ORIGINAL ARTICLE

UDC: 616-074/-078-053::616-002]::616.12
DOI: https://doi.org/10.2298/VSP221130042Z

Age-independent association between high-sensitivity C-reactive protein and blood pressure in middle-aged adults

Povezanost između visoko osetljivog C-reaktivnog proteina i krvnog pritiska nezavisna od životnog doba kod sredovečnih osoba

Huijun Zhao, Yiwen Lu, Junjie Niu, Hong Bian, Xingya Kuang

Tongji University Yangpu Hospital, Department of Occupational Medicine, Shanghai, China

Abstract

Background/Aim. There is growing evidence suggesting that high-sensitivity C-reactive protein (hs-CRP) is a reliable biomarker in patients with hypertension. While the relationship between hypertension and age is well established, the connection between hs-CRP and age remains unclear. The aim of the study was to determine a relationship between hs-CRP and age, body mass index (BMI), and blood pressure in middle-aged people. **Methods.** This cross-sectional survey was conducted in Shanghai, China, and it included data from 1,677 healthy male participants aged 18 to 50 years and 1,127 healthy female participants aged 19 to 49 years recruited during routine health examinations. The hs-CRP, BMI, systolic blood pressure (SBP), and diastolic blood pressure (DBP) were recorded. **Results.** The participants were first separated into four age quartile groups, in which an increase in BMI, SBP, and DBP was observed but not in hs-CRP. Afterward, the participants were divided into four hs-CRP quartile groups, in which an increase in BMI, SBP, and DBP was noted, but not in age. Finally, using Pearson correlation, positive correlations were found between hs-CRP, BMI, SBP, and DBP, but no correlation was discovered between age and hs-CRP. **Conclusion.** The authors showed that age is likely a confounding factor that correlates with SBP, DBP, and BMI, but it does not directly correlate with hs-CRP.

Key words:
age factors; biomarkers; blood pressure; body mass index; c-reactive protein.

Apstrakt

Uvod/Cilj. Sve više dokaza ukazuje na to da je visoko osetljivi C-reaktivni protein (*high-sensitivity C-reactive protein* – hs-CRP) pouzdan biomarker kod bolesnika sa hipertenzijom. Dok je veza između hipertenzije i životnog doba dobro utvrđena, veza između hs-CRP i životnog doba još uvek nije dovoljno jasna. Cilj rada bio je da se utvrdi povezanost između hs-CRP i životnog doba, indeksa telesne mase (ITM) i krvnog pritiska kod osoba srednjih godina. **Metode.** Ova studija preseka sprovedena je u Šangaju, u Kini i uključila je podatke o 1 677 zdravih muških ispitanika, od 18 do 50 godina, i 1 127 zdravih ženskih ispitanika, od 19 do 49 godina, koji su prikupljeni tokom redovnih zdravstvenih pregleda. Beleženi su hs-CRP, ITM, sistolni krvni pritisak (SKP), i dijastolni krvni pritisak (DKP). **Rezultati.** Ispitanici su prvo bili podeljeni prema životnom dobu u četiri grupe, kvartilno, u kojima je utvrđen porast BMI, SKP i DKP, ali ne i hs-CRP. Zatim su ispitanici podeljeni kvartilno u četiri grupe, prema hs-CRP u kojima je utvrđen porast vrednosti BMI, SKP i DKP, ali ne i starosti. Na kraju, korišćenjem Pearson-ove korelacije, nađena je pozitivna korelacija između hs-CRP, ITM, SKP i DKP, ali ne i korelacija između životnog doba i hs-CRP. **Zaključak.** Životno doba je verovatno pridruženi faktor, jer je u korelaciji sa SKP, DKP i ITM, ali nije u direktnoj korelaciji sa hs-CRP.

Ključne reči:
životno doba, faktor; biomarkeri; krvni pritisak; telesna masa, indeks; c-reaktivni protein.

Introduction

C-reactive protein (CRP), a low-weight protein produced by the liver, is considered a classic acute-phase protein that increases in response to stress, inflammation, and various illnesses [1]. CRP detection is a standard test performed in clinical practice. However, standard CRP detection has limited sensitivity with a lower detection limit of 3–8 mg/L, making it an unreliable prediction biomarker [2]. To address this, a more sensitive assay for CRP, known as high-sensitivity CRP (hs-CRP), has been developed and proved to be a useful biomarker in various conditions such as Parkin

Correspondence to: Xingya Kuang, Department of Occupational Medicine, Yangpu Hospital, Tongji University, Shanghai 200 090, China. E-mail: 1400384@tongji.edu.cn

son's disease [3], diabetes [4], postoperative complications [5], sepsis [6], and chronic obstructive pulmonary disease (COPD) [7]. In the realm of hypertension or cardiovascular disease, the hs-CRP has been widely studied and is recognized as one of the key risk factors in assessing cardiovascular risk [8, 9].

Most of the diseases involved in the hs-CRP studies are age-related. Age has typically been considered a confounding factor that is accounted for in hs-CRP studies. However, the relationship between age and hs-CRP has not been thoroughly explored, which results in varying findings from different studies. Some studies have found a positive correlation between hs-CRP and patient age. For instance, Demirbas et al. [10] reported a positive correlation between hs-CRP and age in psoriasis patients. Milan-Mattos et al. [11] reported that the natural aging process increased IL-6 and hs-CRP levels. In patients with carotid intima-media thickness, Kim et al. [12] reported a significant positive correlation between hs-CRP and age. In young children with cardiovascular risk, Rondo et al. [13] reported that age is positively correlated with hs-CRP levels. In infants and young adults with diabetes, Coulon et al. [14] reported a significant correlation between hs-CRP and age or duration of diabetes.

However, other studies did not find any relationship between hs-CRP and age. For instance, there was no relationship between serum hs-CRP and age or weight both in smokers and nonsmokers in COPD patients [15]. In patients with atrial fibrillation, Hermida et al. [16] reported no obvious multiplicative interaction between hs-CRP and age, gender, or race. In an investigation of 213 systemic lupus erythematosus patients and 134 controls, Barnes et al. [17] did not find a relationship between hs-CRP and age, gender, race, etc. Song et al. [3] reported that age is not correlated with hs-CRP in patients with *de novo* Parkinson's disease. Liu et al. [18] reported that age is not correlated with hs-CRP in patients with depression. Feldman and Sbong [19] reported no relation between hs-CRP and age in patients with inflammatory or infectious disorders. Allam et al. [20] found no obvious correlation between serum hs-CRP and age in patients with bronchial asthma.

Moreover, in addition to being a biomarker of a variety of diseases, hs-CRP has been shown to be not only a marker of various illnesses but also a risk factor in healthy individuals for non-alcoholic fatty liver [21], abdominal obesity [22], hypoadiponectinemia [23], etc. Despite this, most studies on hs-CRP and hypertension have focused on patients with the abnormalities, leaving the relationship between hs-CRP level and blood pressure (BP) in healthy individuals largely unstudied.

In this investigation, the relationship between hs-CRP and age, body mass index (BMI), and BP was evaluated by recruiting healthy adults aged 18 to 50 years in Shanghai, China. The recruitment process was conducted during routine physical examinations and involved a medical history inquiry, hematological and clinical chemistry, and electrocardiograph (ECG) by certificate doctors. The levels of hs-CRP, BMI, systolic BP (SBP), and diastolic BP (DBP) were measured in healthy adults and analyzed for any correlations.

Methods

Study population

In total, 1,677 males and 1,127 females aged 18 to 50 years, with a median age of 29 and 28 years, respectively, were recruited from Yangpu Hospital in Shanghai, China, during a routine health examination conducted between April and May 2019. Participants were asked to complete a questionnaire covering their personal information, career, life habits, and medical history. All participants were subjected to physical examination, medical history inquiry, hematology, clinical chemistry, electrocardiograph, urinalysis, etc. After being reviewed by certificated medical physicians, participants who showed no abnormalities in any of the parameters except for BP were included in the study. The investigation complied with the Declaration of Helsinki and was approved by the Ethics Committee of the Yangpu Hospital, Tongji University School of Medicine (No LL-2017-SCI-002). Oral or written informed consent forms were obtained from all the participants in this investigation.

Laboratory measurements

After overnight fasting, body weights and heights were measured in the morning, and body weight mass calculation was conducted using the equation "BMI = body weight (kg)/height (m^2)". After at least 10 min relaxation in the medicine ward of the hospital, the participants were manually measured for SBP and DBP from the right arm by a physician using a mercurial sphygmomanometer (Yuyue Co., Ltd, Jiangsu, China) with a stethoscope. For hs-CRP detection, venous blood (approximately 2 mL) was collected from the participants and processed into serum *via* centrifugation; the samples were kept at 2–8 ˚C until analysis. Then, hs-CRP was detected by using Dimension RXL Analyzer (Siemens Healthcare, Germany) with the method of particle-enhanced turbidimetric immunoassay (PETIA) as described elsewhere [24]. The C-reactive Extended Range Flex reagent was also brought from Siemens (Germany). The detection range was 0.5 to 250.0 mg/L. Calibration and quality control samples were included in each run of the analyses.

Statistical analysis

Data were statistically analyzed using SPSS V20.0 for Windows (SPSS Inc., Chicago, IL, USA). Values below the limit of detection (LOD) were considered negative and given an arbitrary value of LOD/$\sqrt{2}$ [25]. Based on age or hs-CRP levels, participants were divided into four quartile groups: Q1 (1st quartile), Q2 (2nd quartile), Q3 (3rd quartile), and Q4 (4th quartile). The differences in BMI, SBP, DBP, and hs-CRP or age between the groups were examined using one-way ANOVA followed by T-test or *post-hoc* test. Then, a Pearson correlation analysis was applied for the relationship between age, hs-CRP, gender, BMI, SBP, and DBP. Cut-off values for statistical significance were set at $p < 0.05$.

Results

Participants

The results of the measurements are presented in Table 1, revealing that the average age of the participants was 30.9 years, with no significant difference between males (30.9 years) and females (31.0 years, $p > 0.05$). The average hs-CRP level was 1.87 mg/L, with no significant difference between males (1.89 mg/L) and females (1.85 mg/L, $p > 0.05$). The average BMI was 23.4 kg/m^2, with a slightly higher average in males (24.0 kg/m^2) than in females (22.6 kg/m^2, $p < 0.01$). The average SBP was 119.3 mmHg, with a higher average in males (123.0 mmHg) than in females (113.7 mmHg, $p < 0.01$). Similarly, the average DBP was 81.5 mmHg, with a higher average in males (83.1 mmHg) than in females (79.1 mmHg, $p < 0.01$). All participants were considered healthy with no known underlying diseases.

Changes among the age-quartile groups

Initially, the participants were divided into four age-quartile groups: 18–23 years (1st quartile), 24–28 years (2nd quartile), 29–36 years (3rd quartile), 37–50 years (4th quartile). Differences in hs-CRP, BMI, SBP, and DBP were examined between the age-quartile groups. No statistical significance was noted for the hs-CRP between the groups, while data of BMI, SBP, and DBP increased with age from the 1st to the 4th quartile (Table 2).

Changes among the hs-CRP-quartile groups

Similarly, the participants were then divided into four hs-CRP-quartile groups: 0.36–0.95 mg/L (1st quartile), 0.96–1.31 mg/L (2nd quartile), 1.32–1.99 mg/L (3rd quartile), 2.00–3.00 mg/L (4th quartile). Differences in age, BMI, SBP, and DBP were examined between the hs-CRP-quartile groups. No statistical significance was noted for the age between groups, while data of BMI, SBP, and DBP increased as the hs-CRP escalated from the 1st to the 4th quartile (Table 3).

Pearson correlation analysis

Pearson correlation analysis was utilized to assess the interdependence between age, hs-CRP, BMI, SBP, and DBP. Table 4 revealed that age positively correlated with BMI, SBP, and DBP but not with hs-CRP. Similarly, hs-CRP positively correlated with BMI, SBP, and DBP but not with age. Positive correlations were observed between BMI, SBP, and DBP.

Table 1

Summary results of hs-CRP, BMI, SBP, and DBP in the participants

Gender	Number	Age years	hs-CRP mg/L	BMI kg/m^2	SBP mmHg	DBP mmHg
Male	1,677	30.9 ± 7.8	1.89 ± 1.78	24.0 ± 3.7*	123.0 ± 13.4*	83.1 ± 9.7*
Female	1,127	31.0 ± 8. 6	1.85 ± 1.92	22.6 ± 3.5	113.7 ± 13.1	79.1 ± 8.6
Total	2,804	30.9 ± 8.1	1.87 ± 1.84	23.4 ± 3.7	119.3 ± 14.0	81.5 ± 9.5

hs-CRP – high-sensitivity C-reactive protein; BMI – body mass index; SBP – systolic blood pressure; BDP – diastolic blood pressure.
Data are presented as mean ± standard deviation. Student *t*-test was used for comparison between males and females. *$p < 0.01$.

Table 2

Comparisons of hs-CRP, BMI, SBP, and DBP between age-quartile cohorts

Quartile cohort	Age years	Number	hs-CRP mg/L	BMI* kg/m^2	SBP* mmHg	DBP* mmHg
1st	18–23	594	1.88 ± 1.82	22.6 ± 4.0	115.5 ± 12.7	78.4 ± 8.2
2nd	24–28	737	1.83 ± 1.64	23.0 ± 3.8	116.2 ± 13.2	79.7 ± 8.8
3rd	29–36	743	1.94 ± 1.98	23.9 ± 3.6	120.3 ± 14.0	82.1 ± 9.5
4th	37–50	730	1.85 ± 1.89	24.0 ± 3.0	124.4 ± 14.1	85.1 ± 9.9

Data are presented as mean ± standard deviation. A one-way Analysis of Variance (ANOVA) was used for parameter comparison among quartiles. *$p < 0.01$.
For abbreviations, see Table 1.

Table 3

Comparisons of age, BMI, SBP, and DBP between hs-CRP-quartile cohorts

Quartile cohort	hs-CRP mg/L	Number	Age years	BMI* kg/m^2	SBP* mmHg	DBP* mmHg
1st	0.36–0.95	690	30.7 ± 8.3	21.8 ± 3.0	116.3 ± 13.5	79.8 ± 9.0
2nd	0.96–1.31	705	30.7 ± 8.1	22.4 ± 3.1	117.7 ± 13.6	80.2 ± 8.9
3rd	1.32–1.99	701	31.7 ± 8.2	23.9 ± 3.3	120.2 ± 14.0	82.0 ± 9.7
4th	2.00–3.00	708	30.6 ± 7.9	25.5 ± 4.0	122.9 ± 14.1	83.9 ± 9.6

Data are presented as mean ± standard deviation. A one-way Analysis of Variance (ANOVA) was used for parameter comparison among quartiles. *$p < 0.01$.
For abbreviations, see Table 1.

Table 4

Pearson correlation coefficient

Parameters	Age	hs-CRP	BMI	SBP	DBP
Age	1	0.019	0.198*	0.259*	0.270*
hs-CRP		1	0.387*	0.188*	0.167*
BMI			1	0.446*	0.351*
SBP				1	0.736*
DBP					1

Correlation between age, hs-CRP, BMI, SBP, and DBP were analyzed by using Pearson correlation analysis. *$p < 0.01$.
For abbreviations, see Table 1.

Discussion

The aim of this study was to examine the role of hs-CRP as a biomarker of hypertension in young, healthy adults and to assess the impact of age on hs-CRP levels. Results showed that hs-CRP levels were positively correlated with SBP, DBP, and BMI in healthy participants with an average age of 30.9 years (ranging from 18 to 50 years), which was in line with previous studies on hypertension [26] and other cardiovascular disorders [27]. By including young, healthy adults, we sought to minimize the bias between age and underlying disease. Analysis of the data using ANOVA and Pearson correlation analysis revealed that changes in hs-CRP were not related to age, and there was no correlation or trend observed between age and hs-CRP levels.

The hs-CRP level of 1.87 mg/L obtained in this investigation is in line with other studies in Chinese young adults. As reported by Wang et al. [28], the average hs-CRP was determined as 1.89 mg/L in 14,046 healthy adults aged 35 to 64 years. The mean SBP of 119.3 mmHg and the mean DBP of 81.5 mmHg were considered normal values, which is consistent with the results in the nationwide survey conducted in China from October 2012 to December 2015; the mean SBP and DBP in 88,540 adults aged 25–34 years were calculated as 118.9 mmHg and 73.2 mmHg, respectively [29]. The mean BMI in this investigation was 23.4 kg/m^2, which is consistent with the mean BMI (20.8–25.1 kg/m^2) obtained from approximately 100,000 residents in China mainland [30] and the mean BMI of 24.1 kg/m^2 in 2,893 Chinese subjects in Hong Kong [31].

Inflammation is widely recognized as the key contributor to the development of atherosclerosis, which in turn can lead to hypertension. Hs-CRP is a significant marker of inflammation and has been strongly linked to cardiovascular disease. Not only does hs-CRP serve as an inflammatory biomarker, but it also has a direct impact on the pathogenesis of hypertension. That is because hs-CRP can promote vasoconstriction, leukocyte adherence, platelet activation, oxidation, thrombosis, and upregulation of angiotensin type-1 receptor expression. These actions all contribute to the development of hypertension [32].

Although inflammation is observed in many age-dependent diseases, there is no direct correlation between inflammation and age. In healthy children under 12 years old (mean age 5.2 years), the inflammatory cytokines of IL-1Ra, IP-10, and TNF-α decreased with age [33]. In participants aged 24 to 90 years, Lin et al. [34] demonstrated that the rates of change of T cells ($CD4^+$ and $CD8^+$), B cells and NK cells were relatively stable throughout life. In a review including more than 50 studies, researchers did not find evidence of age-related changes in any of the Th1 (IL-2, IFN-γ), Th2 (IL-4, IL-6, and IL-10), or proinflammatory cytokines (IL-1β, IL-8, TNF-α) [35].

Several other risk factors for arterial hypertension are equally important, such as genetics, kidney function, endocrine status, family history, overweight/obesity, poor diet, tobacco use, alcohol consumption, chronic conditions, and gender. The subjects in this investigation with genetic predisposition were from Shanghai, China. The authors separated the parameters of overweight/obesity and gender from the assessment of the relationship between hs-CRP and hypertension. All subjects were considered healthy and free of any abnormalities in the parameters of kidney function, family history, poor diet, tobacco use, and alcohol consumption after being thoroughly reviewed by certified medical physicians. Endocrine status and chronic conditions were not included in the routine physical examination, and their role in both hs-CRP and hypertension has not been addressed in this investigation.

One limitation of this investigation is that the demographic of the participants was not evenly distributed between males and females. The data showed that males had a higher BMI, SBP, and DBP than females. Despite this imbalance, the analysis found no significant differences in hs-CRP between the genders, indicating that this imbalance did not impact the data interpretation. Additionally, participants were considered healthy based on a variety of examinations but not on their BP values. As a result, participants with a BMI ≥ 30 kg/m^2 (159 individuals), SBP ≥ 140 mmHg (204 individuals), and DBP ≥ 90 mmHg (501 individuals) were still included in the investigation, even though they may have underlying health issues.

These individuals were considered part of the targeted population for the investigation.

Conclusion

In the present investigation, by evaluating the levels of hs-CRP, BMI, SBP, and DBP in a sample of young, healthy adults in Shanghai, China, we found that age does not directly correlate to hs-CRP. Instead, hs-CRP may serve as a risk factor that correlates to BP.

Acknowledgement

This study was supported by the National Clinical Key Subject Construction Funds and the Key Disciplines of Occupational and Environmental Health (subject on Prevention and Control of Occupational Poisoning, Foundation No. 15GWZK0201).

The authors would like to thank W.L. Chen, F. Yao, and H. Chen from the Department of Occupational Medicine, Yangpu Hospital, Tongji University, for the health examinations, diagnosis, and sample collection.

Conflict of Interest

The authors declare no conflict of interest.

R E F E R E N C E S

1. *Hansson GK, Robertson AK, Söderberg-Nauclér C.* Inflammation and atherosclerosis. Annu Rev Pathol 2006; 1: 297–329.
2. *Windgassen EB, Funtowicz L, Lunsford TN, Harris LA, Mulvagh SL.* C-reactive protein and high-sensitivity C-reactive protein: an update for clinicians. Postgrad Med 2011; 123(1): 114–9.
3. *Song IU, Cho HJ, Kim JS, Park IS, Lee KS.* Serum hs-CRP levels are increased in de Novo Parkinson's disease independently from age of onset. Eur Neurol 2014; 72(5–6): 285–9.
4. *Petrović M, Dragović T, Petrović S, Obrenčević K, Rančić N, Djurašinović T*, et al. Effect of Vitamin D on proteinuria, lipid status, glycoregulation and C-reactive protein in patients with type-2 diabetes mellitus. Vojnosanit Pregl 2020; 77(6): 582–9.
5. *Marjanović V, Budić I, Slavković A, Radlović V, Simić D.* C-reactive protein and procalcitonin as a predictive factor on appearance of postoperative complications after open appendectomy in children. Srp Arh Celok Lek 2017; 145(5–6): 265–70.
6. *Knežević-Rangelov S, Janković SM.* Accuracy of serum procalcitonin, C-reactive protein, and soluble CD14 subtype levels in diagnosis of sepsis in children. Vojnosanit Pregl 2021; 78(3): 343–6.
7. *Ghobadi H, Fouladi N, Beukaghazadeh K, Ansarin K.* Association of High Sensitive CRP Level and COPD Assessment Test Scores with Clinically Important Predictive Outcomes in Stable COPD Patients. Tanaffos 2015; 14(1): 34–41.
8. *Boshku AA, Panova DI, Ivanovska BZ.* Association of vascular and inflammatory markers with metabolic disorders in women with polycystic ovary syndrome. Vojnosanit Pregl 2019; 76(7): 703–9.
9. *Greenland P, Alpert JS, Beller GA, Benjamin EJ, Budoff MJ, Fayad ZA*, et al. 2010 ACCF/AHA guideline for assessment of cardiovascular risk in asymptomatic adults: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2010; 56(25): e50–103.
10. *Demirbaş A, Kurtipek GS, Tunçez A, Akyürek F, Demirbaş GU.* The role of cystatin-C and fetuin-A in the determination of early atherosclerotic risk in psoriasis patients. Dermatol Ther 2020; 33(6): e13898.
11. *Milan-Mattos JC, Anibal FF, Perseguini NM, Minatel V, Rehder-Santos P, Castro CA,* et al. Effects of natural aging and gender on pro-inflammatory markers. Braz J Med Biol Res 2019; 52(9): e8392.
12. *Kim DJ, Choi SH, Kim SH, Chung SS, Ahn CW, Cha BS,* et al. High sensitive C-reactive protein and carotid intima media thickness in Korean population. Korean Diabetes J 2003; 27(1): 49–62. (Korean)
13. *Rondó PH, Pereira JA, Lemos JO.* High sensitivity C-reactive protein concentrations, birthweight and cardiovascular risk markers in Brazilian children. Eur J Clin Nutr 2013; 67(6): 664–9.
14. *Coulon J, Willems D, Dorchy H.* Increase in C-reactive protein plasma levels during diabetes in infants and young adults. Presse Med 2005; 34(2 Pt 1): 89–93. (French)
15. *Firouzjahi A, Monadi M, Karimpoor F, Heidari B, Dankoob Y, Hajian-Tilaki K*, et al. Serum C-reactive protein level and distribution in chronic obstructive pulmonary disease versus healthy controls: a case-control study from Iran. Inflammation 2013; 36(5): 1122–8.
16. *Hermida J, Lopez FL, Montes R, Matsushita K, Astor BC, Alonso A.* Usefulness of high-sensitivity C-reactive protein to predict mortality in patients with atrial fibrillation (from the Atherosclerosis Risk In Communities [ARIC] Study). Am J Cardiol 2012; 109(1): 95–9.
17. *Barnes EV, Narain S, Naranjo A, Shuster J, Segal MS, Sobel ES*, et al. High sensitivity C-reactive protein in systemic lupus erythematosus: relation to disease activity, clinical presentation and implications for cardiovascular risk. Lupus 2005; 14(8): 576–82.
18. *Liu H, Zhang Y, Gao Y, Zhang Z.* Elevated levels of Hs-CRP and IL-6 after delivery are associated with depression during the 6 months post partum. Psychiatry Res 2016; 243: 43–8.
19. *Feldman M, Shong S.* Is CRP, like ESR, Age and Gender dependent? Rheumatology (Sunnyvale) 2014; 4(2): 134. doi: 10.4172/2161-1149.1000134
20. *Allam MH, Said AF, El Samie Omran AA, Abd El-Reheim DM, Kasem AH.* High sensitivity C-reactive protein: its correlation with sputum cell counts in bronchial asthma. Respir Med 2009; 103(12): 1878–84.
21. *Lee J, Yoon K, Ryu S, Chang Y, Kim HR.* High-normal levels of hs-CRP predict the development of non-alcoholic fatty liver in healthy men. PLoS One 2017; 12(2): e0172666. Erratum in: PLoS One 2018; 13(10): e0206834.
22. *Lapice E, Maione S, Patti L, Cipriano P, Rivellese AA, Riccardi G*, et al. Abdominal adiposity is associated with elevated C-reactive protein independent of BMI in healthy nonobese people. Diabetes Care 2009; 32(9): 1734–6.
23. *Im JA, Kim SH, Lee JW, Shim JY, Lee HR, Lee DC.* Association between hypoadiponectinemia and cardiovascular risk factors in nonobese healthy adults. Metabolism 2006; 55(11): 1546–50.
24. *De BK, Smith LG, Owen WE, Roberts WL.* Performance characteristics of an automated high-sensitivity C-reactive protein assay on the Dimension RXL analyzer. Clin Chim Acta 2002; 323(1–2): 151–5.
25. *Hornung RW, Reed LD.* Estimation of Average Concentration in the Presence of Nondetectable Values. Appl Occup Environ Hyg 1990; 5(1): 46–51.
26. *Jayedi A, Rahimi K, Bautista LE, Nazarzadeh M, Zargar MS, Shab-Bidar S.* Inflammation markers and risk of developing hypertension: a meta-analysis of cohort studies. Heart 2019; 105(9): 686–92.

27. *Clearfield MB*. C-reactive protein: a new risk assessment tool for cardiovascular disease. J Am Osteopath Assoc 2005; 105(9): 409–16.
28. *Wang Z, Wang X, Chen Z, Zhang L, Zhu M*. Distribution of High-Sensitivity C-Reactive Protein and Its Relationship with Other Cardiovascular Risk Factors in the Middle-Aged Chinese Population. Int J Environ Res Public Health 2016; 13(9): 872.
29. *Wang Z, Chen Z, Zhang L, Wang X, Hao G, Zhang Z*, et al. Status of Hypertension in China: Results From the China Hypertension Survey, 2012-2015. Circulation 2018; 137(22): 2344–56.
30. *Zhou B, Wu Y, Yang J, Li Y, Zhang H, Zhao L*. Overweight is an independent risk factor for cardiovascular disease in Chinese populations. Obes Rev 2002; 3(3): 147–56.
31. *Thomas GN, Ho SY, Lam KS, Janus ED, Hedley AJ, Lam TH,* et al. Impact of obesity and body fat distribution on cardiovascular risk factors in Hong Kong Chinese. Obes Res 2004; 12(11): 1805–13.
32. *Sesso HD, Buring JE, Rifai N, Blake GJ, Gaziano JM, Ridker PM*. C-reactive protein and the risk of developing hypertension. JAMA 2003; 290(22): 2945–51.
33. *Decker ML, Gotta V, Wellmann S, Ritz N*. Cytokine profiling in healthy children shows association of age with cytokine concentrations. Sci Rep 2017; 7(1): Article No. 17842.
34. *Lin Y, Kim J, Metter EJ, Nguyen H, Truong T, Lustig A*, et al. Changes in blood lymphocyte numbers with age in vivo and their association with the levels of cytokines/cytokine receptors. Immun Ageing 2016; 13: 24.
35. *Bernstein ED, Murasko DM*. Effect of age on cytokine production in humans. Age (Omaha) 1998; 21(4): 137–51.

Received on November 30, 2021
Revised on October 12, 2022
Revised on April 14, 2023
Accepted on August 8, 2023
Online First August 2023