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Running title: Social support, coagulation activity, and stress

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Abstract

Objective: Lower social support is associated with higher basal coagulation activity and greater norepinephrine stress reactivity, which in turn, is linked with hypercoagulability. However, it is not known if low social support interacts with stress to further increase coagulation reactivity or if norepinephrine affects this association. These findings may be important for determining if low social support influences thrombosis and possible acute coronary events in response to acute stress. We investigated the relationship between social support and coagulation parameter reactivity to mental stress in men and determined if norepinephrine is involved.

Methods: We measured perceived social support in 63 medication-free non-smoking men (mean age ± SEM:36.7±1.7) who underwent an acute standardized psychosocial stress task combining public speaking and mental arithmetic in front of an audience. We measured plasma D-dimer, fibrinogen, clotting-factor-VII activity (FVII:C), and plasma norepinephrine at rest, as well as immediately after and 20 min after stress.

Results: Independent of body mass index (BMI), mean arterial blood pressure (MAP), and age, lower social support was associated with higher D-dimer and fibrinogen levels at baseline (p's < .012) and with greater increases in fibrinogen (β=-.36,p=.001; ΔR^2=.12), and D-dimer (β=-.21,p=.017; ΔR^2=.04), but not in FVII:C (p=.83) from baseline to 20 min after stress. General linear models revealed significant main effects of social support and stress on fibrinogen, D-dimer, and norepinephrine (p's<.035). However, controlling for norepinephrine did not change the significance of the reported associations between social support and the coagulation measures D-dimer and fibrinogen.

Conclusions: Our results suggest that lower social support is associated with greater coagulation activity before and after acute stress, which was unrelated to norepinephrine reactivity.

Keywords: Social support, coagulation, clotting factor VII:C, D-dimer, fibrinogen, psychological stress

Abbreviations

CVD = Cardiovascular Disease

ACS = Acute Coronary Syndromes

BMI = Body Mass Index

MAP = Mean Arterial Blood Pressure

BP = Blood Pressure

SD = Standard Deviation

AUC = Area Under The Curve

TSST = Trier Social Stress Test

FVII:C = Clotting Factor VII Activity

FVIII:C = Clotting Factor VIII Activity

TAT = Thrombin-Antithrombin

vWF = von Willebrand Factor

Introduction

Social support is a context-specific advocative interpersonal process centered on the reciprocal exchange of information on one or more of the following three classes: information leading the person to believe that he or she (1) is cared for and loved, (2) esteemed and valued, and (3) belongs to a network of communication and mutual obligation (1, 2). In the literature, measures of perceived social support are more commonly used than measures of received social support (3). Perceived social support is conceptualized as the subjective appraisal of the degree of match between the amount and type of support needed and amount and type of support available, or the perception that support would be available if needed (3).

Accumulating evidence suggests that social support is associated with health outcomes (2). For example, poor social support prospectively increases the risk of coronary artery disease (CAD) (3-6) with a relative risk 2- to 3-fold and a robust effect observed even after controlling for conventional (e.g. age, body mass index, and high blood pressure), social, and behavioral cardiovascular risk factors (4-7).

Previous research addressed the biological pathways through which low social support increases cardiovascular risk or, alternatively, high social support enhances health. Based on the effects of social support on physiological processes implicated in cardiovascular disease, the so-called "social support-reactivity hypothesis" has been proposed. This view posits that social support maintains cardiovascular health by reducing psychobiological reactivity to stressors, thereby acting as a "stress buffering" variable (8, 9). Indeed, evidence suggests that in healthy individuals social support attenuates psychological and physiological stress responses as indexed by cardiovascular, autonomic, and HPA responses (8, 10-13). In hypertensive and normotensive middle-aged men, greater levels of perceived social support were associated with reduced

catecholamines reactivity to acute psychosocial stress (14). Notably, the accumulation of physiological hyperreactivity to stress throughout a life span – that may occur in individuals with low social support – has been proposed to enhance CAD risk (15-18).

Coagulation and fibrinolysis are implicated as stress-reactive physiological systems important in the development of CAD and acute coronary syndromes (ACS) (19). Patients whose ACS had been triggered by intense emotions showed greater platelet activation in response to psychological stress compared to patients without emotion triggering ACS (20). In healthy individuals, acute mental stress activates both the coagulation and the fibrinolysis components of hemostasis to result in net hypercoagulability (19, 21). Acute psychological stress induced increases in several hemostatic parameters such as FVII:C, FVIII:C and FXII:C, thrombin-antithrombin (TAT) complex, fibrinogen, von Willebrand Factor (vWF), and D-dimer levels have been observed (19).

In contrast to stress affects, higher social support may reduce coagulation activity. Greater social support as assessed via social integration, social isolation, and social network is associated with lower amount of fibrinogen (22-27) even when controlling for cardiovascular risk factors (22, 24, 26, 27). However, the role of social support as a buffer of acute stress for hemostasis is not straightforward. In a small sample of 27 healthy middle-aged men, we recently did not find significant associations between social support as assessed by the German Social Support Questionnaire (F-SozU) and stress-induced changes in coagulation parameters (28). However, in that study, due to the small sample size, we did not control for age, BMI, and blood pressure. In contrast, a study by Steptoe and coworkers assessed associations between social support measures and fibrinogen stress reactivity (27) and found higher fibrinogen levels in socially isolated compared with non-isolated participants before and after acute mild psychological stress

(27). Catecholamines play a role in stress-induced hemostatic changes since catecholamine infusion elicited hypercoagulability in healthy persons (29). In addition, we recently found associations between epinephrine and FVIII:C and between norepinephrine and fibrinogen under resting conditions, independent of age, BMI, and MAP in middle-aged hypertensive and normotensive men (30). Moreover, in the same study, stress-induced changes in D-dimer were predicted by norepinephrine stress change (30). In another study, we found that the stress induced increase in norepinephrine significantly correlated with thrombin formation (31). However, it is unknown whether lower social support is associated with greater catecholamine stress reactivity, which in turn, could induce hypercoagulability. More specifically, the role of norepinephrine in stress-induced D-dimer changes in those with low social support has not previously been examined.

The aim of this study was to extend previous research investigating whether perceived social support is associated with several coagulation parameter levels at rest and throughout a potent acute psychosocial stressor in a sizeable group of medication-free non-smoking men. We hypothesized that lower social support is associated with higher baseline levels and greater increases in response to stress in the coagulation measures fibrinogen and FVII:C, and the hypercoagulability marker D-dimer. Moreover, we examined whether such associations were moderated or mediated by norepinephrine levels.

Methods

Study participants

The study is part of a project studying the biological response in general and coagulation activation in particular to acute psychosocial stress in men as previously described (32, 33).

While our previous report addressed the acute stress-induced increases of the coagulation parameters D-dimer and fibrinogen in relation to age (33), in the present study, we specifically examined the relation of social support to acute stress-induced coagulation changes. In the present study, we also tested whether the relationship between social support and coagulaton activiation to stress would be modulated by norepinephrine. The Ethics Committee of the State of Zurich, Switzerland, formally approved the research protocol. Of the original 66 subjects three persons had to be excluded because of incomplete blood samples for coagulation parameters. The final study sample consisted of 63 subjects who provided written informed consent. The study was conducted between April 2004 and August 2005. We intentionally recruited non-smoking men between 20 and 65 years of age who were in excellent physical and mental health confirmed by an extensive health questionnaire (34) and telephone interview. Specific exclusion criteria were obtained by subjects' self-report and were: regular strenuous exercise, alcohol and illicit drug abuse; any heart disease, varicosis or thrombotic diseases, elevated blood sugar and diabetes, elevated cholesterol, liver and renal diseases, chronic obstructive pulmonary disease, allergies and atopic diathesis, rheumatic diseases, and current infectious diseases. In addition, participants were included only if they reported taking no prescribed and/or over the counter medication, either regularly or occasionally and if their blood pressure was in the normotensive or moderately hypertensive range (systolic BP < 160 mmHg and diastolic BP < 100 mmHg). When the personal or medication history was not conclusive, the subjects' primary care physician was contacted for verification.

Assessment of social support

The first part of the Berlin Social Support Scale (BSSS) consists of 17-items assessing perceived social support (PSS), support seeking (SS), and need for support (NS) (35). Previous literature on social support and cardiovascular disease as well as our own previous findings of greater catecholamine stress reactivity with increasing PSS led us to use the 8-item PSS subscale composed of the two subscales "emotional support" and "instrumental support" in the present study (3, 14). Using a 4-point rating scale ranging from 1 *(completely wrong)* to 4 *(completely right,)* participants were asked whether they agree with certain statements on their perception of social support (e.g. "there are people who help me if I need help"; "there are people cheering me up when I am sad"). The PSS renders scores between 1 (minimum score) and 4 (maximum score). Higher scores mean higher PSS. Cronbachs alpha (N = 437) is .83 for the PSS subscale (35).

Stress protocol

Subjects were tested between 2:00 pm and 4:00 pm. They abstained from physical exercise, alcohol, and caffeinated beverages for at least 24-hours prior to testing. We used the Trier Social Stress Test (TSST) combining a 5-min preparation phase followed by a 5-min mock job-interview, and 5-min mental arithmetic task in front of an audience (36). The TSST evokes reliable physiological responses across different biological systems, including coagulation factors also investigated in the present study (37). During recovery, subjects remained seated in a quiet room for 40 min.

Blood for coagulation and norepinephrine measures was obtained immediately before stress, immediately after stress, and 20 min after stress. Blood pressure was measured immediately before and 40 min after stress by sphygmomanometry (Omron 773, Omron

Healthcare Europe B.V. Hoofddorp, The Netherlands) and mean arterial blood pressure (MAP) was calculated by the formula (2/3 * mean diastolic BP) + (1/3 mean systolic BP).

Biochemical analyses

Venous blood was drawn through an indwelling forearm catheter into polypropylene tubes containing 3.8% sodium citrate and centrifuged at 2,000 X g for 20 min at 4° C. Obtained plasma was immediately aliquoted in polypropylene tubes and frozen at -80°C. All analyses of coagulation factors used the BCS® Coagulation Analyser (Dade Behring, Liederbach, Germany). Determination of FVII:C used standard coagulometric methods using factor-deficient standard human plasma and reagents (Dade Behring) and plasma fibrinogen was determined using a modified Clauss method (Multifibren U, Dade Behring). Plasma D-dimer was measured by means of an enzyme-linked immunosorbent assay (Asserachrom Stago, Asnières, France). Inter- and intra-assay coefficients of variation (CV) were <10% for all coagulation measures.

Blood samples for measurement of plasma norepinephrine were drawn into EDTA-coated monovettes (ethylenediaminetetraacetic acid; Sarstedt, Numbrecht, Germany), and immediately centrifuged for 10 min at 2,000g; plasma was stored at –80°C until analysis. Plasma norepinephrine was determined by means of HPLC and electrochemical detection after liquid–liquid extraction (38, 39). The limit of detection was 10 pg/ml. Inter- and intra-assay variance was <5%. To reduce error variance caused by imprecision of the intra-assay, all samples from one subject were analyzed in the same run.

Statistical analyses

Data were analyzed using SPSS (version 13.0) statistical software package (SPSS Inc., Chicago IL, USA). All tests were two-tailed with level of significance of $p \leq .05$ and level of statistical trends of $p \leq .10$. Using the trapezoid formula, we calculated areas under the total response curves, expressed as area under the measured time-points with respect to ground (AUCg) for all coagulation measures and norepinephrine (40). Prior to statistical analyses all data were tested for normality using the Kolmogorov-Smirnov test. Coagulation values and coagulation AUCs were logarithmically transformed to achieve normal distributions. For clarity, we provide untransformed data.

To assess associations between social support and coagulation activity at baseline and after stress, we first calculated linear regression analyses with the respective coagulation measure as the dependent variable and social support score as a *continuous* independent variable. We used coagulation baseline measures as the dependent variables to assess associations between social support, and coagulation activity at rest. We employed AUC measures of the coagulation parameters to assess associations between social support and stress-induced coagulation changes. In light of previously reported associations between BMI, MAP and age with coagulation parameters at rest and in response to stress (30, 33, 41), we controlled for BMI, MAP, and age. We entered these parameters as predictors in all analyses. All independent variables were simultaneously forced into the regression equations. The optimal total sample size to predict stress reactivity in coagulation parameters was n=59 for detecting a medium to large effect size of f^2=0.25 in multiple regression analyses with a power of 0.80 using 4 predictors. Second, we further tested regression results by performing general linear models with repeated measures for each coagulation parameter as the dependent variable and with social support as the *continuous*

independent variable. In these analyses, we again controlled for BMI, MAP, and age. For illustrative purposes, we categorized the study group based on their social support scores into four groups of subjects with increasing levels of social support termed as follows: lowest (2.75-3.38, n=11), lower (3.50-3.63, n=16), higher (3.75-3.88, n=25), and highest social support scores (4-4, n=11).

To test for associations between social support and norepinephrine stress reactivity we used general linear modelling with norepinephrine levels as repeated dependent factor and levels of social support as the continuous independent factor, while controlling for age, BMI, and MAP. To assess whether associations between social support and coagulation activity at baseline and after stress are related to norepinephrine levels, we again calculated regression analyses. As dependent variables we entered those coagulation measures, which were significantly associated with social support in the linear model. As independent variables, we simultaneously entered social support and norepinephrine to test for a mediation effect of norepinephrine. To test for a moderating effect of norepinephrine, we simultaneously entered social support, norepinephrine, as well as their interaction term (social suppport x norepinephrine) as independent variables. We always controlled for age, BMI, and MAP. Interaction terms were computed on Z-transformed data rendering means of 0 and standard deviations of 1. All regression analyses including interaction terms were performed on Z-transformed data. We calculated Pearson's product-moment correlations to assess associations between social support, age, BMI, and MAP.

Results

Subject characteristics

Social support scores of our 63 study participants ranged between 2.75 and 4 with a mean of 3.66 ± .32 SD. The mean age was 37 years ± 13.7 SD, the mean BMI was 24.8 ± 3.04 SD, and mean MAP was 94.7 mmHg 10.62 SD. Age, MAP, and BMI were intercorrelated (p's < .001) but they did not correlate with social support (p's > .21).

Relation between social support and coagulation activity at rest and in response to stress

Regression analyses

Social support and coagulation activity at rest

D-dimer at rest: Lower social support scores were significantly associated with higher D-dimer levels at rest (β=-.22, p=.012; ΔR^2=.05) independent of MAP (p=.11), BMI (β=.47, p<.001; ΔR^2=.15), and age (β=.51, p<.001; ΔR^2=.17) with the total model explaining 60 % of the variance in D-dimer resting levels.

FVII:C at rest: Social support was not significantly associated with FVII:C at rest (p=.96).

Fibrinogen at rest: Higher fibrinogen at rest was significantly associated with lower social support (β=-.35, p<.001; ΔR^2=.11) independent of MAP (p=.90), BMI (β=.42, p<.001; ΔR^2=.12), and age (β=.33, p=.004; ΔR^2=.08) with the total model explaining 52 % of the variance in fibrinogen resting levels.

Social support and coagulation levels between rest and 20 min after stress

D-dimer area under the curve: Lower social support was associated with higher D-dimer AUC (β=-.21, p=.017; ΔR^2=.04) independent of MAP (p=.07), BMI (β=.42, p<.001; ΔR^2=.13),

and age (β=.56, p<.001; ΔR^2=.21). The whole model explained 59% of the variance in D-dimer AUC.

Fibrinogen area under the curve: Independent of MAP (p=.95), BMI (β=.38, p=.001; ΔR^2=.10), and age (β=.34, p=.005; ΔR^2=.08), lower social support was associated with higher fibrinogen AUC (β=-.36, p=.001; ΔR^2=.12). The whole model explained 48% of the observed variance in fibrinogen AUC.

FVII:C area under the curve: There were no associations between social support and AUC of FVII:C (p=.83).

General linear models

Across all subjects, the TSST elicited significant increases in D-dimer (p=.009, f=.34), fibrinogen (p=.012, f=.32), and FVII:C (p=.046, f=.32) from baseline to immediately after stress while controlling for age, BMI, and MAP. To validate the results from the above regression analyses, we applied general linear models with repeated measures of coagulation factors as dependent variables and social support as a continuous independent variable. After controlling for BMI, MAP, and age, there were significant main effects for social support for repeated D-dimer and fibrinogen levels (D-dimer: F(1/58)=6.0, p=0.018, f=0.31, Figure 1 A; fibrinogen: F(1/58)=13.8, p<0.001, f=0.47, Figure 1 B) while there were no significant interactions between stress and social support (p's >.58). Neither main nor interaction effects were observed in terms of repeated measurements of FVII:C (p's>.24).

For illustrative purposes, Figure 1 (Panel A-B) shows coagulation responses to the TSST in four groups of subjects with increasing levels of social support (lowest (2.75-3.38, n=11), lower (3.50-3.63, n=16), higher (3.75-3.88, n=25), and highest social support scores (4-4, n=11))

based on quartiles (note that subject numbers differ in the four groups because individual PSS values were not balanced above and below the particular cut-off values).

Norepinephrine, social support, and coagulation parameters

Social Support and norepinephrine stress reactivity

The TSST stimulated significant increases in norepinephrine levels ($F(1/61)=94.9$, $p<.001$). General linear modelling with norepinephrine as repeated dependent and social support as continuous independent variable revealed that higher social support was associated with lower norepinephrine levels before and after stress (main effect: $F(1/57)=4.65$, $p=.035$, $f=.27$, Figure 2), while controlling for age, BMI, and MAP. There was no interaction between social support and stress ($p=.33$).

Norepinephrine and associations between social support and coagulation parameters

Table 1 depicts regression results for associations between norepinephrine, social support, and coagulation parameters at rest and in response to stress.

At rest. Regression analyses after controlling for BMI, MAP, and age revealed that resting norepinephrine levels were not significantly related to any of the coagulation parameters (p's>.60), and was determined to not be a significant factor in the associations between social support and resting levels of D-dimer and fibrinogen (Table 1). This suggests that resting norepinephrine levels do not mediate the observed associations between social support and resting levels of D-dimer and fibrinogen. Additionally, entering baseline norepinephine levels social support, plus the norepinephrine-by-social support interaction into the regression equation

revealed that resting norepinephrine levels did not moderate the relationship between social support and both D-dimer and fibrinogen (p's>.69).

Stress reactivity. To determine if norepinephrine secretion mediates between social support and stress reactivity of coagulation factors D-dimer and fibrinogen, regression analyses were recalculated with norepinephrine AUC entered as an independent variable (Table 1). To test for a moderation effect of norepinephrine, its interaction with social support was additionally entered as an independent variable. Controlling for norepinephrine AUC did not significantly affect the observed associations between social support and AUC of D-dimer and fibrinogen. Thus, neither norepinephrine AUC alone nor its interaction with social support were significantly associated with any of the coagulation parameter AUCs (p's>.50). In sum, norepinephrine does not appear be a mediator or a moderator of social support effects on coagulation activity.

Notably, results of the PSS subscales "instrumental support" and "emotional support" were similar to the combined PSS scale in all analyses (data not shown).

Discussion

Research suggests that poor social support is associated with health risks (2) such as coronary artery disease (CAD) (3-6). The mechanisms involved are not known, although over-activation of hemostasis might be one contributing factor. The main objective of the present study was to investigate whether social support is associated with elevated coagulation factor levels at rest and throughout an acute stress process. The coagulation factors fibrinogen and D-dimer were examined at baseline, representing resting activity, and also for the area under the curve (i.e. immediately before stress, immediately after stress, and 20 min after stress) representing the total stress-response course. The results of our study suggest that low social

support is associated with increased fibrinogen and D-dimer levels at rest, and that acute stress and low social support are independently associated with an increased area under the curve. This may indicate that individuals with reduced social support run an even higher atherothrombotic risk during acute stress. Specifically, effects sizes of stress-induced coagulation increases suggest clinical importance. A prothrombotic state of the blood promotes atherosclerosis development and, after rupture of an atherosclerotic plaque, thrombotic occlusion of a coronary artery leading to an ACS (42, 43).

Even though FVII:C was responsive to the TSST, we did not find a significant association between social support and FVII:C both at baseline and throughout the stress period. Clotting factor FVII belongs to the extrinsic system of blood coagulation, whereas fibrinogen is the precursor of fibrin further down in the coagulation cascade after intrinsic and extrinsic coagulation pathways have merged (21). Therefore, it could be that social support is more strongly related to factors involved in the intrinsic pathway of blood coagulation, which reasoning we did, however, not address in the present study. After clot formation, the fibrinolysis system degrades fibrin, whereby fibrin degradation products such as D-dimer are formed. Since it indicates activation of the entire coagulation system (i.e. the step of fibrin formation) and also the fibrinolysis system (i.e. the step of fibrin dissolution), D-dimer is termed a hypercoagulability marker (44). Hypercoagulability markers are more sensitive to change than are individual hemostatic factors (45) providing one explanation for why D-dimer emerged as a significant correlate of social support whereas FVII:C did not. Our findings correspond to previous studies that social support scores were negatively associated with resting fibrinogen levels (19, 21) now extending these findings to D-dimer. These may be important findings in relation to health. Elevated fibrinogen levels are associated with CVD risk (46), and are related to both

atherogenesis and thrombogenesis. For each standard deviation increase in fibrinogen above the mean, it was suggested that there is an 84% increase in the 5-year risk of ischemic heart disease (47). In addition, increased D-dimer levels are associated with greater risk of myocardial infarction (48), cerebrovascular events (49) and peripheral arterial disease (50).

Acute mental stress activates both the coagulation and the fibrinolysis components of hemostasis to result in net hypercoagulability (19, 21). Increased social support has been suggested to act as a buffer to attenuate physiological stress responses, as indexed by cardiovascular, autonomic, and HPA responses (8, 10-13). However, our present findings did not suggest an interaction between social support and stress for hemostatic measures, but that social support and stress are independent factors and therefore may be additive. Higher social support predicted lower D-dimer and fibrinogen AUC from baseline to 20 minutes after the stress task. These findings support a previous study showing that higher fibrinogen levels were found in socially isolated participants both before and after a color-word and a mirror-tracing task (27). The present study extends those results to include D-dimer, which is involved with both coagulation and fibrinolysis. Furthermore, an interpersonal stressor, the TSST, was used in the present research, which expands the range of psychological stress that is found to generate such hemostatic responses. Catecholamines play a role in stress-induced hemostatic changes (30), but their role in social support related changes in coagulation parameters is unclear. In order to examine if norepinephrine mediates or moderates the association between social support and hemostatic changes at rest and in response to stress, fibrinogen and D-dimer were measured at baseline and throughout the stress task (baseline through 20 min post task). Resting norepinephrine levels and the interaction of norepinephine baseline levels with social support did

not predict levels of D-dimer and fibrinogen suggesting that norepinephrine is not associated with hemostatic reactions to stress in relation to social support.

Future studies are needed to examine additional pathways that may mediate social support and health, besides the sympathetic reactivity hypothesis, Anti-stress hormones, inflammatory responses, and sympatho-vagal balance may play roles as alternative mediators. For example, oxytocin was found to have potential anti-stress effects and when combined with social support there was a reduced cortisol response along with increased calmness and decreased anxiety during the TSST (13). In turn, cortisol changes during stress are associated with total fibrin formation (51) suggesting a potential alternate pathway in which social support may buffer stress-induced hemostatic activity and ultimately health. Social networks were associated with reduced inflammatory marker interleukin- 6 responses in male Framingham Heart Study participants (52) and reactivity in interleukin-6 and D-dimer to stress were positively correlated (51). Additionally, in CHD patients, elevated social support is associated with greater probability of sympatho-vagal balance (i.e. reduced heart rate, mean blood pressure, cardiac index, and increased high frequency heart rate variability) during recovery from mental stress (53). In contrast, social isolation was associated with decreased heart rate variability (54) suggesting a reduction in parasympathetic or vagal tone. In women with CHD, we previously observed elevated levels of fibrinogen in association with reduced vagal cardiac control (55). There are also hypotheses about social relationships suggesting that they exhibit main effects on health but do not necessarily interact with stress (56). Lack of social support due to social isolation had a hazard ratio of 1.75 for mortality in heart failure patients (57). Compared with heart failure patients reporting a high social network, hospital readmission was more frequent among those who had moderate (hazard ratio 1.87; CI 1.06-3.29; $P < .05$) and low social networks (HR 1.98;

95% CI 1.07-3.68; P < .05) (58). Similarly, loneliness was significantly associated with elevated systolic blood pressure, but not so with differences in autonomic or endocrine reactivity to stress (59). Comparisons of persons reporting more types of contacts (parents, children, family members, and friends) with those reporting fewer types yielded age- and gender-adjusted hazard ratios of 0.73 (95% confidence interval (CI): 0.64, 0.82) for mortality and 0.75 (95% CI: 0.61, 0.91) for CHD (60). In summary, social support is associated with various factors that might also affect hemostasis and that warrant an investigation as potential pathways linking social support and hemostasis and ultimately health. Alternatively, social relationships may function as a main effect on health. As is often the case, both hypotheses are likely true depending on the situation and factors being measured.

Our study has several strengths, which include recruitment of a sizable group of apparently healthy and unmedicated subjects across a range of perceived social support levels in a natural unselected setting. However, the study has also its limitations. First, its cross-sectional nature does not allow us to interpret the direction of the social support – coagulation - stress link, although we feel it is unlikely that coagulation influences social support. Second, our findings were obtained in a sample of apparently healthy men with BP in the normotensive and mildly hypertensive range and may not be generalized to individuals with more severe hypertension and women. Third, we restricted our analyses to three coagulation parameters and fourth, the significance of low scores on PSS remains to be elucidated and future studies should include assessments of a person's social network.

In conclusion, social support appears to be important for coagulation factor levels such as fibrinogen and D-dimer, which may affect thrombosis and atherosclerotic disease. Lower social support was associated with higher baseline levels of fibrinogen and D-dimer. In addition, lower

social support was independently related to an increase of these hemostatic factors throughout the stress response period. Stress-related alterations in hemostasis might act as a potential trigger for the onset of ACS (19). Although social support did not appear to affect the magnitude of the coagulation factor responses to stress, low social support may have added risk because of its association with greater overall coagulation factor levels. Furthermore, social support does not appear to drive stress associated changes in norepinephrine. Therefore, future studies are needed to examine the mechanisms that are involved in the relationship between social support and hemostasis factors in order to develop interventions that can reduce hemostatic risk factors of CHD related to low levels of social support.

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Table 1. Hierarchical regression analyses for associations between social support and coagulation parameters controlling for norepinephrine

Variables entered	Standardized β-coefficient	t	P	R^2 change
D-dimer at baseline				
Age	.50	4.89	<.001	.17
Body mass index	.47	4.63	<.001	.15
MAP	-.16	-1.61	.11	.02
NEPI at baseline	.02	.20	.84	.00
Social support	-.22	-2.47	.017	.04
Fibrinogen at baseline				
Age	.33	2.89	.005	.07
Body mass index	.41	3.69	.001	.12
MAP	.01	.10	.92	.00
NEPI at baseline	.05	.54	.60	.00
Social support	-.33	-3.45	.001	.10
D-dimer AUC				
Age	.55	5.31	<.001	.20
Body mass index	.42	4.12	<.001	.12
MAP	-.19	-1.88	.07	.03
Norepinephrine AUC	.03	.36	.72	.00
Social Support	-.20	-2.29	.026	.04
Fibrinogen AUC				

Age	.33	2.78	.007	.07
Body Mass Index	.37	3.22	.002	.09
MAP	.00	.02	.98	.00
Norepinephrine AUC	.07	.68	.50	.00
Social Support	-.34	-3.42	.001	.11

AUC, area under the curve; MAP, mean arterial blood pressure; NEPI, norepinephrine; SS, social support score.

Legend to Figure 1 (Panels A-B)

Values are means±SEM. Stress reactivity of D-dimer (Panel A) and fibrinogen (Panel B) across all 63 subjects. We applied general linear models with repeated measures of coagulation factors as dependent variables and social support as continous independent variable while controlling for BMI, MAP, and age in all analyses. The main effect of social support was significant in terms of D-dimer $F(1/58)=6.0$, $p=0.018$, $f=0.31$, Panel A) and fibrinogen ($F(1/58)=13.8$, $p<0.001$, $f=0.47$, Panel B). The figure shows these data for illustrative purposes by four categories of social support scores.

Legend to Figure 2

Values are means±SEM. Stress reactivity of norepinephrine across all 63 subjects. We applied general linear models with repeated measures of norepinephrine as dependent variables and social support as continous independent variable while controlling for BMI, MAP, and age. Higher social support was associated with lower norepinephrine levels before and after stress (main effect: $F(1/57)=4.65$, $p=.035$, $f=.27$). Figure 2 shows these data for illustrative purposes by four categories of social support scores.

Figure 1. Prothrombotic factor levels in four groups of subjects with lowest (2.75-3.38, n=11), lower (3.50-3.63, n=16), higher (3.75-3.88, n=25), and highest social support (SS) scores (4-4, n=11)

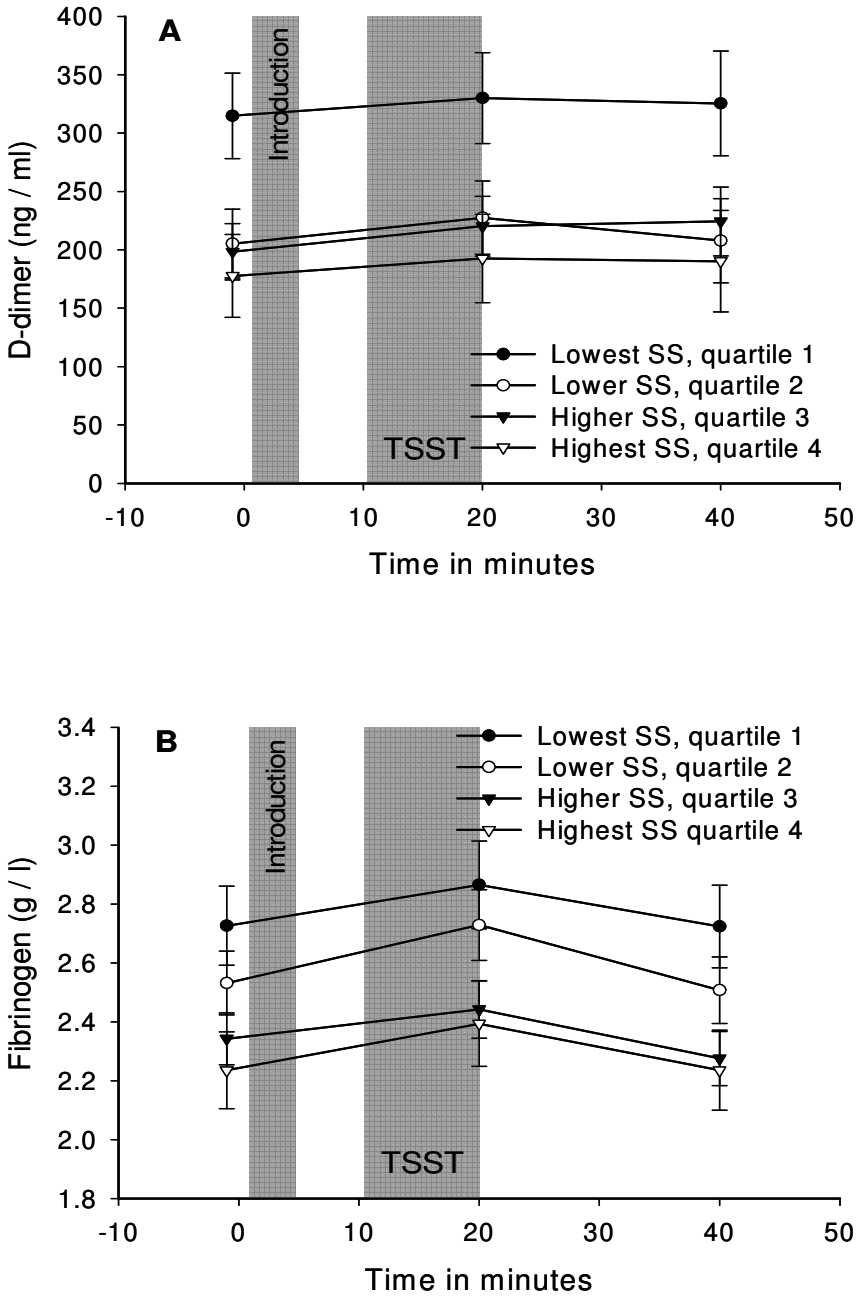

Figure 2. Norepinephrine levels in four groups of subjects with lowest (2.75-3.38, n=11), lower (3.50-3.63, n=16), higher (3.75-3.88, n=25), and highest social support (SS) scores (4-4, n=11)