RESEARCH ARTICLE

Serum carcinoembryonic antigen is positively associated with leukocyte count in Korean adults

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Background: Emerging evidence shows that serum carcinoembryonic antigen (CEA) levels may modestly be increased in non-neoplastic conditions such as cardiometabolic diseases, which are increasingly being seen as inflammatory diseases. Leukocyte count is widely evaluated marker of inflammation in clinical practice and a useful predictor of cardiometabolic disease. In this study, we aimed to determine the relationship between serum CEA levels and leukocyte counts in Korean adults.

Methods: This cross-sectional study included a total of 19 834 individuals enrolled from a health promotion center between November 2006 and July 2010. Multiple linear regression analysis was performed to investigate the association between serum CEA levels and leukocyte counts after adjusting for confounding variables.

Results: According to both stepwise-method and enter-method multiple linear regression analyses, serum CEA levels were positively and independently associated with leukocyte counts ($P < .001$) after adjusting for age, sex, body mass index, systolic blood pressure, diastolic blood pressure, total cholesterol, triglyceride, HDL-cholesterol, cigarette smoking, alcohol ingestion, physical activity, diabetes mellitus, and anti-inflammatory drugs.

Conclusions: We demonstrate a positive relationship between serum CEA levels and leukocyte counts in Korean adults. Our results suggested that an elevated serum CEA level may reflect chronic inflammation state.

KEYWORDS

carcinoembryonic antigen, leukocyte count, subclinical inflammation

1 | INTRODUCTION

Carcinoembryonic antigen (CEA) is a highly glycosylated cell surface glycoprotein and a member of the immunoglobulin supergene family of intercellular adhesion molecules.¹ Previous studies support the broad use of CEA as a tumor marker because it is expressed at greatly increased levels in adenocarcinomas, particularly in colorectal cancer and cancers of other organs including the pancreas, lung, prostate, ovary, and breast.^{2–5} In addition, serum CEA levels may be modestly increased in several non-neoplastic conditions such as aging, renal, and hepatic insufficiency, and may also be increased in smokers.^{2,3,6} CEA

elevation has been identified in hypothyroidism and chronic obstructive pulmonary disease,^{7,8} although at levels not exceeding 10 ng/mL.⁶ Furthermore, recent data have suggested that elevated serum CEA levels are associated with carotid atherosclerosis, type 2 diabetes, insulin resistance, and metabolic syndrome, all of which are conditions associated with oxidative stress and chronic low-grade inflammation.^{9–12}

Leukocyte count is a simple, easy to obtain, and economic marker of inflammation in clinical practice.¹³ In addition to serving as a marker of infection and inflammation, leukocyte count has recently become a useful predictor of certain diseases.¹⁴ Higher leukocyte counts, even within a normal range, are associated with cardiovascular disease

(CVD), type 2 diabetes, and metabolic syndrome.^{15–17} Numerous *in vitro* and *in vivo* studies have shown that some CEA-related cell adhesion molecules (CEACAMs) that interact with CEA are expressed on neutrophils and regulate neutrophil activation.¹⁸ Serum CEA is routinely checked at health check-up centers in many countries to detect malignancy. Although slight elevations in CEA are commonly observed in apparently healthy persons, potential associations between CEA and chronic low-grade inflammation have yet to be documented. In addition, no studies to date have examined the relationship between serum CEA and leukocyte count in a large, population-based study.

The present study was grounded in the hypothesis that CEA levels may be associated with elevated leukocyte counts in states of chronic low-grade inflammation.

2 | MATERIALS AND METHODS

2.1 | Study participants

We retrospectively reviewed the medical records of 20 618 participants aged ≥ 20 years old who underwent a medical examination at the Health Promotion Center of Gangnam Severance Hospital in Seoul, Korea between November 2006 and July 2010. The subjects voluntarily visited the health promotion center to regularly check their health condition. Informed consent was obtained from each participant. This study was conducted in accordance with the ethical principles of the Declaration of Helsinki, and was approved by the Institutional Review Board of Yonsei University College of Medicine, Seoul, Korea. Subjects with leukocyte counts < 3000 cells/ μL or $> 10\,000$ cells/ μL or those with CEA levels > 10 $\mu\text{g/L}$ were excluded to rule out possible cases of bone marrow abnormalities, infection, or hidden malignancy. We also excluded participants who met at least one of the following criteria: missing data; a history of cancer; respiratory, renal, hepatobiliary, thyroid or rheumatologic disease; and not fasting for 12 hours prior to testing. A total of 19 834 Korean adults were included in our final analysis after applying the exclusion criteria.

2.2 | Data collection

Body mass and height were measured to the nearest 0.1 kg and 0.1 cm, respectively, in light indoor clothing without shoes. Body mass index (BMI) was calculated as the weight in kilograms divided by the square of the height in meters (kg/m^2). Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured using the patient's right arm with a standard mercury sphygmomanometer (Baumanometer, W.A. Baum Co Inc., Copiague, NY, USA). All blood samples were obtained from the antecubital vein after a 12-h overnight fast. Fasting plasma glucose, total cholesterol, triglycerides, high density lipoprotein (HDL) cholesterol, and high sensitive C-reactive protein (hsCRP) levels were measured by enzymatic methods using a chemistry analyzer (Hitachi 7600-110; Tokyo, Japan). Serum CEA levels were quantified by chemiluminescence immunoassay using a Unicl DXI 800 analyzer (Beckman-Coulter, Chaska, MN, USA). Leukocyte counts were measured as part of an automated blood cell

count with an ADVIA 120 (Bayer, Tarrytown, NY, USA). Each participant completed a questionnaire about his or her lifestyle and medical history. Self-reported cigarette smoking, alcohol consumption, and physical activity were determined from the questionnaires. Cigarette smoker was defined as who currently smoke. Alcohol drinking was defined as consumption of more than 20 g of alcohol more than once per week. Physical activity was defined as exercise more than once per week. Diabetes mellitus was diagnosed as having fasting plasma glucose ≥ 126 mg/dL or being currently medicated for diabetes. History of taking anti-inflammatory drugs was defined as taking non-steroidal anti-inflammatory drugs, including aspirin.

2.3 | Statistical analysis

Baseline clinical characteristics were presented as the mean and standard deviation (SD) for continuous variables, and numbers and percentages for categorical variables.

To assess the association between leukocyte counts and continuous variables (age, BMI, SBP, DBP, hs-CRP, fasting plasma glucose, total cholesterol, triglyceride, HDL-cholesterol, and CEA), Pearson's

TABLE 1 Characteristics of the study population^a

Total numbers	19 834
Age (years)	46.0 $\pm$ 11.1
Male, N(%)	10 394 (52.4)
Body mass index (kg/m^2)	23.4 $\pm$ 3.1
Systolic blood pressure (mm Hg)	122.5 $\pm$ 15.6
Diastolic blood pressure (mm Hg)	76.3 $\pm$ 10.2
Fasting plasma glucose (mmol/L)	5.2 $\pm$ 1.0
Total cholesterol (mmol/L)	4.9 $\pm$ 0.9
Triglyceride (mmol/L)	1.4 $\pm$ 1.0
HDL cholesterol (mmol/L)	1.4 $\pm$ 0.3
Hs CRP (mg/dL)	1.4 $\pm$ 3.3
Leukocyte count (cells/ μL)	6030 $\pm$ 143.5
CEA ($\mu\text{g/L}$)	1.8 $\pm$ 1.1
Current smoking ^b , N (%)	
Yes	4440 (22.4)
No	14 295 (77.6)
Alcohol ingestion ^c , N (%)	8000 (40.3)
Physical activity ^d , N (%)	11 217 (56.6)
Diabetes mellitus ^e , N (%)	1036 (5.2)
Anti-inflammatory drug ^f , N (%)	461 (2.3)

HDL, high density lipoprotein; CEA, carcinoembryonic antigen; hsCRP, high sensitive C-reactive protein.

^aData are expressed as the mean $\pm$ standard deviation (SD) or number (percentage).

^bCurrent smoker is defined as who currently smoke.

^cAlcohol drinking ≥ 20 g/week.

^dRegular exercise $\geq$ once a week.

^eDiabetes mellitus was diagnosed as having fasting plasma glucose ≥ 126 mg/dL or currently medication for diabetes.

^fAnti-inflammatory drug included non-steroidal anti-inflammatory drugs including aspirin.

simple and partial correlation analysis was conducted after adjusting for age, sex, and BMI. For categorical variables (sex, cigarette smoking, alcohol ingestion, physical activity, diabetes mellitus and anti-inflammatory drugs), the mean values (SD) of leukocytes and mean values (SE) leukocytes adjusting for age, sex, and BMI were calculated and compared using independent *t*-test and analysis of covariance (ANCOVA), respectively.

Participants were categorized into tertiles based on serum CEA levels as follows: $T1 \leq 1.1$; $1.1 < T2 \leq 1.9$; $1.9 < T3 \leq 10$ $\mu\text{g/L}$. ANCOVA and Bonferroni post-hoc test was used to compare leukocyte counts

among the three serum CEA groups after adjusting for age, sex, BMI, SBP, total cholesterol, triglyceride, HDL-cholesterol, cigarette smoking, physical activity, and diabetes mellitus. Stepwise-method multiple linear regression analyses were used to evaluate the independent association between serum CEA level and leukocyte counts after adjusting for age, sex, BMI, SBP, DBP, total cholesterol, triglyceride, HDL-cholesterol, cigarette smoking, alcohol ingestion, physical activity, diabetes mellitus, and anti-inflammatory drugs. After performing these analyses, age, sex, BMI, SBP, total cholesterol, triglyceride, HDL-cholesterol, cigarette smoking, physical activity, and diabetes mellitus

TABLE 2 Correlation coefficients (*r*) and mean leukocyte values $\pm$ SD or SE between leukocyte counts and various variables

	Unadjusted		Adjusted	
	<i>r</i>	<i>P</i> -value [*]	<i>r</i>	<i>P</i> -value ^{**}
Age (years)	-.012	.086	-	
Body mass index (kg/m ²)	.239	<.001	-	
Systolic blood pressure (mm Hg)	.189	<.001	.096	<.001
Diastolic blood pressure (mm Hg)	.181	<.001	.084	<.001
Fasting plasma glucose (mmol/L)	.128	<.001	.082	<.001
Hs-CRP (mg/dL)	.156	<.001	.129	<.001
Total cholesterol (mmol/L)	.086	<.001	.061	<.001
Triglyceride (mmol/L)	.261	<.001	.177	<.001
HDL cholesterol (mmol/L)	-.227	<.001	-.127	<.001
CEA ($\mu\text{g/L}$)	.150	<.001	.107	<.001
	Mean $\pm$ SD	<i>P</i> -value ^{***}	Mean $\pm$ SE	<i>P</i> -value ^{****}
Sex ^a				
Male	5690 $\pm$ 137.9	<.001	-	
Female	6330 $\pm$ 141.6		-	
Cigarette smoking ^a				
Yes	6770 $\pm$ 146.2	<.001	6647 $\pm$ 2.2	<.001
No	5800 $\pm$ 134.6		5841 $\pm$ 1.1	
Alcohol ingestion ^a				
Yes	6190 $\pm$ 143.6	<.001	6038 $\pm$ 1.7	.422
No	5860 $\pm$ 141.7		6017 $\pm$ 1.7	
Physical activity ^a				
Yes	5970 $\pm$ 141.2	<.001	5929 $\pm$ 1.3	<.001
No	6110 $\pm$ 146.0		6477 $\pm$ 1.6	
Diabetes mellitus ^a				
Yes	6520 $\pm$ 146.7	<.001	6381 $\pm$ 4.3	<.001
No	6000 $\pm$ 142.9		6007 $\pm$ 1.0	
Anti-inflammatory drug ^a				
Yes	6100 $\pm$ 142.2	.296	6109 $\pm$ 6.4	.196
No	6020 $\pm$ 143.6		6025 $\pm$ 1.0	

HDL, high density lipoprotein; CEA, carcinoembryonic antigen; hsCRP, high sensitive C-reactive protein.

^aSex, cigarette smoking, alcohol ingestion, physical activity, diabetes mellitus and anti-inflammatory drug use are categorical variables.

*Coefficients (*r*) and *P* values were calculated using Pearson's simple correlation analysis for continuous variables.

**r and *P*-values were calculated by Pearson's partial correlation adjusting for age, sex, and body mass index.

***Mean $\pm$ standard deviation (SD) of leukocytes and *P* values were calculated using independent *t* test for categorical variables.

****Mean $\pm$ standard errors (SE) leukocytes and *P*-values were calculated by analysis of covariance adjusting for age, sex, and body mass index.

FIGURE 1 Leukocyte counts according to serum CEA tertiles. CEA: carcinoembryonic antigen. T1; CEA ≤ 1.1, T2: 1.1 < CEA ≤ 1.9, T3: 1.9 < CEA ≤ 10. Mean and standard error (indicated with error bars). * $P < .001$; calculated by Bonferroni post-hoc test. ^a P -values were calculated using analysis of covariance (ANCOVA) after adjusting for age and sex. ^b P -value were calculated using analysis of covariance (ANCOVA) after age, sex, BMI, SBP, total cholesterol, triglyceride, HDL-cholesterol, cigarette smoking, physical activity and diabetes mellitus

were included in the stepwise-method multiple linear regressions. In addition, we used enter-method multiple linear regression analyses to determine the association between serum CEA levels and leukocyte counts after adjusting for the same confounding factors. To examine the goodness of model fit in multiple regression analysis model of CEA, we compared the R^2 value (17.4%) in the full model (including CEA in step-method analysis) with the R^2 value (17.1%) in the null model (excluding CEA in step-method analysis) using F -statistic. In addition, we conducted path analysis to investigate the mediation effect of the variables (SBP, DBP, fasting glucose, triglyceride, HDL-cholesterol, CRP, and number of metabolic syndrome components) on leukocytes using the R statistical package (version 3.1.3, Institute for Statistics and Mathematics, Vienna, Austria, www.R-project.org) (Appendix 1). The level of statistical significance for all analyses was set as $P < .05$. Statistical analyses were performed using SPSS version 23.0 statistical software (SPSS version 23.0; IBM Corp., Armonk, NY, USA).

3 | RESULTS

The demographic and clinical characteristics of the study population of 19 834 subjects (10 394 men and 9440 women) are presented in Table 1. The mean patient age was 46.0 ± 11.1 years. The mean $\pm$ SD of CEA levels was 1.8 ± 1.1 μ g/L. The proportion of men in the study was 52.4%, and the mean BMI value was 23.4 ± 3.1 kg/m^2 . Correlation analysis identified significantly positive relationships between serum CEA and leukocyte counts both in unadjusted and adjusted models ($r = .150$; $P < .001$ and $r = .107$; $P < .001$) (Table 2). Leukocyte counts were also significantly correlated with BMI, SBP, DBP, hs CRP, fasting plasma glucose, total cholesterol, triglyceride, and HDL-cholesterol. Leukocyte counts were significantly higher in subjects who currently

smoked, did not exercise, and had diabetes mellitus after adjusting for age, sex, and BMI. After adjusting for confounding factors, the higher tertile serum CEA group had significantly higher leukocyte counts (Figure 1). Independent association of serum CEA levels with leukocyte count was assessed using multivariable adjusted models generated from stepwise-method multiple linear regression analyses (Table 3). Serum CEA was identified as a significant independent variable associated with leukocyte count ($\beta = 0.131$; $P < .001$). In addition, the significant association between serum CEA level with leukocyte count persisted in the enter-method multiple linear regression analysis after adjusting for age, sex, BMI, SBP, DBP, total cholesterol, triglyceride, HDL-cholesterol, current smoking, alcohol ingestion, physical activity, diabetes mellitus, and anti-inflammatory drug (Table 3). The R^2 value of the full model was significantly higher than the R^2 value in the null model (17.4% vs 17.1%, $P < .001$). In path analysis, serum CEA was shown to exert direct and indirect effects on leukocyte counts upon consideration of the mediation effects of the following variables: SBP, DBP, fasting glucose, TG, HDL-C, CRP, and number of metabolic syndrome components (Appendix 1).

4 | DISCUSSION

In the present study, we confirmed that serum CEA levels were associated with leukocyte counts in a large population-based cross-sectional study. Serum CEA levels were independently and positively related with leukocyte counts after adjusting for age, sex, BMI, SBP, total cholesterol, triglyceride, HDL-cholesterol, current smoking, alcohol ingestion, physical activity, and diabetes mellitus. Although the R^2 value of the regression analysis was relatively low, the R^2 value of the full model (adjusting for all variables including CEA) was significantly

higher than the R^2 value of the null model (adjusting for all variables excluding CEA).

Our results support the possibility that serum CEA levels are closely related with subclinical low-grade inflammation. In addition, we believe that our findings may suggest a possible mechanism regarding the association between serum CEA levels and cardiometabolic diseases. Specifically, although elevated serum CEA levels have long been regarded as a marker of several neoplastic conditions, they may also be modestly elevated in several non-neoplastic conditions.⁶⁻⁸ Of these, aging and cigarette smoking appear to be major determinants of elevated CEA levels. Tuitou et al.² reported that elderly subjects in apparent good health have elevated CEA levels, while Fukuda et al.³ showed that serum CEA levels are higher in male smokers (3.11 ng/mL) than in male non-smokers (2.14 ng/mL). More recent evidence indicates that elevated serum CEA levels are also related to metabolic syndrome, non-alcoholic fatty liver disease, atherosclerosis, and arterial stiffness, which are conditions closely linked to chronic low-grade inflammation. Lee et al.¹⁰ reported that serum CEA is positively associated with metabolic syndrome in female Korean non-smokers. From the same cohort of 200 healthy Korean adults, CEA was shown to be positively associated with non-alcoholic fatty liver disease.¹⁹ Likewise, Esteghamati et al.²⁰ showed that metabolic syndrome and type 2 diabetes are more prevalent in subjects with high CEA levels. In 4181 Japanese men aged 21-89 years, serum CEA was

independently associated with carotid atherosclerosis.⁹ In addition, Bae et al.²¹ reported that CEA levels are related to arterial stiffness as measured by brachial-ankle pulse wave velocity in healthy Korean adults. Although the underlying biological mechanisms that explain the relationship between serum CEA levels and leukocyte counts are uncertain, there are several lines of evidence to suggest that CEA has the ability to evoke an inflammatory response through direct or indirect pathways. First, Bessa et al.²² reported a potential effect of CEA on leukocyte recruitment by immunoblockade using a polyclonal rabbit antibody. Specifically, serum CEA activates monocytes and hepatic macrophages by binding to the CEA receptor, which results in the production of potent inflammatory mediators such as tumor necrosis factor (TNF)- α , interleukin (IL)-1 β and IL-6. These cascades, in turn, upregulate the cell surface expression of adhesion molecules such as ICAM-1 and E-selectin.^{23,24} These pro-inflammatory cytokines and adhesion molecules mediated by serum CEA may facilitate the proliferation, recruitment, and activation of circulating leukocytes, leading to increased leukocyte counts. Second, CEA, a member of the immunoglobulin superfamily of cell adhesion molecules (IgCAM), has homotypic and heterotypic interactions with CEACAMs,^{18,25} which in turn regulate neutrophil activation and increase neutrophil adhesion to endothelial cells.^{26,27} We have also noted significant mediation effects on CEA for some variables associated with metabolic syndrome and CVD (Appendix 1). The pathophysiologic and clinical significance

TABLE 3 Results of multiple linear regression analysis to assess independent relationships between leukocyte count and CEA and other clinical variables

Variables	Stepwise-method ^a			Enter-method ^b		
	β	SE	P-value [*]	β	SE	P-value ^{**}
CEA(μ g/L)	0.131	0.010	<.001	0.130	0.010	<.001
Age (years)	-0.012	0.001	<.001	-0.012	0.001	<.001
Sex	-0.199	0.028	<.001	-0.192	0.030	.050
Body mass index (kg/m ²)	0.045	0.004	<.001	0.045	0.004	<.001
Systolic BP (mm Hg)	0.008	0.001	<.001	0.007	0.001	<.001
Diastolic BP (mm Hg)	-			0.001	0.002	.555
Total cholesterol (mmol/L)	0.065	0.014	<.001	0.064	0.014	<.001
Triglyceride (mmol/L)	0.168	0.013	<.001	0.167	0.013	<.001
HDL cholesterol (mmol/L)	-0.493	0.041	<.001	-0.496	0.041	<.001
Current smoking	0.031	0.012	.009	0.030	0.012	.012
Alcohol ingestion	-			0.014	0.025	.593
Physical activity	-0.186	0.023	<.001	-0.187	0.023	<.001
Diabetes mellitus	0.229	0.049	<.001	0.230	0.049	<.001
Anti-inflammatory drug	-			0.056	0.069	.417

CEA, carcinoembryonic antigen; BP, Blood pressure; HDL, High density lipoprotein; hsCRP, high sensitive C-reactive protein.

^{*}P-values are calculated by stepwise-method multiple linear regression analyses.

^{**}P-values are calculated by enter-method multiple linear regression analyses.

^aModel variables included age, sex, BMI, systolic blood pressure, total cholesterol, triglyceride, HDL-cholesterol, cigarette smoking, physical activity, and diabetes mellitus.

^bModel variables included age, sex, BMI, systolic blood pressure, diastolic blood pressure, triglyceride, total cholesterol, HDL-cholesterol, current smoking, alcohol ingestion, physical activity, diabetes mellitus, and anti-inflammatory drug.

Full adjusted R^2 (including CEA in step-method analysis)=.174 and null adjusted R^2 (excluding CEA in step-method analysis)=.171, $P < .001$. Nested R^2 comparison was conducted using F -statics.

of these findings, however, requires further study. This association suggests that other mechanisms, at least in part, independent of inflammation may be at play. Some previous studies have shown that serum CEA was associated with increased insulin resistance²⁸ and metabolic syndrome,²⁹ which are closely associated with an increased risk of CVD. Insulin promotes the growth and transition of normal and malignant cells through insulin like growth factor (IGF-1),³⁰ and one study has demonstrated that antisense IGF-1 modulated the expression of CEA in human cells.³¹

Our study has some limitations. First, because of the nature of this cross-sectional study, we were unable to establish a causal relationship between CEA levels and leukocyte counts. Second, only one measurement of leukocyte levels was performed, making it difficult to determine whether the increased leukocyte count was reflective of acute inflammation or chronic inflammation. To reduce these errors, we excluded subjects with leukocyte counts <3000 cells/ μ L or >10 000 cells/ μ L. Third, because the study subjects were volunteers who received their physical examinations in a single hospital and appeared to be slightly healthier than most community-based cohorts, the study population may not represent the general population of Korea. Therefore, the study may have been affected by selection bias.

Despite this weakness, this is the first study to identify a positive association between CEA and leukocyte counts. We can consider the non-malignant condition related to chronic inflammation in interpreting modestly increased serum CEA level.

5 | CONCLUSIONS

We identified a significant association between serum CEA and leukocyte count in the general Korean population. Our findings suggest that serum CEA may be a meaningful marker of chronic low-grade inflammation in clinical practice. Our results also indicate that slightly elevated levels of serum CEA may be not an epiphenomenon.

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APPENDIX 1

	Estimate	CI(lower)	CI(upper)	P-value
Outcome: leukocyte counts				
Model with mediator (CRP)				
CEA → CRP (a)	0.068	0.027	0.108	.001
CRP → leukocyte counts (b)	0.069	0.063	0.075	<.001
CEA → leukocyte counts (c)	0.171	0.153	0.188	<.001
Indirect effect	0.005	0.002	0.008	.004
Direct effect	0.171	0.153	0.192	<.001
Total Effect	0.175	0.157	0.195	<.001
Prop.Mediated	0.027	0.010	0.048	.004
Model with mediator (SBP)				
CEA → SBP (a)	1.686	1.500	1.874	<.001
SBP → leukocyte counts (b)	0.016	0.014	0.017	<.001
CEA → leukocyte counts (c)	0.149	0.131	0.166	<.001
Indirect effect	0.026	0.023	0.030	<.001
Direct effect	0.149	0.132	0.169	<.001
Total Effect	0.175	0.158	0.194	<.001
Prop.Mediated	0.150	0.126	0.179	<.001
Model with mediator (DBP)				
CEA → DBP (a)	1.138	1.016	1.259	<.001
DBP → leukocyte counts (b)	0.023	0.021	0.025	<.001
CEA → leukocyte counts (c')	0.150	0.132	0.167	<.001
Indirect effect	0.026	0.022	0.029	<.001
Direct effect	0.150	0.131	0.168	<.001
Total Effect	0.175	0.156	0.193	<.001
Prop.Mediated	0.146	0.124	0.173	<.001
Model with mediator (Fasting glucose)				
CEA → glucose (a)	0.162	0.150	0.175	<.001
glucose → leukocyte counts (b)	0.139	0.120	0.159	<.001
CEA → leukocyte counts (c')	0.153	0.135	0.170	<.001
Indirect effect	0.023	0.019	0.027	<.001
Direct effect	0.153	0.134	0.171	<.001
Total Effect	0.175	0.156	0.194	<.001

(Continues)

APPENDIX 1 (Continued)

	Estimate	CI(lower)	CI(upper)	P-value
Prop.Mediated	0.129	0.105	0.155	<.001
Model with mediator (Triglyceride)				
CEA → Triglyceride (a)	0.099	0.087	0.111	<.001
Triglyceride → leukocyte counts (b)	0.341	0.322	0.361	<.001
CEA → leukocyte counts (c')	0.141	0.124	0.159	<.001
Indirect effect	0.034	0.028	0.041	<.001
Direct effect	0.141	0.122	0.160	<.001
Total Effect	0.175	0.156	0.194	<.001
Prop.Mediated	0.193	0.158	0.240	<.001
Model with mediator (HDL_cholesterol)				
CEA → HDL-C (a)	-0.014	-0.018	-0.010	<.001
HDL → leukocyte counts (b)	-0.962	-1.023	-0.900	<.001
CEA → leukocyte counts (c')	0.162	0.145	0.179	<.001
Indirect effect	0.013	0.009	0.018	<.001
Direct effect	0.162	0.146	0.180	<.001
Total Effect	0.175	0.158	0.194	<.001
Prop.Mediated	0.075	0.054	0.098	<.001
Model with mediator (MetS components)				
CEA → MetS components (a)	0.122	0.109	0.135	<.001
MetS components → leukocyte counts (b)	0.315	0.296	0.334	<.001
CEA → leukocyte counts (c')	0.137	0.120	0.154	<.001
Indirect effect	0.038	0.034	0.043	<.001
Direct effect	0.137	0.119	0.154	<.001
Total Effect	0.175	0.156	0.193	<.001
Prop.Mediated	0.219	0.190	0.255	<.001