Predictive value of asymmetric dimethylarginine and C-reactive protein for the risk of developing metabolic syndrome in middle-aged men

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A R T I C L E   I N F O

Article history:
Received 5 August 2014
Received in revised form 30 September 2014
Accepted 9 October 2014
Available online 27 October 2014

Keywords:
Asymmetric dimethylarginine
C-reactive protein
Metabolic syndrome
Prediction
Risk factors

A B S T R A C T

Background: We aimed to examine whether serum levels of asymmetric dimethylarginine (ADMA), an endogenous inhibitor of nitric oxide synthase, and C-reactive protein (CRP) are associated with the risk of developing metabolic syndrome in middle-aged men.

Methods: In this longitudinal study, serum ADMA and CRP levels were measured in Japanese men without metabolic syndrome, which was diagnosed according to the currently accepted unified criteria. The subjects were followed-up for a maximum of four years to determine new-onset metabolic syndrome. A Cox proportional hazards model with adjusting for potential confounders was applied to determine the hazard ratio (HR) for developing metabolic syndrome according to serum levels of ADMA and CRP, considered either alone or in combination.

Results: Of the 848 subjects (mean age, 43 ± 6 years), 100 subjects developed metabolic syndrome. High ADMA levels (≥0.45 μmol/L) alone did not show a significant HR for developing metabolic syndrome, while high CRP levels (≥0.3 mg/L) did (HR 1.75, 95% CI 1.12–2.74). The combination of high levels of both CRP and ADMA had a high HR (2.09, 95% CI 1.12–3.76) as compared to low levels of both markers. In contrast, the HR was not significant in the combination of high CRP and low ADMA levels, as well as low CRP and high ADMA levels.

Conclusions: Serum CRP, but not ADMA, levels were associated with the risk of metabolic syndrome. Nevertheless, the risk of metabolic syndrome could be predicted more reliably by considering these two markers together rather than CRP alone.

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1. Introduction

Metabolic syndrome is a cluster of multiple cardiometabolic risk factors including central obesity, elevated blood pressure (BP), elevated glucose levels, and dyslipidemia. The occurrence of metabolic syndrome is therefore a high-risk condition for the incidence of cardiovascular disease (CVD) [1]. From the viewpoint of primary prevention of CVD, it is important not only to clarify its pathophysiological mechanisms but also to seek useful markers for identifying individuals at risk of developing metabolic syndrome.

Nitric oxide (NO) is synthesized from its precursor L-arginine mainly in the vascular endothelium by NO synthase. NO regulates antithrombotic actions of the endothelium such as vasodilation and inhibition of cellular adhesion [2]. In addition to these effects, NO may exert a favorable impact on lipid metabolism, fat accumulation, and glucose metabolism including insulin sensitivity [3]. These findings raise the possibility that NO homeostasis may play a role in preventing metabolic syndrome. Recently, researchers have focused on asymmetric dimethylarginine (ADMA), a methylated form of L-arginine, because it functions as an endogenous inhibitor of NO synthase and can be regarded as a marker of NO availability. Given the possible protective effects of NO on the factors that lead to metabolic syndrome, it is hypothesized that elevated ADMA increases the risk of developing metabolic syndrome. This hypothesis is supported by the results of a previous cross-sectional study that found plasma ADMA levels to be elevated in individuals with metabolic syndrome [4]. However, to our knowledge, whether ADMA predicts future development of metabolic syndrome has not been fully investigated to date.

Inflammation is well known to play a crucial role in the pathogenesis of metabolic syndrome [5]. Previous cohort studies found C-reactive protein (CRP), one of the major inflammatory markers, to predict the risk of developing metabolic syndrome [6,7]. Importantly, experimental
findings have suggested a bidirectional relationship between ADMA and inflammation, i.e., ADMA induces the production of tumor necrosis factor-α (TNF-α) [8], a pro-inflammatory cytokine, while inflammation and oxidative stress facilitate local or systemic ADMA accumulation [9]. However, whether the relationship between ADMA and inflammation is involved in the development of metabolic syndrome remains unclear.

In this study, we examined the predictive value of the serum levels of the two markers, ADMA and CRP, considered either alone or in combination, for the risk of developing metabolic syndrome in middle-aged men.

## 2. Methods

### 2.1. Study population

This study was conducted at a precision equipment manufacturing company in Kanagawa, Japan. Under the Industrial Safety and Health Law of Japan, all employers are required to conduct health examinations of all employees at least once a year. In the baseline survey, male workers above the age of 35 years who had received an annual health examination in 2005 (baseline survey) were selected. Subjects diagnosed with metabolic syndrome or a history or presence of cardiovascular disease, or CRP levels ≥10.0 mg/L at baseline were excluded. Subjects who had incomplete data at baseline as well as those who did not receive any follow-up examinations were also excluded from the analysis. The study protocol was approved by the institutional ethics board of Nippon Medical School, Tokyo, Japan, and all participants gave written informed consent.

### 2.2. Baseline survey

All subjects underwent anthropometric and BP measurements as well as blood sampling. All measurements were conducted in a temperature-controlled room, maintained at 22 °C ± 2 °C. Body mass index (BMI) was calculated as the weight (kg) divided by the square of the height (m²). General obesity was defined as BMI ≥25.0 kg/m². Waist circumference was measured at the level of the umbilicus after expiration. Brachial BP was measured using a mercury sphygmomanometer by well-trained staff members while the subject was seated and at rest for at least 5 min.

A self-reported questionnaire was used to collect data regarding the subjects' smoking habits, frequency of alcohol intake, family history of CVD, exercise habits and medical information, including prescribed drugs. Subjects who smoked a cigarette at least once daily were characterized as current smokers; otherwise, they were categorized as non-smokers. Frequent alcohol intake was defined as alcohol intake at least six days a week. Regular exercise was defined as continuous exercise for at least 15 min at least three days a week for at least one year prior to the interrogation.

### 2.3. Biochemical analysis

At the time of baseline survey, blood samples were obtained from the antecubital vein after overnight fasting (≥8 h of fasting). Standard enzymatic methods were used to measure serum levels of total cholesterol, triglyceride, uric acid, creatinine, and plasma glucose levels. Serum high-density lipoprotein (HDL) cholesterol levels were measured using the direct method. Serum CRP levels were measured using a latex turbidimetric immunoassay (LPIA CRP-H, Mitsubishi Kagaku Iatron, Tokyo, Japan). The lower detection limit of the CRP assay was 0.1 mg/L and the intra-assay coefficient of variation has been reported to be ≤3.4% [10]. Hyperuricemia was defined as serum uric acid levels ≥7.0 mg/dL or under drug treatment for elevated uric acid. After the aforementioned measurements were done, the residual sera were stored at −30 °C for five years, and were used to measure ADMA levels as described elsewhere [11,12]. Briefly, serum ADMA levels were measured by high-performance liquid chromatography using ortho-phthalaldehyde for fluorescence determination at a commercial laboratory (SRL Inc., Tokyo, Japan). The lower detection limit of this assay was 0.06 μmol/L and the intra-assay coefficient of variation was ≤3.0%. The estimated glomerular filtration rate (eGFR) was calculated according to the following equation, as recommended for Japanese men by the Japanese Society of Nephrology [13]:

$$\text{eGFR} (\text{mL/min/1.73m}^2) = 193 \times \frac{\text{serum creatinine (mg/dL)}^{-1.094}}{\text{age(years)}}^{-0.287}.$$  

Chronic kidney disease was categorized into three groups: G1 for eGFR ≥90, G2 for eGFR of 60–89, and G3 — for eGFR <60 [14].

### 2.4. Definition of metabolic syndrome

Metabolic syndrome was defined according to the 2009 unified guidelines from the International Diabetes Federation Task Force on Epidemiology and Prevention [15]. Thus, the subjects were diagnosed with metabolic syndrome if at least three of the following five criteria were fulfilled: (1) central obesity, waist circumference ≥85 cm (for Japanese men); (2) elevated triglyceride, serum triglyceride levels ≥150 mg/dL or under drug treatment for elevated triglyceride; (3) reduced HDL cholesterol, serum HDL cholesterol levels <40 mg/dL or under drug treatment for reduced HDL cholesterol; (4) elevated BP, systolic BP ≥130 mm Hg, diastolic BP ≥85 mm Hg, or under antihypertensive drug treatment; and (5) elevated fasting glucose, fasting plasma glucose level ≥100 mg/dL or under drug treatment for elevated glucose. In this study, data regarding the type of prescribed drugs for dyslipidemia were lacking; therefore, subjects receiving drug treatment for dyslipidemia were considered to have elevated triglyceride levels.

### 2.5. Follow-up examinations

The outcome of this study was the development of metabolic syndrome. The subjects were followed-up every 12 months at the time of annual health examinations to determine the development of metabolic syndrome for a maximum period of four years (from 2006 to 2009). Data were censored at the 4-year follow-up or if subjects were lost to follow-up.

### 2.6. Statistical analysis

All statistical tests were performed using SPSS Statistics software, version 22 (IBM Japan, Tokyo, Japan). Continuous variables with or without a skewed distribution were expressed as the median (interquartile range), or the mean ± SD, respectively. Categorical data were expressed as percentages of the total. The baseline characteristics of the study groups were compared using Student's t-test, or the Kruskal–Wallis test, as appropriate. The correlation between ADMA and CRP was tested by the Spearman’s rank correlation coefficient. Univariate and multivariate Cox proportional hazards models were used to calculate the hazard ratio (HR) and the corresponding 95% CI for developing metabolic syndrome. For Cox analysis, the subjects were first dichotomized into low or high level groups depending on whether the ADMA or the CRP levels were below or above the median values, respectively. They were then divided into quartiles according to the ADMA or CRP levels. In these analyses, two multivariate models were applied; model 1 included ADMA and CRP categories as explanatory variables, while model 2 further included age, general obesity, hyperuricemia, chronic kidney disease stage, frequent alcohol intake, current smoking status, regular exercise, and family history of CVD as explanatory variables. The subjects were also categorized into...
the four subgroups according to the combination of low/high ADMA and CRP: low levels of both, low ADMA and high CRP, or high ADMA and low CRP. For this multivariate analysis, the same explanatory variables as in the model 2 were used. Lastly, the HR of each of the five diagnostic conditions of metabolic syndrome (central obesity, elevated BP, elevated triglyceride, reduced HDL cholesterol, and elevated fasting glucose) was determined in the multivariate Cox model. All statistical tests were 2-sided, and $p < 0.05$ was considered significant.

### 3. Results

Out of the 1084 men initially enrolled, some were excluded because, at baseline, they were diagnosed with metabolic syndrome ($n = 141$), or had CVD ($n = 9$), or had CRP levels $\geq 10.0$ mg/L ($n = 14$). Others were excluded due to incomplete records at baseline ($n = 18$). In addition, 54 subjects were excluded because they did not receive any follow-up examinations. Finally, 848 subjects (mean age $43 \pm 6$ years; range 35–62 years) were included in this analysis. Among the diagnostic conditions of metabolic syndrome, the prevalence of central obesity and elevated BP was approximately 25% in the eligible population, while the prevalence of reduced HDL cholesterol and elevated fasting plasma glucose was $\leq 10%$ at baseline (Table 1). The median values that were applied to differentiate subjects into low or high level categories were 0.45 umol/L for ADMA and 0.3 mg/L for CRP levels. A significant but weak correlation was found between ADMA and CRP levels (Spearman’s $\rho = 0.20$, $p < 0.001$). Baseline characteristics of the study participants according to the low or high level categories of ADMA or CRP are shown in Table 1 and those according to the quartile of ADMA or CRP are shown in Supplemental Tables S1 and S2, respectively.

During the total follow-up of 3119 person-years (mean follow-up period, 3.7 years; median, 4.0 years), 43 subjects were lost to follow-up and 100 subjects were judged to have developed metabolic syndrome.

In the Cox proportional hazards model (Table 2) for developing metabolic syndrome, high ADMA levels showed a significantly high HR, as compared with the low ADMA levels, in the univariate model (HR 1.58, 95% CI 1.06–2.36), but the significance was disappeared in either multivariate model 1 or 2. This trend was also seen in the quartile model of ADMA. In contrast, high CRP levels showed a significantly high HR not only in the univariate model and multivariate model 1, but also in the multivariate model 2 (HR 1.75, 95% CI 1.12–2.74). In the quartile model, the third and the highest quartiles of CRP had a significantly high HR both in the univariate model and multivariate model 1. Further, a significantly high HR was observed in the highest quartile of CRP in the multivariate model 2 (HR 2.55, 95% CI 1.28–5.09).

The effects of the four combinations of low/high ADMA and CRP on the development of metabolic syndrome were next analyzed (Table 3). The combination of high levels of both ADMA and CRP led to a significantly high HR as compared with the reference combination of low levels of both markers, in the univariate model (HR 2.91, 95% CI 1.67–5.08), as well as the multivariate model (HR 2.09, 95% CI 1.16–3.76). Importantly, the combination of low ADMA and high CRP

### Table 1

<table>
<thead>
<tr>
<th>Variable</th>
<th>Overall</th>
<th>ADMA</th>
<th>CRP</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Low (0.33–0.44 μmol/L)</td>
<td>High (0.45–0.79 μmol/L)</td>
<td>Low (&lt;0.1–0.2 mg/L)</td>
</tr>
<tr>
<td>Number of participants</td>
<td>848</td>
<td>430</td>
<td>418</td>
</tr>
<tr>
<td>ADMA, μmol/L</td>
<td>0.45 ± 0.05</td>
<td>0.41 ± 0.03</td>
<td>0.49 ± 0.04d</td>
</tr>
<tr>
<td>CRP, mg/L</td>
<td>0.2 (0.2, 0.5)</td>
<td>0.2 (0.1, 0.4)</td>
<td>0.3 (0.2, 0.6)d</td>
</tr>
<tr>
<td>Age, years</td>
<td>43 ± 6</td>
<td>43 ± 6</td>
<td>43 ± 6</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>22.9 ± 2.6</td>
<td>22.6 ± 2.3</td>
<td>23.2 ± 2.9e</td>
</tr>
<tr>
<td>Waist circumference, cm</td>
<td>81.1 ± 7.0</td>
<td>80.3 ± 6.1</td>
<td>81.7 ± 7.9d</td>
</tr>
<tr>
<td>Central obesity, n (%)</td>
<td>218 (25.7)</td>
<td>84 (19.5)</td>
<td>134 (32.1)d</td>
</tr>
<tr>
<td>Systolic BP, mm Hg</td>
<td>118 ± 12</td>
<td>118 ± 12</td>
<td>118 ± 12</td>
</tr>
<tr>
<td>Total cholesterol, mg/dL</td>
<td>195 ± 26</td>
<td>206 ± 31</td>
<td>108 (26.1)</td>
</tr>
<tr>
<td>Triglyceride, mg/dL</td>
<td>84 (75, 120)</td>
<td>77 (56, 114)</td>
<td>89 (21.3)c</td>
</tr>
<tr>
<td>HDL cholesterol, mg/dL</td>
<td>58 ± 13</td>
<td>59 ± 14</td>
<td>57 ± 12</td>
</tr>
<tr>
<td>Medication for dyslipidemia, n (%)</td>
<td>10 (1.2)</td>
<td>7 (1.6)</td>
<td>3 (0.7)f</td>
</tr>
<tr>
<td>Fasting plasma glucose, mg/dL</td>
<td>90 ± 10</td>
<td>90 ± 13</td>
<td>90 ± 7</td>
</tr>
<tr>
<td>Elevated fasting plasma glucose, n (%)</td>
<td>63 (7.4)</td>
<td>33 (8.1)</td>
<td>28 (6.7)</td>
</tr>
<tr>
<td>Medication for elevated glucose, n (%)</td>
<td>5 (0.6)</td>
<td>5 (1.2)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Uric acid, mg/dL</td>
<td>5.9 ± 1.2</td>
<td>5.8 ± 1.1</td>
<td>6.1 ± 1.2f</td>
</tr>
<tr>
<td>Hyperuricemia, n (%)</td>
<td>154 (18.2)</td>
<td>49 (11.4)</td>
<td>105 (25.1)d</td>
</tr>
<tr>
<td>Medication for hyperuricemia, n (%)</td>
<td>14 (1.7)</td>
<td>14 (1.7)</td>
<td>9 (2.1)</td>
</tr>
<tr>
<td>Serum creatinine, mg/dL</td>
<td>0.83 ± 0.05</td>
<td>0.81 ± 0.12</td>
<td>0.86 ± 0.09</td>
</tr>
<tr>
<td>eGFR, ml/min/1.73 m²</td>
<td>84.0 ± 1.3</td>
<td>85.4 ± 1.4</td>
<td>83.6 ± 1.2e</td>
</tr>
<tr>
<td>CKD stage, n (%)</td>
<td>259 (30.5)</td>
<td>144 (33.5)</td>
<td>115 (27.5)c</td>
</tr>
<tr>
<td>G1</td>
<td>572 (67.5)</td>
<td>281 (65.3)</td>
<td>291 (69.6)</td>
</tr>
<tr>
<td>G2</td>
<td>17 (2.0)</td>
<td>5 (1.2)</td>
<td>12 (2.9)</td>
</tr>
<tr>
<td>G3</td>
<td>231 (27.2)</td>
<td>93 (21.6)</td>
<td>138 (33.0)d</td>
</tr>
<tr>
<td>Current smoking, n (%)</td>
<td>206 (24.3)</td>
<td>108 (25.1)</td>
<td>98 (23.4)</td>
</tr>
<tr>
<td>Regular exercise, n (%)</td>
<td>187 (22.1)</td>
<td>89 (20.7)</td>
<td>98 (23.4)</td>
</tr>
<tr>
<td>Family history of CVD, n (%)</td>
<td>193 (22.8)</td>
<td>81 (18.8)</td>
<td>112 (26.8)c</td>
</tr>
</tbody>
</table>

*Median (interquartile range). $p < 0.05$, $p < 0.01$, and $p < 0.001$ between the groups. $^d p < 0.05$ between the groups across the CKD stages.

*Statistical analysis was not conducted because of small number of subjects in each category.

ADMA, asymmetric dimethylarginine; BMI, body mass index; BP, blood pressure; HDL, high-density lipoprotein; eGFR, estimated glomerular filtration rate; CKD, chronic kidney disease; CRP, C-reactive protein; CVD, cardiovascular disease.
levels showed a marginally higher HR (1.88, 95% CI 1.003–3.51) in the univariate model, but the significance disappeared in the multivariate model. The combination of high ADMA and low CRP levels did not show significant HR either in the univariate or in the multivariate model.

The effects of the above combinations on the development of each diagnostic condition of metabolic syndrome were analyzed (Table 4). Among the five diagnostic conditions, the combination of high levels of both markers showed a high HR only for reduced HDL cholesterol (HR 2.25, 95% CI 1.02–4.74). In addition, a significantly high HR for central obesity was found with the combination of low ADMA and high CRP levels (HR 2.00, 95% CI 1.29–3.09).

4. Discussion

The main findings of this study are as follows. First, high serum CRP levels, but not ADMA levels, were significantly associated with an increased risk of metabolic syndrome. Second, only the combination of high levels of both ADMA and CRP showed a significantly increased risk of metabolic syndrome among the combinations of low/high ADMA and CRP levels. Third, a significant association was observed between the combination of high levels of both markers and the risk of developing reduced HDL cholesterol among the five diagnostic conditions of metabolic syndrome.

The finding of a significant association between CRP levels and the risk of metabolic syndrome is consistent with that reported in previous epidemiological studies [6,7]. Increased visceral adiposity increases the secretion of pro-inflammatory cytokines such as TNF-α and interleukin-6 [16,17]. TNF-α reduces insulin sensitivity [16,18,19], which may in turn impair blood glucose and BP control. These pro-inflammatory cytokines also produce CRP in the liver [20] and adipocytes [21]. Our present finding for the association between CRP levels and the risk of developing metabolic syndrome may be explained by these pathophysiological mechanisms.

NO is reported to have protective effects against developing each diagnostic condition of metabolic syndrome through several mechanisms, such as vascular smooth muscle relaxation, mitochondrial proliferation and activation, improving insulin sensitivity, and inhibiting de novo fatty acid synthesis and decreasing acetyl-CoA carboxylase activity [3]. Therefore, given the function of ADMA as an NO synthase inhibitor, our present results indicating a significant association between the high ADMA levels and increased risk of metabolic syndrome seen in the univariate model are expected findings. Nevertheless, this significance was not maintained when CRP was considered simultaneously with ADMA in the analysis, while CRP levels were significantly associated with the risk of metabolic syndrome. Previous reports showed bidirectional relationship of ADMA and inflammatory responses [8,9]. However, in this study, only 4% (square of correlation coefficient, 0.20) of the variance of ADMA levels can be explained by CRP levels, and vice versa. These findings therefore suggest that in this study, only a weak relationship was demonstrated between reduced NO availability and activated inflammation, and the impact of reduced NO availability on the development of metabolic syndrome is smaller than that of activated inflammation. Further, the lack of data on serum L-arginine levels in this study is thought to be the other explanation for this negative result. Because ADMA competes with L-arginine for binding to NO synthase, the ratio of L-arginine to ADMA is thought to be a more reliable marker of NO availability than ADMA levels alone. In fact, a previous epidemiological study has shown that the combined analysis of L-arginine and ADMA more rigorously stratified their prognosis in community-dwelling participants [22]. The relationship of the combination of L-arginine and ADMA to the risk of metabolic syndrome merits further investigation.

The most important and intriguing findings in this study are that the combination of high levels of both ADMA and CRP, but not the
In contrast, there were no significant differences in the combination of low ADMA and high CRP levels, showing an increased risk of developing metabolic syndrome. As noted above, the effect of reduced NO availability on the development of metabolic syndrome appeared to be smaller than that of activated inflammation. Nevertheless, these observations suggest that the coexistence of these pathological states may be needed to further predispose subjects to an increased risk of metabolic syndrome. From a clinical perspective, the risk of metabolic syndrome could be predicted more reliably by measuring serum levels of CRP and ADMA together rather than CRP levels alone.

The combination of high levels of both ADMA and CRP was significantly associated with an increased risk of reduced HDL cholesterol. In contrast, there were no significant associations between the combination of high levels of both markers and the risk of developing any of the other four diagnostic conditions of metabolic syndrome. These results may be partly explained by an inadequate statistical power due to relatively small number of the study participants in each subgroup (n = 630 to 785). Meanwhile, the HR for central obesity was significantly high for the combination of low ADMA and high CRP levels. The reasons for this unexpected finding are difficult to understand on the basis of current knowledge and need to be further investigated.

This study has a few limitations. First, the study participants included only middle-aged, Japanese male workers from a single company. Therefore, it is unclear whether our results can be extrapolated to other populations, including the elderly, women, and other ethnic groups. Second, as mentioned above, the sample size may be inadequate to examine the true association between ADMA levels and the risk of metabolic syndrome, as well as that between the combinations of ADMA and CRP levels and the risk of developing the diagnostic conditions comprising metabolic syndrome, except for reduced HDL cholesterol. Third, although several potential confounders were examined in the multivariate analysis, other unknown confounders may exist, which may have affected the results.

In conclusion, in a population of middle-aged men, high serum CRP levels, but not ADMA levels, were associated with an increased risk of metabolic syndrome. Furthermore, the combination of high ADMA and high CRP levels increased the risk of metabolic syndrome, whereas the combination of low ADMA and high CRP levels did not increase the risk. These results suggest that activated inflammation rather than reduced NO availability may contribute to an increased risk of metabolic syndrome, but the coexistence of these pathophysiological conditions may further predispose to the development of metabolic syndrome. Hence, the measurement of serum levels of both ADMA and CRP may potentiate the predictive value for developing metabolic syndrome as compared with the measurement of CRP levels alone. In contrast, unexpectedly, the combination of high ADMA and high CRP levels did not predict the development of any condition that comprises metabolic syndrome, except for reduced HDL cholesterol. Further studies are needed to confirm our present results, and address unresolved issues in this study.

**Table 4**

Multivariate HR for developing each diagnostic condition of metabolic syndrome in the combination of low/high ADMA and CRP levels.

<table>
<thead>
<tr>
<th>Central obesity (n = 630)</th>
<th>Elevated BP (n = 636)</th>
<th>Elevated triglyceride (n = 733)</th>
<th>Reduced HDL cholesterol (n = 810)</th>
<th>Elevated fasting glucose (n = 785)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low CRP</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low ADMA</td>
<td>1.00 Reference</td>
<td>1.00 Reference</td>
<td>1.00 Reference</td>
<td>1.00 Reference</td>
</tr>
<tr>
<td>High ADMA</td>
<td>0.93 0.56–1.54</td>
<td>0.89 0.59–1.34</td>
<td>0.95 0.38–2.38</td>
<td>0.87 0.54–1.41</td>
</tr>
<tr>
<td>High CRP</td>
<td>2.00 1.29–3.09</td>
<td>0.79 0.47–1.34</td>
<td>2.30 0.99–5.34</td>
<td>0.99 0.56–1.76</td>
</tr>
<tr>
<td>High ADMA</td>
<td>1.36 0.85–2.18</td>
<td>1.08 0.70–1.64</td>
<td>2.25 1.02–5.00</td>
<td>1.32 0.81–2.17</td>
</tr>
</tbody>
</table>

All models include age, general obesity, hyperuricemia, chronic kidney disease stage, frequent alcohol intake, current smoking status, regular exercise, and family history of cardiovascular disease as explanatory variables.

**HR**, hazard ratio; **ADMA**, asymmetric dimethylarginine; **CRP**, C-reactive protein; **BP**, blood pressure; **HDL**, high-density lipoprotein.

**Supplementary data to this article can be found online at [http://dx.doi.org/10.1016/j.jcme.2014.10.001](http://dx.doi.org/10.1016/j.jcme.2014.10.001).**

**Sources of funding**

None.

**Conflict of interest**

The authors declare no conflict of interest.

**Acknowledgments**

This study was supported in part by the Grant-in-Aid for Scientific Research (C) from the Japan Society for the Promotion of Science (JSPS KAKENHI Grant Number 24590765).

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