

Original Article

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# Relations of Visceral and Abdominal Subcutaneous Adipose Tissue, Body Mass Index, and Waist Circumference to Serum Concentrations of Parameters of Chronic Inflammation

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## Key Words

Chronic inflammation · Visceral adipose tissue · Subcutaneous adipose tissue · Ultrasonography

## Abstract

**Background:** Different measures of body fat composition may vary in their relations to parameters of chronic inflammation. **Methods:** We assessed the relations of visceral (VAT) and subcutaneous adipose tissue (SAT), BMI, and waist circumference (WC) to serum concentrations of high-sensitive C-reactive protein (hs-CRP), tumor necrosis factor alpha (TNF- $\alpha$ ), interleukin-6 (IL-6), resistin, and adiponectin in 97 healthy adults using multivariate linear regression models, adjusted for age, sex, smoking, physical activity, menopausal status, and use of aspirin or non-steroidal anti-inflammatory drugs (NSAIDs). Parameters of chronic inflammation were mutually adjusted. **Results:** VAT ( $\beta = 0.34$ ), SAT ( $\beta = 0.43$ ), BMI ( $\beta = 0.40$ ), and WC ( $\beta = 0.47$ ) were all significantly associated with hs-CRP. BMI was additionally inversely related to adiponectin ( $\beta = -0.29$ ). In exploratory subgroup analyses defined by gender, BMI, smoking, and use of aspirin or NSAIDs, VAT was the strongest indicator for increased levels of IL-6, SAT was the most consistent indicator for increased levels of hs-CRP, and BMI was the most consistent indicator for decreased levels of adiponectin. WC showed to be a weak indicator for increased levels of hs-CRP and decreased levels of adiponectin. **Conclusion:** VAT, SAT, BMI, and WC show distinct associations with parameters of chronic inflammation. Whether these differences reflect differential metabolic risks requires clarification by longitudinal studies.

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Published by S. Karger GmbH, Freiburg

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## Introduction

Obesity is a major public health problem, the prevalence of which has doubled since 1980 in the developed and in many developing parts of the world [1]. Obesity is a strong predictor of diabetes mellitus, hypertension, stroke, and several types of cancer [2–4]. What drives the association between obesity and metabolic diseases remains unclear. Visceral adipose tissue (VAT) has been considered to have multiple endocrine, metabolic, and immunological functions and may be more strongly associated with cardiometabolic risk factors than subcutaneous adipose tissue (SAT) [5–9]. However, data examining potential differences between VAT and SAT with regard to cardiometabolic risk factors are not entirely consistent [10].

In obesity, adipocytes are enlarged, and their secretory properties are altered [11]. Specifically serum levels of tumor necrosis factor alpha (TNF- $\alpha$ ), interleukin-6 (IL-6), and high-sensitive C-reactive protein (hs-CRP) are increased, while adiponectin is decreased [12]. Whether obesity is related to resistin is unclear [13–17]. Systemic inflammation plays a major role in all stages of atherosclerosis, from initiation over progression to rupture of atherosclerotic plaques [18]. Moreover, increased circulating levels of hs-CRP, IL-6, and TNF- $\alpha$  are associated with worse cardiovascular outcomes [19, 20].

Previous studies examining the associations between obesity and inflammatory cytokines used BMI, waist circumference (WC) or waist-to-hip ratio (WHR) as underlying measure of adiposity [16, 17, 21–31]. Because those measures do not differentiate between VAT and SAT, they were unable to fully characterize body fat distribution patterns. Of the studies that did consider body fat distribution, most focused on VAT [24, 26, 32–38], but less is known about the associations between SAT and parameters of systemic chronic inflammation. Specifically the relation between SAT and hs-CRP has been studied to some extent [24, 32–35, 37–39], whereas the associations between SAT and IL-6, TNF- $\alpha$  [33, 34, 37, 38, 40], resistin [41, 42], or adiponectin [35, 40, 43, 44] have not been targeted sufficiently. In addition, results are inconsistent, and only few studies that examined the relation between VAT or SAT and inflammatory parameters [33, 38, 43] reported results from multivariate analyses. Moreover, no study has compared different measures of obesity with regard to their relations to parameters of chronic inflammation. Thus, we sought to examine the relations of VAT, SAT, BMI, and WC to selected parameters of systemic chronic inflammation in healthy adults.

## Material and Methods

### *Study Design and Population*

A cross-sectional study was conducted in Germany between June and August 2011. A total of 97 participants (55 women, 42 men) aged 22–69 years were randomly selected through the local population registry. The study was conducted according to the Declaration of Helsinki guidelines and approved by the local ethics committee. Written informed consent was obtained from all participants.

### *Anthropometric Measurements*

VAT and SAT were quantified using a B-mode ultrasound machine (Mindray DP-50; Mindray Medical Germany GmbH, Darmstadt, Germany) and a 3.5–5.0 MHz convex array transducer. Measurements were performed according to a strict protocol, details of which are described elsewhere [45]. Briefly, the method involved multiple image planes that provided information on adipose tissue thickness. The SAT measurement involved one individual image plane at the median line extending from the skin to the linea alba. VAT was measured using a second image plane reaching from the linea alba to the lumbar vertebra corpus at the median line. All measurements were performed manually by the same examiner at the end of normal expiration applying minimal pressure without displacement of the intra-abdominal contents as verified by the ultrasound image. The parameters from the images were manually extracted using the electronic onboard caliper and were stored directly in a database. Height and weight were measured with participants wearing

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underwear without shoes. BMI was calculated by dividing body weight (kg) by height in meters squared (m<sup>2</sup>). Waist circumference was measured at the mid-point between the lower rib and the iliac crest. Measurements were taken with the participant standing in an upright position.

#### *Serum Analysis*

Non-fasting venous blood was drawn by qualified medical staff. Blood was immediately fractionated into serum, plasma, buffy coat, and erythrocytes and aliquoted into straws of 0.5 ml each according to a standardized protocol. During blood withdrawal and processing, time and room temperature were steadily documented. The straws were stored in conventional tubes at –80 °C. Serum concentrations of TNF- $\alpha$ , IL-6, resistin, and adiponectin were measured using an enzyme-linked immunosorbent assay (Immundiagnostik, Bensheim, Germany), and hs-CRP was determined by immunonephelometry (Behring Nephelometer II, Dade Behring, Marburg, Germany).

#### *Covariate Assessment*

Potential confounding variables including age, sex, current smoking status, physical activity, use of aspirin or non-steroidal anti-inflammatory drugs (NSAIDs), and menopausal status in women were assessed by standardized computer-assisted personal interviews specifically developed for the study. Smoking status was categorized as currently smoking or non-smoking. Physical activity levels were calculated from metabolic equivalents of task (METs) by a 24-hour physical activity recall. Drug use during the previous 7 days was documented by pharmaceutical control numbers using codes of the anatomical therapeutic chemical classification system.

#### *Statistical Analysis*

Descriptive statistics were calculated using direct standardization according to the age distribution of the study population and stratified by VAT and SAT tertiles. The data regarding hs-CRP, TNF- $\alpha$ , IL-6, resistin, and adiponectin were not distributed normally and were therefore log transformed for further analyses. We calculated Pearson correlations between measures of obesity and between selected parameters of systemic chronic inflammation. In addition, we calculated partial correlation coefficients between inflammatory parameters adjusted for age, sex, current smoking status, physical activity, menopausal status, and use of aspirin or NSAIDs.

Multivariate linear regression analysis was performed to estimate relations of VAT, SAT, BMI, and WC to hs-CRP, IL-6, TNF- $\alpha$ , resistin, and adiponectin, adjusted for age (continuous), sex (men; women), smoking status (currently smoking; non-smoking), physical activity (continuous), menopausal status (pre-, peri-, or postmenopausal), and aspirin or NSAID use (drug use during the past 7 days: yes; no). In a second model, all parameters of chronic inflammation were mutually adjusted in addition to the adjustments described in the first model. In a third model, VAT and SAT were mutually adjusted, and BMI and WC were mutually adjusted. We also ran exploratory analyses stratified by sex, BMI, smoking status, and aspirin or NSAID use. Before fitting the linear regression models, all variables (independent and dependent) were standardized by subtracting the mean and dividing by the standard deviation to make relations comparable. When reporting the results from the linear regression models,  $\beta$ -coefficients were considered weak ( $\beta \leq 0.3$ ), moderate ( $\beta > 0.3$  to  $\leq 0.6$ ), or strong ( $\beta > 0.6$ ). All reported p values are two-tailed, and values  $< 0.05$  were deemed statistically significant. IBM SPSS statistics 22 (Chicago, IL, USA) was used for all analyses.

## **Results**

### *Subject Characteristics*

Characteristics of the study population are presented in table 1. The mean age of study participants was 53.5 years. Participants in the upper VAT tertile ( $\geq 8.07$  cm) tended to be older, to be of male gender, to have higher levels of BMI and WC, and to be more likely to report using aspirin or NSAIDs than those in the lower VAT tertile ( $\leq 5.66$  cm). In contrast, study subjects with high VAT were less likely to currently smoke than those with low VAT. There were no appreciable differences in physical activity levels according to VAT. Participants in the upper SAT tertile ( $\geq 2.15$  cm) were more likely to be of female gender, to have

**Table 1.** Age-standardized characteristics of participants according to tertiles of VAT and SAT<sup>a</sup>

| Characteristic              | VAT                     |                                 |                        | SAT                     |                                 |                         |
|-----------------------------|-------------------------|---------------------------------|------------------------|-------------------------|---------------------------------|-------------------------|
|                             | tertile 1<br>(≤5.66 cm) | tertile 2<br>(5.67 to ≤8.06 cm) | tertile 3<br>(≥8.07cm) | tertile 1<br>(≤1.62 cm) | tertile 2<br>(1.63 to ≤2.14 cm) | tertile 3<br>(≥2.15 cm) |
| Number of participants      | 32                      | 33                              | 32                     | 32                      | 33                              | 32                      |
| Age, years                  | 48                      | 55                              | 58                     | 49                      | 59                              | 52                      |
| Sex, % men                  | 29                      | 46                              | 59                     | 47                      | 44                              | 35                      |
| BMI, kg/m <sup>2</sup>      | 23.5                    | 26.1                            | 31.6                   | 24.0                    | 27.6                            | 29.4                    |
| WC, cm                      | 80.9                    | 90.1                            | 105                    | 84.1                    | 92.6                            | 97.6                    |
| Smoking, %                  | 24                      | 19                              | 19                     | 24                      | 23                              | 14                      |
| Physical activity level     | 1.7                     | 1.7                             | 1.7                    | 1.7                     | 1.8                             | 1.7                     |
| Use of aspirin or NSAIDs, % | 5                       | 21                              | 21                     | 11                      | 19                              | 16                      |

<sup>a</sup>Continuous variables values are expressed as mean values and categorical variables are expressed as proportions.

**Table 2.** Markers of systemic chronic inflammation by gender (women: n = 55; men: n = 42)

|                        | Women         | Men           | Total         |
|------------------------|---------------|---------------|---------------|
| Age, years             | 55.55 ± 10.18 | 50.81 ± 14.52 | 53.49 ± 12.41 |
| VAT, cm                | 6.79 ± 3.22   | 8.39 ± 3.64   | 7.48 ± 3.48   |
| SAT, cm                | 2.05 ± 0.77   | 1.89 ± 0.89   | 1.98 ± 0.82   |
| BMI, kg/m <sup>2</sup> | 26.46 ± 4.91  | 27.57 ± 4.39  | 26.94 ± 4.68  |
| WC, cm                 | 86.60 ± 12.30 | 97.83 ± 13.30 | 91.51 ± 13.86 |
| hs-CRP, mg/dl          | 0.15 ± 0.12   | 0.20 ± 0.26   | 0.17 ± 0.19   |
| TNF-α, pg/ml           | 6.18 ± 2.10   | 6.89 ± 2.53   | 6.49 ± 2.31   |
| IL-6, pg/ml            | 2.42 ± 2.48   | 3.00 ± 4.97   | 2.67 ± 3.76   |
| Resistin, ng/ml        | 3.49 ± 1.16   | 3.65 ± 1.07   | 3.56 ± 1.12   |
| Adiponectin, μg/ml     | 14.04 ± 5.25  | 9.34 ± 4.04   | 12.00 ± 5.28  |

Results are expressed as mean value ± SD.

higher levels of BMI and WC, and to be less likely to currently smoke than those in the intermediate (1.63 to ≤2.14 cm) or lower SAT tertile (≤1.62 cm). There were no appreciable differences in physical activity levels according to SAT. The mean concentrations of selected parameters of chronic inflammation were generally higher in men compared to women, with the exception of adiponectin, which was higher in women than in men (table 2).

VAT was significantly positively correlated with SAT ( $r = 0.37$ ;  $p < 0.0001$ ), BMI ( $r = 0.83$ ;  $p < 0.0001$ ), and WC ( $r = 0.79$ ;  $p < 0.0001$ ). As compared to VAT, SAT showed weaker correlations with BMI ( $r = 0.59$ ;  $p < 0.0001$ ) and WC ( $r = 0.51$ ;  $p < 0.0001$ ). BMI and WC were highly correlated with each other ( $r = 0.85$ ;  $p < 0.0001$ ) (data not tabulated).

Hs-CRP was significantly positively correlated with TNF-α ( $r = 0.21$ ;  $p = 0.04$ ) but was not significantly correlated with IL-6, resistin, or adiponectin (table 3). After adjustment for age, sex, smoking, physical activity, menopausal status and aspirin or NSAID use, the only statistically significant partial correlation was that between adiponectin and TNF-α ( $r = 0.31$ ;  $p = 0.02$ ).

Initial multiple linear regression analyses unadjusted for parameters of systemic chronic inflammation showed that VAT was weakly positively associated with hs-CRP ( $\beta = 0.12$ ;  $p = 0.004$ ), moderately positively with IL-6 ( $\beta = 0.33$ ;  $p = 0.002$ ) and weakly inversely associated with adiponectin ( $\beta = -0.20$ ;  $p = 0.048$ ) (table 4). No relations of VAT to TNF-α or resistin were

**Table 3.** Correlation matrix with selected parameters of systemic chronic inflammation

|                                | Log hs-CRP                | Log TNF- $\alpha$         | Log IL-6            | Log resistin       |
|--------------------------------|---------------------------|---------------------------|---------------------|--------------------|
| Log hs-CRP <sup>1</sup>        | 1                         |                           |                     |                    |
| Log hs-CRP <sup>2</sup>        | 1                         |                           |                     |                    |
| Log TNF- $\alpha$ <sup>1</sup> | <b>r = 0.21, p = 0.04</b> | 1                         |                     |                    |
| Log TNF- $\alpha$ <sup>2</sup> | r = 0.18, p = 0.15        | 1                         |                     |                    |
| Log IL-6 <sup>1</sup>          | r = 0.16, p = 0.11        | r = 0.10, p = 0.34        | 1                   |                    |
| Log IL-6 <sup>2</sup>          | r = 0.11, p = 0.42        | r = -0.07, p = 0.58       | 1                   |                    |
| Log resistin <sup>1</sup>      | r = 0.10, p = 0.30        | r = 0.09, p = 0.37        | r = -0.01, p = 0.90 | 1                  |
| Log resistin <sup>2</sup>      | r = 0.09, p = 0.52        | r = -0.01, p = 0.97       | r = 0.03, p = 0.84  | 1                  |
| Log adiponectin <sup>1</sup>   | r = -0.14, p = 0.16       | r = 0.06, p = 0.53        | r = -0.00, p = 0.97 | r = 0.06, p = 0.56 |
| Log adiponectin <sup>2</sup>   | r = -0.11, p = 0.41       | <b>r = 0.31, p = 0.02</b> | r = 0.02, p = 0.89  | r = 0.08, p = 0.53 |

<sup>1</sup>Pearson correlation between parameters of systemic chronic inflammation.

<sup>2</sup>Pearson correlation between parameters of systemic chronic inflammation adjusted for age, physical activity level, sex, menopausal status (women only) smoking, and aspirin or NSAID use.

**Table 4.** Relations of VAT, SAT, BMI, and WC to selected parameters of systemic chronic inflammation

|                                | VAT          |              | SAT         |               | BMI          |              | WC           |              |
|--------------------------------|--------------|--------------|-------------|---------------|--------------|--------------|--------------|--------------|
|                                | $\beta$      | p            | $\beta$     | p             | $\beta$      | p            | $\beta$      | p            |
| Log hs-CRP <sup>1</sup>        | <b>0.12</b>  | <b>0.004</b> | <b>0.60</b> | <b>0.0005</b> | <b>0.39</b>  | <b>0.004</b> | <b>0.46</b>  | <b>0.001</b> |
| Log hs-CRP <sup>2</sup>        | <b>0.33</b>  | <b>0.02</b>  | <b>0.42</b> | <b>0.001</b>  | <b>0.36</b>  | <b>0.013</b> | <b>0.41</b>  | <b>0.006</b> |
| Log hs-CRP <sup>3</sup>        | 0.17         | 0.25         | <b>0.35</b> | <b>0.01</b>   | 0.05         | 0.88         | 0.36         | 0.26         |
| Log TNF- $\alpha$ <sup>1</sup> | 0.14         | 0.31         | -0.07       | 0.61          | 0.01         | 0.94         | 0.08         | 0.61         |
| Log TNF- $\alpha$ <sup>2</sup> | 0.16         | 0.27         | -0.11       | 0.44          | 0.05         | 0.73         | 0.07         | 0.69         |
| Log TNF- $\alpha$ <sup>3</sup> | 0.22         | 0.15         | -0.19       | 0.22          | -0.05        | 0.88         | 0.11         | 0.76         |
| Log IL-6 <sup>1</sup>          | <b>0.33</b>  | <b>0.002</b> | 0.13        | 0.22          | <b>0.22</b>  | <b>0.03</b>  | 0.14         | 0.32         |
| Log IL-6 <sup>2</sup>          | 0.22         | 0.12         | 0.17        | 0.23          | 0.11         | 0.44         | 0.13         | 0.42         |
| Log IL-6 <sup>3</sup>          | 0.18         | 0.24         | 0.10        | 0.50          | 0.03         | 0.92         | 0.10         | 0.77         |
| Log resistin <sup>1</sup>      | -0.09        | 0.49         | 0.15        | 0.26          | -0.05        | 0.73         | -0.05        | 0.74         |
| Log resistin <sup>2</sup>      | -0.14        | 0.38         | 0.15        | 0.33          | -0.07        | 0.66         | -0.09        | 0.62         |
| Log resistin <sup>3</sup>      | -0.22        | 0.20         | 0.22        | 0.18          | 0.04         | 0.91         | -0.13        | 0.74         |
| Log adiponectin <sup>1</sup>   | <b>-0.20</b> | <b>0.048</b> | -0.15       | 0.12          | <b>-0.32</b> | <b>0.002</b> | <b>-0.28</b> | <b>0.012</b> |
| Log adiponectin <sup>2</sup>   | -0.19        | 0.17         | -0.12       | 0.37          | <b>-0.28</b> | <b>0.035</b> | -0.18        | 0.24         |
| Log adiponectin <sup>3</sup>   | -0.16        | 0.26         | -0.06       | 0.68          | <b>-0.58</b> | <b>0.035</b> | 0.39         | 0.19         |

<sup>1</sup>Models are adjusted for age, physical activity level, sex, smoking, menopausal status (women only), and aspirin or NSAID use.

<sup>2</sup>Models are adjusted for age, physical activity level, sex, smoking, menopausal status (women only), aspirin or NSAID use, and mutually adjusted for all parameters of systemic chronic inflammation.

<sup>3</sup>Models are adjusted for age, physical activity level, sex, smoking, menopausal status (women only), aspirin or NSAID use, and mutually adjusted for all parameters of systemic chronic inflammation. In addition, VAT and SAT are mutually adjusted and BMI and WC were mutually adjusted.

found. SAT was moderately positively associated with hs-CRP ( $\beta = 0.60$ ;  $p = 0.0005$ ), but it was unrelated to any of the other parameters. BMI showed a moderate positive association with hs-CRP ( $\beta = 0.39$ ;  $p = 0.004$ ) and a weak positive association with IL-6 ( $\beta = 0.22$ ;  $p = 0.034$ ). A moderate inverse association was found between BMI and adiponectin ( $\beta = -0.32$ ;  $p = 0.002$ ). No relations of BMI were found to TNF- $\alpha$  or resistin. WC was moderately positively

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**Table 5.** Relations of VAT, SAT, BMI, and WC to selected parameters of systemic chronic inflammation in subgroups defined by sex, BMI, smoking status, and use of aspirin or NSAIDs<sup>a</sup>

|                 | Women (n = 55)                        |      |       |      |              |              | Men (n = 42)                          |      |             |             |             |             |              |              |              |             |
|-----------------|---------------------------------------|------|-------|------|--------------|--------------|---------------------------------------|------|-------------|-------------|-------------|-------------|--------------|--------------|--------------|-------------|
|                 | SAT                                   |      | BMI   |      | WC           |              | VAT                                   |      | SAT         |             | BMI         |             | WC           |              |              |             |
|                 | β                                     | p    | β     | p    | β            | p            | β                                     | p    | β           | p           | β           | p           | β            | p            |              |             |
| Log hs-CRP      | 0.18                                  | 0.40 | 0.22  | 0.24 | 0.19         | 0.42         | 0.21                                  | 0.31 | 0.03        | 0.90        | 0.29        | 0.14        | 0.12         | 0.58         | 0.19         | 0.39        |
| Log TNF-α       | -0.03                                 | 0.89 | -0.14 | 0.49 | -0.22        | 0.38         | -0.24                                 | 0.32 | 0.32        | 0.18        | -0.05       | 0.85        | 0.23         | 0.32         | 0.30         | 0.17        |
| Log IL-6        | -0.17                                 | 0.93 | -0.03 | 0.84 | -0.15        | 0.43         | -0.14                                 | 0.46 | <b>0.47</b> | <b>0.01</b> | 0.25        | 0.19        | <b>0.36</b>  | <b>0.049</b> | 0.33         | 0.09        |
| Log resistin    | 0.11                                  | 0.67 | 0.28  | 0.23 | 0.14         | 0.63         | -0.19                                 | 0.85 | -0.44       | 0.07        | 0.02        | 0.95        | -0.25        | 0.32         | -0.22        | 0.39        |
| Log adiponectin | -0.30                                 | 0.14 | 0.05  | 0.79 | <b>-0.42</b> | <b>0.045</b> | -0.16                                 | 0.47 | -0.27       | 0.26        | -0.22       | 0.31        | -0.35        | 0.11         | -0.30        | 0.19        |
|                 | BMI < 25.0 kg/m <sup>2</sup> (n = 36) |      |       |      |              |              | BMI ≥ 25.0 kg/m <sup>2</sup> (n = 61) |      |             |             |             |             |              |              |              |             |
|                 | SAT                                   |      | BMI   |      | WC           |              | VAT                                   |      | SAT         |             | BMI         |             | WC           |              |              |             |
|                 | β                                     | p    | β     | p    | β            | p            | β                                     | p    | β           | p           | β           | p           | β            | p            |              |             |
| Log hs-CRP      | 0.05                                  | 0.83 | 0.38  | 0.11 | -0.22        | 0.40         | 0.22                                  | 0.39 | 0.16        | 0.41        | <b>0.33</b> | <b>0.04</b> | 0.32         | 0.08         | 0.18         | 0.37        |
| Log TNF-α       | 0.05                                  | 0.84 | 0.30  | 0.29 | 0.17         | 0.59         | 0.25                                  | 0.40 | 0.30        | 0.17        | -0.09       | 0.62        | 0.19         | 0.39         | 0.29         | 0.16        |
| Log IL-6        | 0.07                                  | 0.65 | 0.18  | 0.31 | -0.16        | 0.39         | 0.08                                  | 0.64 | <b>0.39</b> | <b>0.03</b> | 0.04        | 0.82        | 0.33         | 0.13         | 0.34         | 0.09        |
| Log resistin    | -0.11                                 | 0.67 | 0.32  | 0.26 | 0.27         | 0.37         | 0.06                                  | 0.84 | -0.22       | 0.30        | 0.15        | 0.46        | -0.34        | 0.14         | 0.00         | 0.99        |
| Log adiponectin | -0.07                                 | 0.78 | 0.28  | 0.29 | -0.42        | 0.10         | -0.15                                 | 0.60 | -0.34       | 0.08        | -0.25       | 0.18        | <b>-0.47</b> | <b>0.02</b>  | <b>-0.46</b> | <b>0.01</b> |

Table 5 continued on next page

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**Table 5.** Continued

|                 | Current non-smoking (n = 78)          |              |             |             |              |              | Current smoking (n = 19)          |              |             |              |             |              |             |                |              |               |
|-----------------|---------------------------------------|--------------|-------------|-------------|--------------|--------------|-----------------------------------|--------------|-------------|--------------|-------------|--------------|-------------|----------------|--------------|---------------|
|                 | VAT                                   |              | SAT         |             | BMI          |              | WC                                |              | VAT         |              | SAT         |              | BMI         |                | WC           |               |
|                 | β                                     | p            | β           | p           | β            | p            | β                                 | p            | β           | p            | β           | p            | β           | p              | β            | p             |
| Log hs-CRP      | 0.18                                  | 0.22         | <b>0.35</b> | <b>0.01</b> | 0.23         | 0.12         | 0.22                              | 0.12         | <b>0.74</b> | <b>0.001</b> | <b>0.49</b> | <b>0.049</b> | <b>0.80</b> | <b>0.00003</b> | <b>0.88</b>  | <b>0.0003</b> |
| Log TNF-α       | 0.19                                  | 0.23         | -0.12       | 0.44        | 0.07         | 0.65         | 0.11                              | 0.48         | 0.34        | 0.18         | -0.25       | 0.34         | 0.08        | 0.74           | 0.29         | 0.30          |
| Log IL-6        | <b>0.36</b>                           | <b>0.01</b>  | 0.13        | 0.39        | <b>0.29</b>  | <b>0.048</b> | 0.24                              | 0.10         | 0.43        | 0.13         | -0.01       | 0.99         | 0.20        | 0.46           | 0.17         | 0.61          |
| Log resistin    | -0.18                                 | 0.28         | 0.13        | 0.41        | -0.08        | 0.66         | -0.06                             | 0.74         | 0.43        | 0.12         | 0.42        | 0.14         | 0.46        | 0.08           | 0.59         | 0.05          |
| Log adiponectin | -0.25                                 | 0.09         | -0.11       | 0.44        | <b>-0.34</b> | <b>0.01</b>  | <b>-0.27</b>                      | <b>0.049</b> | -0.27       | 0.28         | -0.09       | 0.72         | -0.19       | 0.43           | -0.37        | 0.18          |
|                 | Non-use of aspirin or NSAIDs (n = 81) |              |             |             |              |              | Use of aspirin or NSAIDs (n = 16) |              |             |              |             |              |             |                |              |               |
|                 | VAT                                   |              | SAT         |             | BMI          |              | WC                                |              | VAT         |              | SAT         |              | BMI         |                | WC           |               |
|                 | β                                     | p            | β           | p           | β            | p            | β                                 | p            | β           | p            | β           | p            | β           | p              | β            | p             |
| Log hs-CRP      | 0.30                                  | 0.06         | <b>0.41</b> | <b>0.01</b> | <b>0.31</b>  | <b>0.04</b>  | <b>0.31</b>                       | <b>0.04</b>  | <b>0.57</b> | <b>0.04</b>  | 0.53        | 0.13         | 0.63        | 0.12           | <b>0.72</b>  | <b>0.03</b>   |
| Log TNF-α       | <b>0.30</b>                           | <b>0.049</b> | -0.05       | 0.74        | 0.17         | 0.30         | 0.17                              | 0.28         | -0.42       | 0.27         | -0.46       | 0.30         | -0.85       | 0.30           | -0.31        | 0.41          |
| Log IL-6        | <b>0.29</b>                           | <b>0.046</b> | 0.15        | 0.32        | 0.17         | 0.25         | 0.12                              | 0.41         | -0.27       | 0.50         | -0.78       | 0.46         | -0.73       | 0.66           | -0.07        | 0.87          |
| Log resistin    | -0.14                                 | 0.39         | 0.16        | 0.34        | -0.03        | 0.85         | 0.01                              | 0.93         | -0.20       | 0.90         | 0.13        | 0.86         | 0.42        | 0.67           | -0.30        | 0.89          |
| Log adiponectin | -0.26                                 | 0.08         | -0.06       | 0.73        | <b>-0.30</b> | <b>0.04</b>  | -0.24                             | 0.10         | -0.22       | 0.84         | -0.05       | 0.93         | -0.55       | 0.28           | <b>-0.89</b> | <b>0.001</b>  |

<sup>a</sup>Models are adjusted for age, physical activity level, sex, menopausal status (women only), smoking, aspirin or NSAID use, and mutually adjusted for all parameters of systemic chronic inflammation. In these models, VAT and SAT were not mutually adjusted and BMI and WC were not mutually adjusted. In each case, the stratification variable was excluded from the model.



associated with hs-CRP ( $\beta = 0.46$ ;  $p = 0.001$ ) and moderately inversely associated with adiponectin ( $\beta = -0.28$ ;  $p = 0.012$ ).

After mutual adjustment of parameters of systemic chronic inflammation, VAT remained significantly associated with hs-CRP but not with IL-6 or adiponectin (table 4). SAT remained significantly associated with hs-CRP, and BMI remained significantly associated with hs-CRP and adiponectin. WC remained significantly associated with hs-CRP. When VAT and SAT were simultaneously included in the model, only SAT remained significantly associated with hs-CRP. After mutual adjustment of BMI and WC, BMI remained significantly inversely related to adiponectin.

We next conducted an analysis stratified by gender (table 5). In women, we noted a moderate inverse association between BMI and adiponectin ( $\beta = -0.42$ ;  $p = 0.045$ ). In men, we observed moderate positive relations of VAT and BMI to IL-6 ( $\beta = 0.47$ ;  $p = 0.01$  and  $\beta = 0.36$ ;  $p = 0.049$ , respectively). No statistically significant relations were found between VAT, SAT, BMI, or WC and other inflammatory parameters in men or women, although we noted gender differences for all inflammatory parameters. With the exception of SAT, relations of VAT, BMI, and WC to hs-CRP appeared to be stronger in women than in men. Inverse relations of VAT, SAT, BMI and WC to TNF- $\alpha$  and to IL-6 were found in women, whereas in men only SAT was inversely related to TNF- $\alpha$ . Relations of VAT, SAT, BMI and WC to IL-6 were stronger in men than in women.

In non-obese participants, no statistically significant relations were found of VAT, SAT, BMI, or WC to any of the inflammatory parameters (table 5). In overweight/obese participants, VAT showed a moderate association with IL-6 ( $\beta = 0.39$ ;  $p = 0.03$ ), and SAT was statistically significantly associated with hs-CRP ( $\beta = 0.33$ ;  $p = 0.04$ ). BMI and WC showed moderate inverse associations with adiponectin ( $\beta = -0.47$ ;  $p = 0.02$  and  $\beta = -0.46$ ;  $p = 0.01$ , respectively). In general, VAT and BMI showed stronger relations to inflammatory parameters in overweight/obese participants than in normal-weight participants, whereas associations between SAT and inflammatory parameters were stronger in normal-weight than in overweight/obese participants.

In an analysis restricted to current non-smokers, VAT was positively associated with IL-6 ( $\beta = 0.36$ ;  $p = 0.01$ ), and SAT showed a moderate significant association with hs-CRP ( $\beta = 0.35$ ;  $p = 0.01$ ) (table 5). BMI was positively associated with IL-6 ( $\beta = 0.29$ ;  $p = 0.048$ ) and it showed an inverse association with adiponectin ( $\beta = -0.34$ ;  $p = 0.01$ ). WC also showed an inverse association with adiponectin ( $\beta = -0.27$ ;  $p = 0.049$ ). By comparison, in an analysis restricted to current smokers, VAT, BMI, and WC showed strong positive associations with hs-CRP ( $\beta = 0.74$ ;  $p = 0.001$ ,  $\beta = 0.80$ ;  $p = 0.00003$ , and  $\beta = 0.88$ ;  $p = 0.0003$ , respectively), and a moderate positive association was found between SAT and hs-CRP ( $\beta = 0.49$ ;  $p = 0.049$ ). Associations between VAT and inflammatory markers were stronger in current smokers than in non-smokers.

In an analysis limited to non-users of aspirin or NSAIDs, VAT showed moderate positive associations with IL-6 ( $\beta = 0.29$ ;  $p = 0.046$ ) and TNF- $\alpha$  ( $\beta = 0.30$ ;  $p = 0.049$ ) (table 5). SAT, BMI, and WC showed moderate positive associations with hs-CRP ( $\beta = 0.41$ ;  $p = 0.01$ ,  $\beta = 0.31$ ;  $p = 0.04$ , and  $\beta = 0.31$ ;  $p = 0.04$ , respectively). Also, BMI showed a weak inverse association with adiponectin ( $\beta = -0.30$ ;  $p = 0.04$ ). In an analysis restricted to participants using aspirin and NSAIDs, VAT showed a moderate positive association with hs-CRP ( $\beta = 0.57$ ;  $p = 0.04$ ). WC showed a strong positive association with hs-CRP ( $\beta = 0.72$ ;  $p = 0.03$ ) and a strong inverse association with adiponectin ( $\beta = -0.89$ ;  $p = 0.001$ ). In general, VAT, SAT, BMI, and WC were inversely related to TNF- $\alpha$  and IL-6 in users of aspirin or NSAIDs, whereas VAT, BMI, and WC were positively related to these parameters in non-users of aspirin and NSAIDs.



## Discussion

In this population-based study of healthy adults, VAT, SAT, BMI, and WC showed distinct associations with selected parameters of chronic inflammation. Specifically VAT, SAT, BMI, and WC demonstrated a positive relation to hs-CRP. However, the strongest relation was found between SAT and hs-CRP. Compared to the other anthropometric variables, BMI showed a stronger inverse association with adiponectin. Albeit not significant, VAT was the strongest indicator for increased levels of IL-6 and TNF- $\alpha$ . WC was only weakly related to inflammatory parameters. These findings were fairly consistent throughout subgroups defined by gender, BMI, current smoking, and use of aspirin and NSAIDs.

Similar to our results, previous studies among healthy adults reported that VAT, SAT, BMI, or WC were positively associated with CRP [24, 32–34, 38, 46]. Several investigations reported comparable relations of VAT and SAT to CRP [33, 38] or a stronger association with VAT [32, 34, 37], whereas other studies found a stronger relation to SAT [35, 38, 46]. However, none of the aforementioned studies mutually adjusted their analyses for inflammatory parameters or for VAT and SAT [32–35, 37, 38, 46]. When VAT and SAT were mutually adjusted, we found that only SAT remained significantly associated with hs-CRP, indicating that abdominal SAT may have a pathogenic function, as additionally evidenced by endocrine and inflammatory responses [5, 10, 12, 47].

That relations of VAT, BMI, and WC to hs-CRP were stronger in women than in men agrees with previous studies [21, 22, 33, 38] and may be due to enhanced estrogen production in the adipose tissue with upregulation of pro-inflammatory gene expression in women [48, 49]. Our findings in women of similar relations of VAT, SAT, BMI, and WC to hs-CRP suggest that in women associations with CRP are more strongly determined by overall fat mass than by fat distribution. In contrast, in men we noted that SAT, but not VAT, BMI, or WC, was most strongly associated with CRP, which is consistent with previous studies [35, 38, 46] and indicates that adiposity relations with CRP in men may be less strongly influenced by overall fat mass.

Our observation of a more pronounced relation of SAT than of VAT to hs-CRP in overweight/obese subjects has not yet been reported. Only one previous study stratified the examination by BMI and found no significant association between SAT and CRP in obese subjects [37]. In contrast to that study, we considered potential confounding variables in multivariate analyses. In obese individuals, the limited ability of abdominal SAT to store excess energy may cause an increase in free fatty acids (FFA) flux to the portal vein and the systemic circulation [9]. Elevated FFA levels are related to increased CRP [50].

All anthropometric variables showed stronger associations with hs-CRP in current smokers than in non-smokers. Cigarette smoking is associated with increased CRP levels [51], which may partly reflect the mechanisms believed to underlie the adverse effects of smoking on cardiovascular disease and several types of cancer [52]. None of the previous studies that examined the relation between adiposity and CRP reported results stratified by smoking status [24, 32–34, 38, 46]. Also, previous studies examining the relations of obesity to CRP and other inflammatory parameters did not report findings stratified by aspirin or NSAIDs use [24, 32–34, 38, 46]. We found that associations of anthropometric factors to hs-CRP were more pronounced among users of aspirin or NSAIDs. Because NSAIDs down-regulate inflammatory cytokine production including CRP [53, 54], we would have expected to observe less pronounced associations with inflammatory parameters among users than among non-users of aspirin or NSAIDs.

Our findings from multivariate analyses without mutual adjustments for inflammatory parameters or for VAT and SAT are consistent with those from previous studies reporting a positive association between VAT and IL-6 [33, 34, 37, 38, 40] and no relation between SAT

and IL-6 [37, 38, 40]. However, the positive relation of VAT to IL-6 was rendered non-significant after mutual adjustment for other parameters of systemic chronic inflammation and when SAT was included in the model. Significantly positive associations between VAT and IL-6 emerged in additional analyses among men, overweight/obese, current non-smokers, and participants not using aspirin and NSAIDs. In these analyses, we additionally found that associations between VAT and IL-6 were stronger than those between BMI and IL-6, indicating that collecting data on VAT may represent metabolic information captured by IL-6 that is not accounted for by BMI. Only one previous study stratified its population by gender and reported a stronger relation between VAT and IL-6 in women than in men [38]. However, that study was limited to elderly individuals, which may explain the difference from our finding. Men have larger visceral fat depots than women [55, 56], and IL-6 is predominantly expressed and secreted by VAT [57].

We found no overall relations of VAT, SAT, BMI, or WC to TNF- $\alpha$ , which is similar to other studies that addressed these associations [33, 34, 37]. Albeit not significant, we found a stronger relation of VAT to TNF- $\alpha$  compared to the relations of other obesity measures to TNF- $\alpha$ . In further exploratory analyses, we noted significantly positive relations of VAT to TNF- $\alpha$  and IL-6 among non-users of aspirin or NSAIDs, which may be due to NSAID-mediated down-regulation of inflammatory cytokine production [53, 54]. The available literature includes one study that reported a positive relation between VAT and TNF- $\alpha$  in adults aged 70 to 79 years, but no association between SAT and TNF- $\alpha$  [38], and another study that found positive relations of both VAT and SAT to TNF- $\alpha$  among obese adolescents [40]. However, none of these studies mutually adjusted their analyses for inflammatory parameters or for VAT and SAT.

We were unable to detect any associations between adiposity measures and resistin levels. This is consistent with most previous studies that found no correlations between markers of adiposity and resistin [16, 17, 29, 58–63], whereas other studies reported a positive relation of obesity to resistin levels [15, 41, 42, 64–66]. Only one population-based study that examined the relation of VAT and SAT to resistin reported results from multivariate analyses and found similar relations of VAT and SAT to resistin in women and no association between VAT and resistin in men [42]. We found that the relation between SAT and resistin was stronger than the relation of other measures of obesity to resistin. However, resistin is not expressed by adipocytes but is secreted by macrophages located within adipose tissue depots [67]. Hence, circulating resistin is not directly related to adiposity levels but to the degree of inflammation within the adipose tissue depots [9].

Largely similar to our results, previous studies reported that VAT, SAT, BMI, or WC were inversely associated with adiponectin [35, 40, 43, 44, 68]. In our study, the inverse relation of VAT to adiponectin was attenuated and rendered non-significant after mutual adjustment for other parameters of systemic chronic inflammation and when SAT was included in the model. We found that BMI was a stable indicator of decreased adiponectin levels, showing an inverse association in the overall population before and after adjustment for other variables and across a number of stratified analyses. In addition, we found that the relation of BMI to adiponectin was stronger than the relation to other markers of adiposity in all analyses. This suggests that adiponectin may represent metabolic processes that are associated with BMI better than those related to VAT or SAT.

The major strength of our study is that, to the best of our knowledge, it represents the first study to examine associations between several different body fat measures and numerous selected parameters of chronic inflammation in healthy adults. A further asset of our study is that we accounted for correlations between individual parameters of systemic inflammation by mutual adjustment in our multivariate models, which has not been undertaken in any previous study. In addition, we conducted numerous informative exploratory subgroup

analyses. Ultrasound is a less sophisticated method to measure VAT and SAT compared to the gold standard methods of magnetic resonance imaging (MRI) or computer tomography (CT). However, MRI and CT approaches are limited in field conditions due to their associated costs and issues regarding accessibility, contraindications, and in terms of CT examinations, potential adverse effects of radiation. We have recently reported that ultrasound represents a suitable technique to validly and reproducibly assess VAT and SAT in population-based research settings [45]. Our blood samples were non-fasting, but we focused on parameters that are unaffected by fasting status [69, 70].

Limitations of our study include the small sample size, potentially resulting in insufficient statistical power to detect relations, particularly in stratified analyses. Due to the numerous additional analyses performed, some of our findings may have been the result of multiple testing. In addition, the cross-sectional nature of our study design precludes an assessment of cause-effect relationships. Because analyses were based on a single laboratory measurement, they may not represent true long-term average serum concentrations of parameters of chronic inflammation.

In conclusion, we found that VAT, SAT, BMI, and WC showed distinct associations with selected parameters of chronic inflammation. Our study suggests that each of the anthropometric variables provides distinct information regarding metabolic processes related to inflammatory parameters. Compared to VAT, BMI, and WC, SAT was the strongest indicator for increased hs-CRP concentrations. BMI was the strongest indicator for decreased adiponectin levels. Albeit not significant, VAT was the strongest indicator for increased levels of IL-6 and TNF- $\alpha$ . WC represented a less consistent indicator when examining relations to inflammatory parameters. Subgroup analyses showed that gender, BMI, current smoking, and use of aspirin or NSAIDs modify the relations of adiposity measures to the levels of inflammation parameters. The distinct relations of VAT, SAT, BMI, and WC to selected parameters of systemic chronic inflammation emphasize the importance of accurately differentiating between body fat compartments when evaluating the role of adiposity-associated systemic chronic inflammation in the development of metabolic diseases.

## Acknowledgment

This study was conducted within the framework of the pilot studies of the German National Cohort ([www.nationale-kohorte.de](http://www.nationale-kohorte.de)). These studies were funded by the German Federal Ministry of Education and Research (BMBF), grant number 01ER1001A-I, and were supported by the Helmholtz Association, participating universities, and Institutes of the Leibniz Association. The authors' responsibilities were as follows: I.S., B.F., and M.F.L. conceived and designed the study. I.S. and G.B. were responsible for data analysis and I.S. was responsible for data interpretation and writing of the manuscript; all authors were responsible for critical revision of the manuscript and its intellectual content; M.F.L. was responsible for study supervision.

## Disclosure Statement

None of the authors had a conflict of interest.

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