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ORIGINAL ARTICLE

Source-Specific Social Support and Circulating Inflammatory Markers Among White-Collar Employees

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Abstract
Background Despite known beneficial effects of social support on cardiovascular health, the pathway through which sources of support (supervisor, coworkers, family/friends) influence inflammatory markers is not completely understood.
Purpose We investigated the independent and moderating associations between social support and inflammatory markers.
Methods A total of 137 male white-collar employees underwent a blood draw for measurement of high-sensitive C-reactive protein (hs-CRP), interleukin-6 (IL-6), tumor necrosis factor alpha (TNF-α), monocyte and leukocyte counts, and completed a questionnaire on social support.
Results Multivariable linear regression analyses controlling for covariates revealed that supervisor support was inversely associated with IL-6 ($\beta=-0.24$, $p<0.01$) while coworker support was marginally associated with TNF-α ($\beta=-0.16$, $p<0.10$). Support from family/friends was not associated with inflammatory markers.
Conclusion Social support from the immediate supervisor may be a potential mechanism through which social support exerts beneficial effects on inflammatory markers in working men.

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Introduction

Poor social support has been repeatedly found to be associated with an increased risk of various health issues, particularly from cardiovascular disease [1–3]. According to the most recent meta-analysis based on 25 prospective studies, lack of functional and perceived social support was consistently associated with the development and poor prognosis of cardiovascular disease [4]. This has prompted the exploration of specific mechanisms and processes that underlie the benefits of social support to cardiovascular health. Collective evidence from past research suggests that social support is beneficial for: (a) increased health-promoting behaviors, such as smoking cessation, exercising, a healthier diet, and better sleep that may help prevent cardiovascular disease [5–7]; (b) ameliorating cardiac and vascular responses during stress, resulting in suppression of abnormal blood pressure (BP) or heart rate [8–13]; and (c) downregulating inflammatory processes via the neuroendocrine-immune system network [14–20]. Although evidence supporting propositions (a) and (b) are well-documented, there is less evidence showing that inflammatory response is the mechanism through which social support exerts effects on cardiovascular health [2].

To date, clinical and population-based studies have explored the connection between social support and inflammatory markers. Some studies found that greater social support contributes to a decrease of proinflammatory markers as represented by C-reactive protein (CRP) [14–16], interleukin (IL)-6 [17–20], IL-8 [21], or counts/percentage of monocytes in the peripheral blood [22], while a few other studies reported a borderline or no significant relationship between social

support and CRP [23–26], IL-6 [24, 27], tumor necrosis factor alpha (TNF-α) [21, 27], or total leukocytes [22, 26]. For example, in a sample of women aged 61 to 90 years, those with better social relationships and high sleep efficiency had significantly lower levels of IL-6 [19]. A large-scale population study based on the Multi-Ethnic Study of Atherosclerosis reported that perceived emotional support was directly and inversely associated with CRP particularly among men but only weakly related to IL-6 [14]. Similarly, in the Framingham Heart Study, social network quality as measured by the Berkman-Syme Social Network Index (which assesses the type, size, closeness, and frequency of contacts in a respondent's current social network) [28] was inversely associated with serum IL-6 but not with CRP, soluble intercellular adhesion molecule-1, or monocyte chemoattractant protein-1 [17]. In contrast, the Chicago Health, Aging, and Social Relations Study found that perceived social support was not related to plasma CRP levels in a representative sample of middle-aged and older adults [23].

At this time, the relationship between social support and inflammatory markers seems inconsistent. Inconsistency between these studies may be due partly to the differences in conceptualization and measures of social support [29], demographics, study populations, sample sizes, or covariates, as indicated by some researchers [14, 30]. With regard to conceptualization, there seems to be no study that compared different concepts of social support in relation to inflammatory markers but one study reported that "perception" of support was positively associated with natural killer cells while "existence" or "utilization" of support was not associated with natural killer cells [31], suggesting the importance of distinguishing social support concepts in terms of the support-immune relationship. In addition, there are other potentially important factors that were not addressed in the past studies that deserve attention. First, former studies have typically assessed the amount of support provided by collective "others" rather than domain-specific sources like "work-related" or "non-work related," or more specifically, like supervisors, coworkers, family, or friends. A specific source of support may show a tighter association with certain health outcomes than other sources depending on the situation of the respondents. For example, in the working population, several studies have observed a relatively stronger association of workplace social support on health than social support from family or friends because of the more direct relationship of workplace support to work-related demands [32–35]. A meta-analytic review regarding "sources of social support and burnout" indicated that work-related support was more closely associated with exhaustion than non-work-related sources [35]. A study of social support and sleep-related breathing disturbance revealed that a low level of support from supervisors was related to a 3-fold increased prevalence of sleep-related breathing disturbance while reduced support from coworkers or from family was not significantly associated with sleep-related breathing disturbance [32]. These studies suggest the importance of identifying support sources which may be particularly relevant to buffer support-related stress. In a similar context, if the respondents are not working, support from family, relatives, or friends may be the only source of support. Thus, examining the relationship between source-specific social support and proinflammatory markers may help further understanding of the mechanisms of the social support-health relationship as well as development of effective interventions to prevent stress-related disorders such as cardiovascular disease.

A second factor that deserves attention is that except for one recent study [14], past studies relating social support and inflammatory indicators have not addressed the two models by which social support may operate. That is, whether social support exerts an independent effect on inflammatory markers at varying levels of stress (independent/direct model) or whether it exerts a beneficial effect on inflammatory markers at high levels of stress (moderating/buffering model) [36]. Mezuk et al. (2010) have tested these models in relation to inflammatory markers and reported that perceived emotional support has a relatively stronger direct effect than a stress-buffering effect, although the influence of social support itself was found to be only modestly associated with CRP concentrations [14].

In light of the above knowledge, the current study was designed to advance understanding of the association of social support with inflammatory markers in a sample of Japanese daytime white-collar employees. Specifically, our purpose was to clarify the following two questions. First, is source-specific social support, i.e., support from supervisor, coworkers, or family/friends, associated with reduced peripheral blood inflammatory markers? If so, which source of support is associated with the reduction of these markers? Second, is social support independently or interactively associated with inflammatory markers, as measured with the independent and stress-buffering models [36]?

To examine these hypotheses, we measured four established systemic inflammatory markers (high-sensitivity CRP (hs-CRP), IL-6, TNF-α, and total leukocytes), some of which are known to be early indicators of cardiovascular disease [37–39], as well as an independent risk marker of subclinical carotid atherosclerosis, i.e., peripheral monocyte counts [40, 41].

Methods

Study Participants

The study design was cross-sectional and data were collected with a self-administered questionnaire at a trading company in

Japan. The study was conducted as a part of an annual mandatory occupational health examination during April 2004. All participants were full-time, white-collar, Japanese employees working during the daytime (08.30–17.00). A total of 208 employees who underwent health examination were invited to participate in this study and were given the survey questionnaire including purpose, instructions, and informed consent. Overall, 206 employees agreed to participate in the questionnaire survey and blood test, and replied with a signed consent form. Questionnaires and blood samples were collected on the same day. Of the 206 employees, 15 employees were excluded because of missing data in essential study parameters or reporting immune-related disorders or pregnancy (see "Covariates" section for detail). Occasional outliers for covariates (standard deviation>3.0) were excluded from the analyses (the number of excluded outliers were $n=3$ for men). In addition, female employees were excluded from the analysis because of a small sample size ($n=51$) including 18 individuals who had "below the minimum detectable limit" for hs-CRP. The study protocol was reviewed and approved by the Ethical Committee of the Kyushu University, Japan.

Measurements

Social Support

Social support was assessed by a four-item scale included in the Japanese version of the generic job stress questionnaire [32] developed by the U.S. National Institute for Occupational Safety and Health [42], which has been used in various occupational health studies [43–46]. The following questions were asked individually about (1) the immediate supervisor, (2) coworkers, and (3) family/friends. Items for the scale are as follows:

1. How much does each of these people go out of their way to do things to make your work life easier for you (SS1)?
2. How easy is it to talk with each of the following people (SS2)?
3. How much can each of these people be relied on when things get tough at work (SS3)?
4. How much is each of the following willing to listen to your personal problems (SS4)?

Response options were:

(1) don't have any such person, (2) not at all, (3) a little, (4) somewhat, (5) much, (6) very much

Each item response number corresponds to its item score. Social support scores were calculated by adding the scores of SS1 to SS4. The Cronbach α coefficients for supervisor support, coworker support, or family/friends support were 0.90, 0.88, and 0.79, respectively. The test-retest stability over one year (using the data obtained in 2005 with the same sample) for the three different sources of social support ranged between $r=0.61$ and $r=0.64$ ($p<0.001$). Validity was estimated by calculating the correlations between different sources of social support and the covariates, and the relationships were in the expected direction indicating a high convergent validity.

Job Strain

Job strain was defined as the ratio of job demands divided by job control. Job control and job demands were measured using the Brief Job Stress Questionnaire, both scales consisted of three items [47]. Examples of items include "I can work at my own pace (job control)" and "I have an extremely large amount of work to do (job demands)." These scales were developed with a research grant from Japanese Ministry of Labor with reference to Karasek's Job Content Questionnaire and the U.S. National Institute for Occupational Safety and Health Generic Job Stress Questionnaire. The Cronbach α coefficients for job control and job demands were 0.82 and 0.68, respectively.

Inflammatory Markers

Fasting blood samples were collected between 9:00 and 11:00 a.m. from participants to control for diurnal variations. Ethylenediaminetetraacetic acid dipotassium was used as an anticoagulant to collect venous blood from participants to measure circulating CRP, cytokines, and monocyte and total leukocyte counts. All samples were transported and handled at room temperature (i.e., 15–20 °C). We determined counts of monocytes and total leukocytes with an automated cell counter (Coulter Counter SP-IV, Coulter Electronics, Hialeah, Florida, USA). To measure cytokines, whole blood was centrifuged and plasma samples were stored at −80 °C in pyrogen-free plastic tubes until analysis. Plasma hs-CRP concentrations were measured using N-Latex CRP II (Dade Behring, Tokyo, Japan). The minimum detectable level was 0.0155 mg/dl and the values lower than the measurement limit was considered 0.00775 (0.0155/2). In this sample, there were 18 out of 51 women and 12 out of 137 men who had "below the minimal detectable limit" for the hs-CRP. Plasma cytokines (IL-6 and TNF-α) were determined using an enzyme-linked immunosorbent assay kit (Toray Fuji Bionics Inc., Tokyo, Japan). Minimum detectable levels for IL-6 and TNF-α were 0.4 and 2.0 pg/ml, respectively. We did not find any sample that was below the minimal detectable limit for IL-6 and TNF-α. All the measurements were conducted in duplicate and the mean value was taken as the measured concentration. The intra-assay coefficient of variation was less than 10 % in each determination.

Covariates

Covariates measured were age (in years), education (in years), marital status (unmarried/married), smoking (in number of cigarettes smoked per day), alcohol consumption (in grams ethanol per week), leisure-time physical activity, usual sleep duration (in hours of sleep per day), height, weight, depressive symptoms, chronic conditions, medication usage, household financial situation, and occupational grade (managerial or non-managerial).

Alcohol consumption was estimated by asking the usual amount of alcoholic drinks consumed per day multiplied by the number of occasions in a week that alcoholic drinks were consumed. We assessed leisure-time physical activity by calculating the energy expenditure of habitual physical exercise. We asked frequency, type, and length of physical exercise per month and converted these data to metabolic equivalents (METs). Estimated METs were assigned to the physical activities according to their mean intensity levels. One MET corresponds to an energy expenditure of approximately 1 kcal/kg/h. Weekly leisure-time physical activity was calculated from the questionnaire. For example, one hour of moderate intensity physical activity such as bicycling, walking, and calisthenics is equivalent to 3.0 METs, 3.3 METs, and 3.5 METs, respectively, while one hour of vigorous intensity physical activities such as jogging, tennis, and swimming is equivalent to 7.0 METs, 7.0 METs, and 8.0 METs, respectively. If a respondent reported 3 days of bicycling for an hour and one day of tennis for two hours, the total METs/week was calculated by the following formula: 3 days×1 h×3.0 METs+1 day×2 h×7.0 METs=23.0 METs/week. Validity and test-retest reliability were previously confirmed with this questionnaire [48]. Height (in centimeter) and weight (in kilogram) were measured anthropometrically to assess body mass index (BMI), calculated as weight in kilograms divided by the square of height in meters. Depressive symptoms were measured using the Japanese version [49] of the Center for Epidemiologic Studies Depression scale (CES-D) [50]. The 20-item depressive symptom scale measures the level of depressive symptoms experienced in the past week. If there were five or less missing responses on the CES-D, the total CES-D score was calculated based on the following formula: "CES-D score"="sum of item scores answered (X)"×"20/X" [51]. The Cronbach's α of the CES-D was 0.83.

With regard to chronic conditions, participants were interviewed by occupational health doctors/nurses to determine whether they had been diagnosed or treated for any of the following symptoms or disorders at the time of the study: hypertension, diabetes mellitus, depression, asthma, allergies, cancer, angina pectoris, cardiovascular disease, gout, renal disease, colonic polyps, skin disease, autoimmune disorders, anxiety disorders, musculoskeletal disorders, arrhythmia, cholelithiasis, kidney/urinary track diseases, liver disease, cerebrovascular disease, hyperlipidemia, gastric/duodenal ulcer, autonomic imbalance, irritable bowel syndrome, kidney disease, rheumatoid arthritis, hyperthyroidism, common infection, menopausal disorders, hyperlithuria, myoma uterine, or other diseases. If the subjects reported "other diseases," they were asked to specify the condition. As a result, male participants with the following disorders were identified; hypertension (n=9), hyperlipidemia (n=6), diabetes mellitus (n=3), depression (n=1), liver diseases (n=1), kidney/urinary track diseases (n=1), gout (n=4), and the common cold (n=1). In order to eliminate the potential effects of health status on immune parameters we excluded from the analysis employees reporting immune-related disorders (common cold) (n=1). The number of other symptoms or disorders was counted and included as a covariate (no=0, yes=1+). We also obtained information on the use of the following medications; aspirin, β-blockers, acetaminophen, corticosteroids, antidepressants, and other drugs. All participants with immune-related disorders as described above were eliminated, leaving only aspirin or acetaminophen users in the subsequent analyses (n=3). We assessed each participant's household financial situation by asking the following question: Overall, how would you rate your current household financial situation? Response options were "comfortable," "normal or just getting by," and "finding it difficult."

Statistical Analyses

Variables (CES-D score and all inflammatory markers) with skewed distributions were logarithmically transformed to achieve a more normal distribution in values. The CES-D score was scaled for non-negative values by adding 1.

Intercorrelations between social support, inflammatory markers, and covariates (continuous variables) were tested by the Pearson product–moment correlation coefficient. When there was a significant correlation between social support and inflammatory markers by simple correlation, multivariable linear regression analyses were employed to test the main and interactive effects of social support (supervisor, coworker, or family/friends) and job strain on inflammatory markers adjusting for selected covariates (age, marital status, smoking, alcohol consumption, usual sleep duration, BMI, medication usages, financial situation, depressive symptoms, and job strain). The adjusted covariates were selected based on the initial findings which showed marginal associations (p <0.10) with inflammatory markers or social support. To examine the association between social support with inflammatory markers, we utilized moderated regression procedures in which main effects variables were centered [52]. In the analysis, we entered the main effects of social support, job strain, and selected covariates and the social support x job strain cross-products.

In addition, multivariable linear regression analysis was used to test the relationship between social support (dependent variables) and covariates (independent variables). The significance level for all statistical analyses was $p<0.05$ (two-tailed test). We analyzed the data using the Statistical Package for the Social Sciences version 21.0 (SPSS, Inc., Chicago, IL, USA).

Results

Sample Characteristics

Characteristics of the study participants are shown in Table 1. The mean age for the participants was 41 (ranged 23 to 65) years. More than 80 % of participants were married and 94.2 % accomplished more than 16 years (graduate level) of education. Forty-seven percent of participants were current smokers. Participants consumed 144 g ethanol per week, expended 3.6 METs per week, and slept 6 h per day. The average BMI was 23.8 (SD 2.8), CES-D score was 9.8 (SD 6.6), and job strain score was 1.14 (SD 0.44) for this sample. Fifteen percent of participants had chronic condition while 2.2 % reported regular use of over-the-counter medication. There were 4.4 % of participants who reported that their household financial situation is difficult. Nearly 30 % of participants were in a managerial position.

Pearson Correlation Between Social Support, Inflammatory Markers, and Covariates

Intercorrelations between social support, inflammatory markers, and covariates (continuous variables) are shown in Table 2. There was a significant correlation among supervisor, coworker, and family/friends support. Significant inverse relationships between supervisor support and IL-6 as well as coworker support and TNF-α were observed.

Association Between Different Sources of Social Support and Covariates

The relationships between different sources of social support and the covariates are shown in Table 3. The results show that support from one's supervisor, coworkers, and family/friends was associated with covariates in different ways. Supervisor support was positively associated with being married and marginally associated with job strain while coworker support was inversely associated with higher depressive symptoms. Support from family/friends showed a different pattern of relationship with covariates; age, being married, medication usage, depressive symptoms and household financial difficulties were inversely associated while job strain was positively associated with family/friends support at $p<0.10$ level.

Independent and Interactive Associations Between Different Sources of Social Support and Inflammatory Markers

As shown in Table 4, support from one's immediate supervisor [$\beta=-0.21$, $p<0.05$, $F(10, 126)=2.23$, $p<0.05$; $\Delta R^2=0.08$] (Table 4, model 1) and job strain [$\beta=-0.19$, $p<0.05$, $F(10, 126)=1.99$, $p<0.05$; $\Delta R^2=0.07$] (Table 4, model 2) were both significantly associated with a decrease in IL-6. Although the relationship between supervisor support and IL-6 was in an expected direction, the association between job strain and IL-6 was not. With regard to interaction term, no significant supervisor support×job strain on IL-6 was found (Table 4, model 3) but the relationship between supervisor support and IL-6 remained significant [$\beta=-0.24$, $p<0.01$, $F(12, 124)=2.42$, $p<0.01$; $\Delta R^2=0.11$] (Table 4, model 3, Fig. 1a).

Individual contributions of coworker support [$\beta=-0.14$, $p>0.05$, $F(10, 126)=2.13$, $p<p<0.05$; $\Delta R^2=0.08$] (Table 4, model 1) and job strain [$\beta=-0.15$, $p>0.05$, $F(10, 126)=2.14$, $p<0.05$; $\Delta R^2=0.08$] (Table 4, model 2) on TNF-α were not significant while in model 3 the association between coworker support and TNF-α was marginally significant [$\beta=-0.16$, $p<0.10$, $F(12, 124)=2.03$, $p<0.05$; $\Delta R^2=0.08$] (Table 4, Model 3, Fig. 1b).

Discussion

Multiple lines of evidence suggest that lack of social support is reliably associated with higher rates of morbidity and mortality, particularly from cardiovascular disease [1–4]. Inflammatory processes are believed to be one of the potential mediators bridging the relationship between social support and cardiovascular disease [1, 2, 30]. In this cross-sectional study of relatively healthy Japanese white-collar male employees, supervisor support was significantly and inversely associated with IL-6 while coworker support was weakly related to TNF-α. No significant interactive effects of social support× job strain on IL-6 or TNF-α was found. In contrast, social support from family/friends was not related to inflammatory markers. With regard to social support theory, the current results supported a direct pathway for supervisor support on circulating inflammatory markers while there was no evidence supporting the stress buffering hypothesis on inflammatory markers. We conclude that supervisor social support may be a potential biological mechanism through which social support exerts beneficial effects on inflammatory markers among Japanese male employees. However, caution is needed when interpreting the results because we only found significant relationships between supervisor support and IL-6 with a modest effect size.

To our knowledge, there are three studies that explored the relationship between workplace social support and

Table 1 Descriptive statistics for social support, inflammatory markers, and covariates

	Men (n = 137)	
	Mean±SD or n (%)	Range
Social support:		
Support from immediate supervisor (possible range, 4–24)[a]	15.2±3.0	4–20
Support from coworkers (possible range, 4–24)[a]	15.4±2.5	4–20
Support from family/friends (possible range, 4–24)[a]	18.1±3.6	4–24
Inflammatory markers[b]		
CRP (mg/dl)	0.090±0.244	0.0155–2.540
IL-6 (pg/ml)	1.73±0.84	0.60–6.60
TNF-α (pg/ml)	14.1±4.19	5.60–29.10
Monocytes (cells/mm^3)	313±107	121–692
Total leukocytes (cells/mm^3)	5,770±1,446	2,410–10,640
Covariates		
Age (in years)	40.8±11.1	23–65
Education (≥ 16 years)	129 (94.2)	
Married	110 (80.3)	
Current smoker	64 (46.7)	
Smoking (cigarettes smoked/day)	9.7±12.0	0–40
Alcohol consumption (g ethanol/week)	143.6±123.3	0–440
Leisure-time physical activity (METs/week)	3.6±7.1	0–34.5
Usual sleep duration (h/day)	6.0±0.7	5–7
Height (cm)	171.4±5.1	160.8–183.6
Weight (kg)	70.0±8.5	53.2–93.2
BMI (kg/height (m)^2)	23.8±2.8	19.1–32.2
Depressive symptoms (CES-D Scale score)[b,c]	9.8±6.6	0–47
Chronic condition (yes)	21 (15.3)	
Medication usage (yes)	3 (2.2)	
Job control (possible range, 3–12)[a]	8.2±1.6	3–12
Job demands (possible range, 3–12)[c]	8.8±2.1	3–12
Job strain[c,d]	1.14±0.44	0.33–4.00
Household financial situation (difficult)	6 (4.4)	
Occupational grade (managerial)	39 (28.5)	

Note: CRP C-reactive protein, *IL* interleukin, *TNF* tumor necrosis factor, *METs* metabolic equivalents, *BMI* body mass index, *CES-D* Center for Epidemiologic Studies Depression

[a] Positively oriented

[b] Although log-transformed values were used to approximate normal distribution in statistical analyses, mean values, SDs, and ranges are presented without log transformation to allow comparison with other studies

[c] Negatively oriented

[d] Calculated as a ratio of job demands divided by job control

inflammatory markers [24–26]. These studies did not categorize sources of support into supervisor and coworkers, but rather combined them as social support at work. In one study, no significant association was found between social support at work and CRP [24]. Similarly, a study of male Belgium employees free of cardiovascular disease reported no significant relationship between social support at work and CRP [25]. More recently, Shirom et al. prospectively examined the association of social support at work with CRP and total leukocytes, but could not detect any significant relationships [26]. In the present study, when the supervisor and coworker support scores were combined, we could not detect a significant relationship between social support at work and inflammatory markers (data not shown). This finding is consistent with results from the above three studies, but it also tells us the importance of breaking down sources of social support into supervisor and coworkers, as suggested in our main results. Several previous studies have shown that supervisor support and coworker support are differently associated with cardiovascular disease-related outcomes. For instance, a study by Karlin et al. [53] examined the relationship between workplace social support and ambulatory cardiovascular activity and demonstrated that immediate supervisor support was inversely associated with workday systolic blood pressure in women, while coworker support was negatively associated with workday systolic blood pressure in men. Among Japanese male employees, supervisor social support was strongly associated with reduced prevalence of sleep-related breathing disturbance, but coworker support did not show any significant relationship with sleep-related breathing disturbance [32]. Based on the above evidence, studies on the relationship between workplace social support and inflammatory markers

Table 2 Pearson correlation matrix for continuous variables ($n=137$)

Variable	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18
1. Support from immediate supervisor	0.43***	0.20**	−0.06	−0.18*	−0.05	−0.11	−0.09	−0.05	0.09	0.00	0.00	−0.04	0.12	−0.06	0.25**	0.14†	−0.09
2. Support from coworkers	–	0.36***	0.04	−0.11	−0.17*	−0.11	−0.04	−0.36***	0.04	−0.03	−0.03	0.02	0.00	−0.27***	0.05	0.01	−0.06
3. Support from family/friends		–	0.10	−0.09	−0.01	−0.10	−0.05	−0.25**	0.04	−0.08	0.03	0.04	0.13	−0.34***	−0.12	0.05	0.14†
4. CRP[a]			–	0.35***	0.22**	0.20*	0.25**	−0.06	0.02	−0.12	0.08	0.05	0.19*	0.01	−0.20*	−0.22*	−0.04
5. IL-6[a]				–	0.37***	0.23**	0.34***	0.14†	0.23**	−0.01	0.00	0.15†	0.09	0.01	0.02	−0.21*	−0.15†
6. TNF-α[a]					–	0.30***	0.25**	0.17*	0.03	−0.02	0.01	0.00	0.23**	−0.11	0.10	−0.16†	−0.17**
7. Monocytes[a]						–	0.67***	−0.01	0.33***	0.01	−0.01	0.14†	0.15†	0.01	−0.03	−0.08	−0.01
8. Total leukocytes[a]							–	0.02	0.36***	−0.01	−0.04	0.16†	0.22**	0.09	−0.03	−0.02	0.04
9. Age (in years)								–	0.01	0.16†	0.11	0.24**	0.04	0.08	0.19*	−0.15†	−0.21*
10. Smoking (cigarettes/day)									–	0.05	0.04	0.17*	0.04	−0.09	−0.07	0.02	0.13
11. Alcohol consumption										–	0.12	0.09	−0.01	−0.05	0.24**	−0.04	−0.17*
12. Leisure-time physical activity (METs/week)											–	0.13	0.13	−0.21*	0.00	−0.05	−0.03
13. Usual sleep duration (h/day)												–	0.08	−0.02	0.00	−0.25*	−0.20*
14. BMI													–	−0.02	0.09	0.06	0.05
15. CES-D score[a]														–	−0.32***	0.12	0.31***
16. Job control															–	−0.09	−0.69***
17. Job demands																–	0.67***
18. Job strain																	–

Note: *CRP* C-reactive protein, *IL* interleukin, *TNF* tumor necrosis factor, *METs* metabolic equivalents, *BMI* body mass index, *CES-D* Center for Epidemiologic Studies Depression

† $p<0.10$, * $p<0.05$, ** $p<0.01$, *** $p<0.001$

[a] Log-transformed

Table 3 Multiple regression analyses with different sources of social support as dependent variables and covariates as independent variables

	Sources of social supports		
	Immediate supervisor β^a	Coworker β^a	Family/friends β^a
Covariates:			
Age (years)	−0.07	−0.23	−0.26†
Education (1=<16 years, 2=≥16 years)	−0.04	−0.04	−0.13
Marital status (1=unmarried, 2=married)	0.18*	0.04	−0.18†
Smoking (cigarettes smoked/day)	0.09	0.01	−0.07
Usual sleep duration (h/day)	−0.08	0.10	0.11
Alcohol consumption (g ethanol/week)	−0.05	−0.02	−0.10
Leisure-time physical activity (METs/week)	0.03	−0.03	−0.06
BMI (kg/height (m)^2)	0.11	−0.03	0.09
Chronic condition (1=no, 2=yes)	−0.21	−0.08	−0.12
Medication usage (1=no, 2=yes)	−0.00	0.03	−0.16*
Depressive symptoms (CES-D score)[b]	0.02	−0.23*	−0.37**
Job strain	−0.16†	−0.03	0.23*
Household financial situation (1=comfortable, 3=difficult)	0.01	−0.09	−0.14†
Occupational grade (1=non-managerial, 2=managerial)	0.01	−0.10	0.11
Adjusted R^2	0.01	0.16**	0.26***

Note: METs metabolic equivalents, *BMI* body mass index, *CES-D* Center for Epidemiologic Studies Depression

† $p<0.10$, * $p<0.05$, ** $p<0.01$, *** $p<0.001$

[a] Standardized regression coefficient

[b] Log-transformed

may have overlooked the impact of supervisor or coworker support on inflammatory markers.

There has been much less research on the association of source-specific social support with immunological outcomes [24–26, 54–59], and to our knowledge this is the first study that has differentiated multiple (work and non-work) domains of social support in relation to inflammatory markers. We found a disparate association between different sources of social support and inflammatory markers. One possible explanation for our finding is that supervisor support may be directly related to job control (Table 2), and the immediate supervisor may play a more key role in providing practical solutions for restructuring and redesigning job than coworkers and much more than family/friends, which may exert an impact on inflammatory markers. Another possibility is that the support question used in this study asked about the respondent's "immediate" supervisor, who could be a concrete and specific individual who has a close relationship to the respondent, whereas support from coworkers or family/friends is more collective and less specific. Hence, how the sources of support are defined may be relevant to our results.

Our findings may also be interpreted from a socio-cultural context. Many Japanese workers tend to work long hours and have excessive workloads. These working conditions are common among men and excessive work hours are known to be associated with stress-related disorders including

Table 4 Multivariable linear regressions for the association between supervisor support and IL-6 as well as coworker support and TNF-α ($n=137$)

Inflammatory markers (dependent variable)	Model 1 β^a	Model 2 β^a	Model 3 β^a
Lg IL-6			
Social support from immediate supervisor	−0.21*		−0.24**
Job strain		−0.19*	−0.23*
Job strain×supervisor support (interaction)			0.01
Adjusted R^2	0.08*	0.07*	0.11**
Lg TNF-α			
Social support from coworker	−0.14		−0.16†
Job strain		−0.15	−0.15
Job strain×coworker support (interaction)			0.03
Adjusted R^2	0.08*	0.08*	0.08*

Lg logarithmically-transformed, *BMI* body mass index

† $p<0.10$, * $p<0.05$, ** $p<0.01$

[a] Standardized regression coefficient

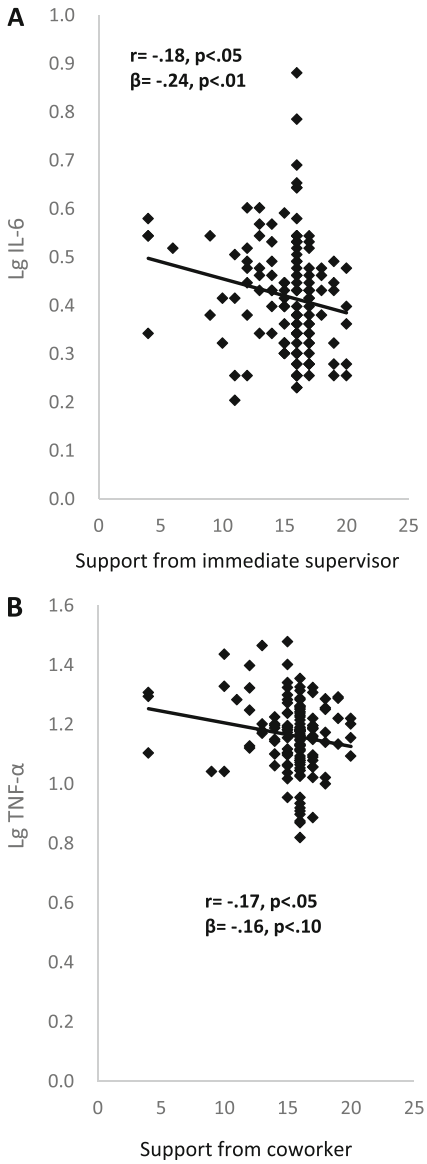

Fig. 1 Scatterplots for the associations between social support from immediate supervisor and IL-6 and coworker support and TNF-α

cardiovascular disease [60]. In addition to extra demands on work, lack of social support from supervisor may add extra burden on the cardiovascular system [61]. Another interpretation is that 28.5 % of men in this sample held managerial positions with high responsibilities and obligations. Such employees may feel it inappropriate or improper to seek supervisor support but rather in a position to provide support to subordinates, making it difficult to solve support-related issues for oneself. Although such assumptions need further confirmation, they may help explanation why supervisor support was more strongly associated with inflammatory markers than support from coworkers or family/friends.

If our findings can be replicated, they may contribute to building strategies to reduce cardiovascular disease risk in the workplace in the future. Supervisor support has been reported to be associated with better cardiovascular disease-related outcomes such as lower BP [53], improved sleep quality [62], less depression [63], and reduced fatigue [64]. In addition, supervisors are identified as a source of emotional, informational, and instrumental social support, and as key individuals in preventing work-related job strain [65]. Based on this fact, researchers have developed supervisor training designed to improve the work environment. This training has been successful in increasing social support as well as improving workplace climate and job autonomy among subordinate workers [66–68]. We think that inflammatory markers could be used as an objective indicator to measure such effectiveness, although further research is warranted.

This study has strengths and limitations that should be considered in the interpretation of the results. Specific strengths of our study are that we examined the association of three different sources of social support with five unique inflammatory markers. In addition, because the current study was undertaken during the mandatory annual health examination, the participation rate was high (>90 %) reflecting low sampling bias. A broad array of potential biobehavioral factors that can affect the measurement of circulating markers of inflammation was considered in the statistical analyses [69]. Limitations of the study were as follows. First, the cross-sectional nature of this study precludes conclusions with regard to causal relationships. With cross-sectional designs, the association could be in either direction, i.e., low social supervisor support may increase inflammatory responses – or higher inflammatory responses may be the cause of lower social support. A study by Cho et al. [70] reported that plasma CRP was a significant predictor of fatigue levels five years later rather than fatigue levels predicting CRP levels, suggesting that low-grade systemic inflammation may have a role in the development of poor work life conditions including social support. Additional studies are required to determine the causal direction of the present findings. Second, the measurement of social support was limited to social support in general, and sources of support were restricted to immediate supervisor, coworkers, and family/friends. It is possible that other support aspects such as "emotional," "instrumental," "informational" or "financial," as well as other support sources such as "relatives," "neighborhood," and "subordinate workers," are more related to inflammatory markers. It is also important to note that the social support scale used in this study showed relatively low test-retest stability which points to a potential limitation. Third, we did not obtain data on concurrent life stressors that may mediate the relationship between social support and inflammation. Life stressors such as marital discord, parenting stress, interpersonal difficulties outside work, family caregiving, and work-family conflict may have a significant impact on inflammatory outcomes [71–74], and further validation including these variables is warranted. Fourth, participants were employees from a specific occupation and

are not representative of the entire Japanese workforce or workers of other racial/ethnic groups; thus, our results may be a culturally-unique finding. Fifth, in view of the fact that simple correlations between support and inflammatory markers had only 2 out of 15 significant findings at the $p < 0.05$ level, the results need to be interpreted with caution. Sixth, we have excluded women from the analyses because of a small sample size and considering the effects of hs-CRP outliers. Thus future studies should be undertaken with a larger sample size taking outliers into account for in Japanese women. Seventh, contrary to our expectations, we found an inverse association between job strain and inflammatory markers which may have contributed to insignificant findings for interactions. And finally, even though we adjusted for a variety of confounders, we could not exclude the possibility that unadjusted factors, i.e., personality traits, genetic components, other social and occupational variables, as well as unknown/unmeasured factors may have affected our findings.

In conclusion, this study examined the relationship between sources of social support and inflammatory status in a sample of Japanese white-collar daytime employees. Although increases in inflammatory markers may not have immediate clinical significance, the results suggested that workplace social support, especially from the immediate supervisor, was directly associated with IL-6. Although the precise mechanisms and pathways underlying the observed associations have yet to be determined, the findings of the present study provide some support for the biological evidence of a relationship between social support and inflammatory markers. Prospective studies are warranted to confirm the relationships between social support, inflammatory markers, and long-term stress-related disorders.

Conflict of interest The authors have no conflicts of interest to disclose.

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