보건학석사 학위논문

Identifying Genetic and Environmental influences on C-reactive Protein and Its correlation with Metabolic Syndrome: The Healthy Twin Study

C-반응성 단백질의 대사증후군 관련성 및 농도에 영향을 미치는 유전요인과 환경요인 분석

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서울대학교 보건대학원

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ABSTRACT

Recently, studies have reported that many chronic complex diseases are closely related to other diseases. For instance, Type 2 Diabetes, Metabolic Syndrome, and Cardiovascular diseases share causes and symptoms in a large proportion. Moreover C-reactive protein(CRP) has also been reported as an associated factor for various kinds of such chronic diseases. Originally, CRP was known as an acute phase inflammation marker. However, after a highly sensitive measurement has been developed, base-line serum CRP concentration has been used as a risk marker when predicting future Cardiovascular diseases. This study aims to confirm the association between CRP concentration and Metabolic Syndrome related characteristics and to identify genetic and environmental contributions to the CRP level.

A total of 2,890 individuals participated in the current study. This number included 640 families, 430 Monozygotic(MZ) Twins, and 97 Dizygotic(DZ) Twins in order to figure out the genetic and environmental contributions to the CRP concentration. To examine the strong association between CRP concentration and Metabolic Syndrome(MetS), different distributions of CRP concentration according to the 5 diagnostic criteria suggested by NCEP and correlations between CRP concentration and MetS related factors were examined. To quantify the life style effect on the CRP concentration, regression and logistic regression analyses using mixed model were conducted. By using variance component model, Intraclass

correlation coefficients and heritability were estimated.

The results showed a strong association between the CRP concentration and MetS related factors, as expected. Also, abdominal obesity was found to be the most relevant index for predicting the CRP concentration among other obesity indices. Along with abdominal obesity, income level showed a close relationship with CRP concentration. The result of Intraclass correlation coeffecients (ICC) and heritability estimates suggest a large proportion of genetic contributions as well as shared environmental contributions to the CRP. Accordingly, obesity, especially abdominal obesity should be given more attention to prevent CRP elevation and other CRP related diseases. When the exact genes regulating CRP concentration are found, it might be possible to apply it to an intervention strategy considering genetic information.

Keywords *: C-reactive protein, Metabolic Syndrome, Heritability, Twin-Family Analysis*

Student ID *: 2010-22085*

CONTENTS

List of Tables

List of Figures

List of Abbreviations

CRP : C-reactive Protein

hsCRP : High sensitivity C-reactive Protein

MetS : Metabolic Syndrome

MZT : Monozygotic Twins

DZT : Dizygotic Twins

ICC : Intraclass correlation coefficient

I. INTRODUCTION

1. Background

C-reactive protein, a typical acute phase inflammation marker, is one of calcium-dependent ligand-binding plasma proteins, and consists of 5 identical polypeptide subunits.[1,2] CRP is mainly originates from the liver and participates in nonspecific immune response against infection.[1,3] In systemic lupus patients, the CRP response does not work properly, which suggests the role of CRP response involved in inborn immunity.[1] It was reported that IL-1, IL-6 and TNF-α regulate CRP concentration. [3-5] Since IL-1, IL-6 and TNF-α are produced from adipocytes, CRP concentration showed a strong association with obesity status in many previous studies. [6-10] When inflammation stimulation such as tissue damaging or infection has occurred, plasma CRP concentration increases rapidly. [11,12] However, after the acute-phase inflammation process, CRP concentration decreases shortly after and base-line CRP concentration is sustained. [1] Since CRP is produced nonspecifically in response to the acute-phase inflammation, infection, and tissue damage, it does not have much information that is clinically significant. On the other hand, increasing sensitivity in detecting base-line C-reactive protein concentration (high sensitivity C-reactive protein, hsCRP) makes CRP useful for cardiovascular disease prediction.[1] Base-line plasma CRP is maintained at diffenrent levels of concentration for different individuals. The factors influencing base-line CRP

concentration have been reported in many previous studies. [6,13-17]

The American Heart Association (AHA) and Centers for Disease Control and Prevention (CDC) analyzed the association between several inflammation markers and cardiovascular disease. As a result, AHA and CDC revealed that base-line high sensitivity C-reactive protein (hsCRP) could be a reliable cardiovascular risk predictor.[18]

Additionally, low grade inflammation is associated with Metabolic Syndrome (MetS) related factors such as waist circumference, triglyceride, HDL cholesterol, fasting plasma glucose, and blood pressure. A strong association between BMI and low grade inflammation (base-line CRP concentration) has been reported. [13,14,19] Furthermore the risk of Type 2 Diabetes and insulin resistance could be predicted by CRP level. [6,20] Some studies have identified the association between CRP level and bone mineral density. [3] For a healthy adult, several studies have agreed on the finding that the median concentration of serum CRP is below 1.0 mg/L.[21,22] The serum CRP concentration could be classified into three levels of cardio vascular disease-related risk groups according to Pearson T. A et al.[18] A serum CRP level of <1.0 mg/L, 1.0-3.0 mg/L, and >3.0 mg/L are considered as low level, intermediate level, and high level group, respectively. [18] It is still unknown whether CRP concentration itself has more importance in regards to health outcome than the class of risk level.

Several environmental factors have been suggested as the causes of serum CRP level elevation. Such environmental factors are obesity, physical activity, smoking status, alcohol consumption, nutrition, socioeconomic status, and etc. Physical activity, smoking status, and alcohol consumption have been reported as environmental factors that affect base-line CRP concentration. [13,15,16] The factors affecting serum CRP level have not been determined, yet. Also, CRP concentration rises with aging,[3,23] and females are exposed to more risk than males according to many reports.[23,24] Koenig et al reported shorter amount of education period to be related to higher levels of CRP concentration. [25] However, in another study there was no statistically significant correlation between education period or income level and CRP concentration.[13] Even though there were several studies that revealed the association between smoking and CRP, the effect of smoking is not fully understood yet, and the results are conflicting. [25-27] Some studies have reported higher levels of CRP concentration for current smokers. [25] However, other studies have shown no significant effect of current smoking on CRP concentration. Instead, it suggested an association between lifetime smoking exposure and CRP elevation. [27]

The existence of genetic influence on CRP concentration was reported in several studies. [20,28-30] Some studies have found CRP level to have hereditary characteristic and showed familial aggregation. [31-34] Some studies have identified genetic information affecting CRP concentration by using genotype

data. [28,30] Some twin studies have presented a significant genetic effect on base-line CRP level, independent of obesity status.[1] On the contrary, other studies have identified the effect of obesity status on CRP level, independent of genetic information.[35]

2. Aims

The current study aims to confirm the association between serum CRP level and other MetS related physiological traits and to identify factors, especially environmental factors and genetic factors, that affect base-line CRP level, and to quantify the effect size of those in general Korean population.

The results of the present would be useful for developing effective intervention, considering personal genetic information, of CRP elevation, and preventing Cardiovascular diseases, and MetS.

II. METHODS

1. Study Population

The Healthy Twin Study, an extended twin and family study of the Korean Twin-Family Register (KTR[36]), is an ongoing prospective and multi-center community-based twin family cohort study that started since 2005. Among the Healthy Twin Study population, 2890 individuals (1165 males and 1725 females) who had serum C-reactive protein concentration data were included in the current study. The study subjects consisted of 640 families including 430 monozygotic twin pairs and 97 dizygotic twin pairs.

2. Data collection

Each of the study participants answered a questionnaire consisting of demographics, past medical history, medications, smoking, drinking habits, physical activity and etc. Height (cm), weight (kg), waist circumference (WC, cm), hip circumference (HC, cm), blood pressure (mmHg) and other physical examinations that were measured using a standardized scale and a stadiometer. BMI (kg/m^2) were obtained from by dividing the weight by squared height. Waist-to-hip ratio (WHR) was derived by dividing the waist circumference by hip circumference. The blood sample of the subjects were attained to test the level of total cholesterol (TC), high density lipoprotein (HDL) cholesterol, low density lipoprotein (LDL) cholesterol, triglyceride (TG), fasting blood sugar (FBS) and high sensitivity C reactive protein (CRP).[37]

3. Statistical Analysis

The summary of demographic data was obtained using SAS 9.3 and presented as mean (SD) for continuous variables and N (%) for categorical variables.

Because generally the distribution of C-reactive protein is skewed to the right and its kurtosis is very high (Fig. 1), performing a natural log transformation would be recommended when used as a continuous variable (Fig. 2), [18,22] or when serum CRP leve isl used in analysis as categorical variables. As mentioned above, serum CRP level can be categorized into 3 classes according to the risk level for cardiovascular diseases -low, intermediate, and high level. When trying to observe the impact of various factors on the risk level, instead of using the concentration itself, the three CRP levels are used as categorical variables. CRP concentration of >10mg/L were excluded from the data, because CRP level above 10mg/L implicate that someone is undergoing an acute phase of inflammation or infection that is not suitable for a study that is trying to identify the impact of base-line CRP concentration.

In order to confirm the association between CRP level and MetS related physiological features, the mean value with standard deviation and the median value with inter-quantile range of serum CRP concentration were compared according to the MetS diagnostic criteria suggested by National Cholesterol Education Program (NCEP).[38] Although there are no definite and only criteria,

the criteria NCEP has suggested are being generally accepted. NCEP suggested 5 criteria related to MetS, and those criteria are as follows: 1) Waist circumference (≥ 90cm for Asian male and ≥ 80cm for Asian female), 2) Triglyceride (≥ 150mg/dL), 3) HDL Cholesterol (≤40 mg/dL for male and ≤ 50mg/dL for female) 4) Blood pressure (≥130mmHg of SBP or ≥85mmHg of DBP), 5) Fasting blood sugar (≥ 100mg/dL, some suggest ≥ 110mg/dL). Those who meet 3 of these criteria would be classified as MetS.[38]

The Spearman correlation coefficients between log-transformed CRP concentration and associated variables were calculated to determine the relationship between CRP level and various obesity indices and MetS related physiological features.

In order to quantify the impact of environmental factors, such as obesity status, regular exercise, smoking status, drinking habit, education level, and income level, regression analyses were performed. When identifying the impact on the serum CRP concentration itself, it was analyzed as a continuous variable in log-transformed value. Familial aggregation was adjusted by using a mixed model in SAS 9.3, and other environmental factors were implemented as independent variables of fixed effect. When being focused on the impact of environmental factors on the class of CRP level (low, intermediate and high), serum CRP level was implemented as a binary variable (low vs. intermediate/high) in generalized linear mixed model in SAS 9.3. Family structure was also adjusted as a random effect, and other independent variables

have remained the same.

Intraclass correlation coefficients according to each relative type such as MZ twins, DZ twins, siblings, and spouse were estimated to detect genetic relevance in serum CRP level. MZ twins share 100% of genetic information with their co-twins, and DZ twins and siblings share 50% of genetic information within their group. Spouse group share none of one's genetic information within groups. Accordingly, differences in ICC according to relative types strongly suggest that there is genetic contribution to the serum CRP level. ICC is defined as proportion of variance explained by within-class variance among total variance. The theoretical formula for the ICC is :

$$\text{ICC} = \frac{\sigma_w^2}{\sigma_b^2 + \sigma_w^2}$$

where σ_w^2 is the within-class variance, and σ_b^2 is the between-class variance. ICC were calculated by using SAS 9.3 mixed procedure.

Another way to identify genetic contribution to the serum CRP level was heritability estimates using family structure. Heritability is defined as the proportion of phenotypic variance explained by additive genetic components. AE model, most fundamental model, assumes that the total phenotypic variance (V_P) is explained by additive genetic effects (V_A) and environmental effects (V_E). In ACE model, environmental effects (V_E) are divided into common environment (V_C) shared by familial relationship and random individual

environment (V_R). Accordingly, heritability can be formulated as follows:

$$h^2 = \frac{V_A}{V_P}$$

Also, c^2 in ACE model can be formulated as follows:

$$c^2 = \frac{V_C}{V_P}$$

The heritability estimation was conducted using variance component method by Sequential Oligogenic Linkage Analysis Routines (SOLAR) software version 6.6.2. All analyses that needed continuous outcome were conducted using log-transformed CRP concentration.

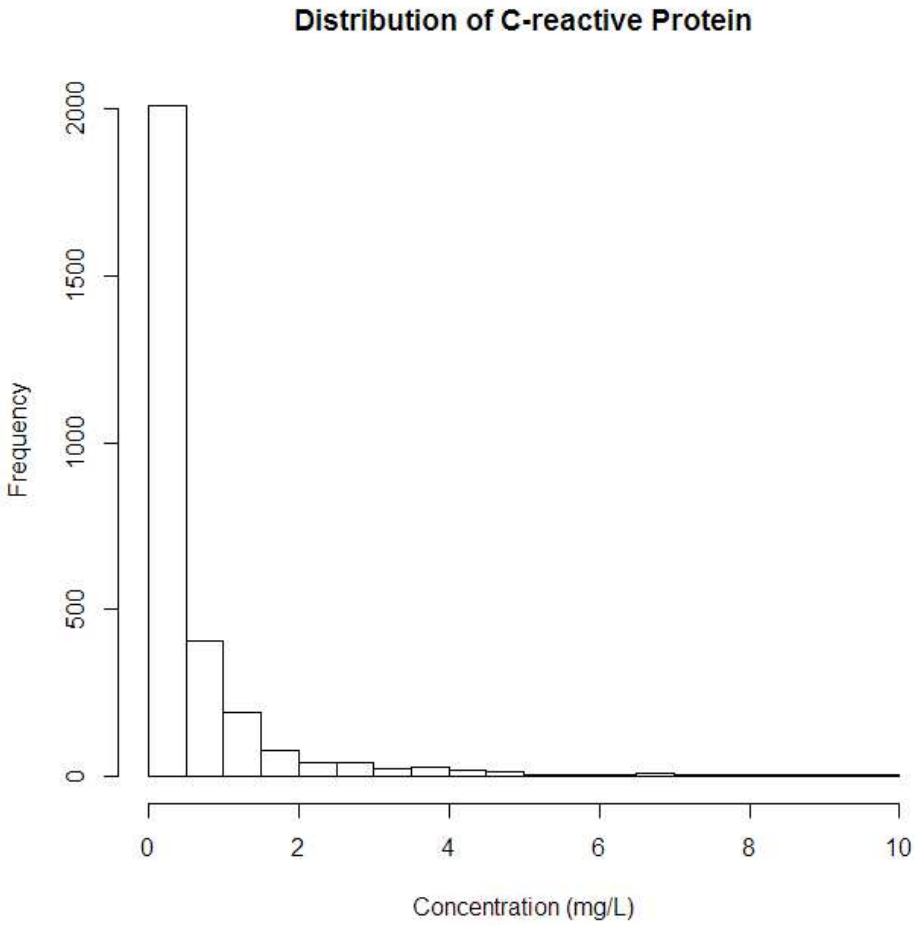


Fig 1. Distribution of CRP concentration

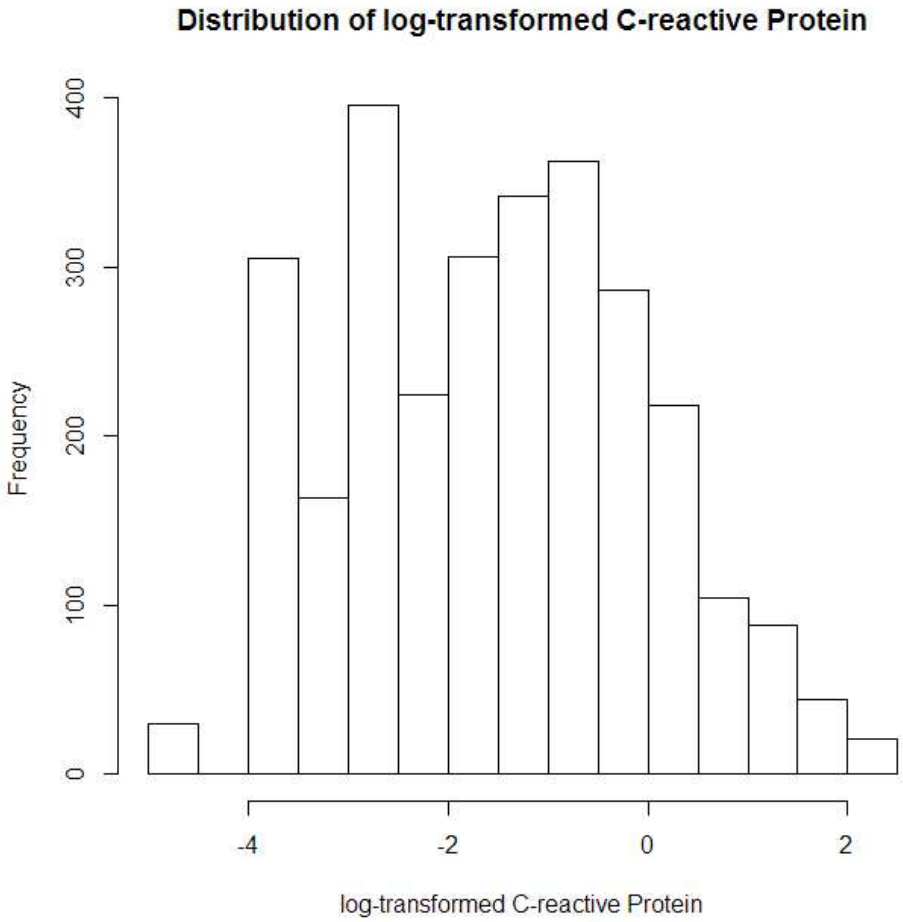


Fig 2. Distribution of log-transformed CRP concentration

III. RESULTS

1. Demographics

The summary statistics of study population are shown in Table 1. The male mean age was 44.57 years and the female mean age was 43.23 years. Serum CRP concentration was significantly higher for male. Most of the physiological characteristics hde significant differences between male and female.

Features of all the variables by 3 groups of CRP level are shown in Table 2. Low level group ($\leq$1mg/dL) showed lower obesity indices, FBS, total cholesterol, LDL cholesterol (higher HDL cholesterol), triglyceride, SBP, and DBP in comparison with intermediate and high level groups. In regards to life style factors, however, no significant difference has been shown except for the income level.

Table 1. Characteristics of the Study population

	Male	Female	P value
N (%)	1165 (40.31)	1725 (59.69)	
Age (yr)	44.57 (13.69)	43.23 (12.63)	0.0076
CRP (mg/L)	0.72 (1.28)	0.58 (1.13)	0.0022
Twin status, *N (%)*			0.0205
MZ	314 (36.51)	546 (63.49)	
DZ	86 (44.10)	109 (55.90)	
Singleton	765 (41.69)	1070 (58.31)	
Obesity-related feature (SD) †			
Weight (kg)	70.87 (10.69)	56.92 (8.56)	<.0001
WC (cm)	85.25 (8.10)	77.67 (9.03)	<.0001
HC (cm)	96.41 (5.88)	93.55 (5.75)	<.0001
BMI (kg/m^2)	24.55 (3.05)	23.09 (3.32)	<.0001
WHR	0.88 (0.06)	0.83 (0.07)	<.0001
MetS related characteristics (SD) ‡			
FBS (mg/dL)	97.07 (20.67)	90.68 (16.81)	<.0001
tCholesterol (mg/dL)	191.11 (35.90)	187.99 (35.64)	0.0215
HDL (mg/dL)	46.69 (11.59)	52.66 (12.83)	<.0001
LDL (mg/dL)	113.82 (31.92)	108.73 (30.88)	<.0001
TG (mg/dL)	142.17 (107.16)	98.81 (64.42)	<.0001
SBP (mmHg)	121.09 (15.89)	113.43 (16.47)	<.0001
DBP (mmHg)	76.50 (10.86)	71.69 (10.44)	<.0001
Life Style, *N (%)*			
Regular Exercise			<.0001
No	695 (37.09)	1179 (62.91)	
Yes	470 (46.26)	546 (53.74)	

Smoking Status			<.0001
Never-smoker	320 (16.99)	1564 (83.01)	
Ever-smoker	845 (84.00)	161 (16.00)	
Drinking Habit¶			<.0001
Moderate	844 (34.25)	1620 (65.75)	
Heavy	321 (75.35)	105 (24.65)	
Education level			<.0001
≤ High School	619 (36.98)	1055 (63.02)	
> High School	546 (44.90)	670 (55.10)	
Income level			0.1324
≤ 1.5 million won	865 (39.53)	1323 (60.47)	
> 1.5 million won	300 (42.74)	402 (57.26)	

† WC, Waist circumference; HC, Hip circumference; BMI, Body mass index; WHR, Waist-to-Hip Ratio

‡ FBS, Fasting blood sugar; tCholesterol, Total Cholesterol; HDL, High density lipoprotein Cholesterol; LDL, Low density lipoprotein Cholesterol; TG, Triglyceride; SBP, Systolic blood pressure; DBP, Diastolic blood pressure

¶Moderate drinking defined as < 24 g/day for male and < 15 g/day for female; Heavy drinking defined as ≥ 24 g/day for male and ≥ 15 g/day for female

Table 2. Distribution of demographic, obesity indices, MetS related factors, and life style variables according to the 3 levels of serum CRP

CRP level	Low level (< 1mg/L)	Intermediate level (≥ 1mg/L & < 3mg/L)	High level (≥3mg/L)
N (%)	2409 (83.36)	352 (12.18)	129 (4.46)
Age	43.26 (12.75)	46.35 (14.09)	46.31 (15.12)
Sex, *N (%)*			
Male	932 (80.00)	172 (14.76)	61 (5.24)
Female	1477 (85.62)	180 (10.43)	68 (3.94)
Obesity index (SD)†			
Weight (kg)	61.53 (11.14)	67.08 (11.95)	69.03 (15.52)
WC (cm)	79.70 (9.11)	85.45 (8.66)	87.02 (10.92)
HC (cm)	94.20 (5.67)	96.88 (6.07)	98.15 (8.34)
BMI (kg/m^2)	23.37 (3.13)	25.08 (3.28)	25.66 (4.42)
WHR	0.85 (0.07)	0.88 (0.06)	0.89 (0.07)
MetS related characteristics (SD)‡			
FBS (mg/dL)	92.52 (17.46)	96.16 (20.45)	99.09 (31.08)
tCholesterol (mg/dL)	188.28 (35.54)	195.00 (37.04)	191.71 (35.10)
HDL (mg/dL)	51.39 (12.43)	44.64 (12.11)	44.39 (13.31)
LDL (mg/dL)	109.98 (31.11)	115.04 (32.74)	114.22 (32.06)
TG (mg/dL)	111.11 (80.91)	142.86 (111.62)	140.40 (100.85)
SBP (mmHg)	115.91 (16.39)	120.08 (17.68)	118.09 (17.61)
DBP (mmHg)	73.02 (10.64)	77.14 (11.72)	75.41 (10.63)
Life Style, *N (%)*			
Regular Exercise			
No	1552 (82.82)	236 (12.59)	86 (4.59)
Yes	857 (84.35)	116 (11.42)	43 (4.23)
Smoking Status			

Never-smoker	1603 (85.08)	206 (10.93)	75 (3.98)
Ever-smoker	806 (80.12)	146 (14.51)	54 (5.37)
Drinking Habit¶			
Moderate	2062 (83.69)	296 (12.01)	106 (4.30)
Heavy	347 (81.46)	56 (13.15)	23 (5.40)
Education level			
≤ High School	1376 (82.20)	219 (13.08)	79 (4.72)
> High School	1033 (84.95)	133 (10.94)	50 (4.11)
Income level			
≤ 1.5 million won	1879 (85.88)	232 (10.60)	77 (3.52)
> 1.5 million won	530 (75.50)	120 (17.09)	52 7.41)

† WC, Waist circumference; HC, Hip circumference; BMI, Body mass index; WHR, Waist-to-Hip Ratio

‡ FBS, Fasting blood sugar; tCholesterol, Total Cholesterol; HDL, High density lipoprotein Cholesterol; LDL, Low density lipoprotein Cholesterol; TG, Triglyceride; SBP, Systolic blood pressure; DBP, Diastolic blood pressure

¶Moderate drinking defined as < 24 g/day for male and < 15 g/day for female; Heavy drinking defined as ≥ 24 g/day for male and ≥ 15 g/day for female

2. Association between CRP and MetS related traits and CRP and Obesity indices

The distribution of serum CRP concentration according to the MetS diagnostic criteria is presented in Table 3. The criterion for waist circumference was closely related to CRP level for both male and female. Those who had above 90 cm (male) or 80 cm (female) of waist circumference had significantly higher mean and median CRP concentration. HDL cholesterol also showed a strong association with CRP level for both sexes. Higher HDL cholesterol was closely related to lower CRP levels. In regards to triglyceride criterion, a strong relationship was found between CRP level and criterion for triglyceride for female, but for males, only border line significance was observed. However, compared to triglyceride, FBS level had an opposite tendency. In this case, a significant association between CRP level and FBS level was found only in males. The least significant association with CRP level among 5 criteria was blood pressure. It only showed borderline significance in females.

Table 3. Distribution of serum CRP concentration according to MetS related physiological characteristics

	Male				Female			
	N	Mean (SD)	Median (IQR)	P value	N	Mean (SD)	Median (IQR)	P value
WC				<.0001				<.0001
Low	857	0.59 (1.06)	0.25 (0.07-0.64)		1107	0.44 (1.03)	0.15 (0.04-0.38)	
High	308	1.09 (1.69)	0.45 (0.13-1.22)		618	0.83 (1.24)	0.40 (0.11-0.95)	
TG				0.0248				<.0001
<150	788	0.66 (1.21)	0.26 (0.07-0.66)		1454	0.51 (1.01)	0.18 (0.05-0.50)	
≥150	377	0.85 (1.39)	0.37 (0.10-1.04)		271	0.95 (1.55)	0.39 (0.12-0.97)	
HDL				<.0001				<.0001
High	844	0.55 (1.00)	0.19 (0.06-0.59)		956	0.40 (0.85)	0.13 (0.04-0.39)	
Low	321	1.18 (1.73)	0.54 (0.25-1.26)		769	0.81 (1.36)	0.31 (0.12-0.87)	
FBS				0.0008				0.0828
<100	858	0.64 (1.14)	0.26 (0.07-0.66)		1505	0.56 (1.11)	0.20 (0.05-0.54)	
≥100	307	0.97 (1.58)	0.40 (0.11-1.01)		220	0.71 (1.22)	0.27 (0.08-0.78)	
BP				0.2394				0.0437
Low	793	0.69 (1.24)	0.30 (0.07-0.73)		1392	0.55 (1.13)	0.19 (0.05-0.52)	
High	372	0.79 (1.36)	0.30 (0.09-0.80)		333	0.69 (1.12)	0.26 (0.08-0.85)	

High waist circumference : ≥ 90 for male and ≥ 80 for female
Low HDL cholesterol : < 40 for male and < 50 for female
High BP : ≥ 130 in SBP or ≥85 in DBP
IQR, Inter-quantile range

Additionally, correlation analyses were conducted in order to quantify how close the relationships between log-transformed CRP level and other variables were. Spearman correlation coefficients between CRP level and other covariates are presented in Table 5. Among 5 obesity-related traits, waist circumference showed the most significant correlation with CRP level for male, female and overall. The least significant correlation was hip circumference for male, female, and overall. Other indices such as weight, BMI and waist-to-hip ratio showed intermediate correlation coefficients. In regards to the MetS related physiological status, all factors – FBS, total cholesterol, HDL cholesterol, LDL cholesterol, TG, SBP and DBP – had statistically significant correlations with log-transformed CRP level for female and overall. For females, the order of correlation coefficients from highest to lowest was as follows: HDL cholesterol, Triglyceride, Total cholesterol, LDL cholesterol, DBP, FBS and SBP. For overall, the order from highest to lowest was as follows: HDL cholesterol, triglyceride, DBP, total cholesterol, FBS, LDL cholesterol, and SBP. For males, the order from highest to lowest was as follows: HDL cholesterol, DBP, Triglyceride, FBS and total cholesterol except for LDL cholesterol, and SBP, which were not significant.

Table 4. Spearman correlation coefficient between log-transformed CRP concentration and obesity and MetS related physiological characteristic

	Male		Female		Overall	
	R	P value	R	P value	R	P value
Obesity indices†						
Weight	0.1809	<.0001	0.2422	<.0001	0.2386	<.0001
WC	0.2400	<.0001	0.3362	<.0001	0.3165	<.0001
HC	0.1593	<.0001	0.2148	<.0001	0.2170	<.0001
BMI	0.1843	<.0001	0.2579	<.0001	0.2506	<.0001
WHR	0.2178	<.0001	0.2993	<.0001	0.2860	<.0001
MetS related characteristics‡						
FBS	0.0983	0.0008	0.0978	<.0001	0.1156	<.0001
HDL	-0.3142	<.0001	-0.3390	<.0001	-0.3404	<.0001
LDL	0.0541	0.0649	0.1364	<.0001	0.1108	<.0001
TG	0.1638	<.0001	0.2742	<.0001	0.2473	<.0001
SBP	0.0489	0.0950	0.0645	0.0074	0.0859	<.0001
DBP	0.1574	<.0001	0.1265	<.0001	0.1573	<.0001

† WC, Waist circumference; HC, Hip circumference; BMI, Body mass index; WHR, Waist-to-Hip Ratio

‡ FBS, Fasting blood sugar; tCholesterol, Total Cholesterol; HDL, High density lipoprotein Cholesterol; LDL, Low density lipoprotein Cholesterol; TG, Triglyceride; SBP, Systolic blood pressure; DBP, Diastolic blood pressure

3. Environmental factors affecting serum CRP level

The result of regression analyses using mixed model is shown in Table 5. The result showed that sex, abdominal obesity, and income level are associated with log-transformed CRP concentration even after adjusting for age. Being a male, in comparison with being a female, can be a risk factor for elevating CRP level, and its β coefficient was 0.2935. Abdominal obesity can cause elevation of CRP level. The β coefficient of the absence of abdominal obesity was -0.6165 when the presesnce of abdominal obesity was being a reference. Regular exercise, smoking status, drinking habit, and education level were not significant environmental factors that affect serum CRP concentration. In regards to the income level, those who earned less than 1.5 million won per month showed decreasing effect compared to those who earned more than 1.5 million won per month. The β coefficient estimate of lower income level was -0.7209.

Table 5. Regression analyses of log-transformed CRP concentration by using mixed model

	β coefficient	SE	P value
Sex			
Male	0.2935	0.0623	<.0001
Female	Ref		
Abdominal Obesity†			
No	-0.6165	0.0560	<.0001
Yes	Ref		
Regular exercise			
No	0.0677	0.0474	0.1535
Yes	Ref		
Smoking Status			
Never-smoker	0.0207	0.0637	0.7446
Ever-smoker	Ref		
Drinking Habit‡			
Moderate	0.0547	0.069	0.4267
Heavy	Ref		
Education level			
≤ High School	0.0818	0.0528	0.1214
> High School	Ref		
Income level			
≤ 1.5 million won	-0.7209	0.0615	<.0001
> 1.5 million won	Ref		

† Abdominal obesity defined as waist circumference ＞ 90cm for male and ＞ 85cm for female
‡ Moderate drinking defined as ＜ 24 g/day for male and < 15 g/day for female; Heavy drinking defined as ≥ 24 g/day for male and ≥ 15 g/day for female

Table 6 shows the distribution of abdominal obesity and life stlye variables according to the two levels of CRP concentration, low level group versus pooled with intermediate and high level group. In this case, two levels of CRP concentration were treated as binary trait and were implemented in logistic regression.

The results of the regression analysis is shown in Table 7. It quantified the risk of being int the intermediate/high level group rather than in low level group for each environmental factor. Abdominal obesity and income level are statistically significant factors that affect CRP level elevation. Male OR value was 1.31 but it was not statistically significant. Those who did not have abdominal obesity showed OR of 0.42. The OR of those who engaged in regular exercise, never smoker, moderate alcohol drinker, and achieved low education level were 1.20, 0.85, 1.13 and 1.05, respectively, though they were not statistically significant. As mentioned above, low income level lower CRP risk level.

Table 6. Distribution of abdominal obesity, and life style variables according to the CRP level (Low vs. Intermediate/High)

	Low level ($<$ 1mg/L)	Intermediate & High level ($\geq$ 1 mg/L)	P-value
N (%)	2409 (83.36)	481 (16.64)	
Age (SD)	43.26 (12.75)	46.34 (14.36)	<.0001
Sex, *N (%)*			<.0001
Male	932 (80.00)	233 (20.00)	
Female	1477 (85.62)	248 (14.38)	
Abdominal Obesity†, *N (%)*			<.0001
No	1726 (87.88)	238 (12.12)	
Yes	683 (73.76)	243 (26.24)	
Life Style, *N (%)*			
Regular Exercise			0.2908
No	1522 (82.82)	322 (17.18)	
Yes	857 (84.35)	159 (15.65)	
Smoking Status			0.0006
Never-smoker	1603 (85.08)	281 (14.92)	
Ever-smoker	806 (80.12)	200 (19.88)	
Drinking Habit‡			0.2539
Moderate	2062 (83.69)	402 (16.31)	
Heavy	347 (81.46)	79 (18.54)	
Education level			0.0499
$\leq$ High School	1376 (82.20)	298 (17.80)	
> High School	1033 (84.95)	183 (15.05)	
Income level			<.0001
$\leq$ 1.5 million won	1879 (85.88)	309 (14.12)	
> 1.5 million won	530 (75.50)	172 (24.50)	

† Abdominal obesity defined as waist circumference $>$ 90cm for male and $>$ 85cm for female
‡ Moderate drinking defined as $<$ 24 g/day for male and < 15 g/day for female; Heavy drinking defined as $\geq$ 24 g/day for male and $\geq$ 15 g/day for female

Table 7. Logistic regression of CRP level by using generalized linear mixed model

	OR¶	95% CI	P value
Sex			
Male	1.31	0.98-1.75	0.0690
Female	1.00		
Abdominal obesity†			
No	0.42	0.33-0.53	<.0001
Yes	1.00		
Regular Exercise			
No	1.20	0.95-1.51	0.1185
Yes	1.00		
Smoking Status			
Never	0.85	0.64-1.15	0.2987
Ever-smoker	1.00		
Drinking Habit‡			
Moderate	1.13	0.82-1.54	0.4651
Heavy	1.00		
Education level			
≤ High School	1.05	0.82-1.34	0.7226
> High School	1.00		
Income level			
≤ 1.5 million	0.49	0.38-0.63	<.0001
> 1.5 million	1.00		

¶ Odds Ratio of having intermediate and high level of CRP
† Abdominal obesity defined as waist circumference $>$ 90cm for male and $>$ 85cm for female
‡ Moderate drinking defined as $<$ 24 g/day for male and < 15 g/day for female; Heavy drinking defined as $\geq$ 24 g/day for male and $\geq$ 15 g/day for female

4. ICC estimates of serum CRP in various relative types

Intraclass correlation coefficient of log-transformed CRP concentration between MZ twins, DZ twins, pooled with DZ twins/siblings, siblings, spouses, and family are shown in Table 8. Each model was adjusted for different covariates, such as age and sex in Model 1, age, sex, and waist circumference in Model 2, and age, sex, waist circumference, regular exercise, smoking status, drinking habit, education level, and income level in Model 3. As more covariates were adjusted, the ICC value decreased gradually. MZ twins had the largest value (0.63-0.71), and DZ twins had the second largest value (0.57-0.66). Pooled with DZ twins/siblings and siblings had similar values (0.41-0.47 and 0.39-0.43, respectively). Spouses had the smallest value (0.33-0.36).

Table 8. Intraclass correlation coefficients of log-transformed CRP concentration by relative types

	MZ	DZ	DZ/Sib	Siblings	Spouse	Family
Model	ICC	ICC	ICC	ICC	ICC	ICC
1	0.71	0.66	0.47	0.43	0.35	0.43
2	0.68	0.66	0.48	0.46	0.36	0.45
3	0.63	0.57	0.41	0.39	0.33	0.41

Model 1 : adjusting age and sex
Model 2: adjusting age, sex and waist circumference
Model 3 : adjusting age, sex, waist circumference regular exercise, smoking status, drinking habit, education level, and income level

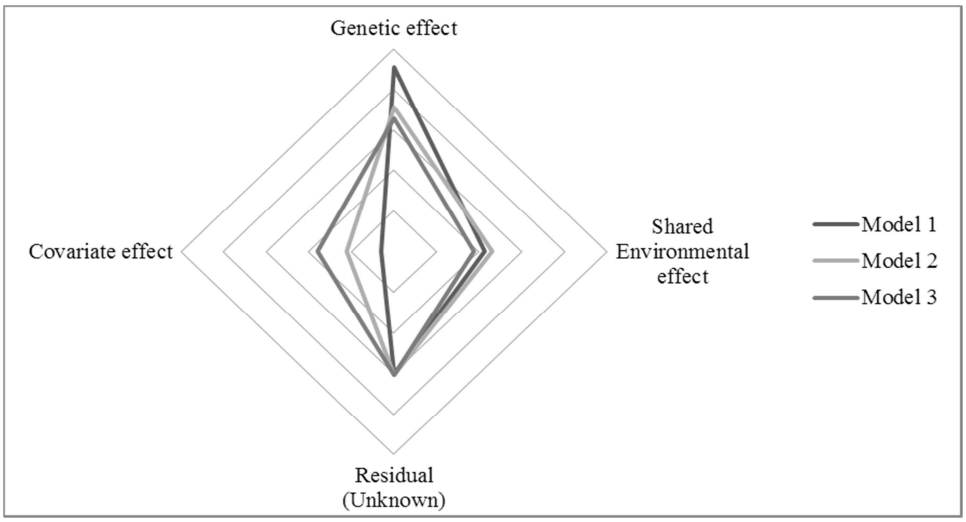
5. Heritability estimates of serum C-reactive protein

Heritability estimates of base-line CRP concentration are shown in Table 9. Various models were implemented and the best fitting model was ACE model with familial common environment adjusted for all covariates including age, sex, waist circumference, regular exercise, smoking status, drinking habit, education level, and income level. A total of 3 models were implemented and the covariates for each model were the same as those of ICC analyses. As a result, the additive genetic effects ranged from 0.40 to 0.47, common environmental effects ranged from 0.22 to 0.26 and random individual environmental effects ranged from 0.31 to 0.37. The proportions of variance explained by covariates were 0.03, 0.11 and 0.18 in Model 1, 2, 3, respectively. Figure 3 is a diagram that shows the associating factors for serum CRP concentration and its variance proportion to the total variance in each model.

Table 9. Heritability estimates of serum CRP level

Model	a^2† (SE)	c^2‡ (SE)	e^2 ¶(SE)	Variance By covariates
1	0.47 (0.04)	0.22 (0.03)	0.31 (0.02)	0.03
2	0.40 (0.04)	0.26 (0.03)	0.34 (0.02)	0.11
3	0.40 (0.04)	0.23 (0.03)	0.37 (0.02)	0.18

† Variance explained by additive genetic effects
‡ Variance explained by shared environmental effects
¶ Random individual effects
Model 1 : adjusting age and sex
Model 2: adjusting age, sex and waist circumference
Model 3 : adjusting age, sex, waist circumference, regular exercise, smoking status, drinking habit, education level, and income level



1) Model 1 : adjusting age and sex
2) Model 2: adjusting age, sex and waist circumference
3) Model 3 : adjusting age, sex, waist circumference, regular exercise, smoking status, drinking habit, education level, and income level
4) Genetic effect : Propotion of variance explained by additive genetic effect
5) Shared Environmental effect : Propotion of variance explained by household effect
6) Covariate effect : Propotion of variance explained by covariates
7) Residual : Propotion of variance explained by random individual factors

Fig 3. Diagram of factors affecting serum CRP level

IV. DISCUSSION

Demographics

Other studies have reported that females usually have higher CRP concentration than males, however; in the current study, the mean and median of male serum CRP concentration was higher than those of females'. Because other variables such as obesity indices, MetS related physiological status, and other life styles factors show different characteristic according to the sex, it is important to consider the sex difference. Also, some other physiological differences between male and female may contribute to those differences. Further studies are needed to determine the sex difference in CRP level.

When categorizing into 3 levels, the majority (83.36%) of subjects were included in low level. There were big differences between low level and intermediate level in many variables, but not much difference between intermediate level and high level. It would help further clarify the results if one could understand the effects of environmental factors that focus on the difference between low level and intermediate/high level not necessarily on the difference among each group.

Association with Metabolic Syndrome

It is confirmed that baseline serum CRP concentration is closely associated with MetS related physiological status. Especially, waist circumference and HDL cholesterol presented a strong association with CRP concentration. The strong association between CRP and MetS implicates that CRP could be considered a more important factor than previously expected not only to cardiovascular diseases, but also in regards to various complex chronic diseases. Still, the exact causal relationship between several MetS related physiological status and CRP concentration need to be established. It is unknown whether a high concentration of serum CRP contribute to the MetS related physiological status or their status affects serum CRP concentration. Therefore, MetS related physiological status were not included in the analyses as adjusting covariates.

Association with Obesity

It is well known that CRP concentration is related to obesity status. [39] Among several obesity indices, waist circumference consistently presented the strongest association for both male and female with CRP concentration in correlation analysis. The results were consistent with the previous studies, too. [8,32] Although further studies are needed to explain the exact mechanisms of how

abdominal obesity work on CRP level or vice versa, it is quite certain that the most relevant obesity index is abdominal obesity – waist circumference. For this reason, every analysis that needed to be adjusted by obesity status, waist circumference or abdominal obesity was implemented as a representative obesity index.

Environmental factors affecting CRP level

A total of 5 life style factors were in the study, including obesity, which is the most closely related factor to serum CRP level. Those life style factors were reported in previous studies as risk factors for cardiovascular diseases or CRP elevation. The results revealed, just as expected, the most substantial influence of abdominal obesity, or waist circumference, among various environmental factors in the study. Regular exercise, smoking status, drinking habit, and education level did not show any statistically significant association with CRP concentration and risk level in the current study. It is well known that smoking increases the risk of cardiovascular diseases, however, smoking status did not seem to affect CRP level. Instead, it actually lowered the CRP level, though statistically not significant. Unexpectedly, higher income level was associated with elevation of CRP. This needs further studies and many factors including stress, and working type should be considered. As for regular exercise, a more

accurate measure of physical activity would be necessary. Also, food consumption or nutritional factor should be considered before determing the effect size of environmental factors. Overall, more accurate and detailed information of environmental factors would be needed in order to identify clearer environmental influences on CRP concentration.

Intraclass correlation coefficients of CRP concentration by relative types

The results of ICC estimation implicate several points. First, it implicate genetic influence on CRP concentration. There is a gradually decreasing trend in ICC value as the genetic distance goes further. The MZ twins who share 100% of their genetic information had 0.71 of intraclass correlation coefficient after adjusting for age and sex. Even after adjusting for all the other life style variables, they still had 0.63 ICC value. On the contrary, spouses who shared no genetic information with each other showed 0.33-0.36 of ICC value that was far lower than that of MZ twins. The second implication is that there was not only genetic effect but also some common environmental effects. This implicates that there might be common environmental effects as well as genetic effects. The correlated CRP level within spouse pairs all resulted from non-

genetic, shared environmental effect. These results were consistent with heritability estimation, mentioned later. This trend implicates that genetic factors have influence on CRP level, and also some common environmental factors were not included in this study may have affected the CRP level. The results are conflicting, however, with previous studies. In previouse studies, CRP seemed not to be influenced by familial shared environment. [31] Overall, the ICC results of the current study were higher than those of previous studies.[33] Especially, in spouse pairs ICC values were higher than those of previous studies. [31,40] Austin et al reported that the ICC of CRP concentration in spouse pairs was not different from zero. [40] Pankow et al also reported no significant intraclass correlation in spouse pairs. [31] However, Sbarra et al suggested that marriage could play a protective role in elevation of CRP concentration in elderly. It showed the influence of marriage on CRP concentration in spouse pairs.[41] Other studies have also shown the correlation of CRP concentration within spouse pairs. [42,43] This discrepancy seems partly due to the difference in participants' age group. In elderly, there was a higher chance of environmental factors affecting CRP concentration. Those conflicting results show the need for further studies to disclose the influence of familial shared environment on CRP concentration.

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Heritability estimates CRP concentration

Heritability estimates support the result of ICC analyses. Heritability analyses revealed the proportion of variance explained by additive genetic effects, shared environmental effects, random individual effects, and covariates effects. After excluding variance that was explained by covariates, about 40% of the total variance was explained by additive genetic effects, that confirmed the genetic contributions to the CRP concentration. Also, a considerable proportion can be explained by shared environment among family members. It could include eating habits, nutritional states, family culture, geography, and religion. Another large proportion remained unexplained in the name of random individual effects, which means that there may still be unknown factors or interactions of factors affecting CRP concentration. Adding up with covariate effects, additive genetic effects made up about 33%, while shared environmental effects made up about 19%. Covariates effects explained 18% of the total variance. Figure 3 is the visualization of the heritability estimation results.

V. CONCLUSION

Baseline serum CRP concentration is closely associated with MetS related physiological status as reported in previous studies. Abdominal obesity most relevantly explains the relationship between CRP concentration and obesity among several obesity indices. Age and sex moderately affect the CRP concentration. Abdominal obesity can increase CRP concentration and the risk level of CRP. Also, higher income level may influence CRP concentration. The results of ICC and heritability analyses strongly support the genetic contributions to the CRP concentration.

The genetic and environmental contributions were partly revealed by the current study, however, the exact factors and its effect sizes need further studies.

Moreover, further studies would be necessary to identify the exact causal relationship among other factors or interaction between factors affecting CRP concentration. Further Genome-wide association analysis may assist in finding out the *Single nucleotide polymorphism* (SNP) or gene, which regulates CRP concentration.

VI. REFERENCE

1. Pepys, M.B. & Hirschfield, G.M. C-reactive protein: a critical update. *Journal of Clinical Investigation* **111**, 1805-1812 (2003).
2. Wessel, J. *et al.* C-reactive protein, an 'intermediate phenotype' for inflammation: human twin studies reveal heritability, association with blood pressure and the metabolic syndrome, and the influence of common polymorphism at catecholaminergic/beta-adrenergic pathway loci. *Journal of Hypertension* **25**, 329-343 (2007).
3. Koh, J.M. *et al.* Higher circulating hsCRP levels are associated with lower bone mineral density in healthy pre- and postmenopausal women: evidence for a link between systemic inflammation and osteoporosis. *Osteoporos Int* **16**, 1263-71 (2005).
4. Weinhold, B. & Ruther, U. Interleukin-6-dependent and -independent regulation of the human C-reactive protein gene. *Biochemical Journal* **327**, 425-429 (1997).
5. Yoshida, N. *et al.* Interleukin-6, tumour necrosis factor alpha and interleukin-1 beta in patients with renal cell carcinoma. *British Journal of Cancer* **86**, 1396-1400 (2002).
6. Chambers, J.C. *et al.* C-reactive protein, insulin resistance, central obesity, and coronary heart disease risk in Indian Asians from the United Kingdom compared with European whites. *Circulation* **104**, 145-50 (2001).
7. Ford, E.S. Body mass index, diabetes, and C-reactive protein among US adults. *Diabetes Care* **22**, 1971-1977 (1999).
8. Brooks, G.C., Blaha, M.J. & Blumenthal, R.S. Relation of C-Reactive Protein to Abdominal Adiposity. *American Journal of Cardiology* **106**, 56-61 (2010).
9. Dehghan, A. *et al.* Genetic variation, C-reactive protein levels, and incidence of diabetes. *Diabetes* **56**, 872-878 (2007).

10. Trayhurn, P. & Beattie, J.H. Physiological role of adipose tissue: white adipose tissue as an endocrine and secretory organ. *Proceedings of the Nutrition Society* **60**, 329-339 (2001).
11. Doumatey, A.P. *et al.* C-reactive protein (CRP) promoter polymorphisms influence circulating CRP levels in a genome-wide association study of African Americans. *Human Molecular Genetics* **21**, 3063-3072 (2012).
12. Clyne, B. & Olshaker, J.S. The C-reactive protein. *Journal of Emergency Medicine* **17**, 1019-1025 (1999).
13. Danesh, J. *et al.* Risk factors for coronary heart disease and acute-phase proteins - A population-based study. *European Heart Journal* **20**, 954-959 (1999).
14. Frohlich, M. *et al.* Association between C-reactive protein and features of the metabolic syndrome - A population-based study. *Diabetes Care* **23**, 1835-1839 (2000).
15. Ford, E.S. Does exercise reduce inflammation? Physical activity and C-reactive protein among US adults. *Epidemiology* **13**, 561-568 (2002).
16. Imhof, A. *et al.* Effect of alcohol consumption on systemic markers of inflammation. *Lancet* **357**, 763-7 (2001).
17. Cushman, M. *et al.* Effect of postmenopausal hormones on inflammation-sensitive proteins - The Postmenopausal Estrogen/Progestin Interventions (PEPI) Study. *Circulation* **100**, 717-722 (1999).
18. Pearson, T.A. *et al.* Markers of inflammation and cardiovascular disease application to clinical and public health practice - A statement for healthcare professionals from the centers for disease control and prevention and the American Heart Association. *Circulation* **107**, 499-511 (2003).
19. Visser, M., Bouter, L.M., McQuillan, G.M., Wener, M.H. & Harris, T.B. Elevated C-reactive protein levels in overweight and obese adults. *JAMA* **282**, 2131-5 (1999).
20. Freeman, D.J. *et al.* C-reactive protein is an independent predictor of risk for the development of diabetes in the West of Scotland Coronary

Prevention Study. *Diabetes* **51**, 1596-1600 (2002).

21. Shine, B., de Beer, F.C. & Pepys, M.B. Solid phase radioimmunoassays for human C-reactive protein. *Clin Chim Acta* **117**, 13-23 (1981).
22. Ridker, P.M. High-sensitivity C-reactive protein - Potential adjunct for global risk assessment in the primary prevention of cardiovascular disease. *Circulation* **103**, 1813-1818 (2001).
23. Worns, M.A., Victor, A., Galle, P.R. & Hohler, T. Genetic and environmental contributions to plasma C-reactive protein and interleukin-6 levels - a study in twins. *Genes and Immunity* **7**, 600-605 (2006).
24. Retterstol, L., Eikvar, L. & Berg, K. A twin study of C-Reactive Protein compared to other risk factors for coronary heart disease. *Atherosclerosis* **169**, 279-82 (2003).
25. Koenig, W. *et al.* C-Reactive protein, a sensitive marker of inflammation, predicts future risk of coronary heart disease in initially healthy middle-aged men: results from the MONICA (Monitoring Trends and Determinants in Cardiovascular Disease) Augsburg Cohort Study, 1984 to 1992. *Circulation* **99**, 237-42 (1999).
26. Mendall, M.A. *et al.* C-reactive protein: relation to total mortality, cardiovascular mortality and cardiovascular risk factors in men. *Eur Heart J* **21**, 1584-90 (2000).
27. Tracy, R.P. *et al.* Lifetime smoking exposure affects the association of C-reactive protein with cardiovascular disease risk factors and subclinical disease in healthy elderly subjects. *Arterioscler Thromb Vasc Biol* **17**, 2167-76 (1997).
28. Vickers, M.A. *et al.* Genotype at a promoter polymorphism of the interleukin-6 gene is associated with baseline levels of plasma C-reactive protein. *Cardiovascular Research* **53**, 1029-1034 (2002).
29. Best, L.G. *et al.* Genetic determination of acute phase reactant levels: the strong heart study. *Hum Hered* **58**, 112-6 (2004).
30. Reiner, A.P. *et al.* Genome-wide association and population genetic analysis of C-reactive protein in African American and Hispanic

American women. *Am J Hum Genet* **91**, 502-12 (2012).

31. Pankow, J.S. *et al.* Familial and genetic determinants of systemic markers of inflammation: the NHLBI family heart study. *Atherosclerosis* **154**, 681-9 (2001).
32. Austin, M.A. *et al.* Heritability of multivariate factors of the metabolic syndrome in nondiabetic Japanese americans. *Diabetes* **53**, 1166-9 (2004).
33. de Maat, M.P. *et al.* Genetic influence on inflammation variables in the elderly. *Arterioscler Thromb Vasc Biol* **24**, 2168-73 (2004).
34. MacGregor, A.J., Gallimore, J.R., Spector, T.D. & Pepys, M.B. Genetic effects on baseline values of C-reactive protein and serum amyloid a protein: a comparison of monozygotic and dizygotic twins. *Clin Chem* **50**, 130-4 (2004).
35. Greenfield, J.R. *et al.* Obesity is an important determinant of baseline serum C-reactive protein concentration in monozygotic twins, independent of genetic influences. *Circulation* **109**, 3022-3028 (2004).
36. Sung, J. *et al.* The Korean Twin Registry--methods, current stage, and interim results. *Twin Res* **5**, 394-400 (2002).
37. Sung, J. *et al.* Healthy Twin: a twin-family study of Korea--protocols and current status. *Twin Res Hum Genet* **9**, 844-8 (2006).
38. Expert Panel on Detection, E. & Treatment of High Blood Cholesterol in, A. Executive Summary of The Third Report of The National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, And Treatment of High Blood Cholesterol In Adults (Adult Treatment Panel III). *JAMA* **285**, 2486-97 (2001).
39. Choi, J., Joseph, L. & Pilote, L. Obesity and C-reactive protein in various populations: a systematic review and meta-analysis. *Obesity Reviews* **14**, 232-244 (2013).
40. Austin, M.A. *et al.* Heritability of C-reactive protein and association with apolipoprotein E genotypes in Japanese Americans. *Ann Hum Genet* **68**, 179-88 (2004).
41. Sbarra, D.A. Marriage protects men from clinically meaningful

elevations in C-reactive protein: results from the National Social Life, Health, and Aging Project (NSHAP). *Psychosom Med* **71**, 828-35 (2009).

42. 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* **8**, 352-9 (2007).

43. Di Castelnuovo, A. *et al.* Cardiovascular risk factors and global risk of fatal cardiovascular disease are positively correlated between partners of 802 married couples from different European countries. Report from the IMMIDIET project. *Thromb Haemost* **98**, 648-55 (2007).

VII. Abstract in Korean (국문초록)

다수의 만성복합질환들이 서로 많은 증상을 공유하며 밀접하게 관련이 있다고 알려지고 있다. 예를 들어 현재 가장 큰 질병 부담을 차지하고 있는 질환들 중 제2형 당뇨병과 대사증후군, 심혈관계 질환들은 많은 부분에서 원인과 증상을 공유하고 있다. C-반응성 단백질은 다양한 만성질환과 관련이 있는 인자로 보고되고 있다. 과거 C-반응성 단백질은 급성기 염증 반응의 중요 표지자로만 알려졌지만, 고감도 측정방법이 개발되면서 C-반응성 단백질을 보다 정확하게 측정할 수 있게 되었고, 사람에 따라 다른 수준으로 평상시 C-반응성 단백질의 농도가 유지되고 있음이 밝혀졌다. 급성기 염증 반응시기가 아닌, 평상시 C-반응성 단백질의 농도는 미래의 심혈관계 질환의 예측인자로 사용된다는 사실은 널리 알려졌다. 본 연구는 그 동안 다수의 연구에서 보고되었던 C-반응성 단백질의 농도와 대사증후군과의 관련성을 확인하고, C-반응성 단백질의 농도에 영향을 미치는 유전적, 환경적 요인들을 밝히고자 한다.

640 가족, 430쌍의 일란성 쌍둥이, 97쌍의 이란성 쌍둥이를 포함하는 2890명을 대상으로 C-반응성 단백질의 농도에 영향을 미치

는 유전적, 환경적 요인들을 확인하였다. 대사증후군과의 관련성을 확인하기 위해 다섯가지의 대사증후군 진단 기준에 따른 C-반응성 단백질의 농도 분포를 확인하였고, 대사증후군 관련 요소들과 C-반응성 단백질 농도와의 상관 분석을 시행하였다. C-반응성 단백질 농도에 영향을 미치는 환경요인을 발견하기 위해 C-반응성 단백질의 농도에 영향을 미칠 것으로 예상되는 생활환경 변수를 이용해서 선형회귀분석과 로지스틱회귀분석을 시행하였다. 환경적 요인과 더불어 C-반응성 단백질에 영향을 미치는 유전적 요인을 발견하기 위해서 다양한 가족관계 내부 상관 분석과 유전율 분석을 시행하였다.

연구 결과, C-반응성 단백질의 농도는 대사증후군과 강한 연관성을 나타낸다는 사실을 확인하였다. 또한 다양한 비만 관련 지표들 중에서 복부비만이 C-반응성 단백질 농도와 가장 깊은 관련성을 갖고 있다는 사실을 발견하였다. 생활환경 요소들 중에서 수입 수준이 C-반응성 단백질과 연관성을 보였다. 가족관계 내부 상관분석과 유전율 분석 결과 유전적 요인이 가족 내 공유 환경과 더불어 C-반응성 단백질의 농도에 상당한 영향을 미치는 것으로 나타났다. 선행연구와 상충되는 결과들도 보고되었기 때문에 환경요인과 유전요인의 정확한 영향을 확인하기 위해서 후속 연구 결과들이 필요하다. 본 연구를

통하여 유전적 요인이 C-반응성 단백질 농도에 매우 큰 영향을 준다는 것을 발견하였고, 유전적 특징을 고려한 C-반응성 단백질의 고위험군 관리의 필요성이 대두되었다. 또한 본 연구의 결과는 C-반응성 단백질 농도의 증가와 이와 관련된 질환을 관리하기 위해서 C-반응성 단백질 농도에 가장 큰 영향을 미치는 요소 중 하나인 비만의 관리, 특히 복부 비만의 관리가 필요하다는 사실을 암시한다. C-반응성 단백질의 농도에 영향을 미치는 유전자의 발현 기작이 정확하게 밝혀진다면 개인의 유전적 정보를 고려한 다양한 만성질환 관리가 가능할 것으로 기대된다.

Keywords: *C-반응성 단백질, 대사증후군, 유전율, 쌍둥이-가족 분석*

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