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Mean platelet volume and prevalence of peripheral artery disease, the National Health and Nutrition Examination Survey, 1999–2004

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Abstract

Objectives—We sought to determine whether mean platelet volume (MPV) is associated with the prevalence of peripheral artery disease (PAD).

Background—Platelets play a pivotal role in the pathogenesis of atherosclerosis and PAD. MPV, a measure of platelet size available in every blood count, is increasingly recognized as an important marker of platelet activity.

Methods—We analyzed data from 6354 participants aged 40 years and older from the 1999 to 2004 National Health and Nutrition Examination Survey (NHANES), a nationally representative sample of the US population. PAD was defined as an ankle brachial index < 0.90 in either leg. Odds ratios and 95% confidence intervals were estimated by logistic regression.

Results—The prevalence of PAD in the cohort was 5.7%. MPV was significantly associated with PAD prevalence (tertile 1 – 4.4%, tertile 2 – 6.1%, tertile 3 – 7.0%, *P* for trend = 0.003). After adjustment for age, sex, and race, the odds ratio of PAD comparing the highest tertile to the lowest tertile was 1.57 (95% confidence interval 1.15–2.13). After further adjustment for smoking status, hypertension, hypercholesterolemia, diabetes, glomerular filtration rate, body mass index, and platelet count the corresponding odds ratio was 1.58 (95% confidence interval 1.14–2.19). The addition of triglycerides, hemoglobin A1c, and C-reactive protein did not affect the results. The significant association between MPV and PAD was unchanged when MPV was used as a continuous variable.

Conclusions—Mean platelet volume is independently associated with PAD. These findings support the hypothesis that platelet size is an independent predictor of increased risk for PAD.

Keywords

Mean platelet volume; Platelets; Peripheral artery disease; Epidemiology

Platelets are essential in the pathogenesis of atherosclerosis and arterial thrombosis [1,2]. Many studies have suggested that platelet activity is a risk factor for cardiovascular disease [3,4]. Increased platelet activity is linked to cigarette smoking, dyslipidemia, hypertension, and diabetes [1], all of which are associated with increased risk for cardiovascular disease. However, the specific role of platelet activity in this constellation of risk factors remains uncertain.

There is considerable controversy over the optimal method of measuring platelet activity [3,5]. Although measuring platelet activity by any of a wide variety of methods has been reported to identify individuals at increased risk for cardiovascular disease [6,7], it remains a research tool, yet to be included in routine clinical decision-making. Potential reasons include the cost and time consuming nature of the analysis, a lack of sufficient data about the optimal method of platelet function testing, unknown optimal cut-off for distinguishing increased risk, and the uncertainty about the interpretation and clinical utility of results [3,5].

Circulating platelets are heterogeneous in size, density and activity [8,9]. Mean platelet volume (MPV), a measure of platelet size available in every blood count, is increasingly recognized as an important marker of platelet activity [10]. Large platelets are more active, contain more prothrombotic material, and are more likely to aggregate compared with smaller platelets [11]. Platelet volume has been found to be increased in patients with myocardial infarction and cerebrovascular disease [11–13], but data in peripheral artery disease (PAD) are lacking.

The aim of this study was to evaluate the relationship between platelet activity and PAD, using the National Health and Nutrition Examination Survey (NHANES) from 1999 to 2004. We hypothesized that MPV is independently associated with the prevalence of PAD.

1. Methods

1.1. Study population

The National Health and Nutrition Examination Survey (NHANES) is an ongoing, cross-sectional survey of the civilian, non-institutionalized population of the United States. For the purpose of this study we combined data from the survey years 1999–2004. NHANES oversampled African Americans, Mexican Americans, and subjects 60 years and older. A total of 7571 subjects 40 years or older had a valid Ankle–Brachial Index (ABI) measured. Participants with an ABI >1.40 ($n = 46$), reflecting non-compressible arteries [14,15], or missing values in the variables of interest ($n = 1171$) were excluded, leaving 6354 individuals eligible for the present study.

1.2. Peripheral artery disease ascertainment

Beginning in 1999, subjects 40 years of age were asked to participate in the ABI section of the lower extremity disease examination. An 8 MHz Doppler ultrasound was used to measure the right brachial artery systolic blood pressure (left if a medical condition precluded measurement) and posterior tibial arteries of both ankles. For individuals 40–59 years of age, ankle pressures were measured twice at each site and once at each site for individuals 60 years or older. The left and right ABI was calculated by dividing the mean ankle systolic blood pressure for each side, respectively by the systolic blood pressure [16]. Prevalence of PAD was defined as an ABI value <0.90 in at least one leg [17].

1.3. Laboratory analysis

The mean platelet volume (MPV), platelet count and other blood cell indices were measured using a Beckman Coulter method of counting and sizing, automatic diluting and mixing [16]. An automated chemical analyzer (Beckman Syncrom LX20, Beckman Coulter, Fullerton, CA) was used to determine non-fasting glucose, serum creatinine, total cholesterol, triglycerides and HDL-cholesterol levels. Fasting glucose was measured using a hexokinase method. Due to a change in assay with subsequent data surveys serum creatinine values from the 1999 to 2000 examination dataset were corrected as suggested in the laboratory documentation files [16]. A latex-enhanced nephelometry method was used to measure C-reactive protein (CRP).

1.4. Other variables of interest

Participants self reported their age, race/ethnicity and gender. Race/ethnicity was recoded as non-Hispanic White, non-Hispanic Black, Mexican American and Other. Hypertension was defined if a subject had a systolic blood pressure ≥ 140 mm Hg and/or diastolic blood pressure ≥ 90 mm Hg, a self reported prescription use for hypertension or diagnosis of hypertension [16]. Hypercholesterolemia was defined if a subject reported use of cholesterol lower prescription, physician diagnosis or if the total serum cholesterol level was ≥ 240 mg/dl. The presence of diabetes was determined if a subject had a fasting glucose ≥ 126 mg/dl, a non fasting glucose ≥ 200 mg/dl, or a self reported physician diagnosis of diabetes or use of oral hypoglycemic medications or insulin. The presence of cardiovascular disease was determined if the subject responded positively to the question “Has a doctor or other health professional ever told you have had a heart attack, congestive heart failure or stroke?”. Chronic kidney disease was defined if an estimated glomerular filtration rate (eGFR) was ≤ 60 ml/min/1.73 m². Each subject had the eGFR calculated based on the abbreviated Modification of Diet in Renal disease Study equation: $175 \times (\text{Serum Creatinine in mg/dl})^{-1.154} \times (\text{Age in years})^{-0.203} \times (0.742 \text{ if female}) \times (1.210 \text{ if Non-Hispanic Black})$ [18]. Smoking status was categorized using a self reported questionnaire. If subjects had a positive response to the question “Do you now smoke cigarettes?” they were labeled as “current smokers”. Subjects who answered no were labeled as “former smokers” if they answer positively to the question “Have you smoked at least 100 cigarettes in your life”. If they never smoked in their lifetime they were labeled as “never smokers”.

1.5. Statistical analysis

NHANES uses a complex, multistage, probability-sampling design to select participants representative of the civilian, non-institutionalized US population. All analyses accounted for the complex sampling method following the NHANES analytic guidelines [16].

Demographics, comorbidities, and other characteristics were compared between subjects with and without PAD. *P*-values were obtained from linear regression for comparing continuous variables across the two groups (PAD vs. non-PAD), or cross tabulations (specifically, Rao-Scott modified Chi-square tests) for categorical variables. For continuous variables that were highly skewed, natural log transformation was applied and *P*-values were obtained comparing the mean of the log transformed variables. For these variables, geometric means and standard errors were calculated as the exponential of the log transformed means and standard errors.

Associations between MPV and selected cardiovascular risk factors were examined using Pearson correlation coefficients. *P*-values were obtained from the regression coefficient by regressing MPV on these risk factors (original scale or log transformed) one by one.

To explore the relationship between MPV and PAD, logistic regression was used with PAD as the dichotomous outcome and MPV as the main predictor. Exploratory analysis showed that the relationship between MPV and the risk of PAD appeared to be linear. Therefore, MPV entered the models as a continuous variable. We also categorized MPV by its tertiles and examined the presence of a linear trend across tertiles. We built models hierarchically for both continuous and categorical MPV. First, we added in demographics such as age, sex, and race into the logistic regression model. This was followed by platelet count. Other confounders such as smoking status, hypertension, hypercholesterolemia, diabetes, glomerular filtration rate, and body mass index were included in the next step. We next examined the impact of potential intermediate biomarkers by adding log triglycerides, log HbA1c, and log CRP as continuous variables one by one, and then all variables together in a model.

To evaluate the consistency of effect of MPV on PAD in subgroups defined by participant characteristics, we fitted a logistic regression model in each subgroup adjusted for other confounders except for the one that was used to define the subgroups. We tested the statistical significance of the interactions between MPV and patient characteristics which was dichotomized for the ease of presentation, adjusting for other confounders. All *P*-values presented are two-tailed; *P* < 0.05 was considered statistically significant. All statistical analyses were performed using SAS 9.2 to account for the complex sampling design. Domain statement was used in all analysis to ensure the correctness of variance estimates.

This manuscript follows the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) recommendations [19]. The authors had full access to and take responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

2. Results

Among the 6354 participants in our sample population, there were 535 with PAD (weighted prevalence 5.7%; 95% confidence interval 5.0–6.4%). Baseline characteristics of participants with and without PAD are summarized in Table 1. Subjects with PAD were older and more frequently female. PAD subjects had a higher prevalence of diabetes, hypertension, and chronic kidney disease than non-PAD subjects. No significant difference in body mass index and total cholesterol was detected between the two groups. Mean platelet volume was significantly higher in PAD subjects than non-PAD subjects, whereas total platelet count did not differ between the groups.

We next examined the association of MPV with selected cardiovascular risk factors (Table 2). Mean platelet volume was significantly although weakly positively correlated with body mass index, HbA1c, and systolic blood pressure. No significant correlation existed between MPV and log transformed CRP, log transformed high density lipoprotein, total cholesterol, log transformed triglycerides, and glomerular filtration rate. As expected, MPV and platelet count were inversely correlated.

Prevalence of PAD increased significantly in a graded fashion with increasing MPV tertiles (tertile 1 – 4.4% [SE = 0.4%], tertile 2 – 6.1% [SE = 0.6%], tertile 3 – 7.0% [SE = 0.8%]; *P* for trend = 0.001) (Fig. 1). In unadjusted and adjusted analyses, tertile of MPV was significantly associated with the prevalence of PAD (Table 3). After adjustment for age, sex, and race, subjects in the highest compared with the lowest tertile of MPV levels had a significantly increased odds of PAD (odds ratio 1.57, 95% confidence interval 1.15–2.13). Further adjustment for traditional risk factors and platelet count did not substantially affect this relationship (odds ratio 1.58, 95% confidence interval 1.14–2.19). This relationship

persisted even after additional adjustment for C-reactive protein (odds ratio 1.58, 95% confidence interval 1.14–2.20).

We next examined the impact of potential intermediary biomarkers on the relation between MPV and the odds of PAD, by sequentially adding these markers to our model, and calculated the multivariable adjusted odds ratio associated with an increase of each femtoliter of MPV. As demonstrated in Fig. 2, after multivariable adjustment, the addition of triglycerides, HbA1c, and CRP did not substantively affect the results.

We repeated our main analysis excluding participants with a history of cardiovascular disease ($n = 980$) and found nearly identical results. The multivariable adjusted odds ratio associated with an increase of each femtoliter of MPV was 1.25 (95% confidence interval 1.08–1.45). Subjects in the highest compared with the lowest tertile of MPV levels had a significantly increased odds of PAD (odds ratio 1.68, 95% confidence interval 1.10–2.55).

Table 4 shows the multivariable adjusted odds ratio of PAD prevalence associated with an increase of each femtoliter in MPV in subgroups of our population. In general, the results were similar in younger and older participants, men and women, and in different strata of cardiovascular risk factors. A borderline significant interaction was detected in subjects of different race/ethnicity ($P = 0.044$). Stratification by CRP (<3 mg/L and ≥ 3 mg/L) influenced the predictive value of MPV for prevalence of PAD (P for interaction = 0.01). In a multivariable adjusted model, MPV was significantly associated with PAD in subjects with a CRP <3 mg/L (odds ratio 1.44, 95% confidence interval 1.17–1.78). However, for those with a CRP ≥ 3 mg/L, the association was no longer significant (odds ratio 0.99, 95% confidence interval 0.83–1.18).

3. Discussion

In a nationally represented sample population, MPV was significantly associated with prevalence of PAD. This association was independent of traditional cardiovascular risk factors for PAD. After multivariable adjustment, the association of MPV and PAD was progressive with no obvious threshold, and consistent for most population subgroups. The significant association with PAD is consistent with the known greater activity of larger platelets [20–26], the role of platelets in the pathogenesis of PAD [27], and the established effects of antiplatelet therapy in the treatment of PAD [28].

Prior studies support the use of MPV as a measure of platelet activity [10,11,13]. Larger platelets are metabolically and enzymatically more active than smaller platelets, containing more pro-thrombotic material with increased thromboxane B_2 per unit volume and glycoprotein IIb/IIIa receptor expression [20,23]. Larger platelets possess greater aggregability in response to ADP and decreased inhibition of aggregation by prostacyclin *in vitro* [22,25]. Larger platelets are denser which contain more alpha granules, which release prothrombotic factors [24,26]. Larger platelets are also associated with increased reticulated platelets, an independent predictor of poor response to dual antiplatelet therapy [21].

Previous investigators have demonstrated a correlation between MPV and certain cardiovascular risk factors [10,11]. A recent systematic review and meta-analysis concluded that MPV was associated with acute myocardial infarction, restenosis following angioplasty and mortality following myocardial infarction [13]. In the largest study to date [29], Martin and colleagues reported that following a MI, MPV was an independent risk factor for recurrent ischemia or death at 2 years of follow-up. Of note, a recent study found that rosuvastatin has MPV reducing properties and this effect is not correlated to changes in lipid values, suggesting a novel potential mechanism of benefit [30].

In the present study, we extended prior work by examining the relationship between MPV and PAD. With more than 6300 patients, this is the largest reported analysis of MPV assessment, and the first in subjects with PAD. We found an approximate 25% increased odds of PAD for each femtoliter increase in MPV, a finding that remained consistent after adjustment for atherosclerotic risk factors, and factors related to platelet activity. In addition, the trend across tertiles was statistically significant in unadjusted and fully adjusted analyses. The significant relationship between MPV and PAD persisted even after additional adjustment for CRP, hemoglobin A1c and triglycerides. Furthermore, the significant association persisted after excluding participants with a history of cardiovascular disease.

As has been seen with other methods for assessing platelet activity, we observed expected associations between MPV and a number of classic cardiovascular risk factors. For example, MPV was significantly correlated with body mass index, hemoglobin A1c, and systolic blood pressure. Importantly, adjustment for these variables did not markedly attenuate the odds of PAD from MPV. Several traditional risk factors were not related to MPV (Table 2). No significant relation existed between MPV and CRP, lipid values, and glomerular filtration rate. A threshold of the grade of platelet activity and the type of platelet activity measured by MPV may explain the lack of any association between MPV and certain cardiovascular risk factors. Furthermore, MPV in this study seems to mainly reflect the thrombophilic and not the inflammatory part of the increased platelet activity. We observed a significant inverse relationship between platelet count and MPV. The relationship between platelet count and MPV is incompletely understood; several studies (including ours) reported an inverse correlation between MPV and platelet count, while one study found that platelet count and platelet volume both increase during stimulated thrombopoiesis, suggesting that platelet count and volume may be regulated by independent mechanisms [31,32]. Consistent with other studies, the present analysis found no significant association between platelet count and PAD (data not shown). The heightened risk of PAD was confined to platelet volume.

Given the significant relationship between inflammation, platelets, and atherosclerosis [33,34], we explored the possibility that CRP (a marker of inflammation) may influence the association between MPV and PAD. Indeed, our analysis demonstrated a significant interaction between MPV and CRP (P for interaction = 0.01). A strong association was detected between MPV and PAD among individuals with CRP <3 mg/L (odds ratio 1.44); however, this association was no longer evident in subjects with CRP ≥ 3 mg/L (odds ratio 0.99). The attenuation of the relationship between MPV and PAD in the presence of elevated CRP may be explained in part by the complex interrelationship of inflammation and platelets in atherosclerotic disease [33]. In individuals with low levels of inflammation, platelet activity may have a relatively large contribution to the development of atherosclerosis. In contrast, in the presence of increased inflammation (e.g. elevated CRP), the relative contribution of platelet activity to the odds of PAD may be diminished. Alternatively, the findings related to CRP may have been due to chance.

The present study has several limitations. Because of the cross-sectional design, we cannot establish causal relations between MPV and PAD; however, our findings support the link between PAD and platelet activity. Second, although MPV is associated with platelet activity, other reasons may contribute to a higher MPV including relative thrombocytopenia. For that reason, we present our data in multiple subgroups (including platelet counts <250) and test for their interaction. Third, we acknowledge that much of the variability in MPV remains unexplained by clinical factors. Fourth, the cohort was US adults greater than 40 years of age; therefore, our findings may not be generalizable to younger individuals and/or populations outside the US. Fifth, MPV was ascertained at a single time point and may be susceptible to short-term variation, which would bias the results toward the null; however,

data suggest that MPV values remain constant when assessed over a period of time [35]. Finally, the variability in the timing and methods of blood sample preparation may have had a significant impact on the measurement of MPV. EDTA has been shown to cause platelet swelling in a time dependent manner [10]. Although specific instructions were given to run the blood count within 2 h, sites were allowed to run the sample up to a maximum of 24 h. However, it is unlikely that this difference in timing would affect those with and without PAD in a non-random manner. Moreover, this would have biased our results toward the null. Nevertheless, further consideration should be given for standardization in future studies.

The present study also has several strengths, including a large sample size and routine ascertainment of coexistent PAD risk factors in a random multiracial sample across the US, which provides excellent power and facilitates adjustment for multiple covariates. In addition, the community-based design reduces selection and referral biases.

In conclusion, this study demonstrated that higher MPV is associated with PAD among a nationally represented sample population of US adults, independent of traditional cardiovascular risk factors. Future longitudinal studies are warranted to provide additional information about the clinical utility of measuring MPV and the pathways connecting platelet activity, cardiovascular risk, and peripheral artery disease.

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Fig. 1.

Weighted prevalence of PAD in increasing MPV tertiles. The range of MPV in tertile 1 was 5.5–7.8 fl (median – 7.4). The range of MPV in tertile 2 was 7.9–8.6 fl (median – 8.2). The range of MPV in tertile 3 was 8.7–13.5 fl (median – 9.1).

Fig. 2.

Estimated odds ratio of peripheral artery disease. Odds ratio of PAD associated with an increase of each femtoliter of MPV after adjustment for triglycerides, hemoglobin A1c, and CRP levels separately, or together. Multivariable adjustment included age, sex, smoking status, hypertension, hypercholesterolemia, diabetes, glomerular filtration rate, body mass index, and platelet count. Triglycerides, CRP and HbA1c were log transformed. The middle point of each bar is the estimated odds ratio and the two ends are the limits of 95% confidence intervals.

Table 1

Demographic information and clinical history in subjects with and without peripheral artery disease.

	PAD (n = 535)	No PAD (n = 5819)	P value
Age (year)	67.8 (0.7)	55.4 (0.2)	<0.0001
Female (%)	57.6 (2.8)	51.1 (0.7)	0.038
Race/ethnicity (%)			0.141
Non-Hispanic White	78.4 (2.3)	78.8 (1.8)	
Non-Hispanic Black	14.2 (2.1)	8.5 (0.9)	
Mexican American	3.3 (1.1)	4.8 (0.8)	
Other	4.0 (1.4)	8.0 (1.2)	
Body mass index (kg/m ²)	28.6 (0.3)	28.4 (0.1)	0.075
Current smoker (%)	24.9 (1.8)	20.3 (0.8)	<0.0001
Diabetes (%)	24.8 (3.1)	11.7 (0.6)	0.005
Hypertension (%)	75.5 (2.5)	46.8 (1.2)	<0.0001
Hypercholesterolemia (%)	60.4 (2.2)	50.9 (0.9)	0.267
Coronary artery disease (%)	21.9 (2.3)	7.0 (0.5)	<0.0001
Cerebrovascular disease (%)	10.4 (1.5)	2.8 (0.3)	<0.001
Chronic kidney disease (%)	34.2 (2.4)	10.4 (0.7)	<0.0001
GFR (ml/min/1.73 m ²)	69.2 (1.0)	80.6 (0.5)	0.002
Hemoglobin A1c ^a	5.9 (1.0)	5.6 (1.0)	0.004
C-reactive protein ^a (mg/L)	3.6 (1.1)	2.1 (1.0)	<0.0001
Total cholesterol (mg/dl)	209.7 (2.9)	210.7 (0.9)	0.494
Triglycerides ^a (mg/dl)	142.0 (1.0)	126.0 (1.0)	0.012
HDL ^a (mg/dl)	49.3 (1.0)	50.8 (1.0)	0.0002
Platelet count (1000 cells/ μ L)	261.8 (3.3)	266.1 (1.4)	0.330
Mean platelet volume (fl)	8.3 (0.1)	8.2 (0.03)	0.001
Ankle brachial pressure index	0.8 (0.01)	1.1 (0.002)	<0.0001

PAD, peripheral artery disease; GFR, glomerular filtration rate. For categorical variables, data are shown as weighted percent (standard error [SE]), and Rao-Scott modified Chi-square test was used for statistical comparison. For continuous variables, data are shown as mean (SE), and *P* values were obtained by linear regression.

^aGeometric means (SE) were used.

Table 2

Univariate correlation coefficients between mean platelet volume and selected cardiovascular risk factors.

Peripheral artery disease risk factors	<i>R</i>	<i>P</i> value
Age	0.025	0.174
Body mass index	0.039	0.011
C-reactive protein ^a	0.006	0.755
Hemoglobin A1c ^a	0.066	<0.001
High density lipoprotein ^a	−0.034	0.055
Total cholesterol	−0.021	0.104
Triglycerides ^a	0.004	0.804
Systolic blood pressure	0.050	0.003
Glomerular filtration rate	−0.020	0.245
Platelet count	−0.385	<0.001

^aLog transformed values were used.

Table 3

Logistic regression analysis of the association between mean platelet volume and peripheral artery disease.

	MPV continuous	Tertile 1	Tertile 2	Tertile 3	P for trend
Range		5.5–7.8	7.9–8.6	8.7–13.5	
Median		7.4	8.2	9.1	
Unadjusted	1.24 (1.10–1.41)	1 (ref)	1.43 (1.10–1.84)	1.65 (1.22–2.22)	0.001
Adjusted for age, sex and race	1.19 (1.07–1.33)	1 (ref)	1.52 (1.14–2.02)	1.57 (1.15–2.13)	0.001
Adjusted for age, sex, race and platelet count	1.27 (1.13–1.43)	1 (ref)	1.62 (1.20–2.17)	1.78 (1.28–2.46)	<0.001
Multivariable adjustment *	1.21 (1.06–1.37)	1 (ref)	1.51 (1.12–2.04)	1.58 (1.14–2.19)	0.004
Multivariable adjustment + CRP *	1.20 (1.05–1.36)	1 (ref)	1.53 (1.13–2.06)	1.58 (1.14–2.20)	0.005

Odds ratios and 95 percent confidence intervals were obtained by logistic regression model with tertile 1 as the reference population.

Adjusted for age, sex, race, smoking status, hypertension, hypercholesterolemia, diabetes, glomerular filtration rate, body mass index, and platelet count.

* CRP was log-transformed.

Table 4Multivariable ^{*} adjusted estimated odds ratio of PAD prevalence for MPV [†]

	Number	OR (95%CI)	P value for interaction
Overall	6354	1.20 (1.05–1.36)	
Age			0.365
<60	3053	1.43 (1.03–2.06)	
60	3301	1.13 (0.97–1.31)	
Sex			0.462
Female	3259	1.33 (1.07–1.65)	
Male	3095	1.09 (0.92–1.30)	
Race			0.044
Non-Hispanic White	3485	1.28 (1.09–1.50)	
Other	2869	0.96 (0.78–1.19)	
Overweight			0.374
BMI <30	4250	1.09 (0.92–1.30)	
BMI ≥30	2104	1.22 (0.97–1.53)	
Current smoker			0.701
No	1213	1.29 (0.97–1.71)	
Yes	5141	1.17 (1.01–1.35)	
Diabetes			0.684
No	5279	1.15 (1.00–1.33)	
Yes	1075	1.37 (0.97–1.92)	
Hypertension			0.350
No	2831	1.45 (1.00–2.11)	
Yes	3523	1.13 (0.98–1.31)	
Chronic kidney disease			0.248
No	5425	1.30 (1.10–1.53)	
Yes	929	0.99 (0.77–1.28)	
Hypercholesterolemia			0.710
No	3055	1.28 (1.04–1.57)	
Yes	3299	1.15 (0.98–1.35)	
CRP level, mg/L			0.010
<3mg/L	3603	1.44 (1.16–1.78)	
≥3mg/L	2751	1.00 (0.84–1.18)	
Platelet count 1000cells/ul			0.391
<250	2962	1.15 (0.91–1.45)	
≥250	3392	1.29 (1.06–1.57)	

^{*} Adjusted for age, sex, race, smoking status, hypertension, hypercholesterolemia, diabetes, glomerular filtration rate, body mass index, platelet count, and log transformed CRP. The particular variable that was used to define the subgroups was not adjusted for.

[†] Effect estimates and P values were obtained using MPV as a continuous variable.