Association between social isolation and inflammatory markers in depressed and non-depressed individuals: Results from the MONICA/KORA study


Helmholtz Zentrum München, German Research Center for Environmental Health, Institute of Epidemiology II, 85764 Neuherberg, Germany

Institute for Clinical Diabetology, German Diabetes Center, Leibniz Center for Diabetes Research, Heinrich Heine University Düsseldorf, 40225 Düsseldorf, Germany

Department of Internal Medicine II – Cardiology, University of Ulm Medical Center, 89081 Ulm, Germany

Department of Psychosomatic Medicine and Psychotherapy, Klinikum rechts der Isar, Technische Universität München, Munich, Germany

**A R T I C L E   I N F O**

**Article history:**
Received 22 February 2011
Received in revised form 27 June 2011
Accepted 28 June 2011
Available online 2 July 2011

**Keywords:**
Depressed mood
Social isolation
CRP
IL-6
Men
Inflammatory response
Combination of depressed mood and social isolation

**A B S T R A C T**

**Introduction:** Depressed individuals not only suffer from chronic low grade inflammation, but also exhibit an inflammatory hyper-responsiveness to acute stress. We investigate whether chronic stress also induces an exaggerated inflammatory response in individuals with increased depression features. As model for chronic stress, social isolation was chosen.

**Methods:** Interleukin (IL)-6 and hs-CRP levels were assessed in 1547 subjects (847 men and 700 women), derived from the population-based MONICA/KORA study. Standardized questionnaires were used to assess depressed mood (depression and exhaustion subscale) and social isolation (social network index).

The relationship between the two inflammatory markers, social isolation and depressed mood was examined taking into account interactions social isolation × depressed mood using multivariable linear regression models, adjusted for age, BMI, smoking, alcohol, and physical activity. Analyses were performed in men and women separately.

**Results:** We observed a significant interaction between depressed mood and social isolation regarding IL-6 and hs-CRP, respectively in men (p-value = 0.02 for IL-6 and <0.01 for hs-CRP), evidencing a substantial synergistic effect of social isolation, and depressed mood on inflammatory responses. Furthermore, depressed and socially isolated men had highly significantly elevated IL-6 levels (geometric mean: 3.76 vs. 1.92 pg/ml, p-value <0.01) and heightened hs-CRP levels (geometric mean: 2.01 vs. 1.39 mg/l, p = 0.08) in comparison with non-depressed and socially integrated men. In women, no significant associations were seen.

**Conclusion:** The interaction of depressed mood and social isolation elicits a substantial synergistic impact on inflammatory markers in men, but not in depressed women.

© 2011 Elsevier Inc. All rights reserved.

1. Introduction

The association between depression, depressive symptoms and elevated levels of proinflammatory cytokines, including interleukin (IL)-6, and C-reactive protein (CRP) has been well described (Howren et al., 2009). Numerous studies have shown the association to be strongest in clinical samples and weaker in community-based samples. Furthermore, associations generally remained significant even after adjustment for metabolic and behavioral factors (Dentino et al., 1999; Emparna et al., 2005; Ladwig et al., 2005; Panagiotakos et al., 2004; Penninx et al., 2003). Hyperactivity of the hypothalamic pituitary adrenal axis (HPA), as indicated by elevated glucocorticoid levels (Plotsky et al., 1998; van Eck et al., 1996) has been observed in depression and the presence of subthreshold depressive symptoms. Although glucocorticoids suppress inflammation in the short term, sustained elevation over time was found to be associated with a widespread resistance of glucocorticoid receptors, which may lead to the increased inflammatory activity in depression (Leonard, 2001; Raison and Miller, 2003). Though numerous studies have led to a better understanding of the association between depression and inflammation, the role of chronic stress in depressed patients has been neglected in the concept.

Acute stress induces inflammation (Heinz et al., 2003; LeMay et al., 1990; Papanicolau et al., 1998). In depressed patients, compared to healthy controls, this inflammatory response to acute stress was found to be increased in two studies (Pace et al., 2006; Weinstein et al., 2010). However, so far no study has investigated the impact of chronic stress on low grade inflammation in...
depressed subjects vs. non-depressed subjects. We aimed to investigate whether depressed subjects show a different association between chronic stress and low grade inflammation compared with non-depressed subjects.

As paradigm of chronic stress we chose social isolation, a potent chronic stress condition (Gripp et al., 2007; Kennedy et al., 1988) that is known to be associated with increased inflammation (Ford et al., 2006; Loucks et al., 2006b). Men and women were analyzed separately, as the associations between social isolation and inflammation as well as depression and inflammation are known to be influenced by sex (Elovainio et al., 2009; Ford and Erlinger, 2004; Ford et al., 2006; Loucks et al., 2006a).

To this end, we analyzed data from a large population-based study in Southern Germany, representing a middle European population.

2. Research design and methods

2.1. Setting

The present study is based on data collected within the population-based MONICA/KORA (MONItoring of trends and determinants in CArdiovascular disease/Cooperative Health Research in the Region of Augsburg) Augsburg Study, conducted between 1984 and 1995 in the area of Augsburg, Southern Germany which was part of the multinational WHO MONICA project. Three independent cross-sectional population-based surveys covering the city of Augsburg and the two adjacent counties were conducted in 1984/1985 (S1), 1989/1990 (S2), and 1994/1995 (S3) to estimate the prevalence and distribution of cardiovascular risk factors. A total number of 13,427 participants (6725 men and 6702 women) in the age range from 25 to 74 years were recruited. Written informed consent was obtained from all participants and the study was approved by the local authorities.

2.2. Study group

Initially in order to study the role of biomarkers in the development of CHD and type 2 diabetes a case-cohort study design was applied (Thorand et al., 2005), including a subsample of 2225 participants (1206 men and 1019 women) randomly selected by sex and survey from a source population based on 9531 participants from S1 to S3 with age range of 35–74 years at baseline and eligible blood samples. In an effort to build a study population without major chronic disease conditions, individuals with a self-reported history of stroke, myocardial infarction, diabetes, cancer or heart failure (n = 343) were excluded leaving a data set of 1882 participants. Furthermore, participants with missing data on hs-CRP, IL-6, blood pressure, body mass index (BMI) and missing information on cigarette smoking, alcohol consumption, physical activity, social network status, and depressed symptomatology (n = 335) were excluded from the data set, leaving a final study population of 1547 subjects (847 men and 700 women). The number of men and women by survey were 340/267, 321/234, and 186/199 for S1, S2, and S3, respectively.

The sample sizes for the subsample by survey were used together with the stratum-specific sizes of the 35–74 year-old source population to compute sampling fractions. The inverse of the sampling fractions yielded the survey and sex-specific sampling weights.

2.3. Assessment of hs-CRP levels

Hs-CRP concentrations were measured using a high-sensitivity immunoradiometric assay (IRMA) (range 0.05–10 mg/dl) [(S1: men aged 45–64; S3) or a high sensitivity latex-enhanced nephelometric assay run on a BN II analyser (DADE Behring, Marburg, Germany) (S1: men aged 35–44 and all women; S2). Both methods gave similar results when the same samples were analyzed (Khuseyinova et al., 2003). The intra- and inter-assay CVs of quality control tests sera for hs-CRP was 4.0% and 12% for the IRMA and 2.5% and 5.1% for the nephelometric assay, respectively.

2.4. Assessment of IL-6 levels

Serum concentrations of IL-6 were measured by sandwich ELISA (CLB, Amsterdam, The Netherlands). The sandwich ELISA was established to meet the following criteria: linearity of signal for the standard curve between optical density (OD) 0.05 and 2.0, difference between expected and measured signal in spiking experiments less than 15%, mean intra-assay variation below 10%, mean inter-assay variation below 10%, lack of signal after freezing and thawing of sera three times less than 20%. All sera were analyzed in duplicate. Measurements were repeated if there was more than 20% difference between the two parallel measurements. Detection limits of cytokine ELISAs were 0.24 pg/ml for IL-6 (Muller et al., 2002).

2.5. Assessment of CHD risk factors

Standardized interviews were conducted by trained medical staff to assess information details on their health behaviors regarding to smoking status, alcohol consumption, physical activity, and sociodemographic information. In addition, standardized medical examinations were conducted. Assessment procedures have been described elsewhere (Evans et al., 2001; Meisinger et al., 2002). Total serum cholesterol and HDL cholesterol were measured by enzymatic methods (CHOD-PAP, Boehringer Mannheim, Germany).

2.6. Psychosocial assessment

Psychosocial information was assessed by a self-administered questionnaire. Depressive symptomatology was assessed by the DEpression and EXhaustion subscale (DEEX scale). The scale combines eight items (fatigability, tiredness, irritability, loss of energy, difficulty in concentrating, inner tension, nervousness, and anxiety) ranging from 0 to 3, leading to a Likert-like scoring range of 0–24. Subjects in the top tertile of the depressive symptom distribution were considered to have a depressed mood. Sex-specific cutoff points were applied (Ladwig et al., 2004).

Social isolation was assessed using the Social Network Index (SNI) initially designed for the Alameda county study (Berkman and Syme, 1979) comprising marital status, contact with friends and relatives, the index of close contacts and informal and formal group associations. The social network index comprises not only the number of social ties, but also the relative importance. Intimate contacts are weighted more heavily than church affiliations and group membership. The social network index comprises four categories of strength of social network.

Subjects in category 4 with the fewest number of social ties were considered to be “socially isolated”. The three other categories were comprised into one category termed “socially integrated”.

2.7. Statistical analysis

For all statistical analyses, the sampling scheme was taken into account by using sex- and survey-specific sampling weights and the appropriate SAS procedure which were developed to estimate correct means, standard errors and p values in case of a weighted analysis.
Skewed variables were natural log-transformed to reach an approximately normal distribution. These include hs-CRP, IL-6, HDL cholesterol, and total cholesterol. All analyses for these variables were conducted using the log-transformed data. All analyses were performed for men and women separately. Means and proportions for baseline demographic characteristics, metabolic characteristics and behavioral risk factors were computed separately for depressed and non-depressed participants. Differences in means were tested by the t-test using the SAS procedure SURVEYREG. Differences in proportions were tested by the $\chi^2$ test using the SAS procedure SURVEYFREQ.

Multivariable linear regression analyses using the SAS procedure SURVEYREG were performed to investigate the association of the two inflammatory markers with social isolation, depressed mood and the possible effect modification between social isolation and depressed mood.

We performed two analyses. In the “continuous and categorial analyses (CCA)” the association of the two inflammatory parameters and all four categories of social network index were investigated by using dummy variables. For depressed mood the continuous score was used.

In the “dichotomous analyses (DA)” social isolation and depressed mood were used as dichotomous variables as it is described in the section “psychosocial assessment”.

First, a raw model was calculated to test for the association between inflammatory parameters and depressed mood (“CCA”: continuous variable, “DA”: dichotomous variable) and the social network index (“CCA”: categories SNI 1–4)/“DA”: dichotomous variable social isolation) without accounting for effect modification. The models were adjusted for age, survey, BMI, and behavioral factors (smoking, alcohol intake and physical activity).

Log-transformed hs-CRP and IL-6 were used as outcome variables.

Subsequently, the interactions terms “SNI 2 $\times$ depressed mood”, “SNI 3 $\times$ depressed mood” and “SNI 4 $\times$ depressed mood were included in the “CCA”. In the “DA” the interaction term “social isolation $\times$ depressed mood” was included. Two levels of adjustment for possible confounding factors were performed: the first model was adjusted for age and survey, the second model was adjusted for age, survey, BMI, and behavioral factors.

To test our assumption that sex modifies the association of social isolation and depressed mood with hs-CRP or IL-6 outcomes, we performed an interaction analysis in the total study population with additionally adding sex and the interaction terms social isolation $\times$ sex, depressed mood $\times$ sex, and social isolation $\times$ depressed mood $\times$ sex as covariates to the linear regression models in the “DA”.

Sex-specific geometric means of hs-CRP and IL-6 levels adjusted for age and survey were calculated for the different combinations of depressed mood and social isolation. The group of individuals who were not depressed and were socially integrated was taken as reference group. Differences between adjusted means of hs-CRP and IL-6 levels in each risk group and the adjusted mean in the reference group were tested by t-tests.

SAS (V9.1) was used for statistical analysis with a significance level of $p < 0.05$ (SAS Institute, Carey, North Carolina).

3. Results

3.1. Descriptive analysis

The clinical, metabolic, behavioral and characteristics of our study group are reported in Table 1. Of the 1547 subjects, 574 subjects were categorized as “depressed mood” (314 men and 260 women).

No significant differences could be seen in metabolic parameters between depressed and non-depressed men. Depressed men were more likely to be physically inactive and had a slightly lower BMI than men who were not depressed. There were no differences in metabolic parameters between depressed and non-depressed women. Depressed women were more likely to be socially isolated.

3.2. Association between hs-CRP and depressed mood (“continuous and categorial analysis (CCA)” and “dichotomous analysis (DA)”)

In a multivariable linear regression analysis, we first tested for the association between hs-CRP, depressed mood (“CCA”: continuous variable, “DA”: dichotomous variable) and social isolation (“CCA”: four categories of social network index, “DA”: dichotomous variable social isolation). Neither in the “CCA” nor in the “DA”, the association between hs-CRP and depressed mood and hs-CRP and the four categories of social network/social isolation was significant. The models were adjusted for age and survey, BMI and behavioral factors. Data are not shown.

3.3. Interaction depressed mood $\times$ four categories of social network/ social isolation

The interaction terms depressed mood $\times$ four categories of social network/social isolation and hs-CRP were tested in two models with different adjustments.

Results are shown for the “DA” (Table 2). The first model was adjusted for age and survey. The second model was adjusted for age, survey, BMI, smoking, physical activity, and alcohol intake. In both models, the interaction term social isolation $\times$ depressed mood was highly significant in men ($p < 0.01$, p-estimate: 0.829 in model 1, 0.779 in model 2).

Table 1

<p>| Characteristics of study subjects (n = 1547), divided into the category “depressed” and “not depressed”. Differences in mean values were compared using t-tests for continuous variables and differences in frequencies were compared using $\chi^2$ test. |
|---------------------------------|-----------------|-----------------|-------------|</p>
<table>
<thead>
<tr>
<th></th>
<th>Not depressed</th>
<th>Depressed</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Men n = 847</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>50.07 $\pm$ 0.47</td>
<td>50.82 $\pm$ 0.61</td>
<td>0.41</td>
</tr>
<tr>
<td>BMI</td>
<td>27.33 $\pm$ 0.17</td>
<td>26.83 $\pm$ 0.19</td>
<td>0.04</td>
</tr>
<tr>
<td>RR syst. (mmHg)</td>
<td>135.22 $\pm$ 0.76</td>
<td>133.25 $\pm$ 1.04</td>
<td>0.09</td>
</tr>
<tr>
<td>RR diastol. (mmHg)</td>
<td>84.14 $\pm$ 0.47</td>
<td>83.05 $\pm$ 0.60</td>
<td>0.14</td>
</tr>
<tr>
<td>Heart rate</td>
<td>73.34 $\pm$ 0.49</td>
<td>72.60 $\pm$ 0.65</td>
<td>0.44</td>
</tr>
<tr>
<td>Total Cholesterol (mg/dl)</td>
<td>231.26 $\pm$ 1.01</td>
<td>230.50 $\pm$ 1.01</td>
<td>0.84</td>
</tr>
<tr>
<td>HDL (mg/dl)</td>
<td>48.12 $\pm$ 1.01</td>
<td>48.86 $\pm$ 1.02</td>
<td>0.35</td>
</tr>
<tr>
<td>CRP (mg/l)</td>
<td>1.36 $\pm$ 1.05</td>
<td>1.23 $\pm$ 1.07</td>
<td>0.23</td>
</tr>
<tr>
<td>IL-6 (pg/ml)</td>
<td>1.95 $\pm$ 1.05</td>
<td>2.06 $\pm$ 1.07</td>
<td>0.50</td>
</tr>
<tr>
<td><strong>Behavioral factors</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Smoker%</td>
<td>30.5</td>
<td>31.9</td>
<td>0.69</td>
</tr>
<tr>
<td>$&gt;$40 g Alcohol/day (%)</td>
<td>38.2</td>
<td>31.5</td>
<td>0.06</td>
</tr>
<tr>
<td>Physically inactive (%)</td>
<td>51.7</td>
<td>63.7</td>
<td>$&lt;$0.01</td>
</tr>
<tr>
<td>Socially isolated (%)</td>
<td>9.2</td>
<td>10.6</td>
<td>0.54</td>
</tr>
<tr>
<td><strong>Women n = 700</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>50.06 $\pm$ 0.48</td>
<td>51.03 $\pm$ 0.63</td>
<td>0.20</td>
</tr>
<tr>
<td>BMI</td>
<td>26.34 $\pm$ 0.21</td>
<td>25.91 $\pm$ 0.26</td>
<td>0.19</td>
</tr>
<tr>
<td>RR syst. (mmHg)</td>
<td>130.91 $\pm$ 0.89</td>
<td>128.26 $\pm$ 1.27</td>
<td>0.09</td>
</tr>
<tr>
<td>RR diastol. (mmHg)</td>
<td>80.15 $\pm$ 0.50</td>
<td>78.73 $\pm$ 0.74</td>
<td>0.11</td>
</tr>
<tr>
<td>HR</td>
<td>74.3 $\pm$ 0.45</td>
<td>74.50 $\pm$ 0.62</td>
<td>0.79</td>
</tr>
<tr>
<td>Total Cholesterol (mg/dl)</td>
<td>232.58 $\pm$ 1.01</td>
<td>230.62 $\pm$ 1.01</td>
<td>0.53</td>
</tr>
<tr>
<td>HDL (mg/dl)</td>
<td>62.98 $\pm$ 1.01</td>
<td>62.80 $\pm$ 1.02</td>
<td>0.85</td>
</tr>
<tr>
<td>CRP (mg/l)</td>
<td>1.31 $\pm$ 1.06</td>
<td>1.21 $\pm$ 1.08</td>
<td>0.41</td>
</tr>
<tr>
<td>IL-6 (pg/ml)</td>
<td>1.87 $\pm$ 1.05</td>
<td>1.71 $\pm$ 1.07</td>
<td>0.31</td>
</tr>
<tr>
<td><strong>Behavioral factors</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Smoker%</td>
<td>21.3</td>
<td>21.6</td>
<td>0.93</td>
</tr>
<tr>
<td>$&gt;$20 g Alcohol/day (%)</td>
<td>22.7</td>
<td>24.4</td>
<td>0.63</td>
</tr>
<tr>
<td>Physically inactive (%)</td>
<td>58.4</td>
<td>62.2</td>
<td>0.33</td>
</tr>
<tr>
<td>Socially isolated (%)</td>
<td>13.9</td>
<td>23.2</td>
<td>$&lt;$0.01</td>
</tr>
</tbody>
</table>

Data are expressed as arithmetic mean $\pm$ SE or as percentage, unless otherwise indicated. p-Value for comparison across the different categories using t-test for continuous variables and $\chi^2$ for categorical variables.

* Geometric mean $\pm$ SE.
In the “CCA” results were similar. The interaction term social network index 4 × depressed mood was highly significant in men (model 1: β-estimate: 0.08, p < 0.01; model 2: β-estimate: 0.08, p < 0.01) whereas the interaction terms SNI 2 × depressed mood and SNI 3 × depressed mood were not significant. Results of the “CCA” are not shown.

3.4. Means of hs-CRP levels by different combinations of depressed mood and social isolation

Hs-CRP levels, adjusted for age and survey, were calculated for the four different groups of combinations of depressed mood and social isolation (Fig. 1). Hs-CRP levels were highest in the group of socially isolated and depressed men (p = 0.08). Hs-CRP levels were slightly but significantly lower in the group of socially integrated but depressed men, compared to the reference group of not depressed, socially integrated men (p = 0.02). In women, no significant difference between the three risk groups and the reference group could be seen.

3.5. Association between IL-6 and depressed mood and social isolation

In the “DA” social isolation was highly significantly associated with IL-6 levels in men (β-estimate: 0.34, p-value < 0.01) but not in women. No significant association was found between IL-6 levels and depressed mood. In the “CCA” SNI 4 was significantly associated with IL-6 levels (β-estimate: 0.31, p-value = 0.03) but neither SNI 3 and SNI 2 nor depressed mood.

3.6. Interaction depressed mood × social isolation

Results of the “DA” are shown in Table 2. In models 1 and 2 the interaction term social isolation × depressed mood was significant in men (p = 0.02, model 1: β-estimate: 0.58, model 2: β-estimate = 0.55). In women, no significant association was found. The associations between depressed mood and IL-6 levels were not significant. Data are not shown. In the “CCA” none of the interaction terms were significantly associated with IL-6 levels, neither in men nor in women.

3.7. Means of IL-6 levels in the different groups of combinations of depressed mood and social isolation

Socially isolated and depressed men had highly significantly elevated IL-6 levels compared with the reference group (socially isolated, depressed: geometric mean: 3.76 pg/ml (CI: 2.42–5.82 pg/ml) socially integrated, not depressed: geometric mean: 1.92 pg/ml (CI: 1.75–2.12 pg/ml), p < 0.01) (Fig. 1). No significant differences between the other two risk groups and the reference group could be seen in men. In women, no significant differences between the three risk groups and the reference group could be seen.

Table 2

<table>
<thead>
<tr>
<th>CRP</th>
<th>Depressed</th>
<th>Socially isolated</th>
<th>Depressed × socially isolated</th>
</tr>
</thead>
<tbody>
<tr>
<td>β-estimate (SE)</td>
<td>p-Value</td>
<td>β-estimate (SE)</td>
<td>p-Value</td>
</tr>
<tr>
<td><strong>Men</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Model 1</td>
<td>-0.197 (0.08)</td>
<td>0.018</td>
<td>-0.266 (0.17)</td>
</tr>
<tr>
<td>Model 2</td>
<td>-0.178 (0.08)</td>
<td>0.021</td>
<td>-0.265 (0.16)</td>
</tr>
<tr>
<td><strong>Women</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Model 1</td>
<td>-0.105 (0.1)</td>
<td>0.293</td>
<td>-0.161 (0.16)</td>
</tr>
<tr>
<td>Model 2</td>
<td>-0.039 (0.09)</td>
<td>0.663</td>
<td>-0.151 (0.14)</td>
</tr>
</tbody>
</table>

Model 1*: adjusted for age and survey.
Model 2*: adjusted for age, survey, BMI, smoking, alcohol, and physical activity.

**Fig. 1.** Mean CRP and IL-6 levels and 95% CIs, adjusted for age and survey in the three different risk groups compared to the reference group “socially integrated, not depressed”. *p < 0.05; **p < 0.01.
3.8. Sex modifies the association of the interaction of social isolation and depressed mood with hs-CRP or IL-6 outcomes

The interaction terms sex × depressed mood × social isolation were significant in both models (hs-CRP: p-value = 0.02, IL-6: p-value <0.05).

4. Discussion

The main finding of this study was a highly significant association between the combination of depressed mood and social isolation and increased IL-6 levels in men but not in women.

Depressed mood yielded no effect on inflammatory parameters. Social isolation was significantly associated with IL-6 levels, but not with hs-CRP levels. However, the interaction of both parameters elicited a substantial synergistic impact on both inflammatory markers.

Previous epidemiological studies have brought evidence of a significant association between social isolation and inflammation (Ford et al., 2006; Loucks et al., 2006a,b). Our results confirm these findings concerning the association of social isolation with inflammation. Lonely people might exhibit increased activity for several genes encoding signaling molecules that promote inflammation and decreased activity for genes that have anti-inflammatory effects (Cole et al., 2007). Interestingly, in our study, significant effects could only be seen in the most isolated group. No effects could be seen in moderate isolation. Results did not change when we reanalyzed data without adjusting for depressed mood.

In contrast to our study, former studies have shown a dose–response relationship between social network size and inflammation (Loucks et al., 2006a,b). We assume that the relation of social network size with inflammation might be not a linear one, but the effect increases with increasing “dose” of social isolation.

The apparent synergistic effect of social isolation and depressed symptomatology on inflammation might be explained by a cytokine-mediated glucocorticoid receptor resistance. Glucocorticoids are crucial in the response to environmental stressors, mobilizing initially the bodily responses and ultimately restraining immune reactions. Cytokines have been shown to induce glucocorticoid receptor resistance (Pace et al., 2007; Pace and Miller, 2009). One might speculate that in the condition of depressed mood and social isolation, increased levels of inflammatory cytokines induce glucocorticoid receptor resistance with the consequence of a further increase in inflammation.

No association was found between depressed mood alone and inflammation. Not all studies investigating the association between depressed mood and inflammation have shown a positive association. Some studies failed to find an association (Janszky et al., 2005; Lesperance et al., 2004; Miller et al., 2005) and some studies even found an inverse association with inflammatory parameters (Whooley et al., 2007). The different regulation of the stress response in depressed and in healthy subjects might explain the inconsistencies in results of studies investigating inflammation in depression.

An alternative explanation of our result might be that an increased reactivity to stress could be the characteristic of a certain phenotype that is generally more likely to develop depression. Carriers of the serotonin transporter SS polymorphism, who are known to have an increased risk for depression, have been shown to have higher inflammatory parameters under control conditions as well as under acute stress (Fredericks et al., 2010). Moreover, polymorphisms in inflammation-related genes have been found to be associated with susceptibility for depression (Wong et al., 2008). These genotypes might be overrepresented in the group of depressed and socially isolated individuals and influence the levels of inflammatory markers in the group of socially isolated and depressed individuals.

In our study, no significant associations could be seen in women. Sex differences have been observed in former studies investigating the association between depression and inflammation with elevation of CRP levels in depressed men but not depressed women (Danner et al., 2003; Ford and Erlinger, 2004). Moreover, Hermes and colleagues showed that male rats but not female rats develop wound healing difficulties caused by a dysregulation of immune response, when exposed to an acute stressor in the presence of chronic social isolation (Hermes et al., 2006).

In humans, a marked sexual dimorphism in the immune system is well established and is reflected in different immunological vulnerabilities of men and women.

Men develop cardiovascular disorders earlier in life than women. Men with low levels of social integration are more vulnerable to disease and death than women (House et al., 1982). However, women have an increased vulnerability to autoimmune inflammatory and allergic disorders (Schuurs and Verheul, 1990).

Sex hormones have been shown to modulate a large variety of mechanisms involved in the immune response. Particularly estrogens have strong immune-modulatory effects. They influence the differentiation, maturation, and emigration of lymphocytes, which are all essential for an adequate immune response (Tanriverdi et al., 2003). They suppress IL-6 production via NF-kB (Pfeilschifter et al., 2002). Estrogens attenuate part of inflammatory responses (Nilsson, 2007), thereby possibly preventing women from a stress-induced inflammatory hyper-responsiveness.

In conclusion, we can only speculate about the reasons why men who are socially isolated and depressed have increased inflammatory parameters. Further studies with longitudinal designs need to be done to better elucidate the mechanisms that lead to the increased inflammation. In clinical cardiology, social isolation clustering together with a depressed mood is a particularly malignant bio-behavioral risk factor for cardiovascular morbidity and mortality (Frasure-Smith et al., 2000; Mookadam and Arthur, 2004; Wang et al., 2006). We have recently shown that leptin is not altered in socially integrated men suffering depressed mood but altered in men who suffer both, depressed mood and social isolation (Hafner et al., 2011). Therefore the extent of psychosocial stressors as well as the amount of support from the patient’s social network has to be taken into account in depressed patients, not only in treatment but also in research.

4.1. Strengths and limitations

Our sample was composed of Caucasians of European ancestry, so generalizations to other ethnicities cannot be made. The cross-sectional design of this study precludes conclusions with regard to causal relationships. Depressed mood was assessed using the DEEX scale. The DEEX scale is not a common instrument to measure depressive symptomatology, but validity within the framework of depression-to-somatic illness concept has been proven to be highly significant (Ladwig et al., 2004). The DEEX scale with equal cut-points has been proven as a reliable instrument to measure depressive symptoms in several publications (Hafner et al., 2011; Ladwig et al., 2003, 2005, 2006). The DEEX scale focuses on symptoms which measure “vital exhaustion” like reduced vitality and weakness. Items reflecting negative self-concepts, or feelings of guilt and distrust were not included, because the depressive symptoms depletion and tiredness rather than feelings of guilt and hopelessness have been found to be predictive for cardiovascular morbidity and mortality (Appels and Mulder, 1988; Kop et al., 2002; Schulz et al., 2000).

No information was available on the menstrual cycle in women. Therefore, we were not able to control for different phases of
menstruation. Unfortunately, we did not measure any neuroendocrine parameters which could have brought more insight into the relation of inflammation and HPA-axis.

Further studies with longitudinal design, neuroendocrine parameters and genetic analyses need to be done to better understand the mechanism that cause the exaggerated inflammation in depressed and isolated individuals.

Despite these limitations, our study has several strengths, the large number of study participants, the population-based design and particularly the detailed information on metabolic variables and behavioral risk factors of study participants.

Conflicts of interest

All authors declare that there are no conflicts of interest.

Acknowledgments

The authors are grateful for the commitment and involvement of all the study participants and for the work and involvement of the MONICA/KORA Augsburg Study staff. The work was financed by the Helmholtz Zentrum München, German Research Center for Environmental Health, Neuherberg, Germany which is supported by the German Federal Ministry of Education and Research, Berlin, Germany. Additional support for this study was received from research grants from the German Research Foundation (TH-784/2-1); by the European Foundation for the Study of Diabetes; the Federal Ministry of Health (Berlin, Germany); the Ministry of Innovation, Science, Research and Technology of the state North Rhine-Westphalia (Düsseldorf, Germany), and by additional funds provided by the University of Ulm, Germany and the German Diabetes Center.

References


Muller, S., Martin, S., Koenig, W., Hanfli-Moghadam, P., Rathmann, W., Haastert, B., Giani, G., Illig, T., Thoran, B., Kolb, H., 2002. Impaired glucose tolerance is associated with increased serum concentrations of interleukin 6 and co-receptor acute-phase proteins but not TNF-alpha or its receptors. Diabetologia 45, 805–812.


