P-selectin and C-reactive protein in relation to home blood pressure and coronary calcification: a SCAPIS substudy

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Short title: P-selectin and home blood pressure

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Abstract

Background: Soluble P-selectin (sP-selectin) and high-sensitivity CRP (hsCRP) have previously been associated with hypertension, but the relation with out-of-office blood pressure (BP) and coronary artery calcification score is unknown. We aimed to examine the relationship between sP-selectin, hsCRP and home BP, as well as coronary artery calcification score and carotid artery plaques.

Methods: In the Swedish CArdioPulmonary bioImage Study (SCAPIS), 5057 randomly selected participants were evaluated with office and home BP using the semi-automatic Omron M10-IT device. For this cross-sectional study, participants with sP-selectin <4 standard deviations above mean and hsCRP <5 mg/L, representing low-grade inflammation, were included. Using generalized linear models, these inflammatory markers were evaluated in relation to BP classifications, as well as coronary artery calcification score and carotid artery plaques.

Results: Of participants, 4548 were included in the analyses. The median age was 57.2 (53.4-61.2) years, and 775 (17.0%) reported taking medication for hypertension. Participants in the highest quartile of sP-selectin (OR 1.67, 95% CI 1.40-1.98, *P* <.001) and hsCRP (OR 2.25, (95% CI 1.89-2.60, *P* <.001) were more likely to have sustained hypertension. Participants in the highest quartile of hsCRP were also more likely to have masked hypertension, OR (95% CI) 2.31 (1.72-3.10), *P* <.001 and carotid artery plaques, OR (95% CI) 1.21 (1.05-1.38), *P* = .007.

Conclusion: Increased sP-selectin and hsCRP were independently associated with sustained hypertension. These findings indicate an association between hypertension and platelet activity, as expressed by sP-selectin.

Keywords

Blood pressure, cardiovascular disease, carotid artery plaque, coronary artery calcium score, c-reactive protein, home blood pressure, selectin.

Abbreviations

BP, blood pressure; CACS, coronary artery calcium score; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; hsCRP, high sensitivity C-reactive protein; eGFR, estimated glomerular filtration rate; hsCRP, high sensitivity C-reactive protein; LDL, low-density lipoprotein; SCAPIS, The Swedish CArdioPulmonary bioImage Study.

1. Introduction

Elevated blood pressure (BP), both at the office and out-of-office, is associated with increased risk of cardiovascular disease [1]. Combining office with out-of-office BP enables the diagnosis of intermediate hypertension phenotypes, including white coat hypertension and masked hypertension [2].

Inflammation is associated with hypertension, cardiovascular disease, and obesity, and with the pathogenesis of type 2 diabetes mellitus [3-5]. Levels of high sensitivity C-reactive protein (hsCRP) correlate to obesity, type 2 diabetes mellitus, BP, atherosclerosis, and arterial stiffness [6-10].

Selectins are proteins that mediate adhesion of blood cells to vascular endothelium [11]. One of these, P-selectin, is expressed by both endothelial cells and activated platelets, and contributes to atherosclerosis and thrombosis [11,12]. Soluble P-selectin (sP-selectin) can be measured in plasma, and increased levels are considered to be of platelet origin [13]. In healthy individuals, sP-selectin correlates strongly with platelet count [13]. Higher levels of both sP-selectin as well as activated platelets displaying P-selectin are found in patients with inflammatory and thrombotic disorders, including hypertension and acute coronary

syndrome [11,13-15]. In individuals without known cardiovascular disease, sP-selectin levels also correlate to the risk of future cardiovascular events [17,18]. However, the relation between sP-selectin and home BP is not known.

The primary aim of our study was to explore sP-selectin in relation to home BP and markers of cardiovascular disease in a large cohort of randomly selected middle-aged individuals.

2. Methods

2.1. Study population

The prospective, observational Swedish CArdioPulmonary bioImage Study (SCAPIS) includes 30,000 men and women aged 50 to 64 years, randomly selected from the Swedish population register [20]. In brief, the study includes data from anthropometric measurements, blood analyses, questionnaires, and imaging studies [20]. Additionally, in a subsample of 5057 participants in Linköping, both office and home BP were measured. In the current study, this subsample was analyzed cross-sectionally.

2.2. Blood pressure measurement and definition of blood pressure classification

BP measurement methodology has been previously described in detail [21]. In brief, participants were instructed to avoid smoking, coffee, and strenuous activity 1 hour before measurements. The semi-automatic Omron M10-IT oscillometric device (Omron, Kyoto, Kyoto prefecture, Japan) was used to measure BP after 5 minutes' rest. Office BP was measured in the supine position on each arm, and the arm with the highest mean of 3 measurements was used for all subsequent analyses. Home BP was measured in the sitting position 3 times in the morning and 3 times in the evening for 7 consecutive days, except for the first day in which no morning measurement was recorded,. The mean values of all systolic and diastolic measurements respectively were used in the analyses.

Categorization of BP has previously been described [22]. In brief, hypertensive office BP was defined as systolic ≥140 mmHg and/or diastolic ≥90 mmHg; and hypertensive home BP was defined as systolic ≥135 mmHg and/or diastolic ≥85 mmHg. BP was then classified as sustained normotension if both office and home BP were normal; white coat hypertension if office BP was elevated, but home BP was normal; masked hypertension if office BP was normal, but home BP was elevated; and sustained hypertension if both office and home BP were elevated.

2.3. Markers of inflammation and platelet activity

Meso Scale Discovery (MSD) platform (Rockville, Maryland, USA), an electrochemiluminescence assay, was used to measure concentrations of sP-selectin in Li-Heparin plasma according to the manufacturer's instructions. Inter-assay coefficient of variations was 2.08% for sP-selectin. Analyses were made by SciLifeLab, Clinical biomarkers facility in Uppsala, Sweden.

For the inflammatory marker hsCRP the lower limit of quantification was 0.15 mg/L.

2.4. Markers of cardiovascular disease

Pulse wave velocity (PWV) was measured using the SphygmoCor® XCEL system (AtCor Medical, Sydney, NSW, Australia), according to a previously published protocol [23].

The presence of carotid artery plaques was investigated bilaterally as previously described [24]. Coronary artery calcifications were assessed using a SOMATOM Definition Flash computed tomography scanner (Siemens Medical Solution, Forchheim, Germany), and quantified using the Agatston score as coronary artery calcification score [25].

2.5. Statistical analyses

In this study analyzing low-grade inflammation, participants with missing values of hsCRP or values at or above 5 mg/L were excluded. Participants with missing values of sP-selectin, or values beyond 4 standard deviations above mean, were also excluded.

Continuous variables, all with skewed distribution, are shown as the median and interquartile range, and categorical variables as the frequency and percentage.

The difference between office BP and home BP ("office-home BP difference") was calculated for each individual by subtracting the home BP from the office BP. Low-density lipoprotein (LDL) was calculated using Friedwald's formula (LDL = total cholesterol – high-density lipoprotein – 0.45 x triglycerides). Estimated glomerular filtration rate (eGFR) was calculated using the 2021 Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation [26]. Coronary artery calcification score was presented both as a continuous variable as well as a dichotomous variable of a total score of less than 100, or a total score of 100 or above, because of its skewedness. The presence of carotid artery plaques was presented as a dichotomous variable of no plaque or one or more plaques [24]. Differences between BP classifications were tested using a Kruskal-Wallis test with pairwise comparisons using Conover's many-to-one test. The Holm-Bonferroni method was used to correct for multiple comparisons.

Analyses using binomial generalized linear models of quartile 4 vs quartiles 1 to 3 of sP-selectin and hsCRP in relation to BP classification and markers of cardiovascular disease were crude (model 1), adjusted for age and sex (model 2), adjusted for model 2 and smoking, and diagnosis of diabetes mellitus and hyperlipidemia (model 3), and adjusted for model 3 and, and hsCRP and sP-selectin respective (model 4 for analysis of sP-selectin and hsCRP respectively). For analyses in relation to markers of cardiovascular disease, adjustments were

the same except that for model 3, diagnosis of hypertension was added to the model. Results were presented as the odds ratios (OR), the 95% confidence intervals (CI) and the *P* values. The associations with sP-selectin and hsCRP for each BP classification were also evaluated using linear regression and presented in figures with the estimates, the 95% CI and *P* value. Statistical tests were two-tailed and *P* values of <.05 were considered statistically significant. R version 4.3.0 (R Core Team, Vienna, Austria) and RStudio version 2023.03.1+446 (Posit Software, Boston, MA, USA) were used for data analyses.

2.5. Ethical considerations

The SCAPIS study was approved by the Regional Ethical Review board in Umeå (Dnr 2010-228-31M) and the Regional Ethical Review board in Linköping (Dnr 2018/478-31) and adheres to the Declaration of Helsinki.

3. Results

Of 5057 participants, 5029 measured home BP. Of those, 123 were excluded because of missing sP-selectin values, 15 were excluded because of sP-selectin values beyond 4 standard deviations above mean (83.9 ng/mL), and 343 were excluded because of hsCRP values at or above 5 mg/L. Thus, a total of 4548 individuals were included in our analysis. The median age was 57.2 (53.4-61.2) years, and 2286 (50.3%) of the participants were men.

Of participants, 775 (17.0%) reported taking medication for hypertension, table 1. Soluble P-selectin was higher in participants with white coat hypertension, masked hypertension, and sustained hypertension vs sustained normotension, median (Q1-Q3) 34.9 (27.3-43.0), 35.8 (28.5-42.4) and 36.8 (29.1-34.1) vs 33.5 (26.7-41.1) ng/mL, *P* = .011 *P* = .030 and *P* <.001 respectively, table 2 and figure 1. Participants with white coat hypertension, masked hypertension, and sustained hypertension vs sustained normotension had higher hsCRP,

median (Q1-Q3) 0.9 (0.4-1.4), 1.2 (0.7-2.1) and 1.2 (0.7-2.3) vs 0.8 (0.4-1.4) mg/L respectively, *P* <.001 for all comparisons, table 2 and figure 2.

Participants in the highest quartile of sP-selectin vs quartiles 1-3 were more likely to have white coat hypertension (OR 1.29; 95% CI, 1.07-1.54; *P* = .007) and sustained hypertension (OR 1.67; 95% CI, 1.40-1.98; *P* <.001) compared with normotension. The results remained after adjustment for age, sex, smoking, diabetes mellitus and hyperlipidemia, and for sustained hypertension also after adjustment for hsCRP, table 3. Using linear regression, higher sP-selectin was associated with an increased proportion of participants with sustained hypertension, estimate of linear regression (95% CI) 0.28 (0.11-0.46), *P* = .002, figure 3.

Participants in the highest quartile of hsCRP vs quartiles 1-3 were more likely to have white coat hypertension (OR 1.37; 95% CI, 1.14-1.64; *P* <.001), masked hypertension (OR 2.31; 95% CI, 1.72-3.10; *P* <.001), and sustained hypertension (OR 2.25; 95% CI, 1.89-2.66; *P* <.001) compared with normotension. The results remained after adjustment for age, sex, smoking, diabetes mellitus, hyperlipidemia, and sP-selectin, table 3. Using linear regression, higher hsCRP was associated with an increased proportion of participants with masked hypertension and sustained hypertension, estimates of linear regression (95% CI) 1.10 (0.31-1.88), *P* = .007 and 4.04 (2.25-5.83), *P* <.001, respectively, figure 4.

Participants in the highest quartile of sP-selectin vs quartiles 1-3 were more likely to have a CACS ≥100, OR (95% CI) 1.26 (1.03-1.55), *P* = .026 and ≥1 carotid artery plaque, OR (95% CI) 1.16 (1.01-1.33), *P* = .035. The observed differences disappeared after adjustment for age and sex. For participants in the highest quartile of hsCRP vs quartiles 1-3 we observed no significant difference in OR for CACS ≥100, OR 1.19 (95% CI, 0.97-1.46), *P* = .097. However, those in the highest hsCRP quartile were more likely to have carotid plaques, OR 1.21 (95% CI, 1.05-1.38), *P* = .007, a finding that persisted after multivariable adjustment for

age, sex, the most established risk factors for cardiovascular disease, and sP-selectin, OR 1.16 (95% CI, 1.00-1.34), $P = .045$.

4. Discussion

In this cross-sectional study of almost five thousand men and women aged 50 to 64 years, we show that individuals with hypertension, whether at the office, at home or both, had higher levels of sP-selectin and hsCRP than those with sustained normotension. Furthermore, sP-selectin was associated with sustained hypertension compared with sustained normotension, also in the multivariable adjusted model. Higher hsCRP increased the likelihoods of having any of the hypertension phenotypes vs sustained normotension, also in the multivariable adjusted model.

Soluble P-Selectin was independently associated with sustained hypertension and associated with white coat hypertension in model 3 but not model 4. High sP-selectin was also related to higher likelihood of CACS ≥100 and carotid artery plaques ≥1. However, this relation was no longer significant after adjusting for age and sex. High sP-selectin is known to be associated with hypertension at the office [14,27,28], resistant hypertension [29], malignant and renovascular hypertension [30], CACS and cardiovascular events [11,13,15,17,18]. Normalization of elevated BP may reduce sP-selectin [31]. However, the above studies of the association between sP-selectin and hypertension were small (less than 200 participants). Furthermore, the associations in our study between sP-selectin and white coat hypertension and sustained hypertension are novel findings which implicate that hypertension may be more closely related with platelet activity and thrombotic disease than previously known. In addition the association appears to go beyond that of inflammation, given that adjustment with hsCRP had little impact on the result.

High sensitivity C-reactive protein was associated with masked hypertension and higher likelihood of at least one carotid artery plaque, but not CACS ≥100. CRP and hsCRP have

previously been associated with obesity, type 2 diabetes mellitus, hypertension, atherosclerosis, and arterial stiffness [6-10]. Levels of hsCRP have also been related to increased risk of future cardiovascular events [6-8]. However, the use of hsCRP in cardiovascular disease risk stratification is debated [33]. Our results confirm the relationship with hypertension, and the relation with carotid artery plaques strengthens the association with atherosclerosis and cardiovascular events.

The association between both sP-selectin and hsCRP with white coat hypertension indicates that isolated hypertension at the office may not be completely benign.

The relationship between inflammation and cardiovascular disease has been thoroughly studied, in terms of both pathophysiology and therapeutics [34-36]. However, whether inflammatory markers are merely elevated as a result of other cardiovascular risk factors, or whether they confer an increased risk themselves, is not clear.

In our study, we excluded participants with hsCRP above 5 mg/L or sP-selectin beyond 4 standard deviations above mean, so that inflammation due to other processes, including acute infections, would not distort any potential association between inflammation and cardiovascular disease. This approach is common, although the specific cut-off level varies between studies[37,38].

There are some limitations to our study. The missing rate was 31% for PWV, compared with an otherwise low missing rate of at most 3% for all other variables, because analysis of PWV was performed only if time permitted. Although home BP was measured in the sitting position, office BP was measured in the supine position. Studies evaluating the difference between supine and sitting measurements have found conflicting results as to the direction and degree of the difference [39-41], but a resulting misclassification of BP in some cases cannot be ruled out. Current medications and previous events were self-reported and thus could include some inaccuracies. Home BP does not capture the same out-of-office BP as

does ambulatory BP measurements, and thus hypertension phenotypes derived based on these two methods are not directly comparable. Finally, causality cannot be determined in this cross-sectional study.

In conclusion, in this large population study of randomly recruited middle-aged individuals, both increased sP-selectin and hsCRP were independently associated with sustained hypertension. Our findings indicate an association between hypertension and platelet activity, as expressed by sP-selectin.

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Figures and Tables

Table 1. Baseline characteristics according to blood pressure classification.

		Sustained normotension (n = 2706)	White coat hypertension (n = 813)	Masked hypertension (n = 209)	Sustained hypertension (n = 820)	Total (N = 4548)
Sex, men, n (%)		1276 (47.2)	377 (46.4)	149 (71.3)	484 (59.0)	2286 (50.3)
Age (years), median (Q1-Q3)		56.4 (53.0-60.5)	59.0 (54.8-62.4)	57.3 (53.8-60.8)	58.7 (54.5-61.8)	57.2 (53.4-61.2)
Ever-smokers, n (%)						
Previous		777 (28.7)	288 (35.4)	63 (30.1)	286 (34.9)	1414 (31.1)
Current		254 (9.4)	50 (6.2)	23 (11.0)	89 (10.9)	416 (9.1)
BMI (kg/m^2), median (Q1-Q3)		25.2 (23.1-27.7)	26.7 (24.3-29.4)	28.2 (26.5-31.2)	28.2 (25.5-31.2)	26.1 (23.7-29.0)
Waist circumference (cm), median (Q1-Q3)		89 (81-97)	94 (85-101)	100 (94-109)	99 (91-106)	92 (83-100)
Fasting glucose (mmol/L), median (Q1-Q3)		5.4 (5.2-5.8)	5.6 (5.3-6.1)	5.7 (5.3-6.2)	5.8 (5.4-6.2)	5.5 (5.2-5.9)
HbA1c (mmol/mol), median (Q1-Q3)		35 (33-37)	35 (33-38)	36 (34-38)	35 (33-38)	35 (33-37)
eGFR (mL/min/1.73 m^2), median (Q1-Q3)		86.4 (77.7-96.5)	86.2 (77.5-96.1)	84.8 (76.5-94.9)	87.5 (77.2-97.6)	86.4 (77.5-96.6)
LDL (mmol/L), median (Q1-Q3)		3.2 (2.6-3.8)	3.3 (2.7-4.0)	3.2 (2.7-3.7)	3.3 (2.7-4.0)	3.2 (2.7-3.9)
HDL (mmol/L), median (Q1-Q3)		1.7 (1.4-2.0)	1.6 (1.3-2.0)	1.4 (1.1-1.6)	1.5 (1.2-1.8)	1.6 (1.3-2.0)
Triglycerides (mmol/L), median (Q1-Q3)		0.9 (0.7-1.3)	1.1 (0.8-1.5)	1.2 (0.9-1.7)	1.3 (0.9-1.8)	1.0 (0.8-1.4)
LDL/HDL ratio, median (Q1-Q3)		1.9 (1.4-2.5)	2.1 (1.5-2.7)	2.4 (1.6-3.1)	2.2 (1.7-2.9)	2.0 (1.5-2.7)
Past event, n (%)	**Myocardial infarction**	49 (1.8)	11 (1.4)	3 (1.4)	14 (1.7)	77 (1.7)
	Stroke	35 (1.3)	12 (1.5)	1 (0.5)	6 (0.7)	54 (1.2)
Current medication, n (%)	**Hypertension**	258 (9.5)	186 (22.9)	65 (31.1)	266 (32.4)	775 (17.0)
	Hyperlipidemia	142 (5.2)	77 (9.5)	25 (12.0)	81 (9.9)	325 (7.1)
	Diabetes mellitus	66 (2.4)	28 (3.4)	19 (9.1)	36 (4.4)	149 (3.3)

		Sustained normotension (n = 2706)	White coat hypertension (n = 813)	Masked hypertension (n = 209)	Sustained hypertension (n = 820)	Total (N = 4548)
Office BP (mmHg), median (Q1-Q3)	**Systolic**	122.0 (114.0-129.0)	145.0 (141.0-152.0)	131.0 (126.0-135.0)	152.0 (144.0-162.0)	130.0 (120.0-143.0)
	Diastolic	78.0 (73.0-82.0)	90.0 (86.0-94.0)	83.0 (80.0-86.0)	96.0 (91.0-101.0)	82.0 (76.0-90.0)
Home BP (mmHg), median (Q1-Q3)	**Systolic**	113.1 (106.4-119.9)	123.5 (117.7-128.7)	132.3 (127.8-137.9)	137.9 (132.7-144.7)	119.5 (110.5-128.9)
	Diastolic	73.4 (69.1-77.7)	79.1 (75.6-82.1)	86.5 (85.3-88.7)	89.0 (86.1-93.0)	77.2 (71.7-83.3)
Office-home BP difference (mmHg), median (Q1-Q3)		8.2 (2.8-14.0)	23.0 (16.2-30.3)	-1.7 (-9.3 to -2.5)	14.3 (6.9-22.6)	10.8 (4.2-18.8)

Values for sex, age, BMI, estimated glomerular filtration rate (eGFR), HDL, triglycerides, all current medication variables, and all BP variables (including the office-home BP difference) were calculated based on all 4548 participants. Values for other variables (smoking status, waist circumference, fasting glucose, HbA1c, LDL, LDL/HDL ratio and past events) were calculated based on 4415-4546 (97-99.96%) of the total population..

BMI, body mass index; BP, blood pressure; eGFR, estimated glomerular filtration rate; HbA1c, glycated hemoglobin; HDL, high-density lipoprotein; LDL, low-density lipoprotein; MH, masked hypertension; SH, sustained hypertension; SN, sustained normotension; WCH, white coat hypertension.

Table 2. Markers of inflammation and cardiovascular disease according to blood pressure classifications.

	Sustained normotension (n = 2706)	**White coat hypertension (n = 813)**	**Masked hypertension (n = 209)**	**Sustained hypertension (n = 820)**	**Total (N = 4548)**	***P* value (for each hypertension phenotype in relation to sustained normotension)**
sP-selectin (ng/mL), median (Q1-Q3)	33.5 (26.7-41.1)	34.9 (27.3-43.0)	35.8 (28.5-42.4)	36.8 (29.1-45.1)	34.3 (27.3-42.3)	<.001 (SH), .030 (MH), .011 (WCH)
hsCRP (mg/L), median (Q1-Q3)	0.8 (0.4-1.4)	0.9 (0.5-1.8)	1.2 (0.7-2.1)	1.2 (0.7-2.3)	0.9 (0.5-1.7)	<.001 (SH, MH, WCH)
PWV, median (Q1-Q3)	8.3 (7.6-9.0)	9.2 (8.4-10.0)	9.3 (8.7-10.1)	9.9 (9.0-10.8)	8.7 (7.9-9.6)	<.001 (SH, MH, WCH)
Total CACS, median (Q1-Q3)	0.0 (0.0-9.0)	0.0 (0.0-28.0)	4.0 (0.0-68.0)	0.0 (0.0-50.3)	0.0 (0.0-17.0)	<.001 (SH, MH, WCH)
Total CACS ≥100, n (%)	217 (8.0)	115 (14.1)	42 (20.1)	142 (17.3)	516 (11.3)	<.001 (SH, MH, WCH)
Carotid artery plaques ≥1, n (%)	1351 (49.9)	499 (61.4)	129 (61.7)	541 (66.0)	2520 (55.4)	<.001 (SH, MH, WCH)

Values for hsCRP, sP-selectin and carotid artery plaques were calculated based on all 4548 participants. Values for CACS and PWV were calculated based on 4416 (97%) and 3134 (69%) respectively of the total population. Differences between blood pressure classifications was tested using a Kruskal-Wallis test with pairwise comparisons using Conover's many-to-one test and the Holm-Bonferroni method to correct for multiple comparisons.

CACS, coronary artery calcium score; hsCRP, high sensitivity C-reactive protein; MH, masked hypertension; PWV, pulse wave velocity; SH, sustained hypertension; SN, sustained normotension; WCH, white coat hypertension.

Table 3. Odds ratio of each hypertension phenotype vs sustained normotension for those with sP-selectin and hsCRP in quartile 4 vs quartiles 1-3. Participants with sP-selectin in quartiles 4 more often had sustained hypertension than sustained normotension, also when adjusted for age, sex, smoking, diabetes mellitus diagnosis and hyperlipidemia diagnosis. Participants with hsCRP in quartile 4 vs quartile 1 more often had white coat hypertension, masked hypertension, and sustained hypertension vs sustained normotension, also when adjusted for age, sex, smoking, diabetes mellitus diagnosis and hyperlipidemia diagnosis.

	SN (ref)	**White coat hypertension (n = 813)**		**Masked hypertension (n = 209)**		**Sustained hypertension (n = 820)**	
sP-selectin Q4 vs Q1-3	**OR**	**OR (95% CI)**	***P* value**	**OR (95% CI)**	***P* value**	**OR (95% CI)**	***P* value**
Crude	1	1.29 (1.07-1.54)	.007	1.20 (0.86-1.67)	.280	1.67 (1.40-1.98)	<.001
Adjusted for age and sex	1	1.24 (1.03-1.49)	.024	1.02 (0.73-1.43)	.893	1.51 (1.26-1.81)	<.001
Adjusted for age, sex, smoking, diagnosis of diabetes mellitus, and hyperlipidemia	1	1.23 (1.02-1.49)	.034	0.88 (0.62-1.25)	.480	1.52 (1.26-1.82)	<.001
Adjusted for age, sex, smoking, diagnosis of diabetes mellitus, hyperlipidemia, and hsCRP	1	1.18 (0.98-1.44)	.086	0.81 (0.57-1.16)	.255	1.41 (1.17-1.70)	<.001
hsCRP Q4 vs Q1-3	**OR**	**OR (95% CI)**	***P* value**	**OR (95% CI)**	***P* value**	**OR (95% CI)**	***P* value**
Crude	1	1.37 (1.14-1.64)	<.001	2.31 (1.72-3.10)	<.001	2.25 (1.89-2.66)	<.001
Adjusted for age and sex	1	1.31 (1.09-1.58)	.004	2.43 (1.80-3.28)	<.001	2.25 (1.89-2.68)	<.001
Adjusted for age, sex, smoking, diagnosis of diabetes mellitus, and hyperlipidemia	1	1.35 (1.12-1.63)	.002	2.41 (1.76-3.28)	<.001	2.23 (1.87-2.66)	<.001
Adjusted for age, sex, smoking, diagnosis of diabetes mellitus, hyperlipidemia, and sP-selectin	1	1.33 (1.10-1.61)	.003	2.42 (1.78-3.31)	<.001	2.18 (1.82-2.61)	<.001

The odds ratios and 95% CI for each hypertension phenotype vs sustained normotension for participants with sP-selectin and hsCRP respectively in quartile 4 vs quartiles 1 to 3 was tested using binomial generalized linear model analyses, and analyses were crude, adjusted for age and sex, adjusted for age, sex, smoking, diagnosis of diabetes mellitus and hyperlipidemia, and adjusted for age, sex, smoking, diagnosis of diabetes mellitus, hyperlipidemia, and hsCRP and sP-selectin respectively.

Abbreviations: CI, confidence interval; hsCRP, high-sensitivity C-reactive protein, OR, odds ratio; ref, reference; SN, sustained normotension; Q1, quartile 1; Q2, quartile 2; Q3, quartile 3; Q4, quartile 4.

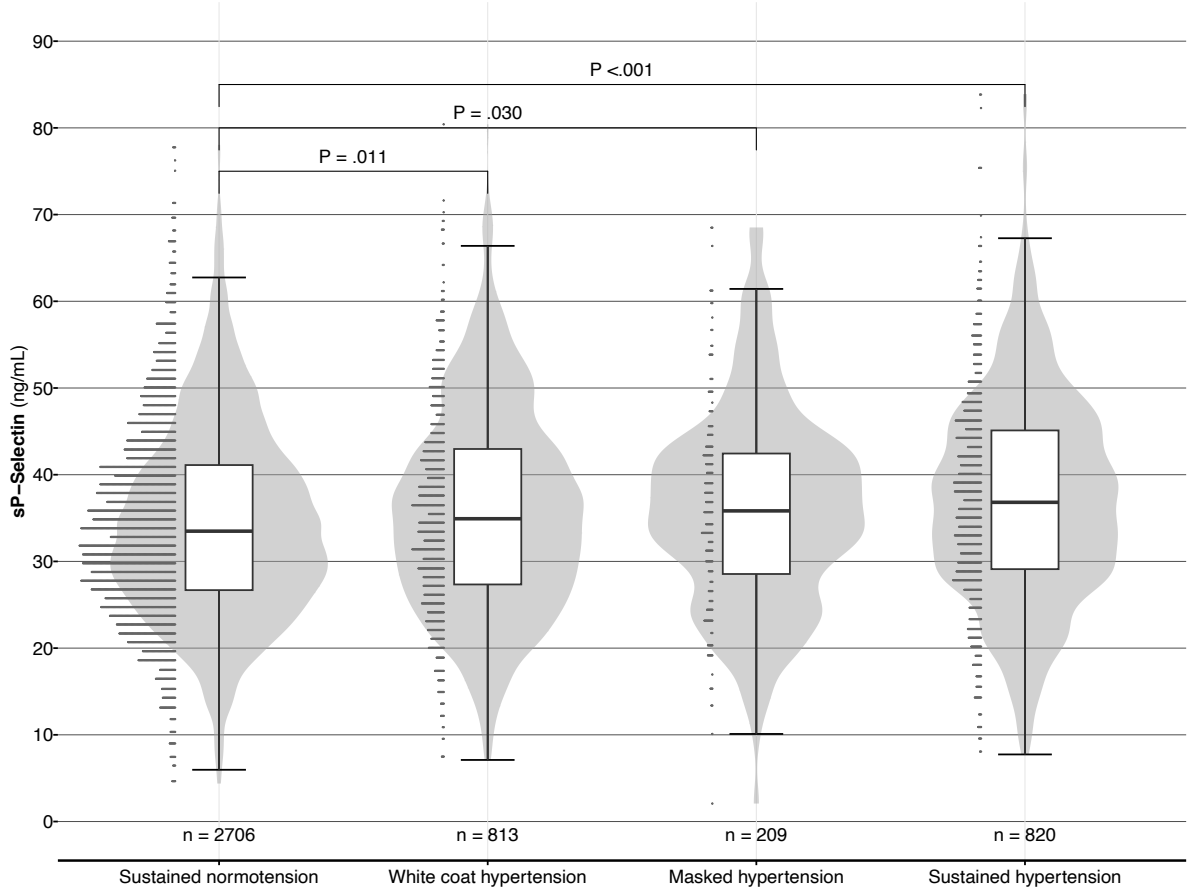
Table 4. Odds ratio of coronary artery calcifications core (CACS) ≥100 and carotid artery plaques ≥1, respectively, for participants with sP-selectin and hsCRP in quartile 4 vs quartiles 1-3. Participants with sP-selectin in quartile 4 more often had CACS ≥100 and carotid artery plaques ≥1, but not when adjusted for age and sex. Participants with hsCRP in quartile 4 more often had carotid artery plaques ≥1, also when adjusted for age, sex, smoking, and diagnosis of diabetes mellitus, hyperlipidemia, and hypertension.

	Coronary artery calcification score (CACS) (n = 4416)			Carotid artery plaques (n = 4548)		
	<100 (ref)	≥100		0 (ref)	≥1	
sP-selectin Q4 vs Q1-3	**OR**	**OR (95% CI)**	***P* value**	**OR**	**OR (95% CI)**	***P* value**
Crude	1	1.26 (1.03-1.55)	.026	1	1.16 (1.01-1.33)	.035
Adjusted for age and sex	1	1.00 (0.81-1.24)	.982	1	1.04 (0.90-1.20)	.586
Adjusted for age, sex, smoking, diagnosis of diabetes mellitus, and hyperlipidemia	1	0.98 (0.78-1.22)	.833	1	1.03 (0.89-1.19)	.679
Adjusted for age, sex, smoking, and diagnosis of diabetes mellitus, hyperlipidemia, and hypertension	1	0.97 (0.77-1.22)	.795	1	1.03 (0.89-1.19)	.710
Adjusted for age, sex, smoking, and diagnosis of diabetes mellitus, hyperlipidemia, hypertension, and hsCRP	1	0.96 (0.77-1.21)	.738	1	1.02 (0.88-1.18)	.787
hsCRP Q4 vs Q1-3	**OR**	**OR (95% CI)**	***P* value**	**OR**	**OR (95% CI)**	***P* value**
Crude	1	1.19 (0.97-1.46)	.097	1	1.21 (1.05-1.38)	.007
Adjusted for age and sex	1	1.18 (0.95-1.46)	.128	1	1.20 (1.04-1.38)	.010
Adjusted for age, sex, smoking, diagnosis of diabetes mellitus, and hyperlipidemia	1	1.10 (0.88-1.37)	.413	1	1.19 (1.03-1.37)	.019
Adjusted for age, sex, smoking, and diagnosis of diabetes mellitus, hyperlipidemia, and hypertension	1	1.04 (0.83-1.30)	.761	1	1.16 (1.01-1.34)	.042
Adjusted for age, sex, smoking, and diagnosis of diabetes mellitus, hyperlipidemia, hypertension, and sP-selectin	1	1.04 (0.83-1.30)	.732	1	1.16 (1.00-1.34)	.045

The odds ratios and 95% CI for CACS ≥100 and carotid artery plaques ≥1 respectively for participants with sP-selectin and hsCRP respectively in quartile 4 vs quartiles 1 to 3 was tested using binomial generalized linear model analyses, and analyses were crude, adjusted for age and sex, adjusted for age, sex, smoking, diagnosis of diabetes mellitus and hyperlipidemia, adjusted for age, sex, smoking, diagnosis of diabetes mellitus, hyperlipidemia, and hypertension, and adjusted for age, sex, smoking, diagnosis of diabetes mellitus, hyperlipidemia, hypertension, and hsCRP and sP-selectin respectively.

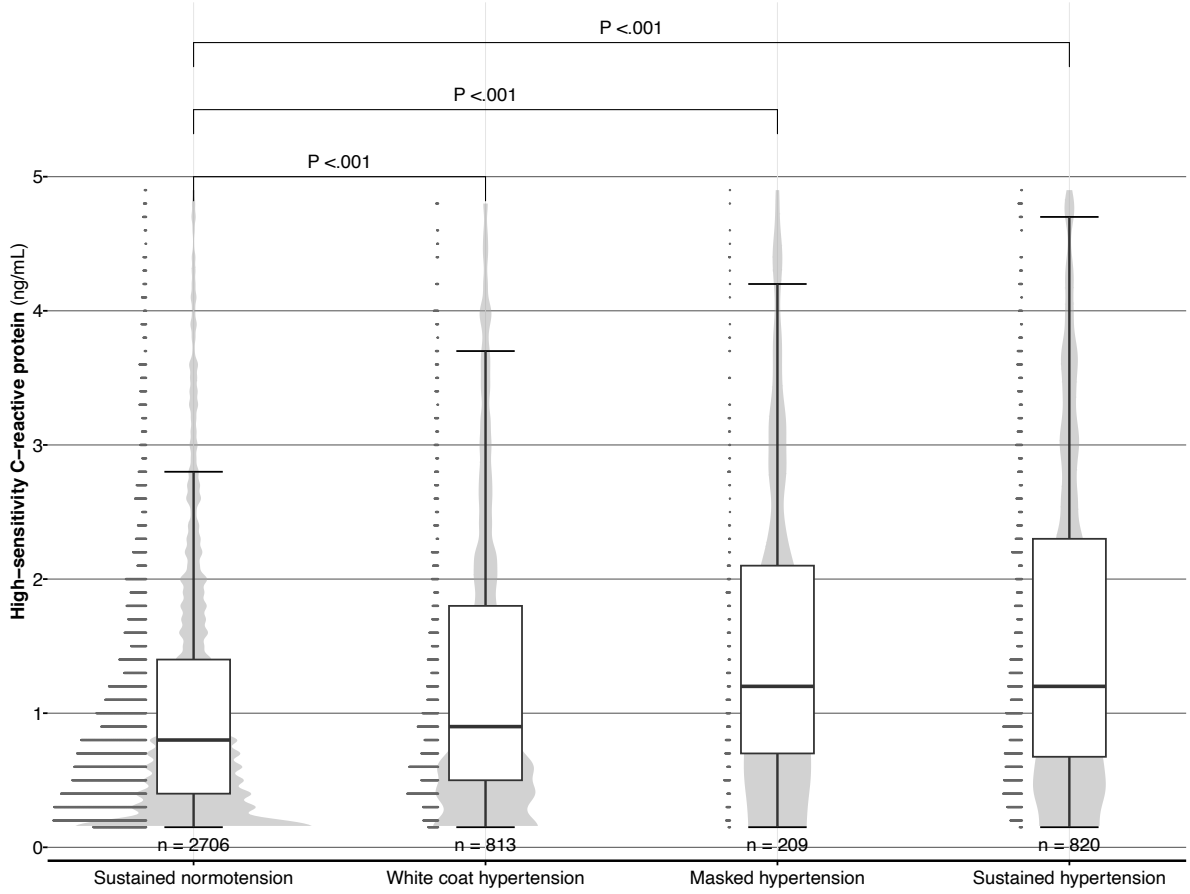
Abbreviations: CACS, coronary artery calcification score; CI, confidence interval; hsCRP, high-sensitivity C-reactive protein; OR, odds ratio; ref, reference; Q1, quartile 1; Q2, quartile 2; Q3, quartile 3; Q4, quartile 4.

Figure 1. Box plot of sP-selectin in relation to blood pressure classification. All hypertension phenotypes had higher sP-selectin than sustained normotension.



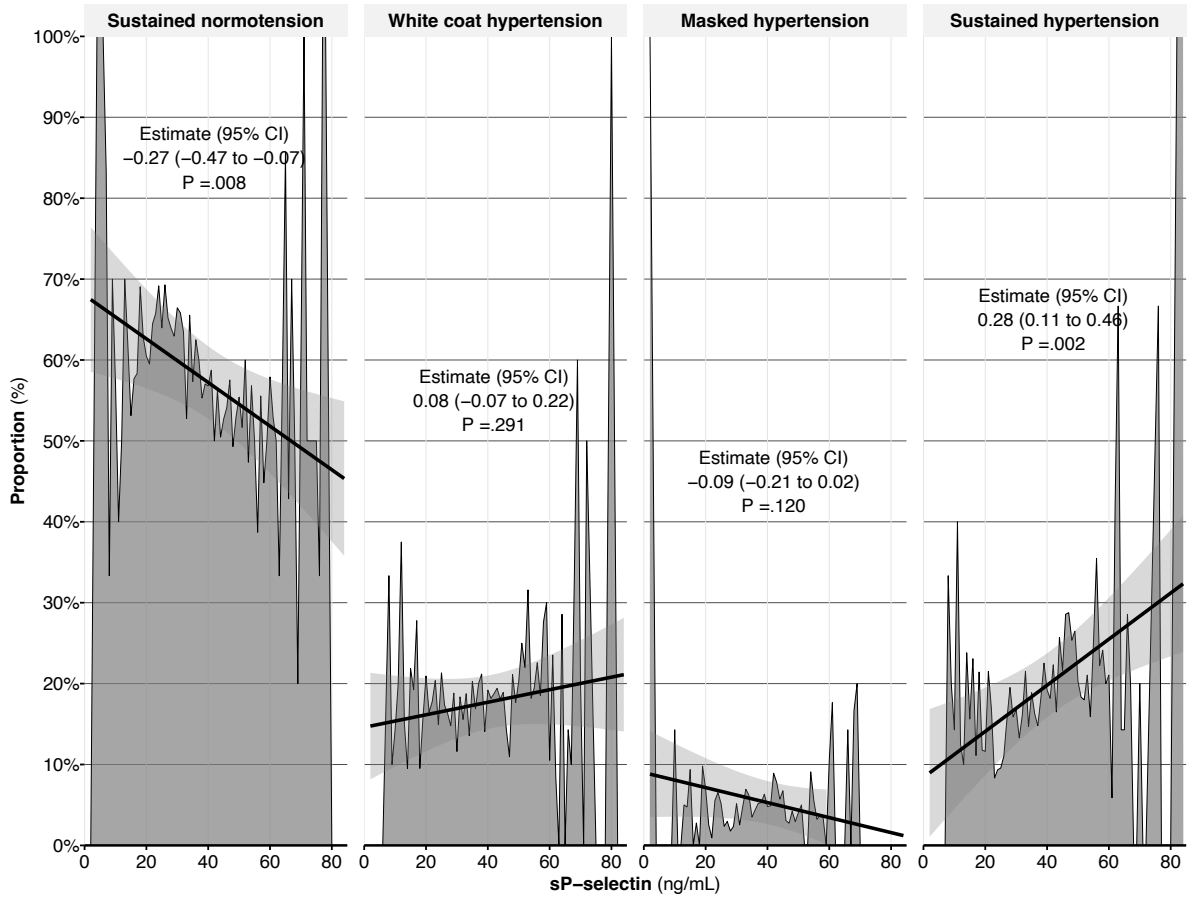
Pairwise comparisons between sustained normotension and hypertension phenotypes were tested using a Kruskal-Wallis test with pairwise comparisons using Conover's many-to-one test and the Holm-Bonferroni method to correct for multiple comparisons.

Figure 2. Box plot of high sensitivity C-reactive protein (hsCRP) in relation to blood pressure classification. All hypertension phenotypes had higher hsCRP than sustained normotension (*P* <.001 for all).



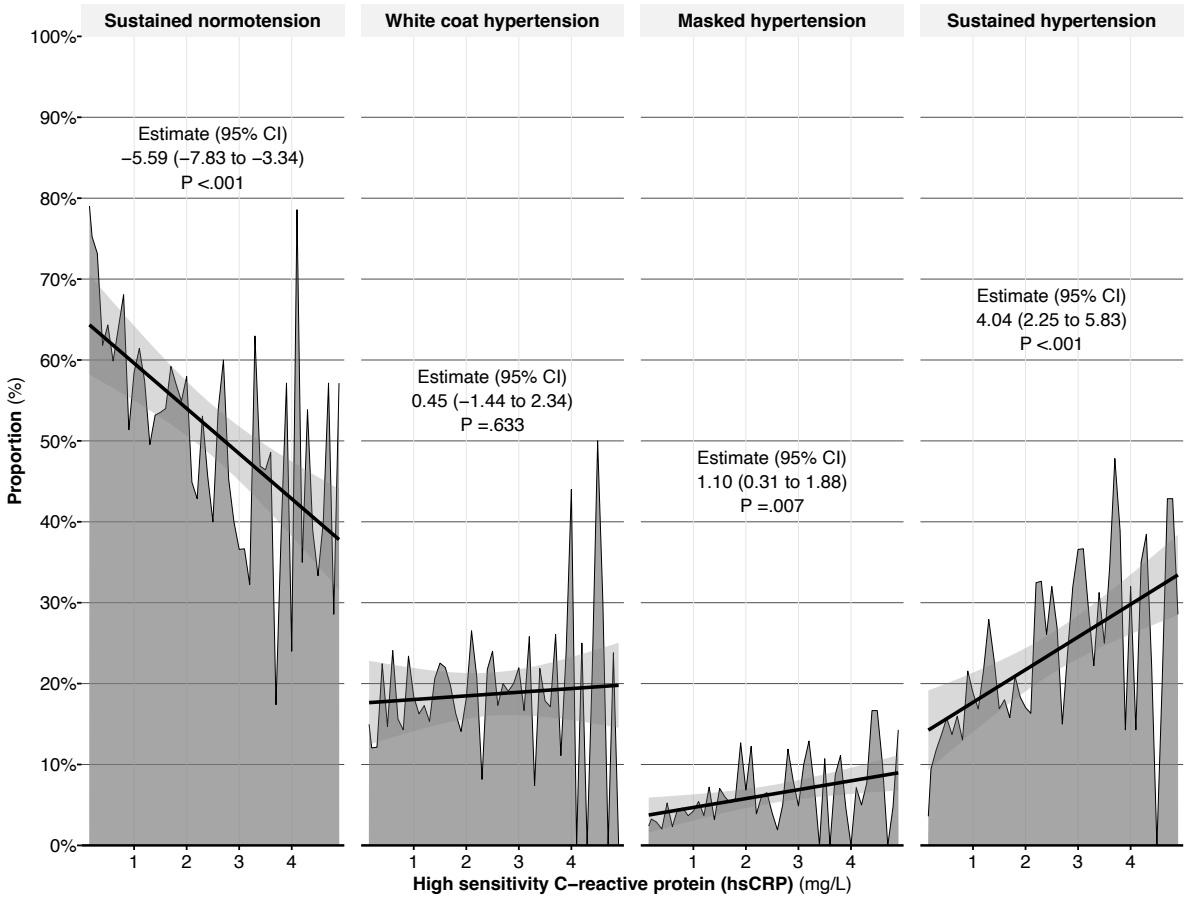
Pairwise comparisons between sustained normotension and hypertension phenotypes were tested using a Kruskal-Wallis test with pairwise comparisons using Conover's many-to-one test and the Holm-Bonferroni method to correct for multiple comparisons.

Figure 3. Proportional area plots of each blood pressure classification in relation to sP-selectin. The fit line (black) and 95% CI (shaded) illustrates the trend of the linear regression with associated estimates, 95% CI and *P* values.



The dark grey areas represent the proportion of the blood pressure classification for each level sP-selectin. The fit line (black) illustrates the estimate of the linear regression for the proportion of the blood pressure classification as the dependent variable, and sP-selectin as the independent variable, with associated 95% CI (shaded).

Figure 4. Proportional area plots of each blood pressure classification in relation to high-sensitivity C-reactive protein (hsCRP). The fit line (black) and 95% CI (shaded) illustrates the trend of the linear regression with associated estimates, 95% CI and *P* values.



The dark grey areas represent the proportion of the blood pressure classification for each level of high-sensitivity C-reactive protein (hsCRP). The fit line (black) illustrates the estimate of the linear regression for the proportion of the blood pressure classification as the dependent variable, and hsCRP as the independent variable, with associated 95% CI (shaded).