

## Psychological, neuroendocrine and immune measures in non spousal carers of disabled elderly in Italy

Mauro Provinciali<sup>1</sup>, Raffaella Moresi<sup>1</sup>, Mario Muzzioli<sup>1</sup>, Denis Tarabelli<sup>2</sup>,  
Cristina Sirolla<sup>2</sup>, Maria Gabriella Melchiorre<sup>2</sup>, Maria Giovanna Tucci<sup>1</sup>,  
Alberto Panerai<sup>3</sup>, Paola Sacerdote<sup>3</sup>, Massimo Mengani<sup>2</sup> & Giovanni Lamura<sup>2</sup>

<sup>1</sup> Immunology Center, I.N.R.C.A., Department of Gerontological and Geriatric Research,  
Via Birarelli 8, 60121 Ancona, ITALY.

<sup>2</sup> Centre of Health Economics, I.N.R.C.A., Department of Gerontological and Geriatric Research,  
Via Santa Margherita 5, 60122 Ancona, ITALY.

<sup>3</sup> Department of Pharmacology, University of Milan, Via Vanvitelli 32, 20129 Milan (ITALY).

*Correspondence to:* Mauro Provinciali, M.D.,  
I.N.R.C.A., Department of Gerontological and Geriatric Research,  
Immunology Center, Via Birarelli 8, 60121 Ancona, ITALY.  
PHONE: +39 071-8004213  
FAX: +39 071-206791  
EMAIL: m.provinciali@inrca.it

*Submitted:* February 2, 2004

*Accepted:* April 8, 2004

*Key words:* **caregivers; disabled elderly; immune system; psychological state; neuroendocrine parameters**

*Neuroendocrinol Lett 2004; 25(5):391-396 NEL250504A10 Copyright © Neuroendocrinology Letters www.nel.edu*

### Abstract

**OBJECTIVES:** The purpose of this study was to determine whether psychological well being as well as metabolic, neuroendocrine and immune functions were different in non spousal primary caregivers of disabled elderly than in controls.

**SETTING AND DESIGN:** We randomly recruited 38 primary family carers of over 65 year old recipients of health home care services and 37 controls stratified according to sex and age.

**METHOD:** Data were collected on psychological wellbeing (including anxiety, depression and self-perceived quality of life), on neuroendocrine and immune conditions (haemanalysis and metabolic signs, plasma ACTH, cortisol, prolactin, intra-lymphocyte content of  $\beta$ -endorphins, NK cell activity and number), as well as on the incidence and severity of influenza disease during previous winter.

**RESULTS:** Caregivers showed greater anxiety, although mean scores did not reach pathological levels. Neither depression nor satisfaction on quality of life did differ significantly, nor differences in haemanalysis and metabolic signs were found, apart from leukocyte and lymphocyte number, which was significantly lower in carers. Plasma levels of ACTH, cortisol and prolactin, the intra-lymphocyte content of  $\beta$ -endorphins as well as the NK cell number and cytotoxicity did not show significant differences. Incidence and severity of influenza episodes was also similar, whereas the duration of influenza disease showed to be significantly longer.

**CONCLUSIONS:** Non spousal caregivers of disabled elderly suffer from only slight alterations of psychological, endocrine and immune parameters, and do not respond very differently to influenza disease. This does not support therefore any generic privilege for them in the allocation of public support or respite services.

## Introduction

An extensive literature has documented that caregiving for disabled elderly fosters psychological distress [7], which, in turn, has been associated with increased morbidity [21], metabolic problems [24] and impairment of the immune system [12,22]. In most of the performed studies, the caregiving subject was the spouse of a patient affected by dementia [6, 11,18,23]. In these individuals, alteration of the hypothalamic-pituitary-adrenal axis, impairment of various immune functions, and down-regulation of the immune response to influenza virus vaccination were associated with increased scores of emotional distress [12,22]. Some studies have shown higher psychological disorders in spousal caregivers in association with behavioural problems of the cared-for person and lack of support networks [17,20], which in turn are to a much greater extent associated with decrements of cellular immunity and more days of infectious illness [9]. Other studies report that, compared to control groups of non caregivers, spousal carers show impaired proliferative capacity of lymphocytes and altered T lymphocyte representation [3] as well as slower wound healing [11]. It has been correctly pointed out that spousal carers of demented patients have two main characteristics that may account for the psychological distress and the neuroendocrine-immune derangement described in the literature. Firstly, spousal carers live a dramatic change of their marital relationship which determines psychological emotional distress which, in turn, may affect endocrine and immune systems. Secondly, spousal carers of older patients are themselves elderly, and it is well known that older individuals have age-related reductions in basal immune efficiency and, more importantly, in the responsiveness of immune cells to stressful stimuli [4]. In this study we concentrated our attention on the impact of family caregiving of the elderly on non spousal carers, for two main reasons. Firstly, very little evidence is available in the literature about the combined psychological, neuroendocrine and immune impact of caregiving on this group of relatives; secondly, Italian national legislation has recently provided a policy framework for supporting families caring for disabled relatives, including measures in favour of working carers, who in most cases are represented by children and children in law of dependent elderly [13]. In order to provide background knowledge on the experience of this group of carers, within a broader survey on the psychological and socio-economic consequences of elderly caregiving, we had the opportunity to carry out a case-control study aimed at recording neuroendocrine and immune functions, as well as the incidence and severity of influenza disease, in a group of non spousal carers of disabled elderly. We hypothesised that non spousal caregivers have worse scores than non carers in terms of psychological distress, impairment of immune system and, as a consequence, vulnerability to influenza, even though not to the extent reported in the literature for spousal carers.

## Materials and Methods

### Subject recruitment procedures and screening criteria

This investigation was approved by the Ethics Committee of the Istituto Nazionale di Ricovero e Cura per Anziani (I.N.R.C.A.), according to current provisions of the Italian National Health System. All participants gave informed written consent. The recruitment procedure of the case-control sample has been carried out in two phases. At first, a random sample of 70 subjects has been extracted from the list of the 559 over 75 year old recipients of the Health Home Care Services (HHCS) provided by the Health District Authority of Senigallia, a middle sized town located in Central Italy. The extracted group of subjects can be estimated to be a representative sample of the over 75 year old disabled elderly population living in the area (which amounts to 4.435 persons, of which 12,6% benefit from the HHCS). Furthermore, the low amount of hours provided by and the health content of the HHCS allow us to assume that the "relief" effect of such services may be very low on caregivers. The selected elderly, together with the family members who were indicated as their main caregivers, were administered a set of assessment scales in order to gain information on health, psychological and socio-economic status. In a second phase, from the initial 70 caregivers only those were selected who presented following characteristics: were not spouses of the cared for person; were between 45 and 75 years old; were not receiving any treatment involving corticosteroids nor immunosuppressant drugs; did not suffer from any infectious, auto-immunising nor neoplastic disease that could affect the variables under investigation. A venous blood sample was drawn from each one of these caregivers in order to assess the endocrine and immune parameters and analyse the association existing between them and the psychological indicators collected through the questionnaire. The same procedure – administration of the questionnaires and drawing of a blood sample – was applied to a control group of non-caregivers, stratified according to sex and age, who were recruited through random sampling from the National Health System list of the residents in the same Health District. Both caregivers and controls were finally interviewed in order to verify: a) who had received an influenza vaccination at the beginning of previous winter, b) who had contracted influenza and, in this case, c) how severe this had been (in terms of presence and peak of temperature, number of days spent in bed and need of hospitalisation). On the whole, complete information (i.e. initial questionnaire, blood sample and final interview on influenza) was collected for 38 caregivers and 37 controls.

### Subjects characteristics

The characteristics of the participants are shown in Table I. The sex ratio resulted similar in both groups, while caregivers' mean age was slightly lower than for controls. Although in both groups a similar, great ma-

majority of subjects were married, a lower percentage of widowed and of divorced/separated persons was observed among carers. According to their profession (a non matched variable), carers showed a significantly higher concentration under the retired status (40%, compared to 30% of controls), being slightly under-represented among working subjects (26% vs. 32%) as well as housewives (34% vs. 38%). Almost half of carers are represented by daughters and about one fourth by daughters-in-law. With regard to this it has to be underlined, for reasons which are dealt with within the discussion of the results, that almost one case out of three (32%) of these relatives were indicated as "primary" carers – i.e., the "relative who provides you the most care" – despite the fact that the spouse of the cared-for was still living. Most carers (72%) cohabited with the cared-for elderly. In connection with the high degree of disability affecting the cared-for persons – who in 50% of cases resulted severely impaired in all ADL/IADL and presented a moderate (18%) or severe (36%) mental deterioration – carers showed an average of 6:40 ( $\pm$  5:50) hours per day dedicated to caring tasks, often for a very long time (mean number of years spent in caring was  $8.1 \pm 6.6$ ). Not surprisingly, 46% of them stated that they could never leave the cared-for elderly unattended. Most carers (61.5%) had to face a progressive form of autonomy loss by their relative, compared to a 38.5% who had to cope with a sudden onset of the disability status in the patient.

**Isolation of plasma and effector cells.** Blood drawings were taken between 8 and 9 in the morning with syringes heparinates. Plasma was separated through centrifugation and stored at  $-80^{\circ}$  C until use. Peripheral blood mononuclear cells (PBMC) were fractionated on Ficoll-Paque (Pharmacia, Uppsala, Sweden) and separated by density gradient centrifugation (400g, 30 min). Cells from the interface of the gradients were washed twice with  $Ca^{2+}$  and  $Mg^{2+}$ - free phosphate buffered saline (Gibco, Life Technologies) and resuspended in RPMI 1640 medium (Gibco) containing penicillin (100 U/ml) and streptomycin (100  $\mu$ g/ml) at a concentration of  $1 \times 10^6$ /ml.

**Phenotype of lymphocytes and flow cytometry.** The phycoerythrin (PE) or fluorescein isothiocyanate (FITC) conjugated monoclonal antibodies anti-human CD16 and anti-CD56 were obtained from Beckton Dickinson (San Jose, CA). Lymphocytes ( $1 \times 10^6$ ) were washed in PBS containing 0.1%  $NaN_3$  plus 5% FCS and labelled with MoAb for 30 min in ice. At the end of the incubation, cells were washed in PBS containing 0.1%  $NaN_3$  and resuspended in Isoton II (Coulter, GMBH) and immediately analysed with a Coulter XL flow cytometer.

**Cytotoxic assay.** Cytotoxic assay was performed by a fluorimetric method as recently reported [16] using carboxyfluorescein diacetate (c'FDA, Molecular Probes, Oregon, USA) (75 $\mu$ g/ml) to label the K562 tumor cell line that was used as target.  $1 \times 10^4$  c'FDA-labelled tumor target cells were incubated with effector cells in 200  $\mu$ l total volume in 96-well round microtiter plates (Nunc, W.G.). Effector: target cell ratios from

Table 1: Subjects characteristics

|                                      | Carers (n = 38) | Controls (n = 37) |
|--------------------------------------|-----------------|-------------------|
| <b>Sex</b>                           | Number          | Number            |
| Men                                  | 8               | 9                 |
| Women                                | 30              | 28                |
| <b>Age</b>                           | Years           | Years             |
| Mean                                 | 53.8            | 57.8              |
| Standard Deviation                   | $\pm$ 7.3       | $\pm$ 7.3         |
| Median                               | 53              | 58                |
| <b>Range</b>                         | 40 – 72         | 36 – 70           |
| <b>Marital status</b>                | %               | %                 |
| Married                              | 84              | 78                |
| Widowed                              | 18              | 14                |
| Divorced or separated                | 0               | 8                 |
| Unmarried                            | 8               | 0                 |
| <b>Relationship to the cared for</b> |                 |                   |
| Daughter                             | 18              | –                 |
| Son                                  | 7               | –                 |
| Daughter in law                      | 10              | –                 |
| Grandchild                           | 3               | –                 |
| Mean years of care (S.D.)            | 8.1 (6.6)       | –                 |

20:1 to 2.5:1 were tested in triplicate. The plates were kept at  $37^{\circ}$  in a humidified 5%  $CO_2$  incubator for 3 h and then centrifuged at 700xg for 5 min. The supernatant was separated from the cellular fraction by rapidly inverting the plate and flicking the supernatants out. Then, 100 $\mu$ l of 1% triton X100 in 0.05 M Borate buffer, pH 9.0 was added to each well. The plate was kept for 20 hr at  $4^{\circ}$ C to allow for solubilization and then was read for fluorescence with a 1420 VICTOR multilabel counter (Wallac, Turku, Finland). The percentage of specific lysis was calculated as follows :

$$\% \text{ Specific Lysis} = [(F_{\text{med}} - F_{\text{exp}}) / F_{\text{med}}] \times 100$$

where F represent the fluorescence of the solubilized cells after the supernatant has been removed; med = F from target incubated in medium alone ; exp = F from target incubated with effector cells. Lytic units ( $LU_{20}/10^7$  cells) were calculated by using a computational method. One LU corresponded to the number of effector cells required to produce 20% of specific lysis.

**Neuro-Endocrine measures.** Adrenocorticotrophic hormone (ACTH), cortisol, and prolactin, were measured using ACTH CT (Radim, Rome, Italy), RIA-Coat Cortisol and IRMA-MAT Prolactin (Byk-Sangtec Diagnostica, GmbH Dietrenbach, Germany) kits by radioimmunoassay according the manufacturer's instructions. For the intracellular determination of  $\beta$ -endorphins,  $5 \times 10^6$  PBMS, separated as above, were centrifuged and resuspended in the protease inhibitor aprotinin (1000 KIU, Trasylol, Bayer) in order to inhibit enzymatic degradation of the peptides. The cells were then stored at  $-20^{\circ}$ C until  $\beta$ -endorphin determination. Pelleted cells were resuspended in 1 ml 0.1N acetic acid, homogenized in a blade homogenizer and sonicated. Samples were centrifuged at 10000 x g for

10 minutes. Supernatants were frozen until assay  $\beta$ -endorphin was measured by radioimmunoassay.

**Psychological measures.** The caregivers were administered following tests: the Montgomery Caregiver Burden Measures (MCBM), aimed at assessing the objective and subjective burden experienced by carers [8]; the Relative's Stress Scale (RSS) [5]; the Zung's Self-rating Anxiety Scale (ZSAS) [26] and Self-Rating Depression Scale (ZSDS) [25] have been chosen to measure anxiety and depression respectively; the short version of the Life Satisfaction Index (LSI-A) [15,1] has been used for the evaluation of the self-perceived quality of life. The latter three scales (ZSAS, ZSDS and LSI-A) have been administered to the control group, too. Both caregivers and controls have been also assessed, through a comprehensive questionnaire, with regard to health conditions, socio-economic status, life styles, use of health and social services as well as available support networks. In order to measure the impact on caregivers due to the typology and severity of the disability suffered by the cared-for elderly, the latter were administered the WHO Functional Autonomy Scale for the assessment of their ADL/IADL impairment; the Short Portable Mental Status Questionnaire (SPMSQ) to evaluate the degree of mental deterioration; the Anxiety Symptom Scale (ASS) and the 15-item Geriatric Depression Scale (GDS-15) as measures of anxiety and depression respectively.

**Statistical analysis.** Univariate analyses of variance and Mann-Whitney test were used to examine differences between caregivers and controls in immune response and neuroendocrine measures, and to analyse differences between subjects with respect to the influenza vaccination as well as to the onset of influenza. Differences in proportions between the two groups were compared by Chi-Square tests. Spearman's rank correlation was used to evaluate the relationships existing between the immune response and neuroendocrine measures and psychological variables. All analyses were carried out using the Statistical Package for the Social Sciences (SPSS v. 9.0).

## Results

As illustrated in Table II, caregivers showed a significantly higher anxiety than controls, though not reaching on the average a pathological level (which is identified by scores of 45 or more). On the contrary, neither depression nor satisfaction on quality of life did differ significantly between the two groups, although depression showed to be strongly correlated with anxiety ( $p < 0.001$ ). Other psychological measures – *per se* applicable only for caregivers – showed a relative high objective burden and moderate, non pathological levels of stress as well as of subjective burden. Haemanalysis and metabolic signs, as evaluated in peripheral blood of caregivers and controls, points out that the number of leukocytes and of lymphocytes was significantly lower in caregivers in comparison with control subjects (leucocytes ( $\times 10^2/\text{mm}^3$ ):  $5.56 \pm 1.26$  vs

$6.34 \pm 1.47$ ,  $p < 0.01$ ; lymphocytes ( $\times 10^2/\text{mm}^3$ ):  $1.810.49$  vs  $2.24 \pm 0.84$ ,  $p < 0.006$ . All other tested haemanalysis and metabolic parameters did not differ between the two groups, as did not (Table III) the NK cell activity and the NK cell number (evaluated as both the absolute and the percentage number of CD16<sup>+</sup> or CD56<sup>+</sup> lymphocytes). No significant differences were observed (Table IV) in the plasma levels of ACTH, cortisol and prolactin as well as the intracellular content of  $\beta$ -endorphins in lymphocytes, which were analysed in order to evaluate stress-associated neuroendocrine alterations. The correlation analysis among psychological, neuroendocrine and immune parameters did not show the existence of any significant relationships. Only inside the group of caregivers, the subjects who felt that they could never leave their disabled relatives alone had a lower percentage of CD56<sup>+</sup> lymphocytes ( $p = 0.04$ ), while those with higher scores of stress performed lower levels of NK cytotoxicity ( $p = 0.04$ ).

The information collected on the incidence, severity and duration of influenza disease in vaccinated and unvaccinated subjects during the previous winter (Table V) showed a higher, albeit non significant incidence of influenza in carers than in controls (29% vs. 16%), mainly due to the difference recorded in unvaccinated subjects. The severity of influenza did not significantly differ in terms of incidence and peak of temperature, nor did the need to keep to one's bed or to be hospitalised but, significantly, a period of temperature longer than 3 days was observed in carers much more frequently than for controls (83% vs. none,  $p = 0.006$ ).

## Discussion

Our findings do not support the initial hypothesis that non spousal caregivers of frail, dependent elderly have worse scores than non carers in terms of psychological distress, impairment of endocrine-immune functions and vulnerability to influenza. The only significant differences observed in comparison with the age- and sex –matched control group were a moderate but non pathologic scores of anxiety, a slight reduction of leukocyte and lymphocyte number, and a longer period of temperature in carers affected with influenza. The correlation existing, within the group of carers, between the feeling of indispensability towards their disabled relatives and the percentage of CD56<sup>+</sup> lymphocytes as well as between stress and levels of NK cytotoxicity does not come to the point of determining objective alterations. Therefore, it might be concluded that there is no evidence of a remarkable impact of caregiving on non spousal carers in terms of psychological, endocrine, and immune alterations, as it has been observed on the contrary in spousal caregivers [7,21,24,12,22,9,3]. The low levels of psychological symptomatology of our sample of carers – despite the severity of the functional and mental impairment of the cared-for patients – can find different explanations, which need to be searched outside the “impairment of the cared for – stress of the caregiver” model

**Table II:** Psychological measuresLegend: S.D.: Standard Deviation; N.A.: Not Applicable; N.S.: Non Significant ( $p > 0.05$ )

|                           | Caregivers |      | Controls |      | p     |
|---------------------------|------------|------|----------|------|-------|
|                           | Mean       | S.D. | Mean     | S.D. |       |
| Anxiety (ZSAS)            | 37.77 ±    | 9.59 | 31.89 ±  | 5.65 | 0.002 |
| Depression (ZSDS)         | 35.77 ±    | 9.80 | 33.89 ±  | 6.76 | N.S.  |
| Life satisfaction (LSI-A) | 9.97 ±     | 4.18 | 8.32 ±   | 4.66 | N.S.  |
| Objective burden          | 4.90 ±     | 2.93 | N.A.     |      |       |
| Subjective burden         | 25.47 ±    | 6.32 | N.A.     |      |       |
| Stress (RSS)              | 27.18 ±    | 8.67 | N.A.     |      |       |

**Table III:** NK cell activity and NK cell number

|                                       | Caregivers |       | Controls |       | p    |
|---------------------------------------|------------|-------|----------|-------|------|
|                                       | Mean       | S.D.  | Mean     | S.D.  |      |
| NK cell activity ( $LU_{20} / 10^7$ ) | 53.03 ±    | 23.90 | 47.47 ±  | 23.20 | N.S. |
| CD 16 <sup>+</sup> (abs. number)      | 0.33 ±     | 0.20  | 0.37 ±   | 0.20  | N.S. |
| CD 16 <sup>+</sup> (% number)         | 18.45 ±    | 9.73  | 17.09 ±  | 7.63  | N.S. |
| CD 56 <sup>+</sup> (abs. number)      | 0.30 ±     | 0.15  | 0.37 ±   | 0.20  | N.S. |
| CD 56 <sup>+</sup> (% number)         | 16.37 ±    | 7.78  | 17.23 ±  | 9.85  | N.S. |

**Table IV:** Neuro – Endocrine parameters

|  | Caregivers |       | Controls |       | p    |
|--|------------|-------|----------|-------|------|
|  | Mean       | S.D.  | Mean     | S.D.  |      |
| ACTH (pg/ml)                           | 15.33 ±    | 12.09 | 19.04 ±  | 14.41 | N.S. |
| Cortisol ( $\mu$ g/dl)                 | 13.17 ±    | 4.85  | 14.27 ±  | 5.18  | N.S. |
| PRL (ng/ml)                            | 7.52 ±     | 4.60  | 7.69 ±   | 4.02  | N.S. |
| $\beta$ -endorphins (pg/ $10^6$ cells) | 37.70 ±    | 22.71 | 41.34 ±  | 26.03 | N.S. |

**Table V:** Incidence of influenza in vaccinated and non-vaccinated subjects

|                         | Caregivers   |        | Controls     |        |
|-------------------------|--------------|--------|--------------|--------|
|                         | Number/Total | %      | Number/Total | %      |
| Subjects with influenza |              |        |              |        |
| Vaccinated              | 2/9          | (22 %) | 1/7          | (14 %) |
| Non-vaccinated          | 9/29         | (31 %) | 5/30         | (16 %) |
| Total                   | 11/38        | (29 %) | 6/37         | (16 %) |

[21]. A first explaining factor might be related to the younger age of non spousal carers – mostly daughters and daughters in law – compared to caring spouses, which implies a better adaptation to age-related endocrine or immune alterations. Psychological morbidity, metabolic, endocrine, and immune alterations reported in studies concerning spousal carers may in fact be dependent on the age-associated defect to adapt to continuously acting stressors [4]. A second reason of the relative well-being characterising the presented sample in comparison to spousal caregivers is the lower psychological impact of non spousal carers who do not live the dramatic change of the marital relationship occurring in spousal caregivers. A further factor is constituted by the possibility that in some cases the recruited caregiver might have represented only one of the different primary carers providing support to the disabled elderly, thus sharing with other persons the burden experienced by carrying out this activity. A comparison between the 11 cases in which the spouse of the cared-for elderly was still alive – the spouse representing generally the most important carer [10] – and the remaining 27 cases shows however no signif-

icant differences for either psychological, metabolic, endocrine or immune variables, apart from an increase in the  $\beta$ -endorphin values of the carers of the elderly with spouse. Despite the concomitant effect of the above factors – and although the limited dimension of the studied cohort suggests a cautious and only partial generalizable interpretation of the illustrated results – the random procedure used to sample the elderly disabled from the general population represents a methodological warranty about the epidemiological significance of the presented data [14]. Furthermore, it should be stressed that the “respite” effect provided towards caregivers by the use of the HHCS by the dependent elderly – albeit it cannot be completely excluded [2] – should have been on the whole extremely low, thus preventing a positively biasing impact on the psychological wellbeing of the sampled caregivers. Therefore, we believe that the reported findings of a low psychological and neuro-immunological morbidity in non spousal carers of Italian dependent elderly may be considered relevant in terms of clinical implications and care services organisation. With respect to this, and beyond the meaning which these

findings might have within the policy framework of the Italian National Health System, our findings support the thesis that health care services for dependent elderly and caregivers' health promotion programmes should be explicitly targeted and implemented in order to take into account of and provide priority support to those groups of carers who are more vulnerable to psychological distress and immune morbidity – such as elderly spousal caregivers – and only secondarily to non spousal carers. Future research in this field should provide more detailed insight into the issue by using longitudinal and more comparative designs, using contrast groups such as spousal vs. non spousal carers as well as service users vs. non users.

## Acknowledgments

The authors would like to acknowledge the support provided by the Italian National Research Council (grants n. n. 96.01583.CT10, n. 97.01296.CT10 and n. 98.01504.CT10) as well as by the European Commission within the research project C.O.P.E. (Carers of Older People in Europe, contract n. BMH-4-98-3374). Also we would like to thank Ms. R. Stecconi, Ms. B. Bartozzi, and Mr. G. Bernardini for their technical assistance.

## REFERENCES

- 1 Adams DL. Analysis of a life satisfaction index. *J Gerontol* 1969; **24**:470–4.
- 2 Bass DM, Noelker LS, Rechlin LR. The moderating influence of service use on negative caregiving consequences. *J Gerontol B-Psychol* 1996; **51B**, S121–S131.
- 3 Castle S, Wilkins S, Heck E, Tanzy K, Fahey J. Depression in caregivers of demented patients is associated with altered immunity: impaired proliferative capacity, increased CD8<sup>+</sup>, and a decline in lymphocytes with surface signal transduction molecules (CD38<sup>+</sup>) and a cytotoxicity marker (CD56<sup>+</sup> CD8<sup>+</sup>). *Clin Exp Immunol* 1995; **101**:487–93.
- 4 Fabris N, Mocchegiani E, Provinciali M. Plasticity of neuro-endocrine-thymus interactions during aging. *Exp Gerontol* 1997; **32**: 415–30.
- 5 Green JG, Smith R, Gardiner M, Timbury GC. Measuring behavioural disturbance of elderly demented patients in the community and its effects on relatives: a factor analytic study. *Age Ageing* 1982; **11**:121–26.
- 6 Haley W, West C, Wadley V, Ford G, White F, Barrett J, et al. Psychological, social and health impact of caregiving: a comparison of black and white dementia family caregivers and non-caregivers. *Psychol Aging* 1995; **10**:540–52.
- 7 Haugh MR, Ford AB, Stange KC, Noelker LS, Gaines AD. Effect of giving care on caregivers' health. *Res Aging* 1999; **21**:515–38.
- 8 Kane RA. Assessment of social functioning: recommendations for comprehensive geriatric assessment. In: Rubenstein L.Z. (ed.) *Geriatric technology assessment. The state of the art.* Milan, Kurtis; 1995. p. 91–110.
- 9 Kiecolt-Glaser JK, Dura JR, Speicher CE, Trask OJ, Glaser R. Spousal caregivers of dementia victims: longitudinal changes in immunity and health. *Psychosom Med* 1991; **53**:345–62.
- 10 Kiecolt-Glaser JK, Malarkey W, Cacioppo JT, Glaser R. In: *Handbook of human stress and immunity*, eds. Glase R & Kiecolt-Glaser JK. Academic, San Diego; 1994. p. 321–339.
- 11 Kiecolt-Glaser JK, Marucha P, Malarkey W, Mercado A, Glaser R. Slowing of wound healing by psychological stress. *Lancet* 1995; **346**:1194–96.
- 12 Kiecolt-Glaser JK, Glaser R, Gravenstein S, Malarkey WB, Sheridan J. Chronic stress alters the immune response to influenza virus vaccine in older adults. *Proc Natl Acad Sci USA: Medical Sciences* 1996; **93**:3043–47.
- 13 Lamura G, Melchiorre MG, Mengani M. Caring for the Caregivers: challenges for Italian Social Policy. In: UN-INSTRAW (editor). *Ageing in a Gendered World: Women's Issues and Identities.* Santo Domingo: United Nations – International Research and Training Institute for the Advancement of Women; 1999. p. 245–272.
- 14 Melchiorre MG, Sirolla C, Quattrini S, Lamura G. Elderly care and respite services: main results of a survey on 400 dependent elderly and their carers living in Central Italy. *Gerontology* 2001; **47**(suppl 1):159.
- 15 Neugarten BL, Havighurst RJ, Tobin SS. The measurement of life satisfaction. *J Gerontol* 1961; **16**:134–43.
- 16 Provinciali M, Di Stefano G, Fabris N. Optimization of cytotoxic assay by target cell retention of the fluorescent dye carboxy-fluorescein diacetate (CFDA) and comparison with conventional Cr51-release assay. *J Immunol Methods* 1992; **155**:19–24.
- 17 Robinson KM. Predictors of depression among wife caregivers. *Nurs Res* 1989; **38**:359–63.
- 18 Russo J, Vitaliano PP, Brewer DD, Katon W, Becker J. Psychiatric disorders in spouse caregivers of care-recipients with Alzheimer's disease and matched controls: a diathesis-stress model of psychopathology. *Journal Abnorm Psychol* 1995; **104**:197–204.
- 19 Sacerdote P, Breda M, Barcellini W, Meroni PL, Panerai AE. Age-related changes of Beta-Endorphin and Cholecystokinin in human and rat mononuclear cells. *Peptides* 1991; **12**:1353–56.
- 20 Schulz R, Williamson A 2-year longitudinal study of depression among Alzheimer's caregivers. *Psychol Aging* 1991; **6**:569–78.
- 21 Schulz R, O'Brien AT, Bookwala J, Fleissner K. Psychiatric and physical morbidity effects of dementia caregiving: prevalence, correlates, and causes. *Gerontologist* 1995; **35**:771–91.
- 22 Vedhara K, Cox NK, Wilcock GK, Perks P, Hunt M, Anderson S, et al. Chronic stress in elderly carers of dementia patients and antibody response to influenza vaccination. *Lancet* 1999; **353**: 627–31.
- 23 Vitaliano PP, Russo J, Niaura R. Plasma lipids and their relationships with psychosocial factors in older adults. *J Gerontol B-Psychol* 1995; **50**:P18–P24.
- 24 Vitaliano PP, Scanlan JM, Krenz C, Schwartz RS, Marcovina SM. Psychological distress, caregiving and metabolic variables. *J Gerontol B-Psychol* 1996; **51B**:P290–P299.
- 25 Wilkin D, Hallam L, Doggett MA. *Measures of Need and Outcome for Primary Health Care.* Oxford, Oxford University Press; 1994. p. 75–80.
- 26 Zung WWK. A rating instrument for anxiety disorders. *Psychosomatics* 1971; **12**:371–79.

---

To cite this article: *Neuroendocrinol Lett* 2004; **25**(5):391–396