Cellular adhesion molecules and blood pressure: interaction with sex in a multi-ethnic population

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Objective **To clarify the association between blood pressure and four different adhesion molecules, adjusting for potential confounders, in men and women from different ethnic origins.**

Design and Methods **The soluble (s) plasma adhesion molecules sP-selectin, sE-selectin, intracellular adhesion molecule-1 (sICAM-1) and vascular cell adhesion molecule-1 (sVCAM-1) were measured in 261 white (120 women), 188 African origin (99 women) and 215 South Asian (99 women) individuals living in England. All were free from coronary heart disease, stroke, other cardiovascular disease and diabetes, and were not receiving drug treatment for hypertension or high lipids, hormone replacement therapy or oral contraceptives.**

Results **After adjustment for age, only sE-selectin concentrations were significantly associated with blood pressure. There was a significant interaction of sex with systolic ($P = 0.013$), diastolic ($P = 0.042$) and pulse ($P = 0.015$) pressures. After adjustment for age, ethnicity, body mass index and smoking, the significant interaction of sex persisted and in women the associations with systolic ($P < 0.001$), diastolic ($P < 0.001$) or pulse ($P = 0.004$) pressure were unchanged, but in men the association with diastolic blood pressure was abolished. Finally, the association appeared to be present in women younger than 50 years, who were likely to be premenopausal.**

Conclusions **The relationship between adhesion molecules and blood pressure is adhesion molecule specific and varies with sex and age, which may partially explain previous inconsistencies in the literature. The mechanisms relating blood pressure to adhesion molecule concentrations are unknown, but they are likely to be modified by the menopause. These differences may relate to the production, clearance or cell-surface shedding of the adhesion molecules.** ***J Hypertens*** **22:705–711 © 2004 Lippincott Williams & Wilkins.**

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Introduction

Formation of atheromatous lesions and subsequent development of coronary heart disease (CHD) can result from the activation and expression of cellular adhesion molecules [1]. Soluble adhesion molecules, which lack cytoplasmic and membrane-spanning domains, are present in the circulation [2]. Although little is known of the processes that govern the shedding and clearance of these molecules, their concentrations in serum or plasma can be readily determined. The circulating concentrations of adhesion molecules are associated with CHD, its risk factors and atherosclerosis *per se* [3–8].

Controversy exists as to whether individuals with hypertension have increased concentrations of circulating adhesion molecules [5,9–13]. Indeed, even in population-based studies, the relationships between adhesion molecules and blood pressure are inconsistent [8,14–16].

In England the incidence of CHD is greater in men than in women and varies widely between different ethnic groups [17,18]. Furthermore, there are significant differences in adhesion molecule concentrations between men and women, and between ethnic groups [7].

The aim of this study was to examine the relationship between adhesion molecule concentrations and blood pressure in both men and women from a multi-ethnic population living in South London.

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Materials and methods

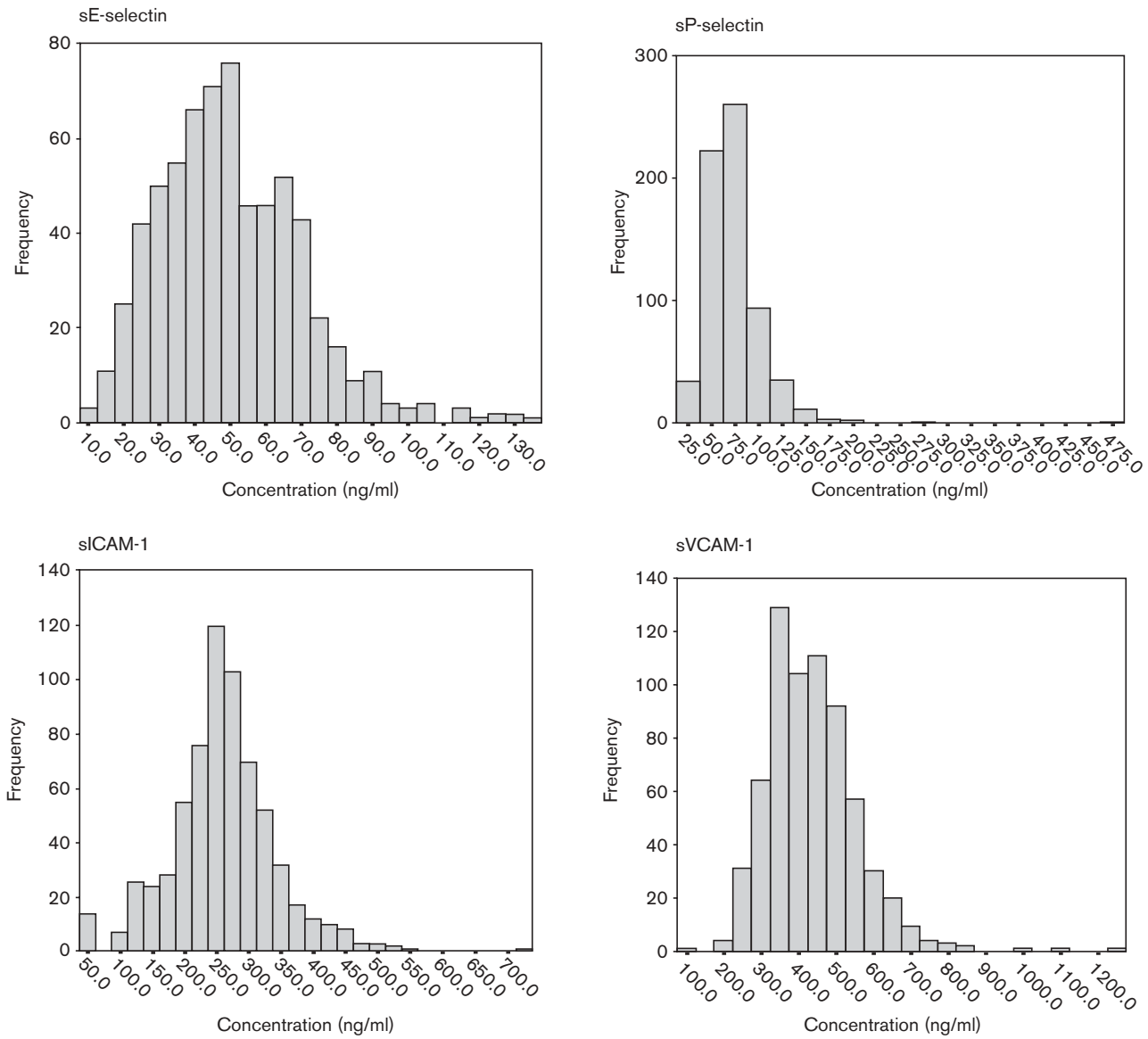
Participants

We studied 664 individuals from the Wandsworth Heart and Stroke Study, as described in detail previously [7,19,20]. They were not receiving antihypertensive or lipid decreasing medication, were not taking the oral contraceptive pill or hormone replacement therapy, and did not have any previous medical history of ischaemic heart disease or stroke. Of the individuals studied, 261 were white (120 women), 188 were of African origin (99 females) and 215 were of South Asian origin (99 women). The Local Ethics Committee approved the study. All participants gave their informed consent to participate.

Methods

Blood was taken between 0800 and 1200 h from seated individuals who had fasted overnight and had refrained from smoking or taking vigorous exercise [19,20]. Height and weight were taken and body mass index (BMI) calculated and expressed as kg/m^2 [19,20]. Blood pressure was taken by standard methods and an auto-

Fig. 1



Frequency distribution of the range of adhesion molecule concentrations in the study population. Plasma concentrations were positively skewed, therefore analyses were performed on log-transformed data. Geometric mean and 95% confidence intervals for each soluble adhesion molecule were as follows: sE-selectin 46.2 ng/ml (range 44.7–47.8 ng/ml); sP-selectin 68 ng/ml (range 66–70 ng/ml); intercellular adhesion molecule-1 (sICAM-1) 245 ng/ml (range 238–252 ng/ml); vascular cell adhesion molecule (sVCAM-1) 420 ng/ml (range 412–429 ng/ml).

mated recorder [19,20]. Pulse pressure was calculated as the difference between systolic (SBP) and diastolic (DBP) blood pressures. Age was used as a proxy for menopausal status, with a cut-off at 50 years. Measurements of the soluble (s) adhesion molecules sE-selectin, sP-selectin, intercellular adhesion molecule-1 (sICAM-1) and vascular cell adhesion molecule (sVCAM-1) were performed using commercially available enzyme-linked immunosorbent assay kits (R& D Systems Europe Ltd, Abingdon, Oxon, UK) [7]. Biochemical measurements were performed as described previously [19,20].

Statistical analysis

Plasma concentrations of sE-selectin, sP-selectin, sVCAM-1 and sICAM-1 were all positively skewed (see Fig. 1), therefore analyses were performed on log-transformed data. Differences between groups (with described adjustments) were tested using analysis of covariance. Results are presented as geometric means and 95% confidence intervals. General linear models with blood pressure as the independent variable were used to estimate the relationship with the adhesion molecules, with adjustment for confounding. Interaction test was used to compare slopes between groups. Because the independent variables had been log-transformed before analysis, the coefficients (β) and 95% confidence interval were elevated to the power of e and expressed as percentage change in adhesion molecule concentrations per 10 mmHg change in blood pressure. A P value less than 0.05 was considered statistically significant.

Results

Detailed characteristics of the population have been reported previously [7]. In brief, the range of blood pressures was 90.5–203 mmHg systolic and 55–123.5 mmHg diastolic. The frequency distribution, geometric mean and confidence intervals for the adhesion molecule concentrations are given in Figure 1.

Analysis of the total group after adjustment for age demonstrated that only sE-selectin concentrations were related to blood pressure, and that these associations were present mainly in women (Table 1). The associations were stronger in women and were significant for SBP ($P = 0.013$), DBP ($P = 0.042$) and pulse pressure ($P = 0.015$) (Table 1). The possibility that ethnicity may affect these associations was also explored. However, the slopes of the associations were not significantly different between the different ethnic groups (test for difference between ethnic groups: $P = 0.55$ for SBP and $P = 0.35$ for DBP). The associations were confined to women and not affected by adjustments for age, ethnicity, BMI and smoking ($P < 0.001$ for SBP, $P < 0.001$ for DBP and $P = 0.004$ for pulse pressure). Furthermore, although the size of the estimate was largely attenuated by multiple adjustments in men, it

Table 1 Relationships between blood pressure and adhesion molecule concentrations in men and women

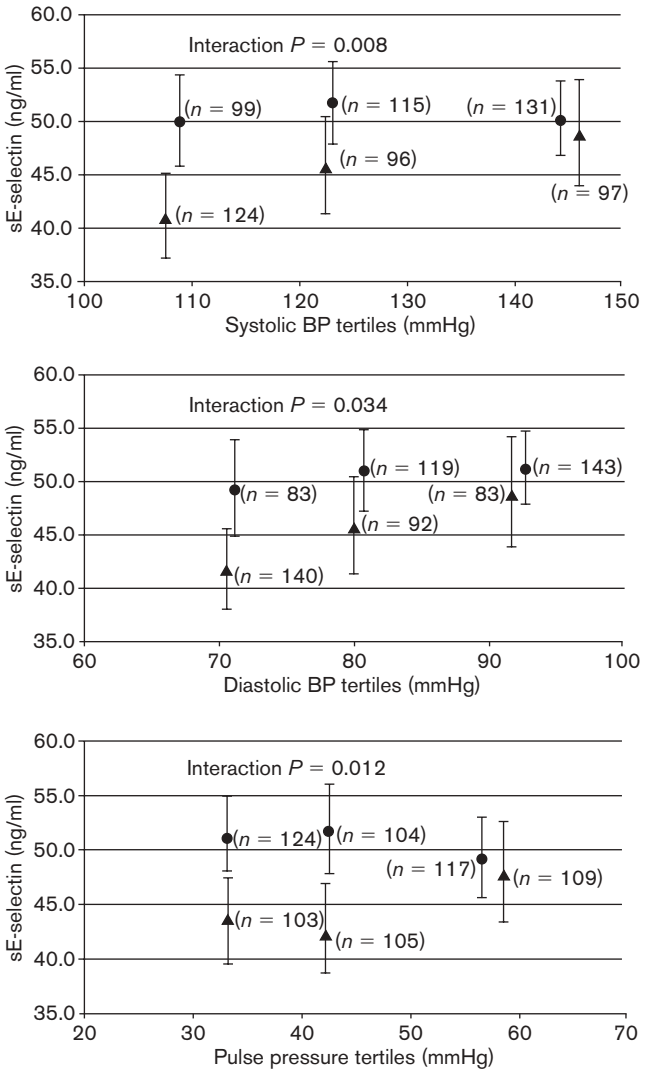
	Men ($n = 346$)			Women ($n = 318$)			Interaction
	Effect (%)[a]	(95% CI)	P	Effect (%)[a]	(95% CI)	P	P
Adjusted for age							
sE-selectin							
SBP	2.0	−0.5 to 4.6	0.122	5.7	3.2 to 8.2	**< 0.001**	**0.013**
DBP	5.1	0.8 to 9.3	**0.019**	10.6	6.0 to 15.3	**< 0.001**	**0.042**
PP	0.4	−0.5 to 4.4	0.836	5.8	2.0 to 9.6	**0.003**	**0.015**
sP-selectin							
SBP	1.9	−0.4 to 4.2	0.104	1.2	−0.9 to 8.2	0.251	0.563
DBP	1.5	−2.3 to 5.4	0.430	0.2	−3.9 to 4.3	0.932	0.552
PP	3.2	−0.4 to 6.7	0.079	2.7	−5.4 to 6.0	0.101	0.716
sICAM-1							
SBP	0.7	−1.6 to 3.0	0.541	0.9	−1.5 to 3.3	0.442	0.761
DBP	0.7	−3.1 to 4.6	0.723	−1.7	−5.6 to 3.3	0.601	0.376
PP	1.1	−2.5 to 6.7	0.542	2.8	−0.7 to 6.4	0.117	0.812
sVCAM-1							
SBP	0.1	−1.6 to 1.9	0.899	0.7	−0.9 to 2.5	0.383	0.480
DBP	−0.6	−3.5 to 2.3	0.674	0.4	−2.5 to 3.2	0.782	0.514
PP	0.8	−1.9 to 3.5	0.559	1.3	−1.0 to 3.6	0.283	0.627
Adjusted for age, ethnicity, BMI and smoking[b]							
sE-selectin							
SBP	0.6	−2.0 to 3.2	0.658	5.4	2.8 to 7.9	**< 0.001**	**0.008**
DBP	2.2	−2.3 to 6.7	0.339	9.7	4.8 to 15.0	**< 0.001**	**0.034**
PP	−0.3	−4.2 to 3.6	0.865	5.6	1.8 to 9.4	**0.004**	**0.012**

[a]Percentage increase in adhesion molecule concentrations per 10 mmHg change in blood pressure.
[b]$n = 317$ for women, because BMI data were missing for one woman of the original 318. CI, confidence interval; s, soluble; SBP, DBP, systolic and diastolic blood pressures; PP, pulse pressure; ICAM-1, intercellular adhesion molecule-1; VCAM-1, vascular cell adhesion molecule-1; BMI, body mass index. Significant values of P are shown in **bold** typeface.

remained virtually unchanged in women. Significant interactions were detected in support of a sex difference in the relationships (Fig. 2).

An age cut-off of 50 years was taken as a crude proxy for menopause. There was no difference in adhesion molecule concentrations (after adjustment for multiple confounders) between women younger than 50 years and those aged 50 years or more (Table 2). The effect of blood pressure on adhesion molecule concentrations in these two groups of women, adjusted for multiple confounders, is shown in Table 3. Consistent with the previous results, the most consistent associations with blood pressure were with sE-selectin, but these were confined to women younger than 50 years, as shown diagrammatically in Figure 3 and by the significant interaction term. Analysis by age demonstrated that, in women, there was an association between pulse pressure and sICAM-1 ($P = 0.005$), which was confined to the women younger than 50 years, as shown by the significant interaction term ($P = 0.046$).

Fig. 2



sE-Selectin concentrations in women (▲) and men (●) by tertile of blood pressure (BP), adjusted for age, ethnicity, body mass index and smoking. Results are geometric means and 95% confidence intervals.

Discussion

Our study shows that blood pressure is significantly and directly associated with circulating concentrations of sE-selectin, but not other adhesion molecules, and that this is confined to women younger than 50 years. These findings were independent of confounders such as ethnic background, smoking and BMI.

Few studies reported in the literature have examined the association between adhesion molecules and blood pressure. However, among those that have there are inconsistencies in the relationships described. These inconsistencies may, in part, reflect differences in the population samples and characteristics, in addition to the adhesion molecules examined.

Of the three studies that have examined the relationship between sE-selectin and blood pressure, one found an association with both SBP and DBP [8], one found an association only with DBP [15] and another reported a possible association with DBP [14]. We found an association between sE-selectin and SBP, DBP and pulse pressure. However, unlike Demerath *et al.* [8], who did not adjust associations for potential confounders, we did not find an association with SBP in men, and even the association with DBP was weak ($P = 0.019$) and was abolished after adjustment for age, ethnicity, BMI and smoking. Moreover, we were able to demonstrate that the associations were independent of ethnic background and were present only in women younger than 50 years. Other studies examined only male individuals [14,16], had too few numbers to permit subgroup analyses [15], did not adjust for potential confounders such as age [15], sex [15], BMI [8,15] or smoking [8,15], did not examine sE-selectin [16], or investigated hypertensive status rather than blood pressure [16]. Demerath *et al.* [8] also demonstrated that there were sex-specific differences in the association between adhesion molecules and some cardiovascular risk factors.

In our study, we did not find a relationship between sVCAM-1 and blood pressure, in agreement with most earlier studies [8,14,15], but not all [10]. In common with most other studies in white individuals, ours also failed to detect a relationship between sP-selectin and blood pressure. However, in contrast with two studies performed in male individuals [8,15], our investigation did not reveal any relationship between sICAM-1 and

Table 2 Characteristics of 317 women aged 40–59 years from the multi-ethnic Wandsworth Heart and Stroke Study population according to age group

	< 50 years ($n = 184$)	⩾ 50 years ($n = 133$)	P[a]
BMI (kg/m^2)	28.3 (27.3 to 29.3)	25.5 (24.1 to 26.8)	0.01
Waist : hip ratio	0.826 (0.810 to 0.843)	0.796 (0.774 to 0.817)	0.08
SBP (mmHg)	125.1 (121.2 to 129.1)	121.8 (116.6 to 127.0)	0.424
DBP (mmHg)	78.6 (76.5 to 80.8)	78.6 (75.8 to 81.4)	0.978
Smoking prevalence (%) (unadjusted for age)			
Current	13	12.7	
Ex-smoker	12	12.7	
Never smoked	75	74.6	
Soluble adhesion molecule concentrations (ng/ml)[b]			
sE-selectin	43.5 (39.1 to 48.3)	46.5 (40.7 to 53.3)	0.494
sP-selectin	65 (59 to 71)	67 (60 to 75)	0.688
sICAM-1	235 (216 to 257)	256 (229 to 286)	0.297
sVCAM-1	405 (380 to 431)	414 (382 to 448)	0.713

Values are means (95% confidence interval) or number, and are adjusted for age unless otherwise specified. There was no more than one value missing from any cell. [a]Test of heterogeneity between age groups by analysis of covariance. [b]Geometric means adjusted for age, body mass index (BMI), ethnicity and smoking ($n = 133$ for women ⩾50 years, because BMI data were missing for one woman in the original group of 134). SBP, DBP, systolic and diastolic blood pressures; s, soluble; ICAM-1, intercellular adhesion molecule-1; VCAM-1, vascular cell adhesion molecule-1.

Table 3 Relationship between blood pressure and adhesion molecule concentrations (adjusted for age, ethnicity, body mass index and smoking) in women younger than 50 years or aged 50 years or more

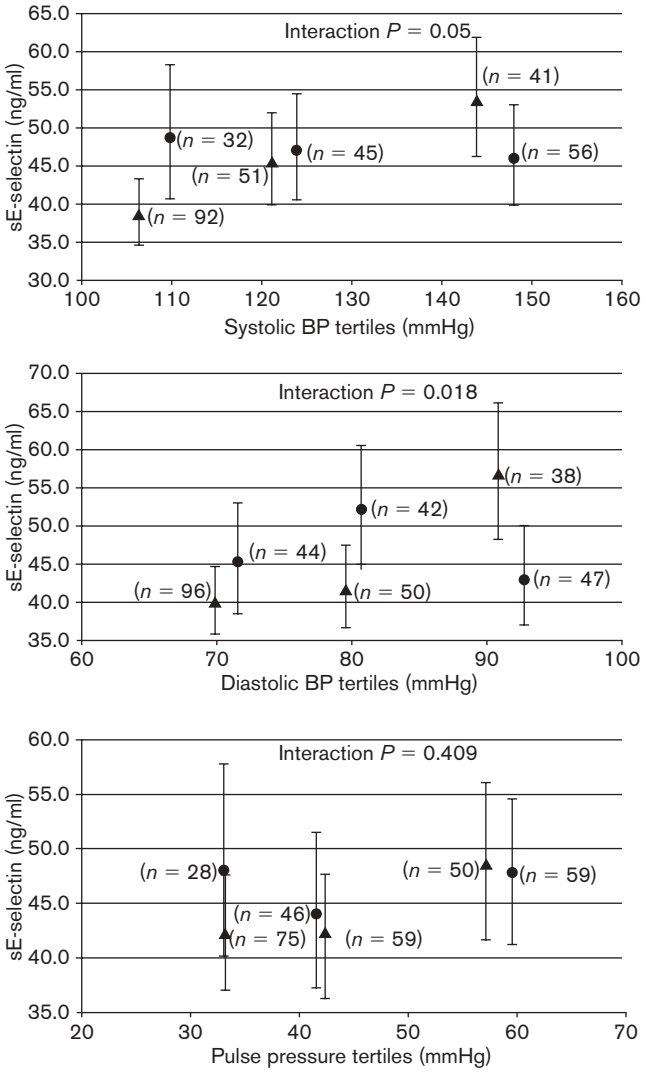
	< 50 years of age ($n = 184$)			⩾ 50 years of age ($n = 133$)[b]			Interaction
	Effect (%)[a]	(95% CI)	P	Effect (%)[a]	(95% CI)	P	P
sE-selectin							
SBP	7.4	0.38 to 11.0	**< 0.001**	2.6	−1.2 to 6.5	0.18	**0.050**
DBP	13.8	7.3 to 20.4	**< 0.001**	3.3	−4.5 to 11.2	0.407	**0.018**
PP	6.8	1.25 to 12.3	**0.016**	3.7	−1.8 to 9.2	0.189	0.409
sP-selectin							
SBP	3.2	−0.08 to 6.3	**0.045**	0.9	−2.3 to 4.03	0.598	0.221
DBP	3.5	−2.1 to 9.2	0.213	1.8	−4.6 to 8.2	0.591	0.560
PP	4.6	−0.05 to 9.2	0.052	0.8	−3.6 to 5.3	0.712	0.189
sICAM-1							
SBP	3.5	0.7 to 6.3	**0.015**	0.3	−3.2 to 3.9	0.859	0.124
DBP	2.5	−2.6 to 7.6	0.329	2.3	−4.8 to 9.5	0.519	0.751
PP	6.0	1.8 to 10.1	**0.005**	−0.5	−5.5 to 4.5	0.841	**0.046**
sVCAM-1							
SBP	1.6	−0.6 to 3.7	0.145	0.05	−2.4 to 2.5	0.965	0.403
DBP	1.3	−2.5 to 5.2	0.491	1.3	−3.7 to 6.3	0.609	0.894
PP	2.6	−0.6 to 5.7	0.112	0.5	−4.0 to 3.0	0.766	0.191

[a]Percentage increase in adhesion molecule concentrations per 10 mmHg change in blood pressure. $n = 133$ for women ⩾50 years, because BMI data were missing for one woman in the original group of 134. CI, confidence interval; s, soluble; SBP, DBP, systolic and diastolic blood pressures; PP, pulse pressure; ICAM-1, intercellular adhesion molecule-1; VCAM-1, vascular cell adhesion molecule-1. Significant values of P are shown in **bold**

systolic blood pressure in men. Becker *et al.* [16] examined the association with hypertensive status in male individuals and also demonstrated a positive association with sICAM-1 concentrations. We have examined the relationship with blood pressure, rather than hypertensive status, and excluded individuals being treated for hypertension. This may have led to an underestimate of the association between adhesion molecules and blood pressure, but it rules out the possibility that drug treatment for hypertension could have influenced adhesion molecule concentrations.

Each adhesion molecule has a specific role in the adhesion pathway. Selectins mediate leucocyte rolling and platelet–leucocyte interaction, whereas firm attachment to, and subsequent migration through, the endothelium require the expression of ICAM-1 and VCAM [21]. Moreover, although P-selectin is present in storage granules, sE-selectin is rapidly synthesized in response to stimulation. Our data support the idea that each adhesion molecule may have a different role in the development of CHD or atherosclerosis, and that they may operate through different mechanisms, espe-

Fig. 3



sE-Selectin concentrations in women younger than 50 years (▲) and those aged 50 years or more (●) by tertile of blood pressure, adjusted for age, ethnicity, body mass index and smoking. Results are geometric means and 95% confidence intervals.

cially in male and female individuals. Studies have demonstrated that oestrogens can decrease the expression of cell adhesion molecules [22] and that hormone replacement therapy can reduce the expression of adhesion molecule [23]. In our study, women receiving hormone replacement therapy or the oral contraceptive pill had been excluded. We did not have a direct hormonal measure of menopausal status, and so used age as a crude proxy. We have clearly shown that there is an interaction between both sex and age, and have demonstrated the relationship between blood pressure and adhesion molecules, especially sE-selectin. Our results would suggest that premenopausal status, possibly acting via oestrogen concentrations, might modify the relationship between circulating adhesion molecule concentrations and blood pressure. We did not observe any difference in adhesion molecule concentrations *per se* according to age group. This is of interest, as it is possible that increasing blood pressures in women younger than 50 years may modulate any protective effect of increased oestrogen concentrations.

The mechanisms underlying the observed association between particular adhesion molecules and blood pressure are unknown. It is possible that increased vascular distension and transmural pressure occurring within the arteries may lead to endothelial activation, with a consequent change in serum concentrations of adhesion molecules [11].

The findings that the relationship between adhesion molecules and blood pressure is adhesion molecule specific, varies with sex and age but not with ethnic origin, and is independent of smoking and body mass may, at least in part, explain previous inconsistencies in the literature. Further studies to investigate the nature of the association between blood pressure and adhesion molecule concentrations are warranted. The selection of individuals for study needs to be considered carefully in the design of such studies, but the possibility that different mechanisms may operate in men and women needs to be explored more fully. Moreover, as a number of adhesion molecule polymorphisms can affect adhesion molecule concentrations [24,25], the influence of genetic determinants on the relationship between blood pressure and adhesion molecules and their interactions needs to be explored further. The outcome of this and other studies to date cannot establish a cause–effect relationship between concentrations of adhesion molecules – in particular, sE-selectin – and blood pressure. However, sE-selectin concentrations may be related to structural vascular changes [26]. In our study in women, a 10 mmHg increase in SBP was associated with a 7.4% increase in sE-selectin concentrations in those younger than 50 years. Therefore, the possibility that circulating sE-selectin concentrations may be a marker for endothelial damage in these individuals cannot be excluded.

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