rhee JA, Lee YH, Nam HS, Jeong SK, Park KS, Kim HY, Ryu SY, Choi SW, et al. APOE polymorphism and carotid atherosclerosis in Korean population: the Dong-gu Study and the Namwon Study. Atherosclerosis 2014; 232: 180-5.
15. Bellosta S, Mahley RW, Sanan DA, Murata J, Newland DL, Taylor JM, Pitas RE. Macrophage-specific expression of human apolipoprotein E reduces atherosclerosis in hypercholesterolemic apolipoprotein E-null mice. J Clin Invest 1995; 96: 2170-9.
16. Thornage FE, Rudel LL, Walzem RL, Williams DL. Low levels of extrahepatic nonmacrophage ApoE inhibit atherosclerosis without correcting hypercholesterolemia in ApoE-deficient mice. Arterioscler Thromb Vasc Biol 2009; 29: 1939-45.
17. Määttäri M, Manninen V, Palouso T, Ehnholm C. Apolipoprotein E polymorphism and C-reactive protein in dyslipidemic middle-aged men. Atherosclerosis 2001; 156: 237-8.
18. Marz W, Scharnagl H, Hoffmann MM, Boehm BO, Winkelmann BR. The apolipoprotein E polymorphism is associated with circulating C-reactive protein (the Ludwigshafen risk and cardiovascular health study). Eur Heart J 2004; 25: 2109-19.

19. Judson R, Brain C, Dain B, Windemuth A, Ruaño G, Reed C. New and confirmatory evidence of an association between APOE genotype and baseline C-reactive protein in dyslipidemic individuals. Atherosclerosis 2004; 177: 345-51.

20. Eiriksdottir G, Aspelund T, Bjarnadottir K, Olafsdottir E, Gudnason V, Launer LJ, Harris TB. Apolipoprotein E genotype and statins affect CRP levels through independent and different mechanisms: AGES-Reykjavik Study. Atherosclerosis 2006; 186: 222-4.

21. Chasman DI, Kozlowski P, Zee RY, Kwiatkowski DJ, Ridker PM. Qualitative and quantitative effects of APOE genetic variation on plasma C-reactive protein, LDL-cholesterol, and apoE protein. Genes Immun 2006; 7: 211-9.

22. Berrahmoune H, Herbeth B, Siest G, Visvikis-Siest S. Heritability of serum hs-CRP concentration and 5-year changes in the Stanislas family study: association with apolipoprotein E alleles. Genes Immun 2007; 8: 352-9.

23. Grönroos P, Raitakari OT, Kähönen M, Hutri-Kähönen N, Marniemi J, Viikari J, Lehtimäki T. Association of high sensitive C-reactive protein with apolipoprotein E polymorphism in children and young adults: the Cardiovascular Risk in Young Finns Study. Clin Chem Lab Med 2008; 46: 179-86.

24. Haan MN, Aiello AE, West NA, Jagust WJ. C-reactive protein and rate of dementia in carriers and non-carriers of Apolipoprotein APOE4 genotype. Neurobiol Aging 2008; 29: 1774-82.

25. Hubacck JA, Peasey A, Pinkhart H, Stavek P, Kubinova R, Marmot M, Bobak M. APOE polymorphism and its effect on plasma C-reactive protein levels in a large general population sample. Hum Immunol 2010; 71: 304-8.

26. Ukola O, Kunnari A, Jokela M, Pääväsalo M, Kesäniemi YA. ApoE phenotype is associated with inflammatory markers in middle-aged subjects. Inflamm Res 2009; 58: 54-9.

27. Kweon SS, Shin MH, Jeong SK, Nam HS, Lee YH, Park KS, Pyu SY, Choi SW, Kim BH, Rhee JA, et al. Cohort Profile: The Namwon Study and the Dong-gu Study. Int J Epidemiol 2014; 43: 558-67.

28. Hixson JE, Vernier DT. Restriction isotyping of human apolipoprotein E by gene amplification and cleavage with HhaI. J Lipid Res 1990; 31: 545-8.

29. Shin MH, Kim HN, Cui LH, Kweon SS, Park KS, Heo H, Nam HS, Jeong SK, Chung EK, Choi JS. The effect of apolipoprotein E polymorphism on lipid levels in Korean adults. J Korean Med Sci 2005; 20: 361-6.

30. Mooijaart SP, Berbée JE, van Heemst D, Havekes LM, de Craen AJ, Slagboom PE, Rensen PC, Westendorp RG. ApoE plasma levels and risk of cardiovascular mortality in old age. PLoS Med 2006; 3: e176.

31. Austin MA, Zhang C, Humphries SE, Chandler WL, Talmud PJ, Edwards KL, Leonetti DL, McNeely MJ, Fujimoto WY. Heritability of C-reactive protein and association with apolipoprotein E genotypes in Japanese Americans. Ann Hum Genet 2004; 68: 179-88.

32. Hong EP, Kim DH, Suh JG, Park JW. Genetic risk assessment for cardiovascular disease with seven genes associated with plasma C-reactive protein concentrations in Asian populations. Hypertens Res 2014; 37: 692-8.

33. Tziakas DN, Challikias GK, Antonoglou CO, Veletza S, Tentes IK, Kortzaris AX, Hatseras DI, Kaská JC. Apolipoprotein E genotype and circulating interleukin-10 levels in patients with stable and unstable coronary artery disease. J Am Coll Cardiol 2006; 48: 2471-81.

34. Drabe N, Zünd G, Grünenfelder J, Sprenger M, Hoorstrup SP, Bestmann I, Maly FE, Turina M. Genetic predisposition in patients undergoing cardiopulmonary bypass surgery is associated with an increase of inflammatory cytokines. Eur J Cardiothorac Surg 2001; 20: 609-13.

35. Verghees PB, Castellano JM, Holtzman DM. Apolipoprotein E in Alzheimer’s disease and other neurological disorders. Lancet Neurol 2011; 10: 241-52.

36. Jofre-Monseny L, Minihane AM, Rimbach G. Impact of apoE genotype on oxidative stress, inflammation and disease risk. Mol Nutr Food Res 2008; 52: 131-45.

37. Rontu R, Ojala P, Hervonen A, Goebeler S, Karhunen PJ, Nikkilä M, Kunnas T, Jylhä M, Eklund C, Hurme M, et al. Apolipoprotein E genotype is related to plasma levels of C-reactive protein and lipid and to longevity in nonagenarians. Clin Endocrinol (Oxf) 2006; 64: 265-70.

38. Carlson CS, Aldred SF, Lee PK, Tracy RP, Schwartz SM, Rieder M, Liu K, Williams OD, Irbarren C, Lewis EC, et al. Polymorphisms within the C-reactive protein (CRP) promoter region are associated with plasma CRP levels. Am J Hum Genet 2005; 77: 64-77.