Brain, Behavior, and Immunity 23 (2009) 684–692

Contents lists available at ScienceDirect

Brain, Behavior, and Immunity

journal homepage: www.elsevier.com/locate/ybrbi

Chronic discrimination predicts higher circulating levels of E-selectin in a national sample: The MIDUS study

Elliot M. Friedman [a,b,*], David R. Williams [d], Burton H. Singer [a,e], Carol D. Ryff [a,c]

[a] Institute on Aging, University of Wisconsin, Madison, Wisconsin, USA
[b] Department of Population Health Sciences, University of Wisconsin, Madison, Wisconsin, 53726, USA
[c] Department of Psychology, University of Wisconsin, Madison, Wisconsin, USA
[d] Department of Sociology and School of Public Health, Harvard University, Boston, Massachusetts, USA
[e] Office of Population Research, Princeton University, Princeton, New Jersey, USA

ARTICLE INFO

Article history:
Received 11 September 2008
Received in revised form 5 January 2009
Accepted 6 January 2009
Available online 11 January 2009

Keywords:
Discrimination
E-selectin

ABSTRACT

Chronic discrimination in both minority and non-minority populations is linked to adverse health outcomes, including increased risk of cardiovascular disease and increased mortality, but the biological processes through which discrimination affects health are unclear. The current study tested the hypothesis that discrimination in a sample of Caucasians would predict elevated serum levels of E-selectin, an indication of endothelial dysfunction which itself is associated with atherosclerosis and cardiovascular disease risk. Participants ($N = 804$) in the biomarker sample from the Survey of Midlife in the United States (MIDUS) provided information about experiences of both major and everyday discrimination at two times separated by a 9–10 year interval. The discrimination measures were designed to assess perceived unfair treatment (e.g. being fired unfairly) independently of the perceived reasons for the unfair treatment (e.g. race, gender). Serum E-selectin was measured at the second wave of data collection. Women reported significantly more instances of major ($P < 0.05$) and everyday $P < 0.001$) discrimination than men. Analyses of Covariance (ANCOVA) showed that both greater lifetime exposure to major discrimination ($P < 0.05$) and chronic exposure to everyday discrimination ($P < 0.05$) predicted higher circulating levels of E-selectin, but only in men. These associations remained statistically significant after adjustments for potential confounding variables, including age, race, socioeconomic status, health status, and health behavior. These results highlight a potential biological mechanism by which exposure to unfair treatment may be related to health, particularly cardiovascular function. Moreover, they add to a growing literature suggesting that unfair treatment in general may predict adverse health outcomes.

1. Introduction

Discrimination has been convincingly linked to a range of adverse health outcomes (Williams et al., 2003; Paradies, 2006), and the ways in which discrimination can affect health are myriad. Institutionalized discrimination, for example, can affect the health of entire segments of the population by way of reduced access to health care, sub-standard living conditions, and diminished opportunities for socioeconomic advancement (Krieger, 2001; Ahmed et al., 2007). At the individual level, exposure to unfair treatment or the perception of unfair treatment may act as a potent stressor that has adverse effects on health and longevity. In community-dwelling samples of African American women, for example, chronic exposure to discrimination is positively associated with risk factors for cardiovascular disease, including elevated blood pressure (Guyll et al., 2001), increased carotid intima media thickness (Troxel et al., 2003), and coronary artery calcification (Lewis et al., 2006). Perceived discrimination is also associated with increased risk of mortality in older adults (Barnes et al., 2008). To date, however, little is known about how — i.e. through what biological processes — unfair treatment is linked to adverse health outcomes, including elevated cardiovascular risk. The current study focuses on E-selectin, a marker for one candidate pathway: endothelial dysfunction.

E-selectin is one of a family of cell adhesion molecules (CAMs) that are expressed on the surfaces of endothelial cells as part of the inflammatory response to endothelial damage, and expression of these proteins is one indication of potential adverse changes in endothelial homeostasis, also known as endothelial dysfunction

* Corresponding author. Address: Department of Population Health Sciences, University of Wisconsin, 624 WARF Office Bldg., 610 N Walnut Street, Madison, WI 53726, USA. Fax: +1 608 263 2820.
E-mail address: friedman1@wisc.edu (E.M. Friedman).

0889-1591/$ - see front matter © 2009 Elsevier Inc. All rights reserved.
doi:10.1016/j.bbi.2009.01.002

(Ross, 1999). Endothelial dysfunction in turn is an initiating step in the process of atherosclerosis, a leading cause of cardiovascular disease (Ross, 1999). Soluble E-selectin and related CAMs are thought to be shed from activated endothelial cells (Pigott et al., 1992) and are associated with atherosclerosis (Bonora, 2006; Galkina and Ley, 2007) as well as cardiovascular disease morbidity and mortality (Hwang et al., 1997; Blann and Lip, 2000; Zethelius et al., 2008). E-selectin in particular was a logical focus for the current study because while other CAMs, such as VCAM and ICAM, are expressed on multiple cell types (Springer, 1990), E-selectin is uniquely expressed by endothelial cells (Erbe et al., 1992), and prior research has linked exposure to discrimination with endothelial pathology (Troxel et al., 2003; Lewis et al., 2006).

While there is no direct evidence to date of a link between psychosocial stress and soluble E-selectin levels, stress exposure has been linked to endothelial dysfunction in human and animal models (Rozanski et al., 1999; Harris and Matthews, 2004; Das and O'Keefe, 2006), and hormones that are released during the stress response have direct effects on endothelial function (Wilbert-Lampen et al., 2006, 2007). For example, disruption of stable social groups of cynomolgus monkeys resulted in damaged endothelial cells, an effect that involved activation of the sympathetic nervous system (Skantze et al., 1998). In healthy men, an experimental speech stressor temporarily impaired the ability of blood vessels to dilate in response to increased blood flow (Ghiadoni et al., 2000). A separate study showed that this effect was reversed by pre-treatment with metyrapone, a glucocorticoid antagonist (Broadley et al., 2005). Cultured human endothelial cells exposed to corticotropin-releasing hormone (Wilbert-Lampen et al., 2006) or beta-endorphin (Wilbert-Lampen et al., 2007), increase their release of endothelin-1, a vasoconstrictor, and (in the case of beta-endorphin) lower levels of nitric oxide, a vasodilator. The aggregate of these effects is unopposed vasoconstriction (Wilbert-Lampen et al., 2006, 2007). Collectively, these prior studies show that ecological and laboratory stressors and exposure to stressor-related hormones both *in vivo* and *in vitro* impair endothelial function. The current study tested the hypothesis that perceived discrimination constitutes a kind of stress that predicts greater endothelial dysfunction, as measured by higher circulating concentrations of E-selectin.

The focus of the present study was perceived discrimination in general, not racism *perse*. While racism is a principal focus of research on the health effects of discrimination in the US, and while racism may be a particularly detrimental form of unfair treatment, recent evidence suggests that unfair treatment of any type may predict poorer health outcomes in minority and non-minority populations alike. While unfair treatment was associated with greater coronary artery calcification among African American women in the Study of Women's Health Across the Nation (SWAN), racial discrimination was not more detrimental than other forms of discrimination (Lewis et al., 2006). Similarly, carotid intima media thickness in the SWAN study was significantly greater among African American women with greater exposure to unfair treatment, but racism specifically was only marginally associated with artery thickness (Troxel et al., 2003). Results from the Chicago Health and Aging Project showed that perceived discrimination was associated with a significantly increased risk of mortality, and this was true for both African American and Caucasian participants (Barnes et al., 2008). In the Survey of Midlife in the United States (MIDUS), perceived discrimination was associated with higher rates of depression in Caucasians than in African Americans (Kessler et al., 1999). In the Whitehall study, perceived unfairness has been related to incident coronary events (De Vogli et al., 2007a,b), incident psychiatric morbidity (Ferrie et al., 2006), and metabolic syndrome (De Vogli et al., 2007a,b). These studies are not framed within the context of discrimination but unfairness is operationalized with measures similar to those used in the discrimination literature. Indeed, perceived discrimination is linked to adverse health outcomes in many diverse groups in a broad range of national contexts (Williams and Mohammed, 2008). Collectively, these results suggest that any form of unfair treatment may increase disease risk, and that diverse groups may be vulnerable to consequent adverse health outcomes. The measures used in the current study were designed to distinguish between perceptions of kinds of unfair treatment (e.g. being denied a promotion; receiving inferior service) and the perceived reasons for receiving such unfair treatment (e.g. race/ethnicity, age, gender (Williams et al., 1997)). Thus, it was possible to test the hypothesis that unfair treatment in general (i.e. for any reason) rather than racism, in particular, would be positively associated with circulating concentrations of E-selectin.

Data for the current analyses are from the Survey of Midlife in the United States (MIDUS), a longitudinal study of health and well-being in community-dwelling adults (Brim et al., 2004). Information on exposure to discrimination was collected in two surveys separated by a 9–10 year interval, and serum samples of E-selectin were obtained as part of the second wave of data collection. Two broad types of discrimination are measured in MIDUS: major lifetime discrimination and everyday discrimination (Williams et al., 1997). The former include experiences that can affect life chances, such as the loss of a job or being denied a bank loan. These experiences were found to be common among MIDUS participants, particularly among those with disadvantaged social status, and were predictive of poorer mental health (Kessler et al., 1999). We hypothesized that participants with greater exposure to such experiences would have higher levels of E-selectin (i.e. a dose-dependent relationship). In contrast, everyday discrimination describes routine unfair treatment, such as being called names or insulted, and while these experiences can be considered relatively minor, such treatment can adversely affect health over time. Chronic, but not acute exposure to everyday discrimination was associated with coronary artery calcification in African American women, for example (Lewis et al., 2006). In the current study we tested the hypothesis that individuals who reported exposure to everyday discrimination in both surveys, thereby demonstrating persistence of this stressor over time, would have higher levels of E-selectin than those reporting no discrimination or discrimination at only one wave of MIDUS data collection. We also examined the potential role of negative affect in mediating any associations between discrimination and E-selectin levels.

2. Methods

2.1. Participants

The MIDUS study comprises telephone and mail surveys that were conducted in 1995–1996 and 2004–2006. A national probability sample of households in the 48 contiguous states with at least one telephone, conducted by the John D. and Catherine T. MacArthur Foundation Research Network on Successful Midlife Development, was selected initially in 1995–1996 (MIDUS 1) using random digit dialing (Brim et al., 2004). The sample of 7120 non-institutionalized adults was stratified in advance by gender and age to achieve equal gender distribution and an age distribution with the greatest number between 40 and 60. An average of 9.2 years later (range 7.8–10.4 years), 75% (adjusted for mortality) of those living from the original sample agreed to participate in a second wave of data collection (MIDUS 2). Participants' responses on measures of everyday discrimination from both waves of MIDUS data collection were used in the current study; samples for measurement of E-selectin were obtained as part of MIDUS 2 data collection.

Biological data collection for MIDUS is ongoing, although a sufficiently large subsample was available to carry out present analyses. Criteria for participating in this part of the investigation were that respondents had to have completed the second wave of telephone and mail surveys (MIDUS 2). They were recruited by letter and a follow-up telephone call. Those who agreed to participate stayed overnight at one of three regional General Clinical Research Centers (GCRC). Upon arrival at the GCRC each respondent provided a detailed medical history interview with a GCRC clinician and completed a set of self-administered questionnaires. Participants were also asked to bring all prescription, over-the-counter, and alternative medications to the GCRC, and these were inventoried by project staff. The following morning fasting blood samples were obtained.

The biomarker sample included in these analyses is based on 887 respondents. Missing questionnaire and/or biomarker data yielded a final sample of 804.[1] Compared to MIDUS 2 respondents who did not complete the biomarker study ($n = 3148$), the biomarker sample was better educated (23.5% had some post-secondary education vs. 17.4% for the full sample, $\chi^2(4) = 41.58$, $P < 0.001$), reported better health (9.9% poor/fair vs. 15.6%, $\chi^2(4) = 21.9$, $P < 0.001$), and was more likely to report at least one instance of major lifetime discrimination (42.6% vs. 36.3%, $\chi^2(2) = 16.3$, $P < 0.001$). There were no differences in everyday discrimination scores, and age, gender, race/ethnicity, and marital status were comparable in the two samples.

2.2. Discrimination measures

Information about perceived unfair treatment of any type was collected using self-administered questionnaires, and two different types of unfair treatment were assessed. These two measures were developed to study racial discrimination in Detroit (Williams et al., 1997) and were largely based on prior qualitative studies of discrimination (Essed, 1991; Feagin, 1991). These same measures were found in MIDUS 1 to predict increased likelihood of depression and anxiety (Kessler et al., 1999).

The first measure, perceptions of major lifetime of discrimination, consisted of 11 specific events, such as not being hired for a job (see Table 1). Participants were asked to indicate how many times they experienced each event and were instructed to count only those instances when they perceived that discrimination of some type was the underlying reason for the event. These items generated 11 variables, each with a distribution of values, the modal value being 0, and a highly positive skew. Given these distributions and the fact that we had no *a priori* hypotheses about specific experiences that would be related to E-selectin, we created a summary measure that consisted of three values: never, 1–2 instances (i.e. a response greater than 0 to any of the 11 items), and 3 or more instances. This summary measure enabled testing the hypothesis that greater exposure to perceived major discrimination of any type would predict greater circulating concentrations of E-selectin. Because this measure assessed lifetime occurrences of each experience, only data from MIDUS 2 (which incorporated both MIDUS 1 responses and any new experiences in the intervening 9–10 years) were included. Participants were also asked to identify the reason for specific type of discrimination they felt they had experienced (e.g. age, gender, race, ethnicity, and height/weight).

The second measure of unfair treatment assessed everyday experiences of relatively minor discrimination, such as receiving poorer service at restaurants or being called names (see Table 1). Using a 4-point scale (1 = never; 4 = often) participants indicated how frequently they experienced 9 different types of everyday discrimination. In contrast to the measure of lifetime discrimination, this scale was designed to assess perceptions of routine, albeit relatively minor, unfair treatment. In order to test the hypothesis that persistent and long-term perceptions of routine unfair treatment would be more biologically detrimental than more limited perceptions of unfair treatment, we used data from both MIDUS 1 and MIDUS 2 to classify participants into one of three categories: never experienced everyday discrimination (i.e. a score of 1 at both MIDUS 1 and MIDUS 2); reported everyday discrimination at either MIDUS 1 or MIDUS 2 (i.e. a score of 1 at either MIDUS 1 or MIDUS 2); reported everyday discrimination at both MIDUS 1 and MIDUS 2 (i.e. scores other than 1 at both MIDUS 1 and MIDUS 2). We took this approach (rather than using a continuous variable) for two reasons. First, the distribution of scores on the scale at both MIDUS 1 and MIDUS 2 was strongly positively skewed because the modal response was "never." While regression analyses showed that greater exposure to everyday discrimination was associated with higher levels of E-selectin, additional analyses involving just those reporting discrimination showed that greater exposure was not associate with higher E-selectin levels – the relevant difference was between those who perceived unfair treatment and those who did not. Transformation of the data did not alter these results. The second reason we took this measurement approach was that averaging across MIDUS 1 and MIDUS 2 scores would not have permitted an assessment of the extent to which chronic exposure specifically was linked to E-selectin levels. Prior research showed that chronic but not acute perceived discrimination was positively associated with coronary artery thickness (Lewis et al., 2006).

2.3. E-selectin

Fasting serum samples from the GCRC were assayed for E-selectin using high-sensitivity enzyme-linked immunosorbent assay (hsELISA) according to manufacturer guidelines (R&D Systems, Minneapolis, MN). The laboratory coefficients of variance (CV) for all assays were in acceptable ranges (typically<10%).

2.4. Covariates

In addition to age, marital status, education, and race, analyses controlled for the influences of health status and health behaviors. These latter domains are also possibly implicated in poor health, which might explain elevated levels of E-selectin. Similarly, smoking and other health behaviors (chronic alcohol use, caffeine consumption) may be related to higher E-selectin levels. By controlling for health status and health behaviors, we sharpened the focus on the extent to which unfair treatment predicts elevated disease risk in individuals whose current health and health behaviors are held constant.

2.4.1. Health status

Health status was assessed using both subjective and objective measures. Subjective health was assessed by single survey question: "In general would you say your physical health is excellent, very good, good, fair, or poor" Scores on this item ranged from 1 ("Excellent") to 5 ("Poor"). Self-rated health is a strong predictor of later morbidity (Idler and Kasl, 1995; Moller et al., 1996) and mortality (Idler and Benyamini, 1997; Franks et al., 2003). The GCRC visit included measurement of height and weight, and body

[1] The biomarker sample included 273 twins, and we took two steps to determine whether the current analyses were influenced by their presence in the sample. First, the associations between both forms of discrimination and E-selectin remained statistically significant in analyses the controlled for twin status. Second, we analyzed the associations of discrimination and E-selectin in the twins and the rest of the sample independently — these analyses showed that the associations were stronger in the non-twins than in the twins. These additional analyses collectively increased our confidence that the presence of the twins in the analytical sample did not materially affect the results.

Table 1
Measures of major lifetime discrimination and everyday discrimination.

Major lifetime discrimination (Participants indicate number of instances of each)
"How many times in your life have you been discriminated against in each of the following ways because of such things as your race, ethnicity, gender, age, religion, physical appearance, sexual orientation, or other characteristics?"
a. "You were discouraged by a teacher or advisor from seeking higher education."
b. "You were denied a scholarship."
c. "You were not hired for a job."
d. "You were not given a promotion."
e. "You were fired."
f. "You were prevented from renting or buying a home in the neighborhood you wanted."
g. "You were prevented from remaining in a neighborhood because neighbors made life so uncomfortable."
h. "You were hassled by the police."
i. "You were denied a bank loan."
j. "You were denied or provided inferior medical care."
k. "You were denied or provided inferior service by a plumber, care mechanic, or other service provider."
Coding: Each item is answered by frequency (# of times) of its happening.

Everyday Discrimination (Participants respond using 4-pt. scale: Often; Sometimes; Rarely; Never)
a. "You are treated with less courtesy than other people."
b. "You are treated with less respect than other people."
c. "You receive poorer service than other people at restaurants or stores."
d. "People act as if they think you are not smart."
e. "People act as if they are afraid of you."
f. "People act as if they think you are dishonest."
g. "People act as if they think you are not as good as they are."
h. "You are called names or insulted."
i. "You are threatened or harassed."

mass index (BMI; weight in kilograms divided by the square of height in meters) was calculated for each participant. A continuous measure of BMI was included in all analyses. Finally, anti-hypertensive, cholesterol-lowering, steroid, and anti-depressant medications have all been shown to lower soluble levels of E-selectin (Alonso et al., 2001; Guzic-Salobir et al., 2001; Serebruany et al., 2003; Sanada et al., 2005). Use of any of these medications was determined from medication inventories obtained during the GCRC visit, and four dummy-coded variables were created for statistical analyses.

2.4.2. Health behaviors

Health behaviors are based on self-reported information from questionnaires completed by respondents during the GCRC visit. Cigarette smoking has adverse effects on endothelial function (Blann and McCollum, 1993). To account for the potential direct effects of smoking on E-selectin levels, a single variable — smoking was coded as never smoked, former smoker, and current smoker — was included in all analyses. Chronic alcohol use has also been linked to elevated soluble E-selectin (Sacanella et al., 1999), and all analyses included a continuous variable indicating on the number of drinks consumed during a typical week. Finally, caffeine consumption has been shown to have an adverse effect on endothelial function acutely (Papamichael et al., 2005), although long-term endothelial effects are less clear (Lopez-Garcia et al., 2006). To control for potential direct effects of caffeine on E-selectin levels, data on frequency of caffeine intake from coffee, tea, or caffeinated beverages were used to calculate average number of caffeinated beverages consumed per day; this continuous variable was included in all analyses.

2.4.3. Neuroticism

While perceived discrimination is hypothesized to act a psychosocial stressor and thereby to affect health, it is possible that those who perceive greater discrimination may do so because of a general negative emotional orientation, which itself may be linked to health. To examine the potential role of the personality dimension of neuroticism, the stable tendency to perceive events negatively, in mediating any associations of perceived discrimination and E-selectin levels, participants completed questions focused on how well four adjectives — moody, worrying, nervous, calm — described them (Rossi, 2001). They responded using a 4-point scale (1 = a lot; 4 = not at all). Scores on the 4 items were then averaged to generate a scale score (range 0–4). Internal consistency for this 4 item scale was good ($\alpha = 0.74$).

2.4.4. Statistical analyses

Associations between perceived discrimination and serum E-selectin levels were examined using analysis of variance (ANOVA). Significant differences in group means were further examined using Tukey's post hoc test. Separate models were estimated for lifetime and everyday discrimination, and analyses of covariance (ANCOVA) were used to examine potential confounding by demographic, socioeconomic, health status, and health behavior variables. The possible mediating role of neuroticism was also tested in bivariate, ANOVA, and ANCOVA analyses. The threshold for identifying statistically significant associations was set at $\alpha = 0.05$.

3. Results

Table 2 provides descriptive statistics for the study sample. Preliminary analyses revealed substantial gender differences in both predictor and outcome variables. For example, women were significantly more likely than men to report instances of both lifetime [$\chi^2(2) = 8.33$, $P < 0.05$] and everyday [$\chi^2(2) = 21.91$, $P < 0.001$] discrimination. This result was somewhat surprising — more often than not, men tend to report higher levels of discrimination than women — but the data are not uniform; a few studies find women are higher (see review by Paradies, 2006). Men, however, had significantly higher circulating levels of E-selectin than women [$t(802) = 4.65$, $P < 0.001$]. There were also significant gender differences for many of the covariates of interest. Men, for example, were more likely than women to be married, to have smoked, to drink more alcohol on a weekly basis, to have more years of education, to be taking cholesterol medication, and to have higher BMI values. Women, in contrast, reported a greater number of chronic health conditions and were more likely to be taking prescription steroid and anti-depressant medications than men (see Table 1), although preliminary analyses showed that medication use was

unrelated to E-selectin levels (data not shown). For these reasons, interaction terms for gender and discrimination were included in all statistical models.

Approximately 35% of the male participants reported at least one instance of major lifetime discrimination with 19% reporting more than 3 instances. The most common forms of discrimination reported were not being hired for a job (19.1%), not being given a job promotion (16.4%), and being denied service or given inferior service (14.7%). The most common reasons given for discrimination were age (48.4% of those reporting discrimination) and race (31.2%; data not shown). Thirty-one percent of men reported never experiencing everyday discrimination, while almost 39% reported chronic experiences of everyday discrimination (Table 2).

Almost half of the female participants reported at least one instance of major lifetime discrimination while nearly 30% reported 3 or more instances (Table 1). As was the case for men, among those reporting discrimination not being hired for a job (20%), not being promoted (16.4%), and being denied service or given inferior service (14.7%) were the most common forms of discrimination, while gender (72%) and height/weight (28.2%) were the principal reasons for discrimination reported (data not shown). Finally, only 20% of women reported no experiences of everyday discrimination while more than half reported chronic everyday discrimination (Table 2).

3.1. Discrimination and E-selectin

Experiences of major lifetime discrimination predicted significantly higher circulating levels of E-selectin [$F(2,802) = 6.65$, $P = 0.001$, $\eta_p^2 = 0.02$], and this association remained statistically significant after inclusion of covariates in the ANCOVA model [$F(2,788) = 4.40$, $P < 0.05$; $\eta_p^2 = 0.02$]. Post hoc testing showed that those reporting 3 or more instances of major discrimination had significantly higher E-selectin levels than those reporting none ($P < 0.05$).

There was also a significant gender $\times$ discrimination interaction in both the ANOVA [$F(2,802) = 4.16$, $P < 0.05$; $\eta_p^2 = 0.01$] and ANCOVA models [$F(2,786) = 6.24$, $P < 0.01$; $\eta_p^2 = 0.01$]. Given this interaction, separate models were estimated for men and women. The results showed that major lifetime discrimination predicted higher E-selectin levels in men [ANOVA: $F(2,383) = 8.14$, $P < 0.001$; $\eta_p^2 = .04$; ANCOVA: $F(2,367) = 4.15$, $P < 0.05$; $\eta_p^2 = 0.02$] but not in women [ANOVA: $F(2,431) = 0.20$, $P > 0.05$; ANCOVA $F(2,415) = 0.06$, $P > 0.05$; Fig. 1]. Post hoc testing showed that men reporting 3 or more instances had significantly higher E-selectin levels than the other two groups ($P < 0.05$). Of the other variables included in the full model, only higher BMI levels were associated with higher E-selectin in men. In women, higher BMI levels and greater daily consumption of caffeine both predicted higher E-selectin levels.

Chronic everyday discrimination significantly predicted higher E-selectin levels [$F(2,802) = 4.19$, $P < 0.05$; $\eta_p^2 = 0.01$], and this association remained statistically significant after the inclusion of covariates [$F(2,786) = 8.51$, $P < 0.001$; $\eta_p^2 = 0.01$]. Post hoc testing showed that those experiencing everyday discrimination chronically (at both MIDUS 1 and MIDUS 2) had higher levels of E-selectin that those reporting no discrimination ($P < 0.05$).

As with lifetime discrimination, there was a near-significant interaction for gender and everyday discrimination in the ANOVA model [$F(2,802) = 2.97$, $P = 0.05$; $\eta_p^2 = 0.01$] and a significant interaction in the full ANCOVA model [$F(2,786) = 15.44$, $P < 0.001$; $\eta_p^2 = 0.01$], and again separate ANCOVAs were estimated for men and women. Chronic everyday discrimination predicted higher E-selectin levels in men [ANOVA: $F(2,383) = 6.40$, $P < 0.01$; $\eta_p^2 = 0.03$; ANCOVA: $F(2,367) = 3.66$, $P < 0.05$; $\eta_p^2 = 0.02$] but not in women [ANOVA: $F(2,431) = 0.32$, $P > 0.05$; ANCOVA: $F(2,415) = 0.07$, $P > 0.05$; Fig. 2], and post hoc tests showed that men who reported everyday discrimination at both MIDUS 1 and MIDUS 2 had elevated levels of E-selectin compared to those who reported no discrimination experiences.

3.2. Relationships with neuroticism

Finally, we examined the extent to which neuroticism mediated the association of perceived discrimination and E-selectin levels. Men and women reporting higher levels of perceived major discrimination [$F(2,863) = 3.26$, $P < 0.05$] and everyday discrimination [$F(2,863) = 15.30$, $P < 0.001$] also had significantly higher scores on the neuroticism scale. However, bivariate analyses showed no association between neuroticism and E-selectin levels ($r = -0.02$, $P > 0.05$), and inclusion of neuroroticism in ANCOVA models did not affect the association E-selectin with either lifetime [$F(2,365) = 3.94$, $P < 0.05$] or everyday [$F(2,365) = 3.22$, $P < 0.05$] discrimination. We also examined possible moderation by neuroticism by including interaction terms for neuroticism and discrimination type, but in neither case was the interaction statistically significant (data not shown).

4. Discussion

This study tested the general hypothesis that perceived unfair treatment would be associated with increased circulating concentrations of the soluble adhesion molecule E-selectin, and the results supported that hypothesis for men, but not for women. Male participants who reported experiencing 3 or more instances of major lifetime discrimination had significantly higher E-selectin levels than those reporting fewer or no instances. Those men who reported everyday discrimination at the time of MIDUS 1 data collection and also 9–10 years later at MIDUS 2, thereby showing persisting experiences of unfair treatment, had significantly higher levels of E-selectin than men reporting no minor discrimination. In our statistical models, potential confounding by age, race, socioeconomic status, subjective and objective health status, health behaviors, and medication use was examined, and none of these variables fully explained the observed associations. In addition, dispositional negative affect, while associated with both forms of perceived discrimination, did not mediate the association of unfair treatment and E-selectin levels. Collectively, these results support the contention that unfair treatment, particularly if it is chronic, may have an adverse impact on endothelial function, which could constitute a pathway to increased risk of vascular disease. Both forms of discrimination accounted for 2–3% of the variance in E-selectin in men, and while this is a small effect size, it is worth noting that BMI, the strongest predictor of E-selectin levels in both men and women, accounted for only 7–8% of the variance (data not shown). The findings represent the first evidence of which we are aware that soluble E-selectin levels are associated with psychosocial experience.

Discrimination has been shown to have an impact on the mental and physical health of stigmatized groups (Krieger, 2001; Ahmed et al., 2007) as well as individuals exposed to unfair treatment (Kessler et al., 1999; Williams et al., 2003; Ferdinand, 2006; Barnes et al., 2008), and cardiovascular disease (CVD), the leading cause of death in the US (Rosamond et al., 2008), provides a compelling nexus for research on the health consequences of discrimination as well as the mechanisms involved. For example, rates of cardiovascular disease are higher in populations who have traditionally experienced discriminatory treatment (Ferdinand, 2006; Rosamond et al., 2008), and indices of risk for CVD, such as vascular pathology, are positively linked to perceived exposure to unfair

Table 2
Descriptive statistics for study sample.

Predictors	Men (n = 385)			Women (n = 419)			p-Value
	Mean (±SE)	Range	%	Mean (±SE)	Range	%	
Lifetime discrimination							
Never			64.5			51.0	<0.05
1–2 instances			16.5			19.3	
3+ Instances			19.0			29.8	
Daily discrimination							
Never			31.1			20.0	<0.001
M1 or M2			30.1			27.9	
M1 and M2			38.7			52.0	
Age	59.0 (0.6)	36–86		57.9	35–86		0.14
Marital status (% married)			80.9			64.0	<0.001
Race/ethnicity (% white)			92.6			93.7	0.16
Education							
<High school			4.3			3.5	<0.001
HS grad or GED			16.9			24.7	
Some college or 2-year degree			29.0			31.0	
College grad			26.0			17.6	
Some grad school or more			23.8			23.2	
Health status and health behavior							
Self-rated health (% fair or poor)			13.7			15.4	0.25
Body mass index (BMI)	29.7 (0.3)	20–57		28.8 (0.3)	15–60		0.05
Smoking status							
Current smoker			11.5			11.6	<0.05
Ex-smoker			38.9			30.4	
Never smoked			49.6			58.0	
Avg. alcoholic drinks per week	4.6 (0.3)	0–56		1.9 (0.2)	0–28		<0.001
Avg. caffeinated drinks per day	2.8 (0.02)	1–3		2.8 (0.0)	1–3		0.23
Blood pressure medication (% yes)			34.8			34.7	0.93
Cholesterol medication (% yes)			37.1			23.3	<0.001
Steroid medication (% yes)			3.6			20.3	<0.001
Anti-depressant medication (% yes)			11.8			17.6	<0.05
Neuroticism	1.96 (0.03)	1–4		2.1 (0.03)	1–4		<0.01
Serum soluble E-selectin (ng/mL)	41.2 (0.9)	9–100		35.8 (0.8)	1–100		<0.001

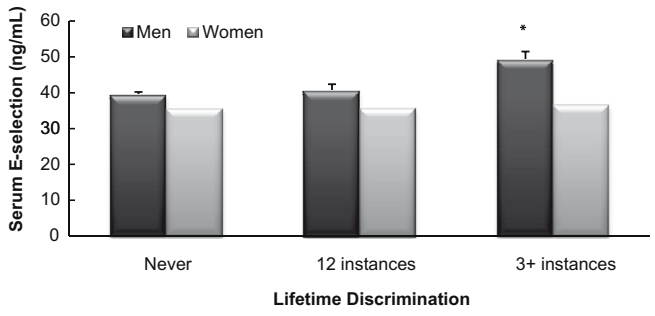

Fig. 1. Relationship between exposure to major lifetime discrimination and serum E-selectin in men and women. Adjusted analyses revealed a significant gender X discrimination interaction [$F(2,786) = 6.24$, $P < 0.01$], and gender-specific analyses showed that among men, exposure to 3 or more instances of any kind of major discrimination (see Table 1) predicted significantly greater E-selectin levels compared to those exposed to fewer or no instances of discrimination [$F(2,367) = 4.15$, $P < 0.05$]. In women, discrimination exposure and E-selectin levels were unrelated.

treatment (Troxel et al., 2003; Lewis et al., 2006). Perceived discriminatory treatment, particularly for reasons of race, has also been linked to greater blood pressure responses to laboratory stressors among African American women (Guyll et al., 2001; Harrell et al., 2003), and greater cardiovascular reactivity may constitute a risk factor for cardiovascular disease (Treiber et al., 2003). Importantly, chronic elevations in blood pressure are associated with greater endothelial dysfunction generally (Ross, 1999) and elevated serum concentrations of E-selectin specifically (Miller et al., 2004). Given these associations, the current results suggest that endothelial dysfunction may be an important mechanism by which discrimination may increase the risk of cardiovascular disease in particular.

Health status and health behaviors represent potential rival explanations for the observed associations. For example, health status, including obesity, may simultaneously explain perceived exposure to discrimination (Andreyeva et al., 2008) and higher circulating levels of E-selectin (Bonora, 2006). Indeed, BMI was a significant predictor of E-selectin levels in all statistical models (data not shown), and women in particular reported height/weight as the basis of unfair treatment almost 30% of the time. Moreover, dis-

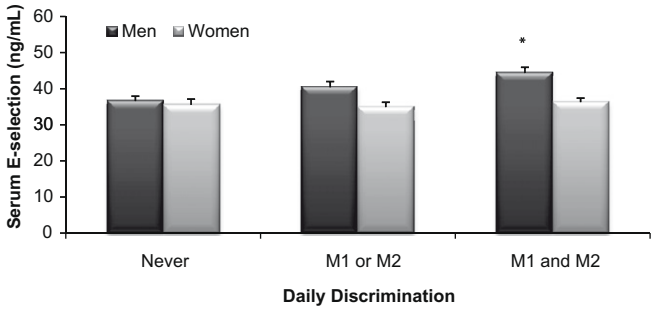

Fig. 2. Relationship between exposure to everyday discrimination and serum E-selectin in men and women. Adjusted analyses revealed a significant gender X discrimination interaction [$F(2,786) = 15.44$, $P < 0.001$], and gender-specific analyses showed that in men, chronic exposure to everyday discrimination (at both waves of MIDUS data collection) predicted significantly higher levels of E-selectin compared to men who never experienced everyday discrimination [$F(2,367) = 3.66$, $P < 0.05$]. In women, everyday discrimination and E-selectin levels were unrelated.

crimination is also thought to result in poorer health behavior and consequently greater likelihood of adverse health outcomes (Ahmed et al., 2007). A number of health behaviors, including smoking, have also been positively linked with endothelial dysfunction and higher levels of soluble E-selectin (Blann and McCollum, 1993; Sacanella et al., 1999; Papamichael et al., 2005). For these reasons, statistical models in the current study adjusted for health status and health behaviors, and the association between perceived discrimination and E-selectin levels remained significant among men. Thus, while health status and health behavior are clearly linked to endothelial dysfunction, they do not constitute rival explanations for the relationship between unfair treatment and E-selectin. That said, it may be fruitful to examine the extent to which the strength of the links between discrimination and adhesion molecules (or other biological markers of disease risk) varies among individuals distinguished by differences in health status, health behaviors, or other characteristics. Such analyses of the interplay among multiple variables will help to identify groups of individuals for whom the association of discrimination and biological risk is particularly strong (or weak).

Gender was a significant determinant of both E-selectin levels and of the relationship between E-selectin and experiences of unfair treatment. A number of previous studies have reported higher E-selectin levels in men compared to women (Blann et al., 1996; Jilma et al., 1996; Bannan et al., 1998; Demerath et al., 2001), although others have observed no such differences (Ponthieux et al., 2004). One potential explanation for this difference may be sex hormones. Pre-menopausal women are at considerably reduced risk of endothelial dysfunction than postmenopausal women (Virdis et al., 2002), and hormone replacement therapies have been shown to improve endothelial function in postmenopausal women (Guzic-Salobir et al., 2001; Colacurci et al., 2003; Prestwood et al., 2004; Salpeter et al., 2006). In additional analyses for the current study, we examined differences in E-selectin levels in pre- and postmenopausal women, and observed no significant group differences between women who reported having a menstrual cycle in the prior 12 months and those who reported none (data not shown). While this analysis suggests that sex hormones did not appear to explain the sex differences observed here, MIDUS does not include the types of data needed for precise classification of menopausal status (Weinstein et al., 2003). For this reason we cannot confidently rule out the possibility that menopausal status may have contributed to sex differences in E-selectin levels in the current study. A second possible source of the sex difference is BMI, which was higher for men than for women. Although BMI strongly predicted E-selectin levels in both men and women, the effect size was almost 30% larger for men ($\eta_p^2 = 0.07–0.08$) than for women ($\eta_p^2 = 0.05–0.06$), suggesting that BMI may be more strongly related to endothelial dysfunction in men than in women.

We found no associations between discrimination and E-selectin levels in women, even though women reported higher rates of both lifetime and everyday discrimination. These results differ from those of prior studies documenting vascular pathology (Troxel et al., 2003; Lewis et al., 2006) and increased cardiovascular reactivity (Guyll et al., 2001) in women reporting greater exposure to discrimination, although links between perceived everyday discrimination and mortality were observed for men and women alike (Barnes et al., 2008). One important difference between this current study and prior ones is the composition of the sample. Data for each of the studies cited above were taken from the SWAN, a national longitudinal study of mid-life Caucasian and African American women. In contrast, as previously noted the MIDUS biomarker sample was predominantly Caucasian. In addition, the age range for the current sample was much broader (35–84 years old) than for the SWAN (42–52 years old). Although like others (Miles et al., 2001) we observed no robust relationship between age and E-selectin levels in the current study (data not shown), it is possible that age-related variables (e.g. health, body habitus) may affect how discrimination and E-selectin are associated over such a large age range in women; future efforts will examine this possibility more closely. Men and women in this sample differed in several ways that could have influenced the link between perceived unfair treatment and E-selectin. A larger percentage of women were taking steroid and anti-depressant medication, although additional analyses showed that medication use was not associated with differences in E-selectin (data not shown). Female sex hormones have also hypothesized to preserve endothelial function, but as mentioned above menopausal status was unrelated to E-selectin levels and thus are unlikely to explain the observed sex differences. Finally, men had higher average BMI and the relationship between BMI and E-selectin was stronger in men than in women; it is possible that obesity may accentuate the relationship between discrimination and E-selectin, even though obesity was not reported as a principle reason for discrimination.

As noted above, psychosocial stressors have been linked to endothelial dysfunction (Rozanski et al., 1999; Harris and Matthews, 2004; Das and O'Keefe, 2006), and while subjective experiences of stress were not examined in the current study, future efforts will examine the extent to which such perceptions are associated with both perceived discrimination and adhesion molecule concentrations. In addition, personality attributes, such as the tendency to view events in a negative light (e.g. neuroticism), have been linked to increased risk of mortality (Almada et al., 1991; Mroczek and Spiro, 2007), particularly from cardiovascular disease (Shipley et al., 2007), and may also increase the likelihood of perceiving unfair treatment (Williams et al., 2003). In the current analyses, neuroticism was higher in those reporting greater perceived discrimination, but it was not associated with E-selectin nor did it mediate or moderate the link between discrimination and E-selectin. These results suggest that the biological signatures of unfair treatment may be independent of the tendency to view the world negatively.

Another way in which the current results differ from prior examinations of discrimination and health is that the MIDUS biomarker sample was almost exclusively Caucasian; only 7% of the sample was non-white. The demographic composition of the sample makes it impossible to extend these results to minority populations or to determine the extent to which racism is unique in its biological signature compared to unfair treatment in general; we intend to pursue these issues in future research using data from an oversample of African Americans in the MIDUS study. As the biomarker sample was also slightly more educated than the full MIDUS sample (23.5% with post-secondary education vs. 17.4% for the full sample), these results may also not extend to those with lower socioeconomic standing. Nonetheless, high proportions of both men and women reported experiences of unfair treatment. This result underscores the value of measuring exposure to discrimination independently of perceived reasons for discrimination. Conflating discrimination and racism, for example, may have masked the association of unfair treatment broadly construed and E-selectin levels. These results also highlight the importance of broadening the consideration of the health impacts of unfair treatment to include populations that are not typically considered stigmatized (e.g. women, obese individuals, the aged). Perceptions of unfair treatment, even among members of privileged racial or ethnic groups, may have significant health consequences. Interestingly, men in the current study cited race/ethnicity as the reason for discriminatory treatment more than 30% of the time, and the most common form of discrimination reported was not being hired. These responses may constitute perceptions of "reverse discrimination" whereby Caucasian men take a negative view of social policies designed to address racial inequities (Fraser and Kick,

2000) and may feel personally disadvantaged by such policies or practices.

In spite of these limitations, however, the present results shed light on a novel mechanism that may link exposure to unfair treatment with adverse health outcomes and also underscore the importance of examining the health consequences of unfair treatment in general.

Acknowledgments

The authors gratefully acknowledge the National Institute on Aging for their support for the present analyses (K01-AG029381 to EMF) and to conduct a longitudinal follow-up of the MIDUS (Midlife in the US) investigation (P01-AG020166). The original study was supported by the John D. and Catherine T. MacArthur Foundation Research Network on Successful Midlife Development.

References

Ahmed, A.T., Mohammed, S.A., et al., 2007. Racial discrimination & health: pathways & evidence. Indian J. Med. Res. 126 (4), 318–327.
Almada, S.J., Zonderman, A.B., et al., 1991. Neuroticism and cynicism and risk of death in middle-aged men: the western electric study. Psychosom. Med. 53 (2), 165–175.
Alonso, R., Mata, P., et al., 2001. Sustained long-term improvement of arterial endothelial function in heterozygous familial hypercholesterolemia patients treated with simvastatin. Atherosclerosis 157 (2), 423–429.
Andreyeva, T., Puhl, R.M., et al., 2008. Changes in perceived weight discrimination among Americans, 1995–1996 through 2004–2006. Obesity (Silver Spring) 16 (5), 1129–1134.
Bannan, S., Mansfield, M.W., et al., 1998. Soluble vascular cell adhesion molecule-1 and E-selectin levels in relation to vascular risk factors and to E-selectin genotype in the first degree relatives of NIDDM patients and in NIDDM patients. Diabetologia 41 (4), 460–466.
Barnes, L.L., de Leon, C.F., et al., 2008. Perceived discrimination and mortality in a population-based study of older adults. Am. J. Public Health 98 (7), 1241–1247.
Blann, A.D., Lip, G.Y.H., 2000. Cell adhesion molecules in cardiovascular disease and its risk factors – what can soluble levels tell us? J. Clin. Endocrinol. Metab. 85 (5), 1745–1747.
Blann, A.D., McCollum, C.N., 1993. Adverse influence of cigarette smoking on the endothelium. Thromb. Haemost. 70 (4), 707–711.
Blann, A.D., Amiral, J., et al., 1996. Circulating endothelial cell/leucocyte adhesion molecules in ischaemic heart disease. Br. J. Haematol. 95 (2), 263–265.
Bonora, E., 2006. The metabolic syndrome and cardiovascular disease. Ann. Med. 38 (1), 64–80.
Brim, O.G., Ryff, C.D., et al., 2004. How Healthy are We? A National Study of Well-Being at Mid-Life. University of Chicago Press, Chicago.
Broadley, A.J., Korszun, A., et al., 2005. Inhibition of cortisol production with metyrapone prevents mental stress-induced endothelial dysfunction and baroreflex impairment. J. Am. Coll. Cardiol. 46 (2), 344–350.
Colacurci, N., Manzella, D., et al., 2003. Endothelial function and menopause: effects of raloxifene administration. J. Clin. Endocrinol. Metab. 88 (5), 2135–2140.
Das, S., O'Keefe, J.H., 2006. Behavioral cardiology: recognizing and addressing the profound impact of psychosocial stress on cardiovascular health. Curr. Atheroscler. Rep. 8 (2), 111–118.
De Vogli, R., Brunner, E., et al., 2007a. Unfairness and the social gradient of metabolic symdrome in the Whitehall II study. J. Psychosom. Res. 63, 413–419.
De Vogli, R., Ferrie, J., et al., 2007b. Unfairness and health: evidence from the Whitehall II study. J. Epidemiol. Commun. Health 61 (6), 513–518.
Demerath, E., Towne, B., et al., 2001. The relationship of soluble ICAM-1, VCAM-1, P-selectin and E-selectin to cardiovascular disease risk factors in healthy men and women. Ann. Hum. Biol. 28 (6), 664–678.
Erbe, D.V., Wolitzky, B.A., et al., 1992. Identification of an E-selectin region critical for carbohydrate recognition and cell adhesion. J. Cell. Biol. 119 (1), 215–227. published erratum appears in J. Cell. Biol. 1993 February 120(4), 1071.
Essed, P., 1991. Understanding Everyday Racism. Newbury Park, California, Sage.
Feagin, J., 1991. The continuing significance of race. anti-black discrimination in public places. Am. Sociol. Rev. 56, 101–116.
Ferdinand, K.C., 2006. Coronary artery disease in minority racial and ethnic groups in the United States. Am. J. Cardiol. 97 (2A), 12A–19A.
Ferrie, J.H., MJ, J.S., Vahtera, J., Marmot, M.G., Kivimaki, M., 2006. Injustice at work and incidence of psychiatric morbidity: the Whitehall II study. Occup. Environ. Med. 63, 443–450.
Franks, P., Gold, M.R., et al., 2003. Sociodemographics, self-rated health, and mortality in the US. Soc. Sci. Med. 56 (12), 2505–2514.
Fraser, J., Kick, E., 2000. The interpretive repertoires of whites on race-targeted policies: claims making of reverse discrimination. Soc. Perspect. 43 (1), 13–28.
Galkina, E., Ley, K., 2007. Leukocyte influx in atherosclerosis. Curr. Drug. Targets 8 (12), 1239–1248.
Ghiadoni, L., Donald, A.E., et al., 2000. Mental stress induces transient endothelial dysfunction in humans. Circulation 102 (20), 2473–2478.
Guyll, M., Matthews, K.A., et al., 2001. Discrimination and unfair treatment: relationship to cardiovascular reactivity among African American and European American women. Health Psychol. 20 (5), 315–325.
Guzic-Salobir, B., Keber, I., et al., 2001. Combined hormone replacement therapy improves endothelial function in healthy postmenopausal women. J. Intern. Med. 250 (6), 508–515.
Harrell, J., Hall, S., et al., 2003. Physiological responses to racism and discrimination: an assessment of the evidence. Am. J. Public Health 93 (2).
Harris, K.F., Matthews, K.A., 2004. Interactions between autonomic nervous system activity and endothelial function: a model for the development of cardiovascular disease. Psychosom. Med. 66 (2), 153–164.
Hwang, S.-J., Ballantyne, C.M., et al., 1997. Circulating adhesion molecules VCAM-1, ICAM-1, and E-selectin in carotid atherosclerosis and incident coronary heart disease cases: the atherosclerosis risk in communities (ARIC) study. Circulation 96 (12), 4219–4225.
Idler, E.L., Benyamini, Y., 1997. Self-rated health and mortality: a review of twenty-seven community studies. J. Health Soc. Behav. 38 (1), 21–37.
Idler, E.L., Kasl, S.V., 1995. Self-ratings of health: do they also predict change in functional ability? J. Gerontol. B Psychol. Sci. Soc. Sci. 50 (6), S344–S353.
Jilma, B., Dirnberger, E., et al., 1996. Sex differences in circulating P-selectin, E-selectin and thrombomodulin. Br. J. Haematol. 95 (3), 575–576.
Kessler, R.C., Mickelson, K.D., et al., 1999. The prevalence, distribution, and mental health correlates of perceived discrimination in the United States. J. Health Soc. Behav. 40 (3), 208–230.
Krieger, N., 2001. The ostrich, the albatross, and public health: an ecosocial perspective–or why an explicit focus on health consequences of discrimination and deprivation is vital for good science and public health practice. Public Health Rep. 116 (5), 419–423.
Lewis, T.T., Everson-Rose, S.A., et al., 2006. Chronic exposure to everyday discrimination and coronary artery calcification in African–American women: the SWAN heart study. Psychosom. Med. 68 (3), 362–368.
Lopez-Garcia, E., van Dam, R.M., et al., 2006. Coffee consumption and markers of inflammation and endothelial dysfunction in healthy and diabetic women. Am. J. Clin. Nutr. 84 (4), 888–893.
Miles, E.A., Thies, F., et al., 2001. Influence of age and dietary fish oil on plasma soluble adhesion molecule concentrations. Clin. Sci. (Lond) 100 (1), 91–100.
Miller, M.A., Kerry, S.M., et al., 2004. Cellular adhesion molecules and blood pressure: interaction with sex in a multi-ethnic population. J Hypertens 22 (4), 705–711.
Moller, L., Kristensen, T.S., et al., 1996. Self rated health as a predictor of coronary heart disease in Copenhagen, Denmark. J. Epidemiol. Commun. Health 50 (4), 423–428.
Mroczek, D.K., Spiro 3rd, A., 2007. Personality change influences mortality in older men. Psychol. Sci. 18 (5), 371–376.
Papamichael, C.M., Aznaouridis, K.A., et al., 2005. Effect of coffee on endothelial function in healthy subjects: the role of caffeine. Clin. Sci. (Lond) 109 (1), 55–60.
Paradies, Y., 2006. A systematic review of empirical research on self-reported racism and health. Int. J. Epidemiol. 35 (4), 888–901.
Pigott, R., Dillon, L.P., et al., 1992. Soluble forms of E-selectin, ICAM-1 and VCAM-1 are present in the supernatants of cytokine activated cultured endothelial cells. Biochem. Biophys. Res. Commun. 187 (2), 584–589.
Ponthieux, A., Herbeth, B., et al., 2004. Biological determinants of serum ICAM-1, E-selectin, P-selectin and L-selectin levels in healthy subjects: the Stanislas study. Atherosclerosis 172 (2), 299–308.
Prestwood, K.M., Unson, C., et al., 2004. The effect of different doses of micronized 17beta-estradiol on C-reactive protein, interleukin-6, and lipids in older women. J. Gerontol. A Biol. Sci. Med. Sci. 59 (8), 827–832.
Rosamond, W., Flegal, K., et al., 2008. Heart disease and stroke statistics–2008 update: a report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Circulation 117 (4), e25–e146.
Ross, R., 1999. Atherosclerosis – an inflammatory disease. N. Engl. J. Med. 340 (2), 115–126.
Rossi, A., 2001. Caring and Doing for Others: Social Responsibility in the Domains of Family, Work, and Community. University of Chicago Press, Chicago.
Rozanski, A., Blumenthal, J.A., et al., 1999. Impact of psychological factors on the pathogenesis of cardiovascular disease and implications for therapy. Circulation 99 (16), 2192–2217.
Sacanella, E., Estruch, R., et al., 1999. Chronic alcohol consumption increases serum levels of circulating endothelial cell/leucocyte adhesion molecules E-selectin and ICAM-1. Alcohol Alcohol. 34 (5), 678–684.
Salpeter, S.R., Walsh, J.M., et al., 2006. Meta-analysis: effect of hormone-replacement therapy on components of the metabolic syndrome in postmenopausal women. Diabetes Obes. Metab. 8 (5), 538–554.
Sanada, H., Midorikawa, S., et al., 2005. Elevation of serum soluble E- and P-selectin in patients with hypertension is reversed by benidipine, a long-acting calcium channel blocker. Hypertens. Res. 28 (11), 871–878.
Serebruany, V.L., Glassman, A.H., et al., 2003. Platelet/endothelial biomarkers in depressed patients treated with the selective serotonin reuptake inhibitor sertraline after acute coronary events: the Sertraline AntiDepressant Heart Attack Randomized Trial (SADHART) Platelet Substudy. Circulation 108 (8), 939–944.
Shipley, B.A., Weiss, A., et al., 2007. Neuroticism, extraversion, and mortality in the UK Health and Lifestyle Survey: a 21-year prospective cohort study. Psychosom. Med. 69 (9), 923–931.

Skantze, H.B., Kaplan, J., et al., 1998. Psychosocial stress causes endothelial injury in cynomolgus monkeys via beta1-adrenoceptor activation. Atherosclerosis 136 (1), 153–161.
Springer, T.A., 1990. Adhesion receptors of the immune system. Nature 346 (6283), 425–434.
Treiber, F.A., Kamarck, T., et al., 2003. Cardiovascular reactivity and development of preclinical and clinical disease states. Psychosom. Med. 65 (1), 46–62.
Troxel, W.M., Matthews, K.A., et al., 2003. Chronic stress burden, discrimination, and subclinical carotid artery disease in African American and Caucasian women. Health Psychol. 22 (3), 300–309.
Virdis, A., Ghiadoni, L., et al., 2002. Endothelial function in hypertension: role of gender. J. Hypertens. Suppl. 20 (2), S11–S16.
Weinstein, M., Gorrindo, T., et al., 2003. Timing of menopause and patterns of menstrual bleeding. Am. J. Epidemiol. 158 (8), 782–791.
Wilbert-Lampen, U., Trapp, A., et al., 2006. Effects of corticotropin-releasing hormone (CRH) on endothelin-1 and NO release, mediated by CRH receptor subtype R2: a potential link between stress and endothelial dysfunction? J. Psychosom. Res. 61 (4), 453–460.
Wilbert-Lampen, U., Trapp, A., et al., 2007. Effects of beta-endorphin on endothelial/monocytic endothelin-1 and nitric oxide release mediated by mu1-opioid receptors: a potential link between stress and endothelial dysfunction? Endothelium 14 (2), 65–71.
Williams, D., Mohammed, S., 2008. Discrimination and racial disparities in health: evidence and needed research. J. Behav. Med. 32 (1), 1–8.
Williams, D., Yu, Y., et al., 1997. Racial differences in physical and mental health: socioeconomic status, stress, and discrimination. J. Health Psychol. 2, 335–351.
Williams, D.R., Neighbors, H.W., et al., 2003. Racial/ethnic discrimination and health: findings from community studies. Am. J. Public Health 93 (2), 200–208.
Zethelius, B., Berglund, L., et al., 2008. Use of multiple biomarkers to improve the prediction of death from cardiovascular causes. N. Engl. J. Med. 358 (20), 2107–2116.