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# Depression, comorbidities and the TNF-α system

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**Abstract**

Depression has frequently been reported to be associated with other physical diseases and changes in the cytokine system. We aimed to investigate associations between a medical history of depression, its comorbidities and cytokine plasma levels in the Bavarian Nutrition Survey II (BVS II) study sample and in patients suffering from an acute depressive episode.

The BVS II is a representative study of the Bavarian population aged 13–80 years. The disease history of its 1050 participants was assessed through face-to-face interviews. A sub-sample of 568 subjects and 62 additional acutely depressed inpatients of the Max Planck Institute of Psychiatry participated in anthropometric measurements and blood sampling. Tumor necrosis factor-α (TNF-α) and soluble TNF receptor (sTNF-R) p55 and sTNF-R p75 plasma levels were measured using enzyme-linked immunosorbent assays.

A history of depression was associated with a higher incidence of high blood pressure, peptic ulcer, dyslipoproteinemia, osteoporosis, allergic skin rash, atopic eczema and thyroid disease.

Within the BVS II sample, participants with a history of depression differed from subjects who had never had depression with regard to sTNF-R p55 and sTNF-R p75 levels even when controlling for age, BMI and smoking status. Acutely depressed inpatients showed even higher levels of sTNF-R p55 and sTNF-R p75 than subjects in the normal population. TNF-α levels were also significantly elevated in acutely depressed patients.

These results confirm earlier studies regarding the comorbidities of depression and support the hypothesis that activation of the TNF-α system may contribute to the development of a depressive disorder.

## 1. Introduction

### *1.1. Comorbidities of depression*

Most general descriptions of depression that date back to Hippocrates have listed gastrointestinal problems, sleep disturbances, headaches, appetite changes as well as aches and pains of a diffuse nature as common features of depression [3]. Additionally, the depressive disorder seems to be associated with other physical diseases such as vascular diseases including high blood pressure [57], myocardial infarction [39] and cerebrovascular insult [13], diabetes, osteoporosis and peptic ulcers [7], asthma [42], inflammatory bowel disease [32] and hypothyroidism [18].

Several mechanisms leading to comorbidity are possible. First, depression might cause another medical condition. For example, cortisol secretion is increased in depressed patients

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[23]; cortisol is a glucocorticoid leading to high blood glucose levels promoting the development of diabetes mellitus. Therefore, depression and its associated symptoms have been found to constitute a major risk factor in the development of type 2 diabetes [36,45]. Second, various medical diseases have been shown to lead to depression. For example, post-stroke depression develops over months after a cerebrovascular insult [13]. Third, one risk factor could lead to both depression and a somatic disorder. For example, it could be shown that the same allelic combination of the angiotensin I converting enzyme and the G-protein β3-subunit C825T polymorphisms increases the risk of myocardial infarction and the vulnerability for a depressive disorder [5].

### *1.2. Cytokines and depression*

Depression and somatic diseases share a number of common symptoms such as tiredness and powerlessness. This raises the possibility that the cytokine system, which is activated in several somatic diseases and leads to sickness behavior, may also be involved in the development of depression [40]. Moreover, the so-called 'cytokine hypothesis of depression' implies that cytokines represent the key factor in the central mediation of the behavioral, neuroendocrine and neurochemical features of depressive disorders [54].

During the last 5 years, it has been established that pro-inflammatory cytokines such as interleukin-1 (IL-1), IL-6 and tumor necrosis factor-α (TNF-α) induce not only symptoms of sickness, but also true major depressive disorders in physically ill patients with no previous history of mental disorders [10]. For example, TNF-α has been found to be increased in depressed female patients when compared with healthy women [29]. And it was hypothesized that these immune alterations associated with depression may contribute to the pathophysiologic processes associated with osteoporosis, dyslipidemia and diabetes [28,29]. But additionally, alterations in plasma cytokine levels have repeatedly been found in patients suffering from affective disorders independent of a physical illness [16,37,38].

Experimental studies applying immune stimulation in humans [50,51] as well as in rodents [35,64] showed that immune stimulation induces depression-like signs and symptoms supporting the view that inflammatory cytokines are causally involved in behavioral alterations of patients with depressive disorders. Moreover, there is evidence for a cytokine-mediated pathogenesis of depression and fatigue in inflammatory diseases of the brain such as multiple sclerosis [12].

Three different mechanisms might link the activation of the cytokine system, of which TNF-α is a part, to the pathophysiology of depression.

At first, as proinflammatory cytokines and serotonergic homeostasis have both been implicated in the pathophysiology of major psychiatric disorders, various authors [49,65] hypothesized that cytokines might also activate neuronal serotonin transporter. This idea would underline the theory of a serotonin deficiency during depression and the pharmacodynamic mechanism of selective serotonin reuptake inhibitors (SSRI) in the treatment of depression, because SSRIs lead to recovery from depression via deactivation of serotonin transporters. Indeed, Zhu et al. found TNF-α stimulated serotonin uptake in both a rat embryonic raphe cell line and in mouse midbrain and striatal synaptosomes. These results provided evidence that proinflammatory cytokines can acutely regulate neuronal serotonin transporter activity. A mitogen-activated protein kinase may be in involved in this mechanism [65].

Second, immune activation with increased production of pro-inflammatory cytokines activates the tryptophan- and serotonin-degrading enzyme indolamine-2,3-dioxygenase (IDO). The increased consumption of serotonin and its precursor tryptophan due to IDO activation may explain the reduced availability of serotonin in depression. This activation of IDO by proinflammatory cytokines additionally leads to the production of glutamatergic agonists. The role of increased glutamatergic neurotransmission in the pathogenesis of depression is increasingly being discussed [44,62].

Third, it has been postulated that the activation of the cytokine system might play a causative role in the depression-related activation of the HPA system [4,38,47,55,56,59].

However, the role of the soluble TNF-α receptors p55 and p55 (sTNF-R p55 and p75) has not been investigated so far in patients with depressive disorder. One single study in patients with heart failure found elevated sTNF-R p55 levels associated with a higher risk for depression [41].

### *1.3. Aim of the present study*

We sought to investigate associations between a medical history of depression, its comorbidities and cytokine plasma levels in a population-based cross-sectional study, the Bavarian Nutrition Survey II (BVS II). We additionally compared plasma levels of TNF-α and soluble TNF-α receptors of this sample with cytokine plasma levels of acutely depressed patients.

Several other studies compared a patient sample with a small group of controls. In this study, we were able to compare a sample of 62 acutely depressed inpatients with 523 normal controls from the same population.

## 2. Subjects and methods

### *2.1. Subjects*

The Bavarian Nutrition Survey II (BVS II) is a representative study of the Bavarian population aged 13–80 years ($N = 1050$) with the primary purpose of assessing food consumption, physical activity, body weight, medical history and several parameters within the blood. From September 2002 until June 2003, 1050 subjects aged 13–80 years were recruited by a three-stage random route sampling procedure from the German-speaking Bavarian population. This recruitment procedure included the selection of 42 communities as so-called sampling points, a random walk with a given starting address, and a random selection of one household member who meets the selection criteria. At baseline, the subject's characteristics, lifestyle, socio-economic and medical history were

assessed by a computerized face-to-face interview. Disease history contained questions regarding high blood pressure, myocardial infarction, stroke, peptic ulcer, chronic inflammatory bowel disease, colon polyps, diabetes, dyslipoproteinemia (high triglyceride levels or hypercholesterolemia), hyperuricemia or gout, osteoporosis, asthma, allergic rhinitis, allergic skin rash, atopic eczema, psoriasis, food allergy, thyroid disease, depression and cancer. The participating subjects were also asked if they had ever received any medication for these medical conditions. For 1033 of these 1050 subjects complete data sets regarding their medical history were available: 439 males (42.5%) and 594 females (57.5%) with a mean age of 46.5 years (±17.1; 13–80 years) and an average BMI of 25.14 kg/m$^2$ (±4.66; 12.80–61.56). Within this sample, 56 subjects (5.4%) who reported a lifetime incidence of depression constituted the cases with a history of depression for the present study. Lifetime history of depression meant that a physician had diagnosed a depressive episode in those subjects. These subjects were not asked whether they were acutely depressed.

The same procedure was chosen regarding asking about antidepressant treatment, which was therefore reported as treatment sometime during their lifetime. An antidepressant was defined as a medication to treat a depressive episode. Within the following 2 weeks, participants were contacted by phone on two workdays and one weekend day for recalling their dietary intake on the day before. Within 6 weeks after recruitment, all adult study subjects (>18 years) who completely provided the requested dietary information were invited to their nearest health office for blood sampling and standardized anthropometric measurements.

A sub-sample of 568 persons followed this invitation and participated in anthropometric measurements and blood sampling. Due to technical reasons, cytokine levels were available from 558 participants, and cytokine plasma level results and clear data regarding a history of depression were available from 543 participants: 231 males (42.5%) and 312 females (57.5%) with a mean age of 48.8 years (±15.2; 19–80 years) and a mean BMI of 25.4 kg/m$^2$ (±4.2; 16.89–51.11). Within this sub-sample, the BMI was measured, whereas for the total sample it was asked for in the interview. Within the subsample, 35 subjects (6.4%) had a history of depression and were treated as cases. Twenty-seven of these 35 subjects (77%) had been treated with antidepressant medication during their depressive episodes.

For characteristics of the sample see Table 1. For pure distribution of cytokines in this sample see [21].

To gain further insight into the relationship between depression and cytokines we also investigated cytokine levels in acutely depressed patients. Sixty-two consecutive referrals to the hospital of the Max Planck Institute of Psychiatry (Munich, Germany) who participated in the Munich Antidepressant Response Signature (MARS) project were included. All patients fulfilled the criteria of a depressive episode according to ICD-10; the individual diagnosis varied according to ICD-10 criteria within the range of affective spectrum disorders (F31, F32, F33). The mean Hamilton (HAMD) score ± SD was 26.81 ± 7.36 and the mean score of the Beck Depression Inventory (BDI) was 25.61 (10.73).

After a complete description of the MARS project, all patients gave written informed consent to participate in the investigation, which had been approved by an independent ethics committee (Ethics Committee of the Medical School at the Ludwig-Maximilians University Munich, Germany). Substance dependence and severe medical conditions with depressive symptoms such as endocrine disorders or dementia prohibited study enrolment. Physical examination, medical history and baseline laboratory investigations did not reveal any acute or chronic inflammation and infection or autoimmunological, cardiac, pulmonary, endocrinological or hematological disease. These diseases were exclusion criteria, because in patients suffering from infectious diseases or cancer, cytokines could promote the development of depression [46]. Nevertheless, we were not able to exclude all important causes of cytokine system alterations such as acute physical [1] or psychological stress [63] or sleep deprivation and insomnia [25], which are also common during depressive episodes.

### 2.2. Experimental procedure

Within both the BVS II sample and the sample of acutely depressed patients on admission, blood was stabilized with sodium ethylene diamine tetraacetic acid (1 mg/ml), centrifuged and the plasma frozen to −80 °C. Cytokines were measured using commercial enzyme-linked immunosorbent assays (TNF-α, sTNF-R p55, sTNF-R p75 and IL-6; Biosource, Brussels, Belgium). In the sample of acutely depressed patients, we determined only TNF-α, sTNF-R p55 and sTNF-R p75 plasma levels. For all assays the intra- and inter-assay coefficients were below 7 and 9%, respectively. Due to technical reasons, results of the cytokine measurement could be obtained only from 62 of 70 patients of the acutely depressed patients sample

Table 1
Characteristics of the BVS II sample

| | BVS II sample | | | BVS II Sub-sample | | |
|---|---|---|---|---|---|---|
| | Never depressed ($n = 988$) | History of depression ($n = 56$) | | Never depressed ($n = 523$) | History of depression ($n = 35$) | |
| Age (mean ± SD) | 45.82 ± 17.21 | 54.59 ± 13.00 | $F_{(1,1043)} = 14.08$* | 48.22 ± 15.30 | 53.97 ± 14.54 | $F_{(1,558)} = 4.66$* |
| Male/female ratio | 420/568 | 21/35 | $\chi^2 = .54$ ns | 227/296 | 11/24 | $\chi^2 = 1.92$ ns |
| BMI (mean ± SD) | 25.86 ± 5.12 | 28.09 ± 5.69 | $F_{(1,1043)} = 9.64$* | 27.03 ± 4.97 | 26.96 ± 3.77 | $F_{(1,558)} = 0.01$ ns |

SD, standard deviation; * denotes a significant difference ($p < .05$); ns, not significant. Differences between cases and non-cases were explored with analysis of variance (age, BMI) and $\chi^2$-tests (male/female ratio).

and 558 persons of the normal population sample. Within the acutely depressed subjects, we did not measure IL-6 levels.

### 2.3. Data analyses

Differences between study participants with a history of depression and BVS II participants who were never depressed were assessed by analysis of variance (age, BMI) and $\chi^2$-tests (gender). In the BVS II sample simple prevalence rates for comorbidities in subjects with a history of depression were compared to never depressed participants using $\chi^2$-tests. Because participants of both groups differed with regard to age and BMI, logistic regressions were performed computing odds ratios adjusted for these parameters.

In a further analysis, we inquired whether study participants with a history of depression differed from BVS II participants who were never depressed with regard to cytokine levels. This analysis used the subsample of BVS II study participants who followed the invitation to have blood drawn. To that end, a multivariate ANCOVA with the dependent variables TNF-α, sTNF-R p55, sTNF-R p75 and IL-6 were computed with the factors history of depression (yes/no), intake of antidepressant medication (yes/no) and smoking (yes/no) controlling for age and BMI. Only if there was a significant overall effect of depression were these effects followed by single ANCOVAs. Because of substantial skewness of all five cytokine parameters, they were log-transformed prior to their inclusion into the analyses. The same procedure was applied to those conditions that were significantly associated with depression in the complete sample, to explore whether these relevant comorbidities are linked to cytokines. Finally, in the case of those comorbidities that were more frequent in persons with depression and were associated with altered cytokine levels, the above detailed analyses were re-computed taking into account these conditions.

To further characterize cytokine levels in depression, we explored differences in TNF-α, sTNF-R p55 and sTNF-R p75 between persons without a history of depression, persons with a history of depression, and acutely depressed patients on admission using a multivariate ANCOVA with the three log-transformed dependent variables and the factors depression (no/life-time history/acute depressive episode on hospital admission) and intake of antidepressant medication (yes/no) controlling for age and BMI. Again, a significant overall effect of depression was followed by single ANCOVAs.

## 3. Results

### 3.1. Age, BMI, gender and comorbidities

In the BVS II sample 56 (5.4%) persons reported a lifetime history of medically diagnosed depression. Compared to the persons without a life-time history of depression they were significantly older and had a higher BMI (see Table 1). Male/female ratios did not differ between the groups. Subjects with a history of depression had a higher incidence of high blood pressure, peptic ulcer, chronic inflammatory bowel syndrome, diabetes, dyslipoproteinemia, osteoporosis, allergic skin rash, atopic eczema and thyroid disease. However, when controlling for age and BMI, a higher incidence was no longer apparent for high blood pressure, diabetes, chronic inflammatory bowel disease and thyroid disease (Table 2).

### 3.2. Cytokines

The pure descriptive statistics of the distribution of cytokines in the BVS II subsample of study participants which had blood drawn has already been published elsewhere [21]. A multivariate analysis of covariance indicated that subjects with a history of depression had both higher sTNF-R p55 and higher sTNF-R p75 levels than participants without a history of depression (Table 3), even when controlling for age, BMI and smoking status. Among the covariates, age ($F_{(5,548)} = 27.29$, $p < 0.001$), BMI ($F_{(5,548)} = 53.09$, $p < 0.001$) and smoking status ($F_{(5,548)} = 3.92$, $p = 0.002$) but not antidepressant medication ($F_{(5,548)} = 1.79$, $p = 0.114$) were significantly related to cytokines.

Since depression was associated with an increased prevalence of peptic ulcer, dislipoproteinemia, osteoporosis, allergic skin rash, and atopic eczema, we also explored whether these conditions were also associated with altered cytokine levels. Among these five comorbid disorders, only allergic skin rash ($F_{(5,549)} = 2.78$, $p = 0.017$) showed an overall effect on cytokine levels. In particular, persons with a history of allergic skin rash had higher sTNF-R p55 levels. To explore whether

Table 2
Prevalence of comorbidities in subjects with and without a history of depression

| Comorbidities | Prevalence % | | Adjusted odds ratio | 95%CI |
|---|---|---|---|---|
| | Never depressed ($n = 988$) | History of depression ($n = 56$) | | |
| High blood pressure | 20.3 | **41.1*** | 1.85 | 1.00–3.45 |
| Myocardial infarction | 2.8 | 3.6 | 0.91 | 0.20–4.07 |
| Stroke | 1.3 | 1.8 | 0.97 | 0.12–7.71 |
| Peptic ulcer | 5.7 | **16.1*** | 2.47* | 1.14–5.37 |
| Chronic inflammatory bowel disease | 1.6 | **5.4*** | 3.03 | 0.84–10.92 |
| Colon polyps | 2.3 | 3.6 | 1.05 | 0.23–4.69 |
| Diabetes | 6.8 | **14.3*** | 1.46 | 0.62–3.45 |
| Dyslipoproteinemia | 18.4 | **37.5*** | 1.96* | 1.09–3.54 |
| Elevation of uric acid levels or gout | 7.8 | 12.5 | 1.14 | 0.48–2.69 |
| Osteoporosis | 3.2 | **12.5*** | 3.42* | 1.38–8.45 |
| Asthma | 4.9 | 8.9 | 2.20 | 0.82–5.88 |
| Allergic rhinitis | 14.0 | 10.7 | 0.92 | 0.38–2.22 |
| Allergic skin rash | 11.7 | **25.0*** | 2.94* | 1.53–5.64 |
| Atopic eczema | 2.6 | **7.1*** | 3.60* | 1.16–11.15 |
| Psoriasis | 2.7 | 7.1 | 2.47 | 0.82–7.44 |
| Food allergy | 5.4 | 5.4 | 1.08 | 0.32–3.62 |
| Thyroid disease | 13.8 | **23.2*** | 1.61 | 0.84–3.10 |
| Cancer | 2.4 | 5.4 | 1.74 | 0.50–6.05 |

*$p < 05$; CI, confidence interval. Comparison of prevalence rates was done with $\chi^2$-tests; odds ratios were derived from a logistic regression analysis and adjusted for age and BMI.

Table 3
Cytokine concentrations in subjects with an acute depressive episode (acute depression), history of depression and without depression (never depressed)

| | (1) Never depressed ($n = 523$) | (2) History of depression ($n = 35$) | (3) Acute depression ($n = 62$) | Test statistics[a], p Group comparisons[c] |
|---|---|---|---|---|
| **TNF-α(pg/ml)[b]** | | | | |
| Mean ± SD | 12.63 ± 6.71 | 13.87 ± 14.50 | 19.83 ± 9.77 | $F_{(2,614)} = 18.11$, $p < 0.001$ |
| Median (IQR) | 11.45 (8.89–14.55) | 10.87 (8.28–14.46) | 17.95 (13.42–23.37) | (1)(2) < (3) |
| **TNF-R p55 (ng/ml)[b]** | | | | |
| Mean ± SD | 1.85 ± 0.53 | 2.12 ± 1.15 | 2.35 ± 1.29 | $F_{(2,614)} = 13.99$, $p = 0.002$ |
| Median (IQR) | 1.76 (1.50–2.08) | 1.96 (1.59–2.16) | 2.20 (1.79–2.55) | (1) < (2) < (3) |
| **TNF-R p75 (ng/ml)[b]** | | | | |
| Mean ± SD | 4.66 ± 1.54 | 5.48 ± 3.00 | 6.10 ± 3.60 | $F_{(2,614)} = 7.74$, $p = 0.018$ |
| Median (IQR) | 4.34 (3.72–5.32) | 4.79 (4.27–6.00) | 5.26 (4.64–6.76) | (1) < (2) < (3) |
| **IL-6 (pg/ml)[b]** | | | | |
| Mean ± SD | 2.49 ± 6.23 | 2.07 ± 1.48 | | $F_{(1,552)} = 0.02$, $p = 0.878$ |
| Median (IQR) | 1.44 (0.96–2.41) | 1.70 (1.12–2.43) | | |

SD, standard deviation; IQR, interquartile range.
[a] Analysis of covariance of log-transformed cytokine concentrations controlling for age, BMI, and medication.
[b] Unadjusted values.
[c] Post-hoc group comparisons.

the increased sTNF-R p55 levels in subjects with depression were independent of their association with allergic skin rash we conducted a further analysis with both conditions and illness-related medication in the same model. While depression was still related to sTNF-R p55 levels ($F_{(1,550)} = 7.74$, $p = 0.006$), allergic skin rash did not show an independent association with sTNF-R p55 levels ($F_{(1,550)} = 2.65$, $p = 0.104$).

Finally, comparing TNF-α, sTNF-R p55 and sTNF-R p75 levels among never depressed subjects, those having a history of depression, and acutely depressed patients, we found that cytokine levels significantly differed between the groups (mANCOVA effect of depression $F_{(6,1226)} = 8.45$, $p < 0.001$). Specifically, TNF-α levels were higher in patients with acute depression than in subjects without depression or with a life-time history of depression. For both sTNF-R p55 and sTNF-R p75, levels were lowest in subjects without a history of depression, significantly increased in subjects with a life-time history of depression, and even higher in acutely depressed patients (Table 3).

## 4. Discussion

### 4.1. Comorbidity of depression

The prevalence of a depressive disorder within the BVS II sample was rather low (around 6%). This is most probably due to the conservative way depression is assessed. Participants were not asked specific symptoms, but whether a physician had already diagnosed a depression.

Depressive persons exhibited a higher incidence of several physical disorders. These comorbidities of depression are in line with previous studies, which have shown associations of depression with high blood pressure [6,14,33], peptic ulcer [26], chronic inflammatory bowel syndrome [26], diabetes [7,11,36,45,53], dyslipoproteinemia [34], osteoporosis [9,28,29], allergic skin rash and atopic eczema. However, from a methodical point of view, one has to take into account that age and BMI influence this comorbidity. Therefore, we calculated odds ratios using a logistic regression taking age and BMI into account. As a result, this higher incidence was no longer apparent for high blood pressure, diabetes, chronic inflammatory bowel disease and thyroid disease. Regarding the relation between high blood pressure and depression, recent data from the Bogalusa Heart Study support the view that depression has a significant indirect effect – mediated through higher levels of BMI – on the prevalence of hypertension [27]. This may explain why depression is no longer associated with hypertension if the mediator of this effect, the BMI, is used as a control variable.

Adjusted for age and BMI, peptic ulcer, dyslipoproteinemia, osteoporosis, allergic skin rash and atopic eczema were still more frequent in study participants with a history of depression than in study participants who have never been depressed. For the prevalence of comorbidities in subjects with or without a history of depression see Table 2.

Regarding the last two diseases, psychiatric and psychological factors play an important role in at least 30% of dermatological disorders [15]. There is also growing evidence for a positive association of allergic disorders and depression [60]. Theories concerning genetic abnormalities in serotonin metabolism, HPA axis dysfunction and histamine metabolism have been used to explain this phenomenon, but an inflammatory hypothesis explaining the association of depression and allergic skin rash has not been investigated before.

In conclusion, the obtained data seem to be plausible, as the results fit into the previous literature regarding the comorbidities of depression.

### 4.2. High TNF-α, sTNF-R p55 and sTNF-R p75 levels in subjects with depression

TNF-α levels were higher in patients with acute depression than in subjects without depression or with a life-time history

of depression. For both sTNF-R p55 and sTNF-R p75, levels were lowest in subjects without depression, significantly increased in subjects with a life-time history of depression, and even further increased in acutely depressed patients, independently of differences in age, BMI and smoking status. The results of this study confirm earlier research with respect to the higher TNF-α levels in acutely depressed inpatients. The new finding is the elevation of both soluble TNF-α receptors in depressed patients.

Major depression has been reported to be associated with an alteration of various aspects of the innate immune system, including cellular components such as macrophages, neutrophils and natural killer cells, and soluble mediators such as acute-phase reaction proteins and cytokines [48]. It seems to become more and more scientifically accepted that cytokines are involved in the development and maintenance of mood disorders [40].

However, as already mentioned in the introduction, the results of previous studies are inconsistent. Increased as well as decreased levels of inflammatory cytokines have been reported in depression [16,37,38]. Therefore, different subtypes of depression may exist, and one subtype may be causally linked to the cytokine system. Additionally, during different states of a depressive episode, different patterns of cytokine expression may appear. Experimentally it has already been shown that cytokines are able to lead to emotional disturbances in humans [51].

In the recently performed study of the Max Planck Institute of Psychiatry, we found lower TNF-α levels in those patients with an acute depressive episode, which showed a more activated hypothalamus–pituitary–adrenal axis (HPA axis) leading to an over-production of cortisol, which suppresses immune cells releasing TNF-α [20]. But the study reported here shows that depressed patients seem to have higher sTNF-R p55 and p75 levels, although an elevated HPA axis may suppress immune cells and cytokine production. Elevated TNF-α receptor levels seem to be associated with an increased risk of depression.

### *4.3. Possible causes of high sTNF-R p55 and sTNF-R p75 levels in subjects with a history of depression*

It is already known that age [24] and obesity [17] are associated with high sTNF-R p55 and sTNF-R p75 plasma levels. Regarding the complete BVS II sample, the appearance of depression was associated with higher age. Age and BMI could therefore mediate the risk of suffering from depression through the elevation of cytokines.

Several physical disorders are also known to lead to an elevation of cytokines. We wanted to investigate whether the disorders found to be comorbidities of depression in the present study sample go along with high sTNF-R p55 and sTNF-R p75 levels and mediate the cytokine elevation found in depressed patients. But this does not seem to be the case systematically. Therefore, one may conclude that the activation of the TNF-α system in depressed patients is independent of the comorbidity with the other diseases investigated.

In this sample, we could not demonstrate an association of antidepressant treatment and cytokine levels, although there are many reports showing an association for specific antidepressant drugs. The reason may be that participants differed in the type of antidepressant medication. For example, mirtazapine increases the plasma levels of TNF-α and both soluble TNF receptors, whereas venlafaxine does not [31]; on the contrary, bupropion, for example, seems to decrease cytokine plasma levels [8].

### *4.4. Possible psychopharmacological consequences*

Given the results we obtained, the question arises, whether it might be intelligent to treat depressive patients with immunomodulators such as the TNF-α antagonist etanercept or the cyclooxygenase-2 inhibitor celecoxib.

In a prospective study reported by Tyring [61] on patients with psoriasis receiving etanercept, this drug led to a tremendous improvement in the HAMD and BDI depression rating scales at week 12 as compared to the placebo group. In a prospective, double-blind, add-on study of patients suffering from an acute depressive episode, reported by Müller et al. [43], additional treatment with celecoxib had significant positive effects on the therapeutic action of reboxetine with regard to depressive symptoms.

These studies underline the relevance of the contribution of the immune system to the development of depression and the possible therapeutic benefit of immunomodulators in the treatment of depression.

### *4.5. Limitations of the study*

This study has some limitations. Participants of the BVS II were only asked whether their physician had already diagnosed a specific disease or symptom. Therefore, we could only prove associations of disease history with cytokine levels. A study participant may have suffered from a disease without knowing his diagnosis, because he had not attended a physician yet. A participant could also have confused the diagnosis. For example he may have said he suffered from allergic skin rash instead of atopic eczema. As subjects were not asked whether they were acutely depressed, the proportion of acutely depressed subjects within the cases with a lifetime history of depression cannot be determined. That means that it cannot be excluded that the elevated sTNF-R p55 and p75 levels in subjects with a lifetime history of depression may be due to high sTNF-R p55 and p75 levels of a subgroup of acutely depressed subjects.

The BVS II was designed with the primary purpose of assessing food consumption, physical activity, body weight, medical history and several parameters within the blood, not with the purpose of assessing the prevalence of acute depressive symptoms or acute depression within the normal population. Nevertheless, we think that this sample and the applied interview served well to investigate epidemiological relations between lifetime prevalence of depression and lifetime prevalence of other diseases. Furthermore, we think that the BVS II

sample served well as a huge control group for the sample of acutely depressed inpatients, although we did not assess for specific symptoms of depression in the BVS II sample.

Unfortunately, we did not ask the participants about the use of anti-inflammatory medication. We only asked for a lifetime history of specific inflammatory or allergic diseases and the lifetime use of medication against these disorders. This may be a limitation for interpreting the data gained from this investigation.

The study was limited to plasma levels of TNF-α and its soluble receptors. Unfortunately, other inflammatory and anti-inflammatory cytokines were not assessed in this study. We chose the TNF-α system, because significant findings regarding its involvement in brain disorders — such as depression, narcolepsy, multiple sclerosis, Alzheimer's and Parkinson's disease — and psychopharmacology have been reported in several study reports. It could be shown that an activation of the TNF-α system might promote the development of psychiatric or neurological symptoms or disorders. Additionally, endocrine changes associated with brain disorders may lead to alterations of the TNF-α system [19]. It would also have been useful to determine the concentration of an anti-inflammatory cytokine such as IL-10 or IL-4 to determine the degree of imbalance between the inflammatory and anti-inflammatory arms of the immune system.

We did not investigate C-reactive protein levels, although this would have been of specific scientific value. However, an investigation of 3884 adults at age 60 and older did not reveal increased CRP levels in depressed subjects after controlling for confounders [58]. In contrast, in the mentioned study and in another study [28], high levels of cytokine IL-6 were associated with depressive disorders. We could not replicate this finding within the BVS II sample. But this negative result should not be over-interpreted as we did not measure IL-6 levels in the sample of acutely depressed patients. And comparing with the result for TNF-α levels in this investigation, the only difference regarding TNF-α levels was found between acutely depressed inpatients and the subjects from the BVS II sample out of the normal population.

Another parameter which would have been interesting to determine is cortisol because of its importance in the psychopathology of depression [23] and co-morbid disorders. Additionally, the hypothalamus–pituitary–adrenal (HPA) axis influences cytokine production and vice versa [2,20,30,52]. Although this additional parameter would have been desirable, we focused on the TNF-α system and IL-6 plasma levels in this study and did not determine cortisol levels.

As this is a cross-sectional but not a longitudinal study, caution is recommended regarding conclusions about causality. The conclusion that elevated cytokine levels may contribute to the pathogenesis of depression is derived from earlier literature, but cannot be substantiated from our data. Therefore, it would be necessary to strengthen experimental and longitudinal research in animals and humans investigating the effect of cytokines on mood over a certain period of time.

Psychotropic drugs influence the TNF-α system by normalizing the HPA axis changes [20] associated with psychiatric diseases and inducing weight gain [66] and liver damage [22]. Several side effects of psychotropic drugs resemble brain disorders in which the TNF-α system plays an important pathogenetic role [19].

Therefore, another limitation of the study is that participants of the BVS II and the MARS study were not necessarily free of psychotropic drugs. Although there were no statistical hints for an overall effect of antidepressant medication in both study groups, effects of specific medication may not be considered.

## 5. Conclusion

These results confirm the outcome of previous studies that depression is associated with several other physical diseases. The novel finding of this study is that subjects with a history of depression differed from never depressed subjects with regard to sTNF-R p55 and sTNF-R p75 levels, and that acutely depressed inpatients showed even higher levels of sTNF-R p55 and sTNF-R p75 than persons from the normal population.

TNF-α levels were also significantly elevated in acutely depressed patients. These results support the hypothesis that an activation of the TNF-α system may contribute to the development of a depressive disorder.

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