Perceived social support and inflammatory markers over the life course: evaluating the buffering vs. direct effects hypotheses of social support using the Multi-Ethnic Study of Atherosclerosis

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EXTENDED ABSTRACT

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The interrelationships between the social environment and physical health have been the subject of numerous empirical investigations, and it has been established that low emotional support and social isolation are associated with increased mortality, particularly from cardiovascular disease (CVD). Despite the compelling epidemiologic evidence of a strong and clinically significant association between social support and CVD morbidity and mortality, the mechanisms underlying this relationship remain unspecified. Clearly, characteristics of the social environment must affect physiologic states in order to have an effect on CVD risk, and several researchers have speculated that neuroendocrine hormones (i.e., cortisol, inflammatory cytokines, catecholamines), which have been implicated in CVD and other chronic conditions, may be a mechanism by which social support affects health. However, even if social support is associated with neuroendocrine markers, it is unclear whether this relationship is due to a *direct* influence on physiology, or if support simply *buffers* the effect of negative experiences (e.g., exposure to chronic stress) on health. Evidence suggests both models are operating in the population, but whether the relative importance of these processes changes over the life course has not been extensively examined, although there are suggestive reports that the "direct-effects" model is more pronounced in older individuals. A lifespan framework is useful for understanding how social support may influence health, as social roles change over the life course (i.e., marriage, parenthood) and many conditions, such as CVD, develop over decades before symptoms manifest.

The goal of this paper is to explore the relationship between perceived social support (PSS) and two markers inflammation that have been implicated in CVD, interleukin-6 and C-reactive protein, using the Multi-Ethnic Study of Atherosclerosis. We evaluated whether these associations are consistent with the hypothesized links between PSS and health, and investigated two main questions: (1) *Does the association between support and inflammatory markers strengthen over the life course – that is, is the association is stronger among older age cohorts relative to younger ones?* and (2) *Do the relative importance of the buffering versus the direct-effects models of support change over the life course?* We hypothesized that if buffering is predominant, the association between PSS and inflammation will be stronger among those experiencing chronic stress relative to those not exposed. However, if the direct model is predominant, the association will not vary by chronic stress status. Finally, because the receipt and provision of social support is gendered (i.e., women are more likely to experience loss of a spouse) and changes in social relations over the life course are likewise gendered, we evaluated whether these relationships varied by sex.

Methods

The Multi-Ethnic Study of Atherosclerosis (MESA) is an on-going study of the individual and environmental predictors of subclinical cardiovascular disease and used a unique sampling frame to develop a diverse (40% non-Hispanic white, 30% African American, 20% Hispanic, and 10% Asian) sample of middle and older age (range: 45-84) adults. The sample is 53% women. All MESA participants were free of clinical CVD at baseline. This report is restricted to the baseline survey and to those participants with complete data on the measures of social support, chronic stress, and markers of inflammation (N = 6,153, 90% of the baseline sample).

The two primary independent variables were perceived social support (PSS) and chronic stress. PSS was measured by an index (range: 6 – 30) of six likert-scored items concerning availability of emotional support (i.e., *Is there someone available to you whom you can count on to listen to you when you need to talk?*). Chronic stress was measured by a composite of six dichotomous items concerning on-going stressors in several domains (e.g., personal health, health of a friend/relative, work-life, financial matters, relationship with friend/relative). The two factors investigated as moderators of the relationships between PSS and inflammation were gender and age-cohort. The moderating influences of these factors were assessed using Analysis of Variance (ANOVA) and both interaction terms and stratification in the regression analyses. The primary outcomes are two markers of inflammation, C-reactive protein (CRP) and interleukin-6 (IL-6), although only the results from the IL-6 analyses are discussed in detail below. Values of the inflammatory markers were log-transformed in order to

normalize their distributions to better meet the assumptions of the linear regression modeling. These markers have been shown to be associated with risk of cardiovascular morbidity and mortality. We conducted separate analyses with each marker as an evaluation of the robustness and generalizability of the relationships to other inflammatory markers. The MESA sample was free of clinical CVD at baseline, and thus it is well-suited for examining the relationship between social support and physiology isolated from the confounding effects of pre-existing cardiovascular disease that may mask true associations or create spurious ones. While alterations in these neuroendocrine markers may not have immediate clinical significance, they may be early indicators of cardiovascular disease risk.

Results

Overall, the sample reported high levels of perceived social support (PSS), with a median (IQR) of 26 (22 – 29) for men and 25 (21 – 28) for women out of a total possible score of 30. As shown by **Table 1**, higher levels of PSS were associated with older age, being married, higher income, higher educational attainment, and lower reports of chronic stress (all $P<0.01$).

We used ANOVA to evaluate differences in mean log-transformed IL-6 by chronic stress (dichotomized at the median), perceived social support (categorized as quartiles), sex (males and females), age cohort (four groups, 45-54, 55-64, 65-74 and 75-84), and the interaction between PSS and chronic stress. The ANOVA indicated a main effect of chronic stress ($F = 5.68$, $df = 1$, $P<0.02$), sex ($F = 19.00$, $df = 1$, $P <0.001$) and cohort ($F = 82.64$, $df = 3$, $P < 0.001$) but not of PSS ($F = 0.25$, $df = 1$, $P =0.62$). The lack of a direct association between PSS was confirmed with the CRP analysis (data not shown). The two-way interaction between chronic stress and PSS was not significant ($F = 1.06$, $df = 1$, $P = 0.30$), indicating that in the sample overall, mean IL-6 did not vary differentially by perceived social support and exposure to stress.

In the regression models there was no evidence to support the buffering hypothesis either in the sample overall or among the strata by sex or age alone (data not shown). Chronic stress was associated with higher log-transformed IL-6 in the sample as a whole. As shown by **Table 2**, the interaction between PSS and chronic stress was only significant among the oldest (aged 75-84) cohort of men, indicating that greater stress was associated with higher IL-6 among those with low social support (mean difference in IL-6 per SD increase in stress 0.15 pg/ml) but was not associated with IL-6 in those with high social support (mean difference -0.07 pg/ml, P for interaction 0.039). Results for the CRP analyses were similar (data not shown).

Conclusion

The main finding from this study is that perceived social support has little influence, either through direct or stress-buffering pathways, on inflammatory markers. There was evidence to support the buffering hypothesis only for older men. The men in this group reported less chronic stress but higher levels of support relative to the younger cohorts, which indicates that the observed buffering effect may be due to differences in vulnerability to the effects of these stressors rather than an accumulation of stressors with older age.

The findings from this study are consistent with the null results from interventions that aimed to reduce CVD morbidity and mortality by providing social support (e.g., the Enhancing Recovery in Coronary Heart Disease patients (ENRICHD) trial), which indicated that social support alone is not sufficient to alter disease progression or outcome. While these findings are surprising in light of the consistent epidemiologic relationships between social support and heath, they indicate that other mechanisms may be more important determinants of CVD risk. It may be that other measures of social life, such as integration and isolation, are stronger predictors of these pre-clinical inflammatory markers. Alternately, social support may operate on health not through physiology, but through other pathways such as improved access to services (i.e., having supportive friends/relatives may facilitate treatment seeking and utilization).

Table 1: Selected Study Population Characteristics by Tertiles of Perceived Emotional Support for Men and Women, MESA 2000 – 2002

	MEN				WOMEN			
	Low (n = 927)	**Middle** (n = 1123)	**High** (n = 875)	**p-value**	**Low** (n = 1308)	**Middle** (n = 1230)	**High** (n = 690)	**p-value**
Perceived social support	18.42 (4.19)	25.95 (1.48)	29.73 (0.44)	0.001	18.67 (4.01)	26.02 (1.43)	29.65 (0.48)	0.001
Age (years)	61.47 (10.26)	61.99 (10.14)	62.64 (9.94)	0.012	61.28 (10.34)	62.05 (9.91)	62.16 (10.14)	0.036
Non-Hispanic white N (%)	355 (38.3%)	461 (41.1%)	351 (40.1%)	0.442	520 (39.8%)	478 (38.9%)	252 (26.5%)	0.367
Married N (%)	512 (55.4%)	856 (76.3%)	753 (68.8%)	0.001	499 (38.2%)	699 (56.8%)	459 (66.5%)	0.001
At least some college (>12 yrs) N (%)	647 (30.1%)	806 (71.8%)	579 (33.8%)	0.025	816 (62.4%)	753 (61.2%)	400 (58.0%)	0.154
Employed full or part-time N (%)	495 (53.5%)	581 (51.8%)	445 (50.9%)	0.528	585 (44.8%)	541 (44.0%)	329 (47.8%)	0.268
Household income (<$50,000/yr) N (%)	540 (60.1%)	551 (50.6%)	382 (45.7%)	0.001	907 (71.4%)	756 (63.4%)	379 (57.9%)	0.001
Current NSAID use N (%)	161 (17.4%)	201 (17.9%)	145 (16.6%)	0.739	382 (29.2%)	360 (29.3%)	188 (27.3%)	0.584
BMI (kg/m^2)	27.8 (4.6)	27.7 (4.3)	28.1 (4.4)	0.109	28.6 (6.0)	28.8 (6.4)	28.9 (6.1)	0.430
Current smoker N (%)	199 (21.5%)	214 (19.1%)	118 (13.5%)	0.001	202 (15.4%)	114 (9.3%)	51 (7.4%)	0.001
MET Leisure activity/week	1652.1 (1109.0)	1580.4 (1051.2)	1658.8 (1040.2)	0.505	1818.4 (1225.8)	1759.7 (1169.4)	1726.5 (1193.6)	0.074
Chronic stress events (any)	1.40 (1.31)	0.97 (1.06)	0.77 (0.91)	0.001	1.68 (1.30)	1.21 (1.19)	0.97 (1.03)	0.001
Chronic stress events (6+ mons)	1.28 (1.28)	0.86 (1.01)	0.70 (0.88)	0.001	1.53 (1.27)	1.08 (1.14)	0.85 (0.97)	0.001
C-reactive protein (mg/L)*	2.08 (1.95)	1.94 (1.86)	1.98 (1.83)	0.657	2.75 (2.35)	2.81 (2.40)	3.03 (2.51)	0.060
Interleukin-6 (pg/mL)	1.50 (1.18)	1.43 (1.18)	1.48 (1.16)	0.873	1.58 (1.20)	1.55(1.23)	1.61 (1.17)	0.635

Values are mean (standard deviation) unless otherwise noted.
CRP excluding values >10 mg/L.
NSAID use includes OTC NSAID and Cox-2 inhibitors.
Current smoking status includes cigarettes, cigars and pipes
P-value for non-parametric trend across tertiles of emotional support for continuous variables and chi-squared test for categorical variables.

Table 2: Mean difference in ln(Interleukin-6) per standard deviation increase in chronic stress by age and sex

Women Age 45-54	**Mean Change in Ln(IL-6)**	**p-value***
All	0.21	0.012
Low perceived social support	0.13	0.176
High perceived social support	0.07	
Women Age 55-64		
All	0.02	0.863
Low perceived social support	0.04	0.744
High perceived social support	0.05	
Women Age 65-74		
All	-0.01	0.959
Low perceived social support	0.03	0.577
High perceived social support	0.07	
Women Age 75-84		
All	-0.14	0.296
Low perceived social support	-0.02	0.227
High perceived social support	0.07	
Men Age 45-54		
All	0.03	0.765
Low perceived social support	0.03	0.949
High perceived social support	0.03	
Men Age 55-64		
All	0.17	0.097
Low perceived social support	0.07	0.161
High perceived social support	-0.01	
Men Age 65-74		
All	0.11	0.347
Low perceived social support	0.06	0.572
High perceived social support	0.03	
Men Age 75-84		
All	0.44	0.032
Low perceived social support	0.15	0.039
High perceived social support	-0.07	

*P-value for main effect of standard deviation increase in chronic burden (All) and interaction term between PSS score and standardized level of chronic burden.
Low perceived social support refers to 10^{th} percentile (PSS score = 17). High perceived support refers to the 90^{th} percentile (PSS score = 30)
Adjusted for age and race.