# TNF-α, soluble TNF receptor and interleukin-6 plasma levels in the general population

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**ABSTRACT. The cytokines tumor necrosis factor-α (TNF-α), soluble TNF receptors p55 and p75, and interleukin 6 (IL-6) are involved in host defense against several microbiological agents, in the process of inflammation and also in body weight regulation. In the present study, we sought to assess the influence of age, gender, smoking, and body mass index on plasma levels of TNF-α, TNF receptors, and IL-6 in more than 550 adult subjects randomly selected from the Bavarian population. None of the cytokine parameters had a normal distribution and all distributions were significantly skewed. The cytokine plasma levels investigated increased significantly with age, while gender had a relatively weaker influence on the plasma levels. Plasma levels of TNF-α, TNF receptors, and IL-6 correlated significantly with the BMI. The study provides insights into factors influencing the cytokine levels investigated in a randomly chosen study sample.**

**Keywords:** TNF-α, TNF receptor, IL-6, BMI, age

Tumor necrosis factor-α (TNF-α) was originally characterized as an antitumor agent inducing cachexia and inflammation [1]. It is now clear that it plays an important role in the defense against viral, bacterial, and parasitic infections as well as in autoimmune responses and energy homeostasis. Physiological induction of TNF-α production is protective, but its overproduction may be detrimental and even lethal to the host [2]. Apart from cardiovascular [3, 4], inflammatory [5], infectious [6] and psychiatric diseases [7], age [8-10] and body fat mass [11-13] seem to influence plasma levels of TNF-α as well.

However, much less is known about serum levels of its soluble receptors sTNF-R p55 and sTNF-R p75. In a first normative study conducted by Maier *et al*. [14], who investigated plasma levels of sTNF-R p55 and sTNF-R p75 in 113 healthy patients, the concentration range of these molecules in the plasma was as follows: sTNF-R p55: 0.2–2.6 ng/mL and sTNF-R p75: 0.7–5 ng/mL.

Similar to TNF-α, IL-6 is a multifunctional, proinflammatory cytokine produced by both lymphoid and nonlymphoid cells [15].

We sought to assess the influence of age, gender, smoking, body mass index (BMI), and the effect of selected diseases on plasma levels of TNF-α, its soluble receptors p55 and p75, and IL-6 in more than 500 adults randomly chosen from the Bavarian population.

## METHODS

### *Patients*

The second Bavarian Nutrition Survey (BVS II) is a representative, cross-sectional study of the Bavarian population aged 13-80 years (n = 1050). From September 2002 until June 2003, 1050 subjects were recruited from the German-speaking Bavarian population by a three-stage random route sampling procedure including the selection of 42 communities as sample points (stratified by county and community characteristics), a random walk (every third household) with a given start address, and a random selection of one household member. At baseline, subjects' characteristics, lifestyle, and medical history were assessed by a computerized, face-to-face interview. Within six weeks of recruitment, all adults (18 years or older) who completed the baseline interview (n = 879) were invited to their nearest public health office for blood sampling and standardized anthropometrical measurements.

Five hundred and sixty eight people accepted this invitation and participated in the anthropometrical measurements and blood sampling. Due to technical reasons, cytokine plasma levels were only able to be measured in 558 participants (235 males and 323 females, age: 51 + 16 years (mean + SD); range: 19-80 years).

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BMI was calculated as measured weight divided by the square of measured height (kg/m$^2$). For details of this sample and medical history including diabetes, hypertension, chronic inflammatory bowel disease, and cancer see *table 1*. The study was approved by an independent ethics committee (Bayerische Landesärztekammer).

### *Procedure*

Blood was stabilized with sodium ethylenediamine tetraacetic acid (1 mg/mL) and aprotinin (300 kIU/mL) and immediately centrifuged; the plasma was frozen to -20°C. Cytokines were measured with commercial enzyme-linked immunosorbent assays (TNF-α, sTNF-R p55, sTNF-R p75 and IL-6 [Biosource, Brussels, Belgium]). For all assays, the intra- and inter-assay coefficients were below 7 and 9%, respectively.

### *Data analyses*

Minimum and maximum, as well as selected percentiles (5%, 25%, 50%, 75%, 95%), were determined for each parameter. The distribution of cytokine levels was tested for normality using the Kolgomorov-Smirnov (K-S) test, and suitable transformations across the ladder of powers were sought to achieve normality of the data and thus allow for parametric modelling including the evaluation of possible interaction effects. Because of a bi-modal distribution, age was categorized into 6 groups: 19 to 29, 30 to 39, 40 to 49, 50 to 59, 60 to 69, and 70 years or above. BMI was categorized into 3 groups: normal weight (BMI < 25 kg/m$^2$), overweight (BMI 25-30 kg/m$^2$), and obese (BMI ≥ 30 kg/m$^2$). BMI was analysed as a categorical variable in all analyses. In a first analysis, the influence of age and gender was determined with a 2 (gender) x 6 (age group) analysis of variance (ANOVA). In a second analysis, the influence of BMI, smoking status, and lifetime history of hypertension and diabetes were assessed by ANOVA controlling for potential confounders such as age or gender. Two-way interaction effects were considered in all analyses. Significant effects were followed up with *post hoc* comparisons (Bonferroni corrected).

### *Distribution of cytokine levels*

None of the parameters (TNF-α, sTNF-R p55, sTNF-R p75, and IL-6) had a normal distribution (K-S test, $p < 0.05$) and all were significantly skewed. $Log_{10}$ transformations were used to normalize the distribution for TNF-α (K-S, $p = 0.217$) and sTNF-R p55 (K-S, $p = 0.230$), whereas the $log_{10}$-transformed values of sTNF-R p75 and IL-6 were still not normally distributed (K-S, $p = 0.070$ and K-S, $p = 0.030$, respectively). A power transformation with -1 resulted in a normal distribution for sTNF-R p75 (K-S, $p = 0.325$). For IL-6, 5 outliers were detected with exceptionally high values: while for 552 subjects, IL-6 levels ranged between 0.25 and 11.64 pg/mL, the levels of those five outliers were substantially higher (51.5 pg/mL, 61.8 pg/mL, 68.92 pg/mL, 93.62 pg/mL, and 620.6 pg/mL). After exclusion of these outliers and $log_{10}$ transformation, the IL-6 levels no longer deviated from a normal distribution (K-S, $p = 0.272$).

**Table 1**
Description of the study sample

| | Male | | Female | | Total | |
|---|---|---|---|---|---|---|
| | N | % | N | % | N | % |
| Age group (years) | | | | | | |
| 19-29 | 23 | 9.8 | 35 | 10.8 | 58 | 10.4 |
| 30-39 | 43 | 18.3 | 85 | 26.3 | 128 | 22.9 |
| 40-49 | 40 | 17.0 | 82 | 25.4 | 122 | 21.9 |
| 50-59 | 40 | 17.0 | 47 | 14.6 | 87 | 15.6 |
| 60-69 | 61 | 26.0 | 48 | 14.9 | 109 | 19.5 |
| ≥ 70 | 28 | 11.9 | 26 | 8.0 | 54 | 9.7 |
| BMI (kg/m$^2$) | | | | | | |
| ≤ 25 | 69 | 29.4 | 145 | 44.9 | 214 | 38.4 |
| >25-30 | 107 | 45.5 | 112 | 34.7 | 219 | 39.2 |
| > 30 | 59 | 25.1 | 66 | 20.4 | 125 | 22.4 |
| Smoking status | | | | | | |
| Current smoker | 71 | 30.2 | 67 | 20.8 | 138 | 24.8 |
| History of smoking | 70 | 29.8 | 60 | 18.6 | 130 | 23.3 |
| Never smoked | 94 | 40.0 | 195 | 60.6 | 289 | 51.9 |
| Life time history | | | | | | |
| Hypertension | 59 | 25.1 | 63 | 19.5 | 122 | 21.9 |
| Diabetes | 18 | 7.7 | 20 | 6.2 | 38 | 6.8 |
| Chronic inflammatory bowel disease | 3 | 1.3 | 4 | 1.2 | 7 | 1.3 |
| Cancer | 7 | 3.0 | 9 | 2.8 | 16 | 2.9 |

## RESULTS

### *Association of cytokine levels with gender and age*

Log-transformed TNF-α levels were significantly associated with gender and age *(table 2)*. Gender explained 0.9% of the variation, and females showed slightly lower TNF-α levels than males. Differences between the age groups accounted for 14.1% of the variation in TNF-α levels. *Post hoc* comparisons revealed that subjects in the oldest age group (≥ 70 years) had significantly higher TNF-α levels than all other groups ($p < 0.05$, for medians and interquartile ranges see *table 2*, for pairwise comparisons see *figure 1*).

Log-transformed sTNF-R p55 levels were significantly associated with age and gender. Differences between males and females explained 1.0% of the variance of TNF-R p55 levels, with females showing lower levels than males. Age accounted for 22.1% of the variance, and mean sTNF-R p55 levels increased across the age groups. Similarly to TNF-α, the oldest subjects (≥ 70 years) had the highest levels *(table 2*, *figure 1)*.

Levels of sTNF-R $p75^{-1}$ were also only associated with age, which accounted for 17.3% of the variance, but not with gender. sTNF-R p75 levels were again lowest in the younger age groups (19-49 years) and highest in the oldest (≥ 70 years) age group (*post hoc* comparisons, $p < 0.05$, *table 2*).

Log-transformed IL-6 levels were associated with age (accounting for 18.7% of the variance), but not with gender. IL-6 levels were again lowest in the youngest age groups (19-49), which had significantly lower levels than each of the older age groups (50 ≥ 70).

### *Association of cytokine levels with BMI, smoking status, hypertension, and diabetes*

Cytokine levels were not associated with smoking status, history of diabetes or hypertension when controlled for age, gender, and BMI. TNF-α levels were not associated with BMI, but for sTNF-R p55, sTNF-R p 75, and IL-6 the levels increased with increasing body weight even when controlling for age and gender *(figure 1*, for F-values and test statistics see *table 2)*. *Post hoc* comparisons revealed that for both sTNF-R p55 (3.5% explained variance) and sTNF-R p75 (1.8% explained variance) cytokine levels were significantly higher in overweight and obese subjects when compared to normal-weight individuals. IL-6 levels were significantly higher in overweight subjects compared to normal weight individuals and even higher in obese subjects (*post hoc* comparisons $p < 0.05$).

## DISCUSSION

### *Influence of age and gender on cytokine plasma levels*

In the present study, we show that levels of TNF-α, sTNF-R p55, sTNF-R p75, and IL-6 increase with age, and that gender has only a minor influence on the plasma levels of these cytokines. Age predicted cytokine levels significantly, strongly, and independently of the BMI.

According to Bruunsgaard *et al*., chronic low-grade inflammation in aging promotes an atherogenic profile and is related to age-associated disorders such as Alzheimer's disease, atherosclerosis, type 2 diabetes, and an enhanced mortality risk [16]. Inflammatory mediators seem to be strong predictors of mortality [17]. Thus, a dysregulated production of inflammatory cytokines seems to play an

**Table 2**
TNF-α, sTNF-R p55, sTNF-R p75, and IL-6 plasma levels stratified by age and the ANOVA results, showing the influence of age, gender and BMI on these cytokine levels

| Age group | n | Median | IQR | 5-95% | ANOVA (F, p) |
|---|---|---|---|---|---|
| **TNF-α** | | | | | |
| 19-49 | 307 | 10.30 | 7.91-12.73 | 5.45-19.86 | Age: $F_{5,550} = 18.13$, $p < 0.01$ |
| 50-69 | 196 | 12.71 | 9.82-15.13 | 6.92-22.84 | Gender: $F_{1,550} = 4.84$, $p = 0.03$ |
| > 70 | 54 | 16.48 | 13.73-20.54 | 9.20-39.06 | BMI: $F_{1,548} = 2.56$, $p = 0.08$ |
| **sTNF-R p55** | | | | | |
| 19-49 | 308 | 1.63 | 1.44-1.89 | 1.19-2.27 | Age: $F_{5,551} = 31.22$, $p < 0.01$ |
| 50-69 | 196 | 1.88 | 1.59-2.18 | 1.30-2.73 | Gender: $F_{1,551} = 5.33$, $p = 0.02$ |
| > 70 | 54 | 2.47 | 1.98-2.92 | 1.59-5.07 | BMI: $F_{1,549} = 9.83$, $p = < 0.01$ |
| **sTNF-R p75** | | | | | |
| 19-49 | 308 | 4.03 | 3.47-4.69 | 2.82-5.94 | Age: $F_{5,552} = 23.07$, $p < 0.01$ |
| 50-69 | 196 | 4.78 | 4.04-5.61 | 3.32-6.86 | Gender: $F_{1,551} = 2.87$, $p = 0.09$ |
| > 70 | 54 | 6.21 | 4.77-7.50 | 4.02-11.31 | BMI: $F_{1,549} = 5.02$, $p = 0.01$ |
| **Il-6** | | | | | |
| 19-49 | 186 | 1.13 | 0.76-1.80 | 0.43-5.61 | Age: $F_{5,546} = 25.17$, $p < 0.01$ |
| 50 to ≥ 70 | 122 | 2.05 | 1.32-3.09 | 0.85-5.69 | Gender: $F_{1,545} = 3.43$, $p = 0.06$ |
| | | | | | BMI: $F_{1,543} = 28.64$, $p < 0.01$ |

IQR: interquartile range, BMI: body mass index.

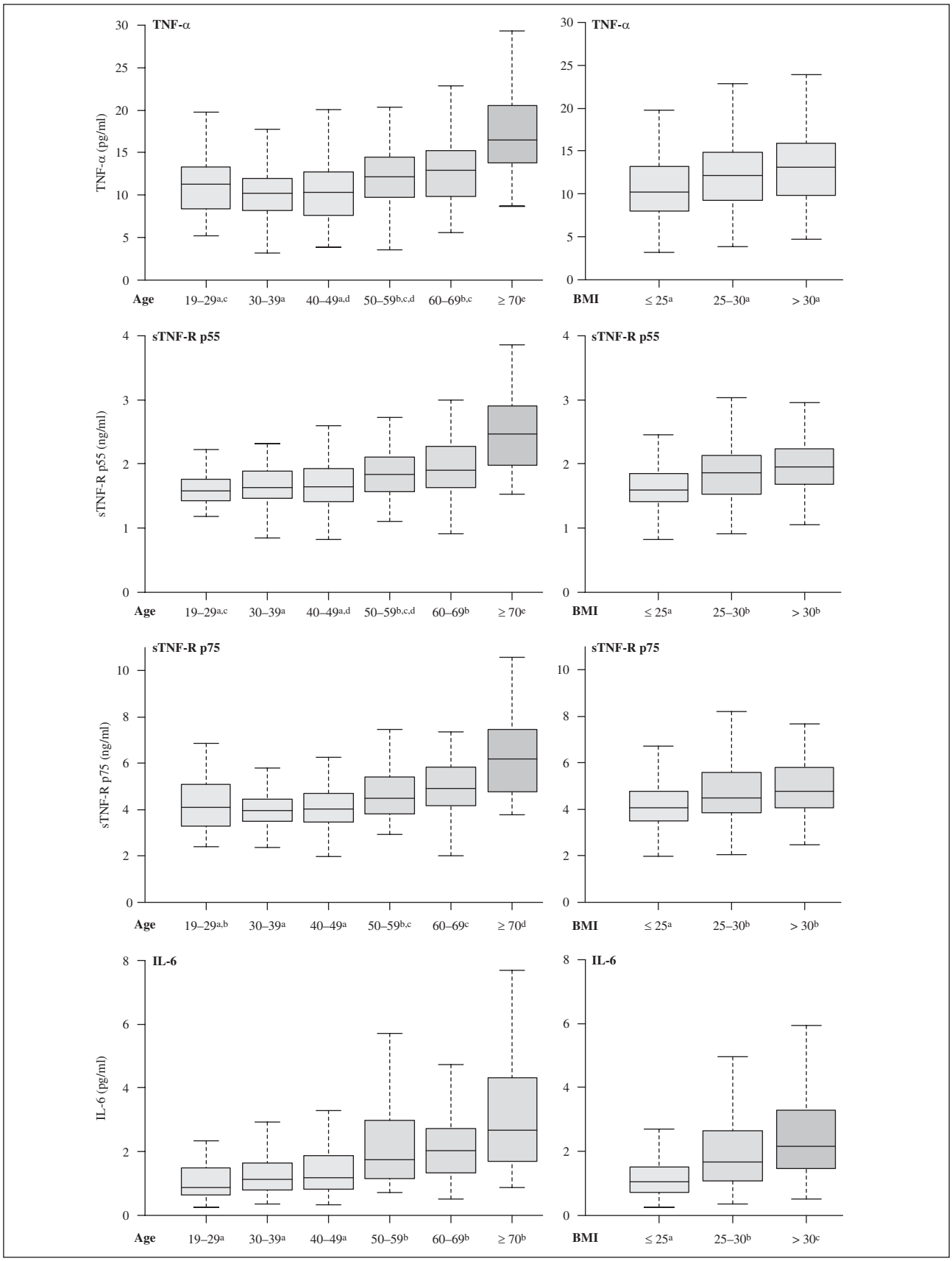


**Figure 1**

Boxplots of cytokine levels in relation to age and BMI. The boxes show the median of the cytokine levels as a line and the first (25th percentile) and third quartile (75th percentile) of the distribution as the lower and upper parts of the box. The whiskers represent the 5$^{th}$ and 95$^{th}$ percentile values. Group labels that share the same superscript (**A**-**E**) do not differ from each other (*post hoc* pairwise comparisons, Bonferroni corrected). Colour-coding of boxes for age groups refers to descriptive statistics given in *table 2*, colour-coding for BMI refers to group differences.

important role in the process of aging. Some other causes as to why plasma levels of TNF-α and its receptors, as well as IL-6 plasma levels increase with age, may be the increasing body fat mass during aging [18, 19], changes in sex hormones such as the decline of testosterone levels in aging men [20], and the loss of muscle mass during aging [12].

### *Influence of BMI on cytokine plasma levels*

The BMI was found to be associated with plasma levels of the sTNF-Rs and IL-6. This finding is in accordance with previous studies [11-13, 21, 22], which also found an impact of BMI on inflammation markers. Adipocytes may produce and secrete several proteins including TNF-α, its receptors, and IL-6, but recent data indicate that white adipose tissue is infiltrated by macrophages, which may be a major source of locally-produced pro-inflammatory cytokines [22].
As increased proinflammatory cytokine levels are known to be associated with cardiovascular disease [23-25], silent brain infarctions [26], and a worse prognosis after stroke [27], Park *et al*. concluded that the positive associations of obesity and visceral adiposity with elevated cytokine levels suggest the importance of reducing obesity and visceral adiposity to prevent elevations in cytokine levels and associated diseases [11].

### *Diabetes, hypertension, and cytokine plasma levels*

Diabetes and hypertension are both reported to be associated with higher cytokine levels [28], but these findings could not be reproduced in the present study sample. Indeed, in our study the positive association between cytokine levels and these disorders disappeared when controlling for age and BMI. The methodological limitations given by the cross-sectional study design do not allow for investigating the influence of cytokines on these disorders independently of the anthropometrical measures. In the present study, information on diabetes and hypertension was derived from interviews rather than blood pressure measurements or oral glucose tolerance testing, which reduces the reliability of these data.

### *Methodical issues*

A weakness of this study is that only one assay was used to assess TNF, TNF-R p55, and p75 levels, although it is known that variations between methods may occur; additionally, for the same method, variations may occur between different commercial kits. Thus, research groups using R&D system kits [4, 6, 8, 23] report normal levels below 5 pg/mL, whereas groups using the Biosource kits – as we did in this study – report higher levels. Therefore, comparisons between other studies are difficult, and these data have only restricted usefulness as references values.

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