Relationship between perceived social support and immune function

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Abstract

Background: Although a previous meta analysis showed some substantial relationships between social support and immune function, there is still no knowledge about the effects of social support on natural killer (NK) cell number. In this study we examined the direct relationships between peripheral lymphocyte subpopulations and several aspects of social support.

Method: We administered the Japanese version of the Stress and Coping Inventory (SCI) by Rahe et al to 98 male workers with a written informed consent. Blood samples were collected at 10:00a.m. in the morning. Lymphocytes subsets were measured by flowcytometry using CD3, CD16, and CD56 antibodies.

Result: Partial correlation coefficient controlled by age and smoking between social support and immune cells revealed that there were weak but significant correlations between perceived social support and the numbers of CD3-/CD16+and CD3-/CD56+ NK cells (r=0.25,0.26). There was no correlation between social support and percentage of NK cells.

Conclusion: Positive correlation of perceived social support with NK cell numbers suggested that perceived social support has a direct effect on NK cells and that increased social support might accompany with high natural immunity. Further investigation should be undertaken to elucidate why only the perceived social support was correlated to NK cells.

Introduction

Since social support has been proved to have effects on mortality and incidence of diseases, this psychosocial entity has attracted attention from many researchers of social psychology, health psychology, sociology and medicine. House [1] suggested that individuals isolated from society have shorter life expectancy and that social support has stronger effects on mortality than other risk factors i.e. smoking, Type A behavior.

It is also known that social support has effects on psychological parameters such as depression and anxiety. Previous studies using various populations such as psychotic depression patients[2], normal adult workers [3] and college students[4], revealed that there was a negative correlation between social support and depression. Studies on HIV positive patients [5], normal adult workers [6], and the people in the islands of the Southern Pacific Ocean [7] showed that there was a negative correlation between social support and anxiety.

Several interventional studies on cancer and AIDS patients examined the effects of social support on one's health [8-9]. These studies proved that social support improved their prognosis and depressive mood. Although researcher in various fields have shown that social support influences on the status of one's health, the mechanisms through which social support has effects remain to be unclear.

While many researchers proposed several hypotheses for the mechanisms, there is no definite explanation. Cohen and Wills proposed a hypothesis that social support has an effect on one's appraisal of stressors. Consequently social support indirectly affects stress reactions such as anxiety and depression [10]. Another finding notes that social support influences indirectly on one's health via direct influences on health-related behaviors such as physical exercise [11]. The above two pathways can be classified into the hypothesis of indirect effects. On the other hand, the direct effect hypothesis is also presented because there is some evidence relevant to direct effects of quality of social relationships on immune function in the field of psychoneuroimmunology, highlighted as an area of research to investigate the effects of psychological parameters on physiological ones [12].

Uchino et al [13] concluded that social support has a substantial relationship to immune function on the basis of meta analysis on the researches of social support. With respect to psychological parameters that affect immunity, Irwin reported that depression has a negative correlation with the number of natural killer (NK) cells (CD16+) [14]. To our best knowledge, however, no one has examined the relationship between social support and NK cell number. Although it was observed that there was no correlation between social support and the percentage of NK cells [15], it is feasible that the results were biased since the sample size was small and the authors did not use the number but percentage of NK cells. In the present study, in addition to measuring the NK cell number we examined the direct correlation hypothesis of social support on NK cell number in a cross sectional design with controlling for age and smoking as major two confounding factors of immunity.

Methods

Participants

A total of 98 male workers (mean age: 46.1±7.25) were recruited from a private company in Japan and psychological questionnaires and immunological assessments were executed with written informed consent. In our study there was no shift worker. The influence from circadian rhythm to immune system in this study was seemed to be slight, since sample subjects were seemed to have almost homogeneous working hours.

Assessment of social support

The Japanese version of Stress Coping Inventory (SCI) was administered in order to evaluate the level of social support. Rahe developed SCI [16] and Fukunishi standardized the Japanese version of SCI [17]. SCI is a self-administered questionnaire composed of 4 subscales, that is, health-related behaviors, and response to stress, social support, and life satisfaction. For the present study, social support scale was utilized from the Japanese version of SCI. The scale is classified into 3 subscales, namely individual social support network, utilization of social support, and perceived social support. The respective subscale consists of 6 items with 0-3 Likert scale.

Immunological assessments

Blood samples were collected in heparinized tubes (Beckton-Dickson, New Jersey, USA) at

10:00 am and stored at a room temperature for no longer than 24 hours before the assays. To determine white blood cell (WBC) subset counts, total numbers of WBC and leukocyte differential counts were determined using a Coulter counter (Beckman Coulter, Inc, Fullerton, CA, USA). Lymphocyte subsets were measured by flowcytometry analysis (EPICS XL, Beckman Coulter, Inc, Fullerton, CA, USA) according to standard methods. Enumeration of the following cells by flowcytometry was conducted using three combinations of two collar analysis: T cells and NK cells (CD3/fluoresein isothyocyanate (FITC) and CD16/phycoerythrin (PE), and, CD3/FITC and CD56/PE). All antibodies were purchased from Beckman Coulter, Inc (Fullerton, CA, USA).

Statistical analysis

Partial correlation coefficients were calculated to assess the associations of social support with indices of immune function. All differences were significant at a $p < 0.05$, using two-tailed tests. The analysis was conducted with SPSS for windows version 10.0.

Results

Descriptions of the variables used in the present study are shown (Table 1). We

Table1 Description of the variables

	n subjects	mean	S.D.
AGE	98	46.09	7.25
Total score of social support	95	30.81	7.82
Existence of social support	95	11.38	3.36
Utilization of social support	95	8.23	2.73
Perception of social support	95	11.19	2.74
CD3-CD16+ /μl	95	268.13	179.80
CD3-CD56+ /μl	95	292.09	187.81

conducted partial correlation analysis controlling for age and smoking so as to examine the relations between social support and immune functions. As psychological scales, we used individual social support network, utilization frequency of social support, and perceived social support. As indices of immune cells, we used the numbers and percentages of CD3-/CD16+, and CD3-/CD56+. There were significant correlations between perceived social support and the numbers of CD3-/CD16+ cells and CD3-/CD56+ cells. Perceived social support had a positive correlation with CD3-/CD16+ number ($r=0.25$, $p<0.05$: $n=78$) and with CD3-/CD56+ number ($r=0.26$, $p<0.05$: $n=78$) (Table2). The other immune

Table2 Partial correlation between social support and immunological parameters(cell counts) (N=78)

	existense of support	utilization of support	perception of support
CD3-CD16+ /μl	0.17	0.16	0.25*
CD3-CD56+ /μl	0.17	0.15	0.26*

* p<.05　　controlled by age and smoking
Level of significance was adjusted by Bonferroni's corrections with each column

parameters were no significantly correlated with any social support indices. No statistically significant correlations between social support and the percentage of lymphocyte subsets were observed (Table3).

Table3 Partial correlation between social support and immunological parameters(%) (N=98)

	existense of support	utilization of support	perception of support
CD3-CD16+(%)	0.11	0.13	0.20
CD3-CD56+(%)	0.10	0.12	0.20

* p<.05　　controlled by age and smoking

Discussion

Schlesinger [15] reported that there was no relationship between social support and the percentage of NK cells. We also observed the

same null findings in terms of percentages of NK cells, and observed that perceived social support had a weak but significant positive correlation with CD3-/CD16+ and CD3-/CD56+ NK cell numbers after controlling for age and smoking. Percentages of particular lymphocyte subsets should be recognized as representing the consequences of cell differentiation rather than the strength of the immunity. To evaluate the immune function of the circulating blood, one should count the cell numbers per unit. Thus our results are consistent with our hypothesis that social support correlates the increase in NK cell number and might be relevant to augmenting the natural immunity although we cannot tell any causal relationship due to our cross sectional design. Although we tried to include as many confounding factors as possible, the present study has limitations because we did not assess the intercurrent virus infections which might increase NK cell numbers.

Cohen et al 〔18〕 showed that susceptibility to common cold was associated with the social network diversity as an index of social bondage. The subjects with low social network diversity had higher susceptibility to common cold. They hypothesized that the mediators of the link between social support network and susceptibility to virus infection were attributed to health related behaviors, such as smoking, alcohol intake and exercise, and endocrinolo-immunological system. However, they did not find any correlation between social support network diversity and NK cell activity, which plays an important role to defend against the virus infections. They had to assume immunological factors other than NK cell activity to explain their own results. In our study we also failed to find any correlation between NK cell numbers and social support network but found the correlation with perceived social support. In terms of virus infection, perceived support might be a better predictor.

The results presented showed no relation between social support and the numbers of T cells (CD4+ and CD8+) and B cells (CD19+). It is consistent with a previous review by Uchino [13] in which there was no correlation between CD4+ number and social support in studies conducted both on 33 (healthy) female [19] and on 221 HIV positive male [20] that simply examined a correlation.

Among three categories of social support, significant positive correlation with NK cell number exists only in the perceived social support. Uchino [13] proposed that, of perceived support, emotional support especially correlates with cardiovascular responses and has strong effects on mental health such as depression, anxiety, and so on. This proposal could be endorsed in part by the results of the present study that perceived social support correlated with NK cell number in terms of psycho-neuro-endocrine-immune system. As it is possible to interpret that both support network and utilization frequency are parts of perceived support, the results may be biased by the questionnaire method.

Cohen and Willis [10] proposed two hypotheses for the mechanism of the effect of social support on one's health: the direct and buffering hypothesis. The former is that social support has a direct effect on one's health. The latter is that support has an influence just after an exposure to stressors. The results presented here seem to support the direct hypothesis in terms of NK cells. In the previous studies, the direct hypothesis was confirmed when the researchers used social integration as an tool for assessing social support, while the indirect hypothesis was confirmed when the functional indexes such as perceived support were used as a research tool. However, our results were different from the previous studies. This difference may be due to the kinds of physiological parameters evaluated since

the indirect hypothesis was often confirmed in the relationship between the reactivity of cardiovascular functions and social support.

In the future, it is necessary to investigate the reason that perceived support specifically correlates with NK cell number with controlling for potential confounders.

References

1 House JS, Landis KR, Umberson D: Social relationships and health. *Science* 1988 Jul 29; 241(4865):540-5

2 Thakur M, Hays J, Krishnan K, Ranga R: Clinical, demographic and social characteristics of psychotic depression. Psychiatry Research 1999 May; 86(2): 99-106

3 Frese M: Social support as a moderator of the relationship between work stressors and psychological dysfunctioning: A longitudinal study with objective measures. Journal of Occupational Health Psychology. 1999 Jul; 4(3): 179-192

4 Mallinckrodt B, Leong FT: Social support in academic programs and family environments: Sex differences and role conflicts for graduate students. Journal-of-Counseling-and-Development. 1992 Jul-Aug; 70(6): 716-723

5 Bettoli VE, Brown RT, Brown JV, Baldwin K: Psychological adjustment and adaptation of siblings and mothers of children with HIV/AIDS. Families Systems and Health. 1998 Fal; 16(3): 249-266

6 Williams S, Cooper C: Measuring occupational stress: Development of the Pressure Management Indicator. Journal of Occupational Health Psychology. 1998 Oct; 3(4): 306-321

7 Ginter EJ, Glauser A, Richmond BO: Loneliness, social support, and anxiety among two South Pacific cultures. Psychological Reports. 1994 Jun; 74(3, Pt 1): 875-879

8 Garssen B, Goodkin K: On the role of immunological factors as mediators between psychosocial factors and cancer progression. Psychiatry Research. 1999 Jan; 85(1): 51-61

9 Goodkin K, Blaney NT, Feaster DJ, Baldewicz T, Burkhalter JE, Leeds B: A randomized controlled clinical trial of a bereavement support group intervention in human immunodeficiency virus type 1-seropositive and -seronegative homosexual men. Archives of General Psychiatry. 1999 Jan; 56(1): 52-59

10 Cohen S, Wills TA: Stress, social support, and the buffering hypothesis. *Psychol Bull* 1985 Sep;98(2):310-57

11 Steptoe A, Wardle J, Fuller R, Holte A, Justo J, Sanderman R, Wichstrom L: Leisure-time physical exercise: prevalence, attitudinal correlates, and behavioral correlates among young Europeans from 21 countries. *Prev Med* 1997 Nov-Dec;26(6):845-54

12 Suzanne CS, Margaret EK, Mark LL: Individual Difference Factors in Psychoneuroimmunology; in Robert A, David LF, Nicholas C(ed):Psychoneuroimmunology, New York, ACADEMIC PRESS,2000,vol2,pp87-109

13 Uchino BN, Cacioppo JT, Kiecolt-Glaser JK: The relationship between social support and physiological processes: a review with emphasis on underlying mechanisms and implications for health. *Psychol Bull* 1996 May;119(3):488-531

14 Irwin M: Depression and Immunity; in Robert A, David LF, Nicholas C(ed):Psychoneuroimmunology, New York, ACADEMIC PRESS,2000,vol2,pp383-398

15 Schlesinger M, Yodfat T: The impact of stressful life events on natural killer cells. Stress Medicine, 7, 53-60

16 Rahe RH: The Stress and Coping Report Workbook. Health Assessment Programs, Nevada, 1994

17 Fukunishi I, Nakagawa T, Nakagawa H, Sone Y, Kaji N, Hosaka T, Rahe RH: Validity and reliability of the Japanese version of the Stress and

Coping Inventory. *Psychiatry Clin Neurosci* 1995 Aug;49(4):195-9
18 Cohen S, Doyle WJ, Skoner DP, Rabin BS, Gwaltney JM Jr. : Social ties and susceptibility to the common cold. 1997: JAMA, 277(24), 1940-4.
19 McNaughton ME, Smith LW, Patterson TL, Grant I: Stress, social support, coping resources, and immune status in elderly women. *J Nerv Ment Dis* 1990 Jul;178(7):460-1
20 Perry S, Fishman B, Jacobsberg L, Frances A: Relationships over 1 year between lymphocyte subsets and psychosocial variables among adults with infection by human immunodeficiency virus. *Arch Gen Psychiatry* 1992 May;49(5):396-401

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Associations of Perceived Social Support and Structural Support With Natural Killer Cell Activity in Older Adults.

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Abstract

Authors attempted to conduct a social support intervention for older people. The final goal is to increase their natural killer (NK) cell activity by modulating perceived social support. This article presents base-line associations between social support and NK cell activity in older people (54 men, 76 women). Perceived friend support was positively correlated with NK cell activity ($p < .01$). Interactions of perceived spouse support by gender ($p < .05$) and perceived family support by current illness ($p < .05$) were significant for NK cell activity. Frequent contacts with close friends and relatives had a tendency to increase NK cell activity, whereas a greater number of close friends and relatives had a significant decreasing effect ($p < .05$). The results suggest that the effects of social support on immune changes depend on the sources and types of support.

Key words: perceived social support, NK cell activity, older people, a cross-sectional study.

Immune alteration is proposed as one of the possible pathways by which social support influences health. Thus, many studies examined the associations between social support and numerical and functional measures of the immune system (Uchino, Cacioppo, & Kiecolt-Glaser, 1996).

Natural killer (NK) cells play a pivotal role in immune surveillance against cancer and viral infection (Talmadge, Meyers, Prieur, & Starkey, 1980; Trinchieri, 1989). Prospective studies showed that low NK cell activity was a predictor of the subsequent incidence of cancer (Imai, K., Matsuyama, Miyake, Suga, & Nakachi, 2000) and infection (Ogata et al., 2001). Particularly, infections lead to serious health consequences in older people compared to younger people (Statistics and Information Department, Minister's Secretariat, Ministry of Health and Welfare, Japan). Solana, Alonso, and Pena (1999) argued that NK cell activity could be a candidate for a biomarker of healthy aging. These facts and opinions emphasize the importance of the studies on social support and NK cell activity in older people. Of a

limited number of studies in older population (Uchino et al., 1996), Esterling, Kiecolt-Glaser, Bodnar, and Glaser (1994) showed in a study in caregivers of Alzheimer's disease and controls that high emotional and tangible support was associated with high NK cell activity via cytokine stimulation in vitro.

Most of social support interventions have been designed to improve mental symptoms by increasing enacted support. All the interventions, however, have not been successful. Some studies showed that increased enacted support was associated with favorable outcomes (Bloom, Hodges, & Caldwell, 1982; Vachon, Lyall, Rogers, Freedman-Letofsky, & Freeman, 1980), whereas other studies showed no positive effect of interventions (Clarke, Clarke, & Jagger, 1992; Dadds & McHugh, 1992; Heller, Thompson, Trueba, Hogg, & Vlachos-Weber, 1991). To our knowledge, few interventions have demonstrated an enhancement of perceived social support (Brand, Lakey, & Berman, 1995). In addition, Brand et al. (1995) assessed no objective indicator of health.

We planed to conduct a social support intervention for older people with NK cell activity as a health outcome. Our final goal is to increase their NK cell activity by increasing perceived social support. This article presents the cross-sectional data at an initial assessment. The objectives of this study is to examine (a) whether perceived social support is associated with increased NK cell activity, (b) whether the effect of perceived social support depends on the sources of the support (spouse, family, and friends), and (c) which subpopulations will receive the efficacy of increased perceived social support from the perspectives of immunology.

Methods

Participants

The subjects were recruited from 605 older people over 65 years living at home at central areas of Nakakawane Town, a rural community in Shizuoka Prefecture, Japan. We (T.M., N.K.) hold a meeting at the town office to elucidate the procedure of the study. Among the 605 people, 493 attended the meeting in response to the public announcement through the town office and 112 people stayed away from the meeting. Several days later, we sent a document explaining the procedure of the study and a questionnaire for screening social support to 605 people by mail. Five hundred and nine people (231 men, 278 women) answered and returned the questionnaire, *Mean* age = 73.2 years (*SD* = 5.9 years, *Range* = 65-93 years) for men and 73.7 years (*SD* = 7.5 years, *Range* = 65-96 years) for women. Because we were attempting an intervention at the town office, we measured immune functions in people living within 1.5 km of the town office. Among 151 people who were candidates for intervention, 130 (54 men, 76 women) responded to the questionnaire and agreed to give us blood samples (response rate = 86.7%). *Mean* age was 73.5 years (*SD* = 6.06 years, *Range* = 65-93 years) for men and 71.7 years (*SD* = 4.65 years, *Range* = 65-87 years) for women. The analyses were conducted on data for the 130 people.

This study was performed with written informed consent and approved by the ethics committee at National Center of Neurology

and Psychiatry, Japan.

Measures

Perceived social support

The revised version of the Jichi Medical School Social Support Scale [JMS-SSS] was used (Tsutsumi, A. et al., 2000). This scale was designed to measure perceived social support from spouse, family, and friends in a community sample. For each source of support, identical 10 questions were provided, with a 4-point scale (1 = *strongly disagree*, 2 = *disagree*, 3 = *agree*, 4 = *strong agree*). Perceived social support from spouse, family, and friends were scored by summing up the ratings on the 10 questions. Tsutsumi, A. et al. (2000) recommended that the ratings on two questions should be excluded on scoring perceived spouse support because these had significant positive correlations with the Social Desirability Scale (Crowne & Marlowe, 1960). Cross validity was confirmed in the original version of the JMS-SSS including the same 10 questions as the revised version with a 2-point anchor rating (0 = *disagree*, 1 = *agree*)(Tsutsumi, A. et al., 1994). Perceived social support from spouse and family evaluated by the original version of the JMS-SSS was associated with favorable health behaviors in men (Tsutsumi, A., Tsutsumi, K., Kayaba, & Igarashi, 1998) and decreased depressive symptoms in women (Tsutsumi, K., Tsutsumi, A., & Matsuzaki, 1999). Perceived social support evaluated by the revised version in 1999 significantly correlated with that evaluated by the original version in 1992-1994, $r(314) = .43$ for spouse support, $r(189) = .28$ for family support, $r(356) = .41$ for friend support. The revised version of the JMS-SSS assesses emotional, tangible, and informational support, but factor analysis showed a single dimension of the scale (variance accounted for by the first principal component = 57.0% for spouse support, 68.2% for family support, and 67.0% for friend support). In this study, the Cronbach's alphas were 0.91 for spouse support, 0.92 for family support, 0.93 for friend support.

Structural measures of social support

The number of close ties was assessed by an open-ended question: "How many close friends and relatives do you have?". Because of a skewed distribution, natural log (ln) of the number of close ties was used in data analyses.

Frequency of social contacts ("How often do you contact with close friends and relatives?") was rated on 6-point likert scale ranging from 1 = *less than once per year* to 6 = *almost every day*.

Mediating variables

Empirical studies have found that depression (Herbert & Cohen, 1993) and health-related behaviors (Kusaka, Kondou, & Morimoto, 1992) influences immune functions. We assessed depressive symptoms and health behaviors to examine their mediating effect on the associations between social support and NK cell activity.

Depression. The 15-item version of the Geriatric Depression Scale [GDS] was used to assess depressive symptoms (Yatomi, 1994). The alpha was 0.70.

Health behaviors. The Morimoto's Health Practice Index was used (Kusaka et al., 1992). This scale is a modification of the Breslow's Health Practice Index (Belloc & Breslow, 1972; Belloc, 1973; Berkman & Breslow, 1983). The Morimoto's Index is scored by summing up the ratings (0 = *no*, 1 = *yes*) on

the 8 health behaviors: not smoking; not consuming excess amount of alcohol; eating breakfast; sleeping 7 to 8 hours every day; working less than 10 hours per day; exercising twice or more per week; eating a nutritionally balanced diet; and keeping a moderate level of mental stress. Kusaka et al. (1992) showed that a higher score on Morimoto's Index was associated with increased NK cell activity in men between 30 and 60 years of age.

Covariates

Covariates included age (in years), gender (0 = *men*, 1 = *women*), income, health status, and life events.

Income. Annual income of husband and wife was assessed on 3 levels: low (-¥99,999, n = 26); middle (¥1,000,000-¥2,999,999, n = 59); and high (¥3,000,000-, n = *31*) (US$1 is about ¥120 in March, 2002). We did this because from taxable and tax-deductible income reports, the 25th and the 75th percentile of the family income for people over 65 years at Nakakawane Town were estimated as ¥1,200,000 and ¥3,000,000, respectively (Tax Office, Nakakawane Town, Shizuoka, Japan). Middle- and high-income groups in our sample did not differ in immunological and psychological measures (data not shown). In addition, Vitaliano et al. (2001) showed that emotional support was associated with higher NK cell activity only in older adults with income of less than the 25th percentile. Therefore we recoded income into 2 categories (0 = -¥99,999, 1 = ¥1,000,000-).

Health status. Self-reported past/current illness and medications were evaluated. People without any current illness were coded as 0 and people with any current illness were coded as 1. This study addressed neither types nor numbers of illness. Exceptionally, people with a past history of malignancy were coded as 1.

Life events. The Holmes and Rahe Schedule of Recent Events was used (Holmes & Rahe, 1967). Because this study was conducted in older people, 25 events were included. Sixty-four people experienced no event, 31 people experienced one event, and 35 people 2 through 10 events. We coded people who experienced no event as 0 and people who experienced one or more events as 1.

Missing values

Among people who indicated spouse, family, and friends as the sources of support, 52 (48.1%), 47 (45.6%), and 53 (44.1%) completed all the questions, respectively. Prevalence of missing data on questions except for income was 0-7.7%. Between people with and without valid data on the relevant questions, no significant difference in the other psychological measures was detected (data not shown). For these missing data, the means of valid data were allocated. Because people with missing data on income (10.8%) reported significantly low perceived family and friend support compared to people with valid data, people with missing data on income were excluded from the analyses.

NK cell activity

NK cell activity was measured against K562 using a standard 4h-^{51}Cr release assay. Target cells were labeled with [^{51}Cr] sodium chromate (New England Nuclear, Boston, MA) at 37 °C for 1h, washed, and resuspended at 2×10^5 /ml in RPMI 1640 medium containing 10% FCS, 2 mM glutamine, 100 U/ml penicillin and 100 U/ml

streptomycin. Labeled target cells were incubated with effector cells at E:T=20:1 in U-bottom 96-well plates at 37 °C for 4h. Radioactivity in the supernatant was determined by a gamma counter. The assay was performed in quadruplicate. The percentage of specific lysis as cytotoxicity was determined according to the formula: specific lysis (%) = (mean experimental cpm release - mean spontaneous cpm release)/(mean maximal cpm release - mean spontaneous cpm release).

Results

Table 1 summarizes descriptive statistics. In the following analyses, a p value < .05 was considered to indicate statistical significance. All tests were two-tailed.

Prior to multiple regressions, intercorrelations among variables were examined (see Table 2). The number of close ties was negatively correlated with NK cell activity. Perceived social support was not related with NK cell activity. Perceived social support had moderate correlations with structural measures of support, depression, and health behaviors. Except that perceived friend support was higher in women than in men, perceived social support was not related with demographic variables. Moderate to medium correlations were observed among perceived social support scales.

To examine the associations between perceived social support from different sources and NK cell activity, we performed three hierarchical regressions on NK cell activity (see Table 3, 4, & 5). All continuous variables were centered (Aiken & West, 1991).

In step 1, covariates (age, gender, current illness, income, and life events) were forced into the models. Low income was associated with decreased NK cell activity (See Table 3, 4, & 5).

In step 2, structural measures of support (number of close ties and frequency of social contacts) were included, which significantly contributed to the model (5.1-7.6% of variance). In each of three equations, the number of close ties was negatively correlated with NK cell activity (see Table 3, 4, & 5). Frequency of social contacts had a tendency to increase NK cell activity in people with spouse or family as the sources of support (see Table 3 & 4).

In step 3, perceived social support was entered into the models. Only perceived friend support was positively correlated with NK cell activity and accounted for about 4% of variance (see Table 5).

To examine the two-way interactions of perceived social support and other variables (gender, current illness, income, life events, the number of close ties, and frequency of social contacts), we then included the product terms of these variables in forward, stepwise regressions (inclusion criteria = p < .10). Interactions of perceived spouse support by gender (see Table 3) and perceived family support by current illness (see Table 4) were significant for NK cell activity. No significant interaction of perceived friend support and other variables was detected though a product term of perceived friend support and life events stayed in the equation (see Table 5).

In a last step, we included depression and health behaviors to examine whether they partially mediated the effects of social support on NK cell activity. Addition of mediating variables did not contribute significantly to

the model and had little, if any, influence on the associations between social support and NK cell activity, $\Delta F(2, 86) = .11$, $p = .90$ for spouse support, $\Delta F(2, 81) = .12$, $p = .89$ for family support, $\Delta F(2, 97) = .26$, $p = .78$ for friend support. Thus, depression and health behaviors were excluded from the models.

To identify the nature of interactions (perceived spouse support by gender and perceived family support by current illness), we tested the significance of simple slopes within each level of the categorical variables (Aiken & West, 1991).

Figure 1 presents a scatter plot with regression lines representing interaction of perceived spouse support and gender for NK cell activity controlling for age, illness, income, number of close ties and frequency of social contacts. For neither men, $t(97) = -1.45$, $p > .10$, nor women, $t(97) = 1.43$, $p > .10$, the simple slopes of the regression lines differ from 0. The point of intersection (perceived spouse support of 32.9) fell beyond the possible range of 8-32 and a distance between 2 lines was wider at a low level of support than that at a high level of support. The results indicate that NK cell activity in men did not differ from NK cell activity in women at a high level of spouse support, whereas men had a higher NK cell activity than women at a low level of spouse support.

Figure 2 illustrates interaction of perceived family support and current illness for NK cell activity controlling for age, gender, income, number of close ties and frequency of social contacts. In each group, perceived family support was not significantly correlated with NK cell activity, $t(82) = 1.50$, $p > .10$ for people with current illness and $t(82) = -1.27$, $p > .10$ for people without current illness.

To examine which aspect of perceived social support influences NK cell activity, we examined correlations among 28 items for perceived social support and NK cell activity controlling for age, gender, illness, income, life events, number of close ties, and frequency of social contacts. Results showed that the following 3 items for friend support were significantly correlated with NK cell activity: "Do you think that your friends help you with your housework?", $r(100) = .25$, $p < .01$; "Do you think that you and your friends communicate your feelings well to each other?", $r(100) = .21$, $p = .03$; and "Do you think that your friends are pleased to hear your happiness?", $r(100) = .28$, $p < .01$. No item for spouse or family support was related with NK cell activity.

Table 1

Descriptive statistics (N = 130)

Variable	*n*	*Mean*	*SD*
Age	130	72.47	5.33
Gender	130		
0 = Men	54	41.5%	
1 = Women	76	58.5%	
Current illness	130		
0 = No	60	46.2%	
1 = Yes	70	53.8%	
Income	116		
0 = - ¥99,999	26	22.4%	
1= ¥1,000,000 -	90	77.6%	
Life events	130		
0 = Not experienced	64	50.8%	
1 = Experienced	66	49.2%	
Depressive symptoms	130	3.90	2.62
Health behaviors	130	6.72	1.11
No. of close ties	130	16.28	16.45
Frequency of social contacts	130	3.69	1.22
Perceived spouse support	108	28.03	4.04
Perceived family support	104	34.26	4.74
Perceived friend support	120	27.46	5.97
NK cell activity (%)	130	52.01	16.40

Note. No. of close ties indicates a geometric mean.

Table 2

Correlations among psychological and immunological variables (n = 83-130)

Variable		1		2		3	
1	NK cell activity	———					
2	Age	.15		———			
3	Gender	-.15		-.17	*	———	
4	Current illness	.08		.03		-.19	*
5	Income	.15		-.42	***	-.14	
6	Life events	.07		-.00		-.11	
7	Depressive symptoms	-.02		.07		.11	
8	Health behaviors	.11		-.04		.02	
9	No. of close ties	-.28	**	-.19	*	.15	
10	Frequency of social contacts	.09		.00		.16	
11	Perceived spouse support	.05		.02		-.02	
12	Perceived family support	.04		-.02		.07	
13	Perceived friend support	.14		-.16		.23	*

Note. Pearson's correlation coefficients.

*p < .05. *p < .01. ***p < .001.

(Table 2. *continued*)

Variable	4	5	6	7		8		9	
4	———								
5	.07	———							
6	.01	.03	———						
7	.03	-.14	.06	———					
8	-.02	.03	-.09	-.26	**	———			
9	-.02	.17	-.13	-.18	*	.02		———	
10	.01	-.12	.16	.02		-.03		.02	
11	.02	.03	-.09	-.25	**	.05		.08	
12	-.04	.07	-.14	-.33	***	.24	*	.22	*
13	-.14	.05	-.06	-.25	**	.14		.20	*

(Table 2 *continued*)

Variable	10	11	12	13
10	———			
11	.23*	———		
12	.19	.58***	———	
13	.32***	.21*	.51***	———

Table 3

Results of Hierarchical Regression Analysis for Evaluating the Associations of Perceived Spouse Support and Other Variables with NK Cell Activity (n = 98).

Step	Independent variable	B	SE	B	p
1	Age	0.36	0.35	0.11	
	Gender	-6.57	3.56	-0.20	
	Current illness	-2.06	3.28	-0.06	
	Income	11.26	4.64	0.26	*
	Life events	0.06	3.45	0.00	
2	No. of close ties	-6.96	2.46	-0.29	**
	Frequency of social contacts	2.48	1.43	0.18	[a]
3	Perceived spouse support	-0.81	0.55	-0.20	
4	Perceived spouse support x Gender	1.70	0.84	0.28	*

Note. Adjusted R^2 = .064 for Step 1, $F(5, 92) = 3.65$, $p = .049$; Adjusted R^2 = .115 for Step 2, $F(7, 90) = 2.80$, p = .01; Adjusted R^2 = .105 for Step 3, $F(8, 89) = 2.43$, p = .02; Adjusted R^2 = .135 for Step 4, $F(9, 88) = 2.69$, $p = .008$.

[a] $p = .09$.

*$p < .05$. *$p < .01$.

Table 4

Results of Hierarchical Regression Analysis for Evaluating the Associations of Perceived Family Support and Other Variables with NK Cell Activity (n = 93).

Step	Independent variable	B	SE	B	p
1	Age	0.52	0.33	0.18	
	Gender	-4.43	3.63	-0.13	
	Current illness	2.27	3.46	0.07	
	Income	11.87	4.45	0.31	**
	Life events	-0.66	3.47	-0.02	
2	No. of close ties	-6.32	2.95	-0.23	*
	Frequency of social contacts	3.06	1.48	0.22	*
3	Perceived family support	-0.79	0.53	-0.22	
4	Perceived family support x Illness	1.42	0.71	0.29	*

Note. Adjusted R^2 = .036 for Step 1, $F(5, 87) = 1.69$, $p = .14$; Adjusted R^2 = .102 for Step 2, $F(7, 85) = 2.49$, p = .02; Adjusted R^2 = .091 for Step 3, $F(8, 84) = 2.15$, p = .04; Adjusted R^2 = .122 for Step 4, $F(9, 83) = 2.425$, $p = .02$.

*$p < .05$. *$p < .01$.

Table 5

Results of Hierarchical Regression Analysis for Evaluating the Associations of Perceived Friend Support and Other Variables with NK Cell Activity (n = 109).

Step	Independent variable	B	SE	B	p
1	Age	0.61	0.33	0.19	
	Gender	-3.98	3.25	-0.12	
	Current illness	1.22	3.06	0.04	
	Income	10.23	4.18	0.25	*
	Life events	0.40	3.12	0.01	
2	No. of close ties	-8.25	2.34	-0.33	***
	Frequency of social contacts	1.10	1.41	0.08	
3	Perceived friend support	1.14	0.39	0.40	**
4	Perceived friend support x Life events	-0.91	0.52	-0.23	[a]

Note. Adjusted R^2 = .027 for Step 1, $F(5, 103) = 1.60$, $p = .17$; Adjusted R^2 = .103 for Step 2, $F(7, 101) = 2.78$, p = .01; Adjusted R^2 = .141 for Step 3, $F(8, 100) = 3.21$, p = .003; Adjusted R^2 = .158 for Step 4, $F(9, 99) = 3.25$, $p = .002$.

[a] $p = .08$.

*$p < .05$. *$p < .01$.

Figure 1. Interactions of perceived spouse support and gender on NK cell activity ($n = 98$).

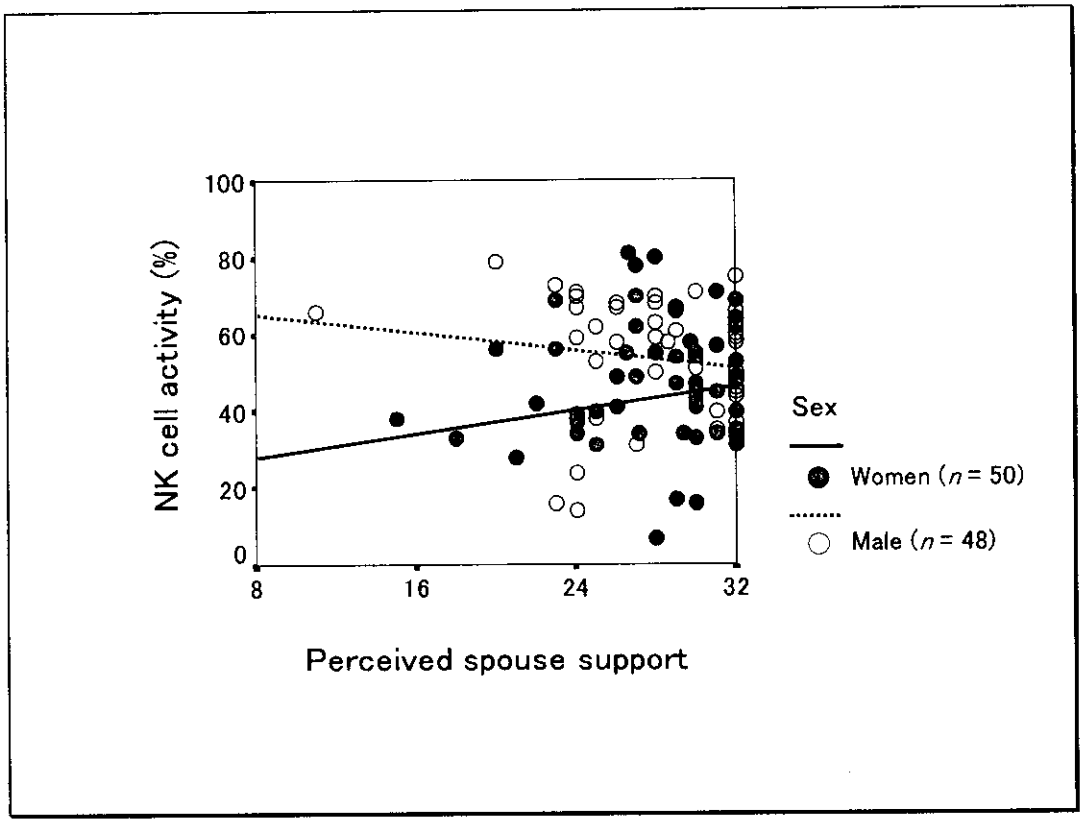
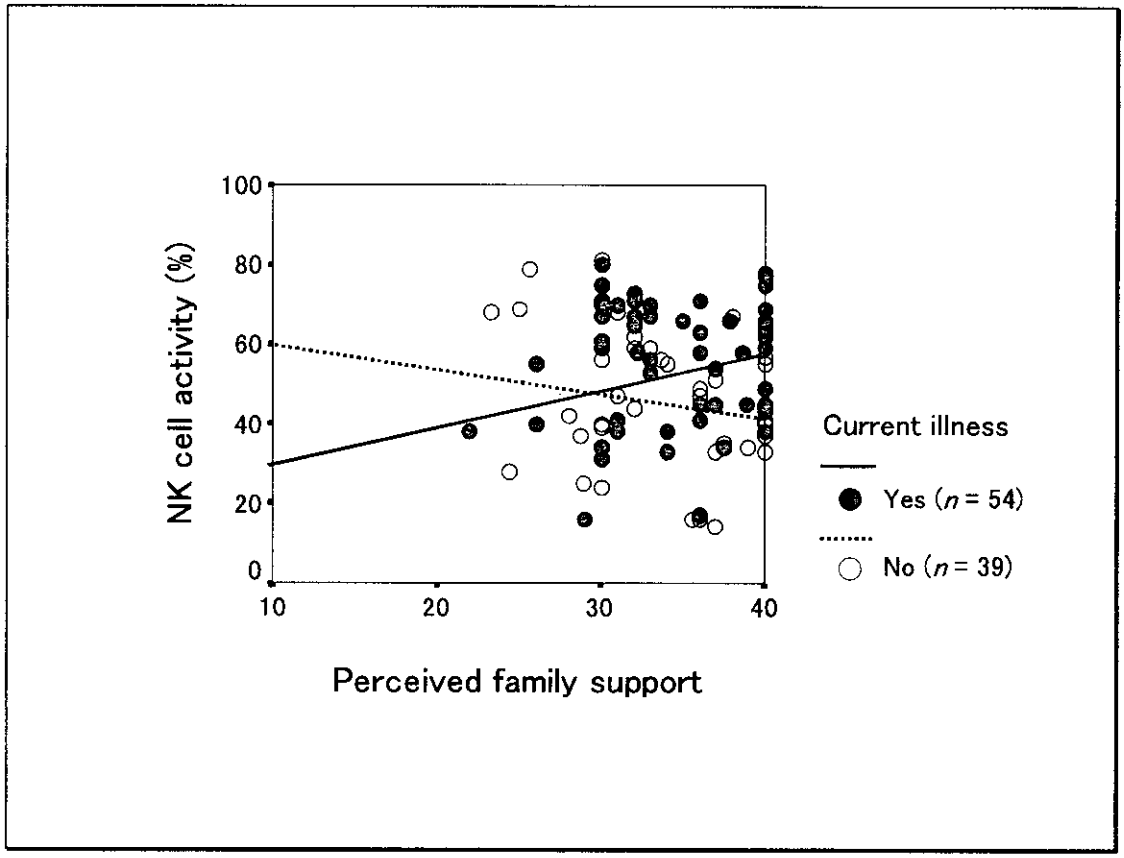


Figure 2. Interactions of perceived family support and current illness on NK cell activity ($n = 93$).



Discussion

This cross-sectional study in older people showed that perceived friend support was positively correlated with NK cell activity, independent of possible confounding variables. Neither perceived spouse nor family support had a linear relationship with NK cell activity by itself, but they interacted with gender and current illness, respectively. The results suggest a possibility that an intervention to increase perceived social support will do a favor all people with friends and some of people with spouse and family. In contrast, contradictory findings were observed on the associations between structural social support and NK cell activity. Frequency of contacts with friends and relatives tended to increase NK cell activity, whereas the number of close friends and relatives was strongly and negatively correlated with NK cell activity. Our findings indicate that the effects of social support on NK cell activity in older people depend on the sources and types of support and that a social support intervention for older people should take into consideration these differential effects.

We confirmed in our sample that perceived friend support was associated with increased NK cell activity. Because most people in the present study indicated friends as the sources of support, it seems reasonable that an

intervention scheduled should be designed to increase perceived social support mainly from friends rather than from spouse and family. In addition, of 10 items for perceived friend support, help for housework and mutual understanding of the feelings were positively correlated with NK cell activity. Brand et al. (1995) showed in their intervention that a greater degree of self-esteem and self-reinforcement increased perceived social support. Changes in the ways in which people think about themselves and the world around them may serve as factors that facilitate a reconstruction of positive relationships with others. Our intervention will be in accordance with their findings.

Many studies investigated the associations between social support, stressors (e.g., life events), and mental health. Some studies confirmed the main-effect hypothesis (Aneshensel & Stone, 1982; Wildes, Simons, & Harkness, 2002) and others confirmed the buffering hypothesis (Brown, Andrews, Harris, Adler, & Bridge, 1986; Cohen, L. H., McGowan, Fooskas, & Rose, 1984; Cohen, S. & Hoberman, 1983; Dalgard, Bjork, & Tambs, 1995; Kaniasty & Norris, 1992). As a study by Tijhuis, Flap, Foets, & Groenewegen (1995), this study interpreted illness as a stressor. Although perceived family support was not related with NK cell activity in people with or without current illness, the product term of perceived family support and current illness contributed significantly to the regression. It may be possible to say our results endorsed to some extent a buffering effect of perceived family support.

Men had a higher NK cell activity than women at a low level of perceived spouse support. Although previous studies have not yet generated a conclusive remark about gender differences in the associations between social support and health (Shumaker & Hill, 1991), Acitelli & Antonucci (1994) showed in a study in older couples that "perceptions of social support in marriage was more strongly related to the marital satisfaction and general well-being of wives than husbands" (p. 688). One possible suggestion by our findings is that an intervention for women with low spouse support may raise their NK cell activity to a level equivalent to that in men.

Longitudinal studies have shown that restriction of social network is a risk factor of increased mortality (Berkman & Syme, 1979). Our results showed that frequent contacts with close friends and relatives tended to have an enhancing effect on NK cell activity, but that a greater number of close friends and relatives had a significantly decreasing effect. The size of the latter effect was comparable to that of the positive effect of perceived friend support. Berkman (1985) and House, Landis, & Umberson (1988) argued that in the Eastern countries in which people are closely connected with others, negative effects of social network are great and its positive effects could be underestimated. Studies in the Japanese people have found weaker associations between network size and mortality than those observed in the Western people (Fujita & Hatano, 1990; Yasuda & Ohara, 1989). Our findings may reflect a negative effect of a greater size of social network. However, intercorrelations with other psychological variables did not provide an evidence for

negative aspects of social network. The number of close ties was positively correlated with perceived social support from family and friends and was negatively correlated with depressive symptoms (see Table 2). Network size may influence health by pathways other than changes in NK cell activity.

No mediating effect of depressive symptoms and health behaviors on the association between social support and NK cell activity was observed. This is consistent with the results from previous studies (Uchino et al., 1996, p. 251). However, we did not find their main effects on NK cell activity. A greater proportion of our sample reported a low level of depression (GDS of more than 6 = 15.4%) and desirable health practices (Health Practice Index of more than 6 = 68.5%). Skewed distributions of these factors may contribute to our results.

In summary, this study found a positive association between perceived friend social support and NK cell activity. A structural aspect of social relationships had a negative effect on NK cell activity and that the size of this effect was equivalent to the positive effect of perceived social support. There is possibility that positive reappraisal of personal relationships (e.g. by increasing self-esteem) will attenuate the negative effects of social network. These cross-sectional data support our primary policy that a social support intervention should be designed to change the perception of social support.

References

Acitelli, L. K. & Antonucci, T. C. (1994).Gender differences in the link between marital support and satisfaction in older couples. *Journal of Personality and Social Psychology, 67,* 688-698.

Aiken, L. S., & West, S. G (1991). *Multiple regression: Testing and interpreting interactions.* Newbury Park, CA: Sage.

Aneshensel, C. S. & Stone, J. D. (1982). Stress and depression: a test of the buffering model of social support. *Archives of General Psychiatry, 39,* 1392-1396.

Belloc, N. B. & Breslow, L. (1972). Relationship of physical health status and health practices. *Preventive Medicine, 1,* 409-421.

Belloc, N. B. (1973). Relationship of health practices and mortality. *Preventive Medicine, 2,* 67-81.

Berkman, L. F. (1985). The relationship of social networks and social support to morbidity and mortality. In S. Cohen & L. Syme (Eds.), *Social support and health* (pp. 241-262). Orlando: Academic Press.

Berkman, L. F. & Syme, S. L. (1979). Social networks, host resistance, and mortality: a nine-year follow-up study of Alameda County residents. *American Journal of Epidemiology, 109,* 186-204.

Berkman, L. F. & Breslow, L. (1983). *Health and ways of living: The Alameda County Study.* NY: Oxford University Press.

Bloom, B. L., Hodges, W. F., & Caldwell, R. A. (1982). A preventive program for the newly separated: initial evaluation. *American Journal of Community Psychology, 10,* 251-264.

Brand, E. F., Lakey, B., & Berman, S. (1995). A preventive, psychoeducational approach to increase perceived social support. *American Journal of Community Psychology, 23,* 117-135.

Brown, G W., Andrews, B., Harris, T., Adler, Z., & Bridge, L. (1986). Social support, self-esteem and depression. *Psychological Medicine, 16,* 813-831.

Clarke, M., Clarke, S. J., & Jagger, C. (1992). Social intervention and the elderly: a randomized controlled trial. *American Journal of Epidemiology, 136,* 1517-1523.

Cohen, L. H., McGowan, J., Fooskas, S., & Rose, S. (1984). Positive life events and social support and the relationship between life stress and psychological disorder. *American Journal of Community Psychology, 12,* 567-587.

Cohen, S. & Hoberman, H. (1983). Positive events and social supports as buffers of life change stress. *Journal of Applied Social Psychology, 13,* 99-125.

Crowne, D. P. & Marlowe, D. (1960). A new scale of social desirability Independent of psychopathology. *Journal of Consulting Psychology, 24,* 349-354.

Dadds, M. R. & McHugh, T. A. (1992). Social support and treatment outcome in behavioral family therapy for child conduct problems. *Journal of Consulting and Clinical Psychology, 60,* 252-259.

Dalgard, O. S., Bjork, S., & Tambs, K. (1995). Social support, negative life events and mental health. *The British Journal of Psychiatry, 166,* 29-34.

Esterling, B. A., Kiecolt-Glaser, J. K., Bodnar, J. C., & Glaser, R. (1994). Chronic stress, social support, and persistent alterations in the natural killer cell response to cytokines in older adults. *Health psychology, 13,* 291-298.

Fujita, T. & Hatano, S. (1990). [Factors predicting mortality in two years among the elderly at home in three different socioeconomic areas]. *Japanese Journal of Public Health, 37,* 1-8.

Heller, K., Thompson, M. G, Trueba, P. E., Hogg, J. R., & Vlachos-Weber, I. (1991). Peer support telephone dyads for elderly women: was this the wrong intervention? *American Journal of Community Psychology, 19,* 53-74.

Herbert, T. B., Cohen, S. (1993). Depression and immunity a meta-analytic review. *Psychological Bulletin, 113,* 472-486.

Holmes, T. H. & Rahe, R. H. (1967). The Social Readjustment Rating Scale. *Journal of Psychosomatic Research, 11,* 213-218.

House, J. S., Landis, K. R., & Umberson, D. (1988). Social relationships and health. *Science, 241,* 540-545.

Imai, K., Matsuyama, S., Miyake, S., Suga, K., & Nakachi, K. (2000). Natural cytotoxic activity of peripheral-blood lymphocytes and cancer incidence: an 11-year follow-up study of a general population. *Lancet, 356,* 1795-1799.

Kaniasty, K. & Norris, F. H. (1992). Social support and victims of crime: matching event, support, and outcome. *American Journal of Community Psychology, 20,* 211-241.

Kusaka, Y., Kondou, H., & Morimoto, K. (1992). Healthy lifestyles are associated with higher natural killer cell activity. *Preventive Medicine, 21,* 602-615.

Ogata, K., An, E., Shioi, Y., Nakamura, K., Luo, S., Yokose, N., Minami, S., & Dan, K. (2001). Association between natural killer cell activity and infection in immunologically normal elderly people. *Clinical and Experimental Immunology, 124,* 392-397.

Shumaker, S. A. & Hill, D. R. (1991). Gender differences in social support and physical health. *Health Psychology, 10,* 102-111.

Solana, R., Alonso, M. C., & Pena, J. (1999).