Social relationships and inflammatory markers: An analysis of Taiwan and the U.S.

Dana A. Glei [a,*], Noreen Goldman [b], Carol D. Ryff [c], Yu-Hsuan Lin [d], Maxine Weinstein [a]

[a] Centre for Population and Health, Georgetown University, Washington DC, USA
[b] Office of Population Research, Princeton University, USA
[c] Institute on Aging, University of Wisconsin, Madison, USA
[d] Population and Health Research Center, Bureau of Health Promotion, Department of Health, Taiwan

ARTICLE INFO

ABSTRACT

We evaluated the association between two aspects of social relationships and six inflammatory markers in Taiwan and the U.S. These two countries share similar levels of current life expectancy, but exhibit important differences in social structure. The data comprised population based samples from Taiwan (aged 53+; $n = 962$) and the U.S. (aged 35–86; $n = 990$) collected between 2003 and 2009. Circulating levels of interleukin-6 (IL-6), C-reactive protein (CRP), fibrinogen, and soluble forms of intercellular adhesion molecule 1, E-selectin, and IL-6 receptor (sIL-6R) were measured in fasting blood samples. A social integration score was based on marital status, contact with family and friends, church attendance, and other social participation. A perceived social support index was based on questions regarding the availability of care and support from family and friends. Linear regression models tested the association between these two measures and each inflammatory marker controlling for sociodemographic characteristics, obesity, medication use, and baseline health status. After adjusting for potential confounders, social integration had a significant but weak inverse association with CRP in Taiwan. Perceived social support was significant in two of 12 models, and the coefficient was *positive* (i.e., higher support was associated with higher CRP and sIL-6R in the U.S.). We found no evidence that the coefficients for social relationship measures varied by sex or age. Our results yielded limited evidence of a weak association between two dimensions of social relationships and six inflammatory markers in Taiwan and the U.S. Given that the literature suggests a strong link between social relationships and mortality, and that inflammation plays an important role in the leading causes of death, we had expected to find consistent and moderately strong associations between social relationships and inflammatory markers. The small effect sizes and lack of robustness across markers were surprising.

© 2012 Elsevier Ltd. All rights reserved.

Introduction

A recent meta-analysis concludes that the link between social relationships and mortality is as strong or stronger than other well known risk factors such as smoking, physical activity, and drug treatment for hypertension (Holt-Lunstad, Smith, & Layton, 2010). Yet the physiological and behavioral pathways through which social relationships affect survival are not well understood. Among studies that examine the link between social relationships and physiological parameters, markers of immune function and/or inflammation yield the most consistent effects (Kiecolt-Glaser, Gouin, & Hantsoo, 2010; Uchino, 2006). Chronic inflammation is a significant predictor of mortality and plays an important role in

the development of cardiovascular disease and other conditions (Kiecolt-Glaser et al., 2010; Pearson et al., 2003), although it remains unclear whether this association is causal. Prior studies of social relationships and inflammation are based largely on samples of U.S. or European populations. Most rely on a small number of subjects, examine only one inflammatory marker, or include only one dimension of social relationships.

Measures of social relationships are typically based on the existence of social ties, or on the function or perceived quality of those networks (Cohen, 1988). Holt-Lunstad et al. (2010) finds that measures of social integration that incorporate multiple components (e.g., marital status, network size, network participation) yield the strongest association with mortality. Among measures of the quality of social relationships, perceived social support and loneliness also exhibit notable associations with mortality (Holt-Lunstad et al., 2010). The two main pathways through which social relationships may affect inflammation—and in turn,

health—involve behavioral and psychological processes (Cohen, 1988; Uchino, 2006). Social relationships may influence health behaviors and health care by providing information and tangible resources or by indirect means and may also have psychological effects on affect, self-esteem, personal mastery, sense of life purpose and perceptions of stress.

Differences in social structure across cultures could contribute variation in both the nature of social relationships and how those relationships affect health. Americans favor self-expression and independence in relationships with others, whereas Chinese value interdependence and social harmony (Markus & Kitayama, 1991). Social ties with family are likely to be more prevalent in Taiwan compared with the U.S. Divorce rates are lower than in the U.S. Older Taiwanese are more likely than their U.S. counterparts to live with or in close proximity to their married children or other relatives. In Taiwan, adult sons are expected to provide financial support for their elderly parents.

This study uses data from large population based samples of adults in Taiwan and the U.S. to examine associations between social relationships and six inflammatory markers: interleukin-6 (IL-6) and its soluble receptor (sIL-6R), C-reactive protein (CRP), fibrinogen, soluble intercellular adhesion molecule 1 (sICAM-1), and soluble E-selectin (sE-selectin). Given the complexity of the immune system, no single marker can adequately capture inflammatory processes. Our analyses allow us to determine the consistency of patterns across multiple measures of inflammation, for different dimensions of social relationships, and between countries. Prior studies of the link between social relationships and inflammation have focused on IL-6, CRP, or fibrinogen, while the other markers considered here have rarely been examined. Given that the six inflammatory markers are biologically related, we anticipate similar associations. However, we hypothesize that the associations with inflammation will be stronger for integration than for perceived support given its stronger association with mortality (Holt-Lunstad et al., 2010). Taiwan and the U.S. provide interesting contexts for investigating these questions because they experience similar levels of life expectancy and patterns of chronic disease, but as noted above, differ substantially in social structure, particularly with regard to self-other relations. Although these differences in the social environment may lead to variations in the estimates between the two countries, we expect to find significant associations between social relationships and inflammation in both populations.

Methods

Taiwan

The Taiwan data came from the 2006 wave of the Social Environment and Biomarkers of Aging Study (SEBAS) and the 2003 wave of its parent study, the Taiwan Longitudinal Study of Aging (TLSA). TLSA began in 1989 with a nationally representative sample of persons aged 60 and older; younger refresher cohorts were added in 1996 and 2003. In 2000, a random sample of those interviewed in the 1999 TLSA was selected for SEBAS; the oldest cohort and urban residents were oversampled. Among the 1497 respondents who completed the in-home interview, 1023 (68%) participated in a physical examination.

The sampling frame for the 2006 follow-up included those who completed the 2000 SEBAS exam (aged 60+) and a random sample of the younger cohort (aged 53–60) first interviewed in 2003. Among the 1284 respondents who completed the 2006 interview, 1036 (81%) participated in the physical examination; 3 died before the exam, 32 were not eligible because of a health condition, and 213 declined. [See Supplemental Fig. S1, which shows response rates and attrition.]

Analyses presented elsewhere document the predictors of exam participation (Goldman, Glei, Lin, & Weinstein, 2010; Goldman, Lin, Weinstein, & Lin, 2003): average self-reported health status was almost identical for exam participants and non-participants. We also found that exam participants did not differ significantly from non-participants in terms of the social relationship measures (data not shown). Written informed consent was obtained for participation in both the in-home interview and hospital visit, which entailed a medical examination.

The hospital-based physical examination, including collection of a fasting blood specimen, occurred several weeks after the home interview. Blood specimens were analyzed at Union Clinical Laboratories (UCL) in Taipei. In addition to routine standardization and calibration tests, triplicate sets of specimens were contributed by 10 individuals outside the target sample: two sets were sent to UCL and the third set was sent to Quest Diagnostics in the US (San Juan Capistrano, CA). The results indicated high intra-lab reliability (≥ 0.83) and strong inter-lab correlations (≥ 0.90) for CRP, IL-6, and fibrinogen; data were not available for sICAM-1, sE-selectin, or sIL-6R. Additional details about the study are provided elsewhere (Chang, Glei, Goldman, & Weinstein, 2007; Glei, Goldman, Lin, & Weinstein, 2011). The SEBAS data collection (Taiwan) was approved by human subjects committees in Taiwan and at Georgetown University and Princeton University.

United States

The U.S. data came from the Midlife Development in the United States (MIDUS) National Study (Ryff et al., 2007). MIDUS began in 1995 with a sample of non-institutionalized, English speaking residents of the contiguous United States, aged 25–76. National random digit dialing was used to select the main sample ($n = 3487$) and a sample of twin pairs ($n = 1914$). The study also included a random subsample of siblings of individuals in the main sample ($n = 950$) and oversamples from five metropolitan areas in the U.S. ($n = 757$). The response rate for the phone interview ranged from 60% for the twin subsample to 70% for the main sample.

Between 2004 and 2006, a follow-up phone interview was completed by 4963 of the MIDUS I participants (75% of survivors). Of those, 81% ($n = 4041$) also returned the mail-in self-administered questionnaire (SAQ). Among the original MIDUS I cohort, participation in MIDUS II was higher among whites, females, and those who were married, better educated, and in better health (Radler & Ryff, 2010).

Participants in the biomarker component of MIDUS II made a two-day visit to one of three clinical research centers (East coast, Midwest, West coast) during 2004–2009, where they completed health assessments, a fasting blood draw, and an overnight 12-h urine collection. Respondents from the main and twin subsamples who completed the phone interview and SAQ ($n = 3018$) were recruited for the biomarker component. Of these, 338 respondents were deemed ineligible because existing health information suggested that travel to the clinic would entail excessive risk to the respondent or project staff (Love, Seeman, Weinstein, & Ryff, 2010). Clinic visits were completed by 1054 participants (39% of those eligible; 42% of those contacted). This sample does not include the new city-specific (Milwaukee) oversample of African-Americans added in MIDUS II ($n = 201$ participated in the clinic visit). Although siblings and city oversamples were not generally recruited, a small number ($n = 26$) of clinic participants came from these sources. All participants provided informed consent. The MIDUS data collection (U.S.) was approved by the institutional review boards at the University of Wisconsin-Madison, UCLA, and Georgetown University.

Analyses presented elsewhere (Love et al., 2010) indicate that respondents in the biomarker sample did not differ significantly from those in the interview sample in terms of age, sex, race, marital status, income, or various health indicators, but they were more likely to have a college degree, less likely to be a current smoker, and more likely to use alternative medicine compared with the national sample. Clinic participants also reported significantly higher levels of social integration and perceived availability of social support than those who did not complete the clinic visit (data not shown). IL-6 and sIL-6R were assayed at the MIDUS BioCore Lab (University of Wisconsin, Madison), while other inflammatory markers were assayed at the Laboratory for Clinical Biochemistry Research (University of Vermont, Burlington).

Because assays were performed by different laboratories, caution is warranted in making direct comparisons of the laboratory results for Taiwan and the U.S. Nonetheless, differences in the absolute levels do not hinder comparisons of the associations between social relationships and those biomarkers.

Measures

Inflammatory markers

Outcomes include circulating levels of IL-6 and its soluble receptor (sIL-6R), CRP, fibrinogen, sICAM-1, and sE-selectin; higher values denote greater inflammation. The inflammatory cascade is initiated by primary proinflammatory cytokines (e.g., IL-1, TNF-α) that elicit production of "messenger" cytokine, IL-6, which in turn, stimulates the synthesis of acute phase proteins (e.g., CRP, fibrinogen) in the liver (Libby & Ridker, 1999). IL-6 forms a complex with sIL-6R in the blood that activates inflammatory processes (Jones, Horiuchi, Topley, Yamamoto, & Fuller, 2001; Knupfer & Preiss, 2008): sIL-6R is believed to enhance the effect of IL-6 by prolonging its half-life and by activating cells that are not normally responsive to IL-6 (Jones et al., 2001; Jones & Rose-John, 2002). CRP is a non-specific marker of systemic inflammation and fibrinogen aids in blood clotting. The primary cytokines also activate the expression of cell adhesion molecules (e.g., ICAM-1, selectins), which in turn, target the transfer of leukocytes to inflamed areas and allow interactions between leukocyte and endothelial cells (interior of blood vessels) (Walzog & Gaehtgens, 2000). sICAM-1 and sE-selectin are soluble forms that are shed by activated cells and are measurable in blood (Blankenberg, Barbaux, & Tiret, 2003).

For both surveys, inflammatory markers were based on fasting blood specimens collected during the hospital/clinic visit (see Supplemental Table S1, which lists assay methods and lower detection limits). There were a few respondents for whom values were outside the detectable range (SEBAS: $n = 28$ for IL-6, $n = 1$ for sICAM-1; MIDUS: $n = 32$ for CRP, $n = 1$ for sE-selectin, $n = 1$ for sICAM-1). These values were recoded to the detection limit or just below. To normalize markers with a skewed distribution, we applied a log transformation to IL-6, CRP, sIL-6R, & sE-selectin; and a square root transformation to fibrinogen and sICAM-1.

Among these inflammatory markers, ln(CRP) was moderately correlated with $\ln(IL - 6)$ ($r = 0.42$ in Taiwan, 0.45 in the U.S.) and $\sqrt{\text{fibrinogen}}$ ($r = 0.40$ in Taiwan, 0.45 in the U.S.). The correlation between $\sqrt{\text{fibrinogen}}$ and $\ln(IL - 6)$ was stronger in the U.S. ($r = 0.35$) than Taiwan ($r = 0.21$), while the reverse was true for the correlation between $\sqrt{\text{sICAM} - 1}$ and $\ln(\text{sE} - \text{selectin})$ ($r = 0.45$ in Taiwan, 0.11 in the U.S.). With a few exceptions, the remaining correlations were between 0.10 and 0.27.

Social relationships

Marital status was determined at the 2006 SEBAS interview for Taiwan and at the clinic visit for the U.S. The lag between the 2006 SEBAS interview and collection of biomarkers was about one month

(mean $= 4.6$ weeks, range $= 0$–12.1). Other indicators of social relationships came from the 2003 TLSA (Taiwan) and the SAQ (U.S.). The lag between these measurements and the collection of the biomarkers was similar for the two samples: an average of 3.0 years (range $= 2.6$–3.3) for Taiwan; an average of 2.2 years (range $= 0.0$–5.2) for the U.S. Given the potential for reverse-causality (e.g., ill health may affect social engagement), our lagged measures of social relationships support the implied temporal order of predictor and outcome.

We combined multiple components to create a measure of social integration similar to the Berkman-Syme Social Network Index used in other studies (Ford, Loucks, & Berkman, 2006; Loucks et al., 2006). One point was assigned for each of the following components, resulting in a score ranging from 0 to 4 (see Supplemental Table S2, which lists the survey questions):

1. Respondent was married or lived with a partner/companion;
2. Respondent had weekly contact with at least one non-resident family member and at least one friend/neighbor;
3. Respondent attended church/temple at least sometimes/monthly; and
4. Respondent participated in some other social group.

Our measure of perceived social support was based on questions regarding the availability and quality of care and support from friends and family. The U.S. questions explicitly excluded the spouse/partner, whereas the Taiwan questions referred to family and friends more generally (see Supplemental Table S3, which provides details regarding items and construction). The resulting index had a potential range of 0–3 and good psychometric properties (alpha $= 0.77$ for Taiwan; 0.86 for the U.S.). The correlation between social integration and perceived support was small ($r = 0.13$ for Taiwan and 0.33 for the U.S., not shown).

Health behaviors

Smoking history was asked during the 2006 home interview in Taiwan and during the clinic visit in the U.S. Alcohol intake was asked during the hospital/clinic visit and referred to consumption over the past six months for the Taiwan sample and over the past month for the U.S. sample. In Taiwan, the response categories for alcohol intake comprised never, sometimes, and frequently. To create comparable categories for the U.S. sample, we defined frequent use as five or more days a week.

Control variables

Sociodemographic controls included sex, age, educational attainment, and race/ethnicity. Educational attainment was determined at the baseline wave of TLSA for Taiwan and during the phone interview of MIDUS II for the U.S. Because the distributions differed greatly by country (Table 1), the regression models included a set of dummy variables where the highest category in Taiwan comprised those with 13 or more years and the lowest category in the U.S. included those with 12 or fewer years. In Taiwan, we defined ethnicity as Taiwanese versus Mainlander. In the U.S., race/ethnicity was defined as non-Hispanic white versus all others.

Because obesity may have affected immune markers (O'Connor et al., 2009) as well as social relationships, we adjusted for waist circumference measured at the time of the hospital/clinic exam. We also controlled for use of three types of medication (antihypertensives, lipid-lowering agents, and hormones/steroids) that may have affected levels of inflammation. Information about medication use came from the 2006 SEBAS interview (Taiwan) and the MIDUS clinic visit (U.S.). Finally, we included controls for baseline health status (2003 for Taiwan; at the time of the phone interview or SAQ

Table 1
Descriptive statistics for analysis variables by country.

	Taiwan[a] (n = 961)	United States (n = 970)
Control variables		
Age, mean (SD), y	65.2 (9.1)	57.9 (11.5)
Education		
6 Years or less, no. (%)	624 (64.9)	1 (0.1)
7−11 Years, no. (%)	110 (11.5)	34 (3.5)
H.S. graduate/GED, no. (%)	117 (12.1)	202 (20.8)
13−15 years, no. (%)	47 (4.9)	277 (28.6)
College graduate, no. (%)	57 (5.9)	225 (23.2)
Graduate school, no. (%)	6 (0.6)	231 (23.8)
Mainlander, no. (%)	97 (10.1)	N/A
Hispanic, nonwhite or mixed race, no. (%)	N/A	116 (12.0)
Waist circumference, mean (SD), cm	83.9 (9.8)	96.5 (16.7)
Antihypertensive medication, no. (%)	272 (28.3)	336 (34.6)
Lipid-lowering medication, no. (%)	63 (6.6)	283 (29.2)
Hormone/steroid medication, no. (%)[b]	41(4.2)	150 (15.5)
Self-assessed health status (1−5), mean (SD)	3.3 (1.0)	3.7 (0.9)
CES-depression scale (0−30), mean (SD)	4.3 (5.1)	N/A
CIDI-SF depressive symptoms (0−7), mean (SD)	N/A	0.6 (1.8)
Functional limitations (0−6), mean (SD)	1.0 (1.6)	1.7 (2.0)
Measures of social relationships		
Married or lives with a partner, no. (%)	756 (78.7)	718 (74.0)
Weekly contact with non-resident family, no. (%)	903 (94.0)	844 (87.0)
Weekly contact with friends, no. (%)	745 (77.5)	783 (80.7)
Weekly contact with both family and friends, no. (%)	705 (73.4)	701 (72.3)
Attends church/temple at least sometimes/monthly, no. (%)	571 (59.4)	543 (56.0)
Participates in some other social group, no. (%)	444 (46.2)	634 (65.4)
Social integration (0−4), mean (SD)	2.6 (1.0)	2.7 (1.1)
Score = 0, no. (%)	20 (2.1)	23 (2.4)
Score = 1, no. (%)	122 (12.6)	128 (13.2)
Score = 2, no. (%)	285 (29.6)	241 (25.0)
Score = 3, no. (%)	355 (36.9)	323 (33.4)
Score = 4, no. (%)	182 (18.9)	252 (26.1)
Perceived social support (0−3), mean (SD)	2.5 (0.4)	2.4 (0.5)
Score = 0−0.9, no. (%)	4 (0.5)	14 (1.4)
Score = 1−1.9, no. (%)	70 (7.3)	141 (14.5)
Score = 2−2.9, no. (%)	688 (71.4)	651 (67.3)
Score = 3, no. (%)	201 (20.9)	162 (16.7)
Health behaviors		
Never smoked, no. (%)	604 (62.9)	516 (53.2)
Former smoker, no. (%)	169 (17.6)	341 (35.2)
Current smoker, no. (%)	188 (19.6)	113 (11.7)
Never drink alcohol, no. (%)	692 (72.0)	313 (32.3)
Sometimes drink alcohol, no. (%)	212 (22.0)	518 (53.4)
Frequently drink alcohol, no. (%)	57 (6.0)	139 (14.3)
Inflammatory markers		
C-reactive protein, mean (SD), mg/L	1.6 (1.7)	2.1 (2.1)
IL-6, mean (SD), pg/mL	3.3 (5.2)	2.6 (2.5)[c]
Soluble IL-6 receptor, mean (SD), ng/mL	43.4 (17.1)	36.5 (10.3)[c]
Fibrinogen, mean (SD), mg/dL	324.5 (65.0)	336.4 (79.8)
Soluble ICAM-1, mean (SD), ng/mL	268.1 (94.7)	285.7 (98.7)[c]
Soluble E-selectin, mean (SD), ng/mL	43.2 (34.7)	41.3 (20.6)[c]

Abbreviations: ICAM-1, intercellular adhesion molecule 1; IL-6, interleukin-6.

[a] Data for Taiwan are weighted to adjust for oversampling and for differential response rates by age, sex and other covariates.

[b] Includes corticosteroids, androgens, estrogens, and progestins (including hormonal contraceptives). In Taiwan, the variable also includes thyroid and hypophysis (pituitary) hormones; the data are not sufficiently detailed to distinguish between these hormones and steroids. Thus, this measure captures use of steroidal anti-inflammatories (e.g., dexamethasone, prednisone), but data are not available in both surveys to identify use of nonsteroidal anti-inflammatories (e.g., ibuprofen, aspirin, naproxen).

[c] One respondent from MIDUS is missing data for IL-6, sIL-6R, sICAM-1, and sE-selectin.

for the U.S.): self-assessed health status, depressive symptoms, and functional limitations.

Analytical strategy

The analysis sample for Taiwan was based on respondents who completed the 2006 SEBAS exam (*n* = 1036). For the U.S., analyses were based on respondents who participated in the biomarker component of MIDUS II (*n* = 1054). Because very high levels of CRP (>10 mg/L) are likely to reflect acute rather than chronic inflammation (Pearson et al., 2003), we excluded respondents with such values (SEBAS, *n* = 41; MIDUS, *n* = 31). A few additional respondents were excluded because of missing data for CRP (SEBAS, *n* = 4; MIDUS, *n* = 14) or one of the covariates (SEBAS, *n* = 30; MIDUS, *n* = 39), leaving an analysis sample of 961 for Taiwan and 970 for the U.S.

Using linear regression, we estimated two models for each inflammatory marker (transformed as described above). The first model included social integration, perceived social support, and control variables. The second model added health behaviors, which may mediate the link between social relationships and inflammation. Prior to model fitting, we standardized the outcome variables and the measures of social relationships to have a mean of zero and a standard deviation of one to facilitate comparisons of effect size. Models for Taiwan controlled for urban residence and included a random level effect for primary sampling unit (PSU) to account for the multi-stage sampling design. Models for the U.S. included a family-level random effect to account for sampling multiple individuals from the same family.

Results

Descriptive statistics for all variables in the analysis are shown in Table 1. The mean ages for the two study samples reflected the younger range of the U.S. sample (35−86) compared with the Taiwan sample (53−97). As noted earlier, the educational distributions also differed: the majority of the Taiwan sample, but less than 1% of the U.S. sample, had six or fewer years of education; the percentage with post-graduate education was less than 2% in Taiwan but nearly one-quarter in the U.S. The older age of the Taiwan sample contributed to the educational disparity because the oldest Taiwanese cohorts received little education. By contrast, educational attainment among today's young Taiwanese is high.

As expected, the Taiwanese reported stronger social ties with family than Americans: they were more likely to be married and have regular contact with family members (*p* < 0.05 for both differences). On the other hand, Americans were more likely to participate in other social groups than the Taiwanese (65% versus 46%, respectively, *p* < 0.001). Yet, overall levels of social integration and perceived social support were very similar between countries.

Based on models that control for potential confounders (Tables 2−5, Model 1), there was a significant inverse association between social integration and CRP in Taiwan. But the magnitude was modest: a one SD increase in social integration was associated with 0.07 of a SD decrease in log(CRP)—that is, a 7% decrease in CRP. Perceived social support was significant in two cases, but the coefficients were *positive*: higher levels of support were associated with higher levels of CRP and sIL-6R among U.S. respondents.

We found no evidence that the associations between social relationships and inflammatory markers varied by sex or age. Sex interactions with the two measures of social relationships were not significant for any outcome in either country (data not shown). Similarly, no interaction between age and social relationship measures was significant.

Because the measure of social integration did not represent an underlying latent construct (i.e., the components were not highly

Table 2
Coefficients from linear regression models predicting IL-6, CRP, & fibrinogen, Taiwan ($n = 961$).

	ln(IL − 6)		ln(CRP)		√fibrinogen	
	(1)	(2)	(1)	(2)	(1)	(2)
Urban resident	−0.16	−0.13	0.08	0.07	0.22**	0.18
Female	0.52	0.59	2.02***	2.26***	1.23**	1.29**
Age	0.02***	0.02***	0.02***	0.02***	0.02***	0.02***
Age × female	−0.01	−0.01	−0.03***	−0.03***	−0.02**	−0.02**
Mainlander	−0.07	−0.10	−0.26**	−0.26**	−0.25*	−0.27**
(<6 years education)						
7−11 years education	0.13	0.11	0.01	0.00	0.01	−0.00
12 years education	−0.15	−0.17	−0.33***	−0.33***	−0.19*	−0.20*
13+ years education	−0.14	−0.16	−0.28**	−0.27**	−0.12	−0.10
Waist circumference	0.02***	0.02***	0.03***	0.03***	0.00	0.00
Antihypertensive medication	0.08	0.10	0.07	0.08	0.11	0.11
Lipid-lowering medication	0.22	0.19	0.09	0.08	0.32**	0.29*
Hormone/steroid medication	0.09	0.11	0.04	0.04	−0.13	−0.14
CES-D	0.00	0.00	0.00	−0.01	−0.01	−0.01
Self-assessed health status	−0.05	−0.05	0.00	0.00	0.00	0.00
Functional limitations	0.01	0.01	0.01	0.01	0.02	0.03
Social integration	−0.05	−0.04	−0.07*	−0.07*	−0.03	−0.01
Perceived support	0.04	0.05	−0.02	−0.02	0.00	−0.01
(Never smoked)						
Former smoker		0.14		0.12		0.17
Current smoker		0.26**		0.25**		0.35***
(Never drinks alcohol)						
Sometimes drinks alcohol		0.13		0.15*		−0.02
Frequently drinks alcohol		−0.33*		−0.15		−0.26*
Constant	−2.73***	−2.78***	−3.47***	−3.70***	−1.41**	−1.47**
Overall R^2	0.12	0.14	0.13	0.14	0.06	0.08

Abbreviations: CRP, C-reactive protein; sICAM-1, soluble intercellular adhesion molecule 1; IL-6, Interleukin-6; sE-selectin, soluble E-selectin; sIL-6R, soluble IL-6 receptor.
$*p < 0.05$; $**p < 0.01$; $***p < 0.001$.
Note: Outcome variables and measures of social relationships were standardized (to mean = 0 and SD = 1 for the pooled sample) prior to model fitting. The model includes a random level effect for PSU to account for the multi-stage sampling design.

Table 3
Coefficients from linear regression models predicting IL-6, CRP, & fibrinogen, U.S. ($n = 970$).[a]

	ln(IL − 6)		ln(CRP)		√fibrinogen	
	(1)	(2)	(1)	(2)	(1)	(2)
Female	0.74*	0.71*	0.70*	0.66*	0.61	0.59
Age	0.02***	0.02***	0.00	0.00	0.01**	0.01**
Age × female	−0.01	−0.01	0.00	0.00	0.00	0.00
Hispanic/nonwhite/mixed race	−0.08	−0.08	−0.10	−0.11	0.15	0.15
(H.S. graduate or less)						
Some college	−0.02	−0.02	−0.03	−0.04	−0.16	−0.17
College graduate	−0.10	−0.09	−0.17	−0.16	−0.16	−0.14
Graduate school	0.00	0.02	−0.05	−0.02	−0.13	−0.11
Waist circumference	0.02***	0.02***	0.03***	0.03***	0.02***	0.02***
Antihypertensive medication	0.14*	0.15*	0.05	0.06	−0.03	0.00
Lipid-lowering medication	0.04	0.04	−0.18*	−0.17*	0.11	0.12
Hormone/steroid medication	0.06	0.07	0.40***	0.42***	−0.12	−0.10
CIDI-SF	0.01	0.01	−0.01	−0.02	0.01	0.00
Self-assessed health status	−0.09*	−0.08*	−0.10*	−0.09*	−0.04	−0.03
Functional limitations	0.03	0.03	0.03	0.03	−0.01	−0.02
Social integration	−0.04	−0.04	−0.04	−0.03	−0.03	−0.02
Perceived support	0.03	0.02	0.06*	0.06*	0.03	0.03
(Never smoked)						
Former smoker		0.04		0.03		−0.03
Current smoker		0.16		0.22*		0.18
(Never drinks alcohol)						
Sometimes drinks alcohol		−0.03		0.04		0.01
Frequently drinks alcohol		−0.05		−0.05		−0.18
Constant	−2.67***	−2.72***	−2.33***	−2.45***	−2.15***	−2.25***
Overall R^2	0.19	0.20	0.23	0.23	0.11	0.11

$*p < 0.05$; $**p < 0.01$; $***p < 0.001$.
Note: Outcome variables and measures of social relationships were standardized (to mean = 0 and SD = 1 for the pooled sample) prior to model fitting. The model includes a family-level random effect to account for sampling multiple individuals from the same family.
[a] Analyses are based on 969 respondents for IL-6.

Table 4
Coefficients from linear regression models predicting sICAM-1, sE-selectin, & sIL-6R, Taiwan ($n = 961$).

	$\sqrt{sICAM-1}$		ln(sE − selectin)		ln(sIL − 6R)	
	(1)	(2)	(1)	(2)	(1)	(2)
Urban resident	−0.05	−0.06	0.04	0.00	−0.23*	−0.21**
Female	0.65	0.75	0.52	0.58	0.44	0.47
Age	0.02**	0.02**	0.00	0.00	0.01	0.01
Age × female	−0.01	−0.01	−0.01	−0.01	−0.01	0.00
Mainlander	−0.11	−0.10	−0.30**	−0.32**	−0.06	−0.04
(< 6 years education)						
7−11 years education	−0.13	−0.12	−0.21*	−0.23*	−0.06	−0.06
12 Years education	−0.17	−0.13	−0.04	−0.05	−0.14	−0.17
13+ Years education	−0.29**	−0.25*	−0.35**	−0.36**	−0.16	−0.16
Waist circumference	0.01**	0.01**	0.03***	0.03***	0.01*	0.01*
Antihypertensive medication	0.01	0.02	0.14	0.16*	0.08	0.08
Lipid-lowering medication	0.22	0.22	0.14	0.07	0.16	0.14
Hormone/steroid medication	0.23	0.22	−0.21	−0.21	−0.08	−0.10
CES-D	0.01	0.01	0.01	0.01	−0.01	−0.01
Self-assessed health status	−0.03	−0.03	−0.06	−0.07	−0.10**	−0.10**
Functional limitations	0.00	0.00	−0.04	−0.03	0.00	0.01
Social integration	−0.05	−0.04	−0.01	0.01	−0.05	−0.05
Perceived support	−0.01	−0.01	0.05	0.05	0.05	0.06
(Never smoked)						
Former smoker		0.10		0.12		0.07
Current smoker		0.33**		0.13		0.23*
(Never drinks alcohol)						
Sometimes drinks alcohol		−0.11		0.04		−0.10
Frequently drinks alcohol		0.12		0.11		−0.25
Constant	−1.96***	−1.97***	−1.81***	−1.82***	−0.60	−0.55
Overall R^2	0.07	0.09	0.14	0.41	0.07	0.08

*$p < 0.05$; **$p < 0.01$; ***$p < 0.001$.
Note: Outcome variables and measures of social relationships were standardized (to mean = 0 and SD = 1 for the pooled sample) prior to model fitting. The model includes a random level effect for PSU to account for the multi-stage sampling design.

intercorrelated), we considered whether the association was driven by particular components. We estimated an auxiliary set of models that included a dichotomous variable for each of the four components (not shown). All of the coefficients were small and only a few attained statistical significance. Having a spouse/partner was inversely associated with IL-6 in the U.S. Contact with family and friends was not significant in any model, but when we included separate indicators for family and for friends we discovered that

Table 5
Coefficients from linear regression models predicting sICAM-1, sE-selectin, & sIL-6R, U.S. ($n = 969$).

	$\sqrt{sICAM-1}$		ln(sE − selectin)		ln(sIL − 6R)	
	(1)	(2)	(1)	(2)	(1)	(2)
Female	0.44	0.36	−0.58	−0.60*	−0.07	−0.04
Age	0.01**	0.01**	−0.01*	−0.01*	0.00	0.00
Age × female	−0.01	0.00	0.01	0.01	0.00	0.00
Hispanic/nonwhite/mixed race	−0.25*	−0.26**	0.15	0.15	−0.19*	−0.19*
(H.S. graduate or less)						
Some college	−0.02	−0.03	0.01	0.00	−0.04	−0.04
College graduate	−0.23*	−0.18*	−0.01	0.00	−0.09	−0.10
Graduate school	−0.19*	−0.14	−0.03	−0.01	−0.12	−0.13
Waist circumference	0.01***	0.01***	0.01***	0.01***	0.01**	0.01**
Antihypertensive medication	−0.12	−0.10	0.08	0.09	−0.04	−0.05
Lipid-lowering medication	0.01	0.01	0.00	0.01	−0.07	−0.07
Hormone/steroid medication	−0.13	−0.07	−0.26***	−0.24**	−0.13	−0.14
CIDI-SF	0.00	−0.01	0.00	0.00	0.02	0.02
Self-assessed health status	−0.08*	−0.06	0.02	0.02	0.01	0.00
Functional limitations	0.00	−0.01	0.02	0.02	0.02	0.03
Social integration	−0.05	−0.02	0.04	0.05	0.02	0.01
Perceived support	−0.01	−0.01	0.01	0.00	0.06*	0.06*
(Never smoked)						
Former smoker		0.05		−0.01		−0.05
Current smoker		0.68***		0.20*		−0.14
(Never drinks alcohol)						
Sometimes drinks alcohol		−0.08		0.02		0.00
Frequently drinks alcohol		0.00		0.01		−0.02
Constant	−1.16**	−1.44***	−0.51	−0.63	−0.85*	−0.79*
Overall R^2	0.08	0.11	0.08	0.08	0.04	0.04

*$p < 0.05$; **$p < 0.01$; ***$p < 0.001$.
Note: Outcome variables and measures of social relationships were standardized (to mean = 0 and SD = 1 for the pooled sample) prior to model fitting. The model includes a family-level random effect to account for sampling multiple individuals from the same family.

contact with family was inversely associated with two markers in Taiwan (IL-6 & sE-selectin); there was no such relationship in the U.S. The coefficient for contact with friends was significant in only one case and *positive*: contact with friends was associated with *higher* levels of sE-selectin in the U.S. Church attendance was significant in 2 out of 12 models, both in the U.S.; it was associated with lower levels of sICAM-1, but *higher* levels of IL-6. Finally, participation in non-religious social groups had a significant inverse association with two inflammatory markers (sICAM-1 & sIL-6R) in Taiwan. Thus, in each country 4 out of 30 coefficients (13%) were significant, but in the U.S. two of those were not in the expected direction. The association between social integration and inflammation was more consistent in Taiwan than in the U.S., but the results remained sporadic and weak.

In Model 2, the addition of health behaviors had little effect on the coefficients for social relationship measures. However, current smoking was generally associated with higher levels of inflammation.

To test the robustness of our results, we explored several alternative models. First, we reestimated the models shown in Tables 2–5 including respondents with high levels of CRP. The results for Taiwan remained unchanged, but in the U.S. the coefficient for social integration became significant for sICAM-1 ($\beta = -0.07$, $p \sim 0.04$). Second, we created dichotomous indicators for low social integration (≤ 1 of 4) and for low perceived support (<2 of 3) to test for a threshold effect of social isolation. For social integration, we found small but significant inverse associations (i.e., low levels associated with more inflammation) with CRP and fibrinogen in Taiwan only. Low perceived support had the opposite relationship with IL-6 in Taiwan and sIL-6R in the U.S. (i.e., low support associated with *lower* inflammation). In sum, these alternative models suggested that the results were sensitive to specification.

Discussion

After evaluating the relationship between two dimensions of social relationships and six inflammatory markers in the U.S. and Taiwan, we found only a few statistically significant associations. Given that the literature suggests a strong link between social relationships and mortality, and that inflammation plays an important role in the leading causes of death, we had expected to find consistent and moderately strong associations between social relationships and inflammatory markers. The small effect sizes and lack of robustness across markers were surprising.

Our measure of social integration exhibited a small inverse association with CRP in Taiwan. The two previous studies of the link between social integration and CRP, both based on U.S. samples, showed mixed results: one reported no association with CRP (Loucks et al., 2006), while the other found significant associations with CRP for some sex-age combinations but not others (Ford et al., 2006). We identified only one prior study of social integration and IL-6, which showed an inverse association in a U.S. sample (Loucks et al., 2006). In previous research focusing on the effects of social integration, the most consistent relationship was reported for fibrinogen (Loucks, Berkman, Gruenewald, & Seeman, 2005; Rosengren et al., 1990; Steptoe et al., 2003; Wamala et al., 1999), with only one study reporting no association (Helminen, Rankinen, Vaisanen, & Rauramaa, 1997). In our study, there was no association with fibrinogen.

We found no evidence that higher perceived support was associated with lower inflammation. Two previous studies that evaluated the relationship between overall perceived support and IL-6 also found no significant effect in adjusted models (Costanzo et al., 2005; Mezuk, Diez Roux, & Seeman, 2010), although

Costanzo et al. (2005) did find a significant association for one (social attachment) of the six subscales tested. In the case of CRP, we discovered a significant association in the U.S. but not in the expected direction (perceived support was related to more inflammation); there was no such relationship in Taiwan. Among two prior studies, both based on U.S. samples, one reported no association (McDade, Hawkley, & Cacioppo, 2006) and the other found perceived support inversely associated with CRP, but it was significant only for men (Mezuk et al., 2010). For fibrinogen, two previous studies showed a significant inverse association (Davis & Swan, 1999; Mezuk et al., 2010), while a third found the opposite relationship (Helminen et al., 1997). We found no significant association between perceived social support and fibrinogen in either the U.S. or Taiwan.

We found one prior study that investigated the link between social relationships and sICAM-1. Loucks et al. (2006) reported a significant association between social integration and sICAM-1, but only for men. There were no prior studies of the association with sE-selectin or sIL-6R. Here, we found only one significant association between social relationships and these three markers in either country: perceived support was associated with *higher* sIL-6R in the U.S.

As expected, the evidence supporting an association between social relationships and lower inflammation was stronger for social integration than for perceived support. There are several plausible explanations. Measures of relationship quality may be more susceptible to response bias and to cultural differences. For example, respondents may sometimes provide socially desirable responses for perceived support. Very few respondents in either country gave negative answers to these questions. The limited variability in this measure of perceived support may have contributed to the weak results. Moreover, if those in ill health were more likely to report the availability of such support, perhaps because they felt a greater need, this reporting pattern could generate the unexpected positive association with CRP and sIL-6R that we observed in the U.S. On the other hand, perceived support could be counterproductive in a society that values self-reliance (e.g., U.S.), while being viewed more favorably in a culture that favors interdependence (e.g., Taiwan) (Uchida, Kitayama, Mesquita, Reyes, & Morling, 2008).

The analysis could be improved by better measures of relationship quality. First, such measures could encompass negative (e.g., social conflict, loneliness) as well as positive aspects of relationships. Second, they could reflect not only social support provided *by* others, but also support provided *to* others, which may be especially important in collectivistic cultures. Third, data could be obtained regarding the quality of the respondent's closest relationships. The nature of such relationships may differ across cultures and may change as people age. For example, Taiwanese were more likely than Americans to participate in non-religious social groups. Levels of church attendance appeared similar, but followed different patterns with age: in Taiwan, church attendance decreased at older ages, while the opposite was true in the U.S. The Taiwan advantage in contact with family and the U.S. advantage in contact with friends, church attendance, and participation in other social groups were greater at older ages (65+) than at younger ages.

It is also possible that social relationships moderate the effects of stressors on health, as posited by the stress-buffering hypothesis (Cohen & Wills, 1985; Wheaton, 1985). The theory proposes that the perceived level of stress is a product of exposure to stressors and the resources one can mobilize to cope with those stressors (Cohen & Wills, 1985). Thus, perceived stress may absorb whatever buffering effect social support might have (i.e., those with more support have lower levels of perceived stress). A recent study evaluated the

extent to which perceived social support moderates the effects of stress on CRP, IL-6, and fibrinogen and found little evidence of such stress buffering (Mezuk et al., 2010). However, the measure of stress appeared to reflect perceived stress rather than exposure to potentially stressful events. A better test of the stress-buffering hypothesis would be to investigate the interaction with exposure to potential stressors.

The link between social relationships and inflammation is likely to involve complex pathways that vary by individual and environmental characteristics. Some prior studies suggested that the association may be stronger for men than women (Loucks et al., 2005, 2006; Mezuk et al., 2010) and another indicated that the effect may depend on age (Ford et al., 2006). We found little evidence that the effect of social relationships differs by sex or age. The absence of age interactions suggests that differences in the age ranges of the two samples do not account for inter-country differences in the effects of social relationships.

To the best of our knowledge, our results provide the first comparison between an individualistic and a collectivistic culture of the linkages between social relationships and multiple markers of inflammation. Given that both social relationships and biomarkers are dynamic, we should not be surprised that a single snapshot fails to reveal dramatic effects. This study focused on basal operating levels of biomarkers, but those basal levels are likely to be the result of dynamic processes over a long period of time. Longitudinal data with repeated assessments over time may yield a stronger signal. In line with the stress-buffering hypothesis, we may need to look more directly at how social relationships condition stress-induced reactivity. Some short term laboratory based studies have demonstrated that social support reduces cardiovascular responses to stressors (see review by Uchino, 2006), but more attention is needed on the reactions across multiple, inter-related systems. Still, identifying how best to quantify the dynamics of physiological systems in people's everyday lives with measures that are feasible for large-scale study is a big challenge. Strategies for blending experimental approaches with longitudinal surveys could represent a promising approach. Untangling these physiological pathways will require a companionable marriage between small studies that can identify the pathways that appear to be important and large scale, population based studies that can test the viability of those explanatory pathways.

Role of funding

Conflicts of interest

None of the authors have a conflict of interest that could inappropriately influence the results of this study.

Acknowledgments

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.socscimed.2012.02.020.

References

Blankenberg, S., Barbaux, S., & Tiret, L. (2003). Adhesion molecules and atherosclerosis. *Atherosclerosis, 170*, 191–203.

Chang, M., Glei, D., Goldman, N., & Weinstein, M. (2007). The Taiwan biomarker project. In M. Weinstein, J. W. Vaupel, & K. W. Wachter (Eds.), *Biosocial surveys. Committee on Advances in Collecting and Utilizing Biological Indicators and Genetic Information in Social Science Surveys, Committee on Population, Division of Behavioral and Social Sciences and Education* (pp. 3-1–3-16). Washington, DC: The National Academies Press.

Cohen, S. (1988). Psychosocial models of the role of social support in the etiology of physical disease. *Health Psychology: Official Journal of the Division of Health Psychology, American Psychological Association, 7*, 269–297.

Cohen, S., & Wills, T. A. (1985). Stress, social support, and the buffering hypothesis. *Psychology Bulletin, 98*, 310–357.

Costanzo, E. S., Lutgendorf, S. K., Sood, A. K., Anderson, B., Sorosky, J., & Lubaroff, D. M. (2005). Psychosocial factors and interleukin-6 among women with advanced ovarian cancer. *Cancer, 104*, 305–313.

Davis, M. C., & Swan, P. D. (1999). Association of negative and positive social ties with fibrinogen levels in young women. *Health Psychology: Official Journal of the Division of Health Psychology, American Psychological Association, 18*, 131–139.

Ford, E. S., Loucks, E. B., & Berkman, L. F. (2006). Social integration and concentrations of C-reactive protein among US adults. *Annals of Epidemiology, 16*, 78–84.

Glei, D. A., Goldman, N., Lin, Y., & Weinstein, M. (2011). Age-related changes in biomarkers: longitudinal data from a population-based sample. *Research on Aging, 33*, 312–326.

Goldman, N., Glei, D. A., Lin, Y. H., & Weinstein, M. (2010). The serotonin transporter polymorphism (5-HTTLPR): allelic variation and links with depressive symptoms. *Depression and Anxiety, 27*, 260–269.

Goldman, N., Lin, I. F., Weinstein, M., & Lin, Y. H. (2003). Evaluating the quality of self-reports of hypertension and diabetes. *Journal of Clinical Epidemiology, 56*, 148–154.

Helminen, A., Rankinen, T., Vaisanen, S., & Rauramaa, R. (1997). Social network in relation to plasma fibrinogen. *Journal of Biosocial Science, 29*, 129–139.

Holt-Lunstad, J., Smith, T. B., & Layton, J. B. (2010). Social relationships and mortality risk: a meta-analytic review. *PLoS Medicine, 7*, e1000316.

Jones, S. A., Horiuchi, S., Topley, N., Yamamoto, N., & Fuller, G. M. (2001). The soluble interleukin 6 receptor: mechanisms of production and implications in disease. *The FASEB Journal: Official Publication of the Federation of American Societies for Experimental Biology, 15*, 43–58.

Jones, S. A., & Rose-John, S. (2002). The role of soluble receptors in cytokine biology: the agonistic properties of the sIL-6R/IL-6 complex. *Biochimica et Biophysica Acta, 1592*, 251–263.

Kiecolt-Glaser, J. K., Gouin, J. P., & Hantsoo, L. (2010). Close relationships, inflammation, and health. *Neuroscience and Biobehavioral Reviews, 35*, 33–38.

Knupfer, H., & Preiss, R. (2008). sIL-6R: more than an agonist? *Immunology and Cell Biology, 86*, 87–91.

Libby, P., & Ridker, P. M. (1999). Novel inflammatory markers of coronary risk: theory versus practice. *Circulation, 100*, 1148–1150.

Loucks, E. B., Berkman, L. F., Gruenewald, T. L., & Seeman, T. E. (2005). Social integration is associated with fibrinogen concentration in elderly men. *Psychosomatic Medicine, 67*, 353–358.

Loucks, E. B., Sullivan, L. M., D'Agostino, R. B., Sr., Larson, M. G., Berkman, L. F., & Benjamin, E. J. (2006). Social networks and inflammatory markers in the Framingham heart study. *Journal of Biosocial Science, 38*, 835–842.

Love, G. D., Seeman, T. E., Weinstein, M., & Ryff, C. D. (2010). Bioindicators in the MIDUS national study: protocol, measures, sample, and comparative context. *Journal of Aging and Health, 22*, 1059–1080.

Markus, H. R., & Kitayama, S. (1991). Culture and the self: implications for cognition, emotion, and motivation. *Psychological Review, 98*, 224–253.

McDade, T. W., Hawkley, L. C., & Cacioppo, J. T. (2006). Psychosocial and behavioral predictors of inflammation in middle-aged and older adults: the Chicago health, aging, and social relations study. *Psychosomatic Medicine, 68*, 376–381.

Mezuk, B., Diez Roux, A. V., & Seeman, T. (2010). Evaluating the buffering vs. direct effects hypotheses of emotional social support on inflammatory markers: the multi-ethnic study of atherosclerosis. *Brain, Behavior, and Immunity*, .

O'Connor, M. F., Bower, J. E., Cho, H. J., Creswell, J. D., Dimitrov, S., Hamby, M. E., et al. (2009). To assess, to control, to exclude: effects of biobehavioral factors on circulating inflammatory markers. *Brain, Behavior, and Immunity, 23*, 887–897.

Pearson, T. A., Mensah, G. A., Alexander, R. W., Anderson, J. L., Cannon, R. O., 3rd, Criqui, M., et al. (2003). Markers of inflammation and cardiovascular disease: application to clinical and public health practice: a statement for healthcare professionals from the Centers for Disease Control and Prevention and the American Heart Association. *Circulation, 107*, 499–511.

Radler, B. T., & Ryff, C. D. (2010). Who participates? Accounting for longitudinal retention in the MIDUS national study of health and well-being. *Journal of Aging and Health, 22*, 307–331.

Rosengren, A., Wilhelmsen, L., Welin, L., Tsipogianni, A., Teger-Nilsson, A. C., & Wedel, H. (1990). Social influences and cardiovascular risk factors as determinants of plasma fibrinogen concentration in a general population sample of middle aged men. *BMJ (Clinical Research Edition), 300*, 634–638.

Ryff, C., Almeida, D. M., Ayanian, J. S., Carr, D. S., Cleary, P. D., Coe, C., et al. (2007). *Midlife development in the United States (MIDUS II), 2004–2006* [Computer file]. No. ICPSR04652-v1. Ann Arbor, MI: Inter-university Consortium for Political and Social Research [Distributor].

Steptoe, A., Kunz-Ebrecht, S., Owen, N., Feldman, P. J., Rumley, A., Lowe, G. D., et al. (2003). Influence of socioeconomic status and job control on plasma fibrinogen responses to acute mental stress. *Psychosomatic Medicine, 65*, 137–144.

Uchida, Y., Kitayama, S., Mesquita, B., Reyes, J. A., & Morling, B. (2008). Is perceived emotional support beneficial? Well-being and health in independent and interdependent cultures. *Personality and Social Psychology Bulletin, 34*, 741–754.

Uchino, B. N. (2006). Social support and health: a review of physiological processes potentially underlying links to disease outcomes. *Journal of Behavioral Medicine, 29*, 377–387.

Walzog, B., & Gaehtgens, P. (2000). Adhesion molecules: the path to a new understanding of acute inflammation. *News in Physiological Sciences: An International Journal of Physiology Produced Jointly by the International Union of Physiological Sciences and the American Physiological Society, 15*, 107–113.

Wamala, S. P., Murray, M. A., Horsten, M., Eriksson, M., Schenck-Gustafsson, K., Hamsten, A., et al. (1999). Socioeconomic status and determinants of hemostatic function in healthy women. *Arteriosclerosis, Thrombosis, and Vascular Biology, 19*, 485–492.

Wheaton, B. (1985). Models for the stress-buffering functions of coping resources. *Journal of Health and Social Behavior, 26*, 352–364.