Prediction of circulating adipokine levels based on body fat compartments and adipose tissue gene expression

**Supplementary Material**

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# Supplementary Text

## Text S1: Assessment of blood pressure and standard anthropometric measures

This study was conducted in the EPIC Potsdam substudy comprising 1472 participants within the large European Prospective Investigation into Cancer and Nutrition (EPIC) study [1–3].

Blood pressure was measured in a sitting position. The measurement was carried out in three repetitions at the non-dominant arm, in each case at intervals of three minutes by means of a fully automatic measuring device ("M5 Professional", OMRON, Mannheim, Germany), and the blood pressure was calculated as the mean value of the last two measurements. The measurement was repeated manually, if the blood pressure exceeded the value of 160/95 mmHg or the device showed an error message.

Standard anthropometric measures were obtained according to standardized protocols following the WHO guidelines [4]: waist circumference (WC) was measured at the midpoint between the distal border of the lowest rib and the superior border of the iliac crest and was measured to the nearest 0.1 cm. Hip circumference (HC) was measured at the widest point of the buttocks and was measured to the nearest 0.1 cm. Both WC and HC were measured 3 times and a mean value was calculated. Waist–hip–ratio (WHR) was calculated as the ratio of WC and HC, and body mass index (BMI) as weight (kg) divided by height squared (m2).

## Text S2: Assessment of adipose tissue and skeletal muscle tissue mass

Whole–body MRI scans excluding head and arms were performed in the clinical Ernst von Bergmann center in Potsdam on a Siemens 1.5T Avanto scanner using a 2–point Dixon technique with a 3D gradient echo sequence. Adipose tissue (AT) and skeletal muscle tissue (SMT) measures were obtained using a fully–automated segmentation approach including image–processing methods and statistical shape models. Available measures include the amount of AT in the visceral (in the abdominal cavity i.e. around and between the organs in the abdomen; VAT), subcutaneous (fat tissue beneath the skin; SAT), and coronary (fat tissue around the heart and heart vessels; CAT) compartments, SMT, and the total body volume (TBV).

In more detail, in the first processing steps after performing a 15–minute standardized MRI protocol, whole–body images were generated by integrating all acquired MRI sections, whole–body masks were created using the Otsu technique [5] to compute optimal thresholds between foreground and background, corrections for swap–phase artifacts in the lower extremities were performed separately for each leg, and arms were removed since they were often outside of the image due to hardware limitations.

Then, AT compartments were segmented based on statistical shape models and appearance models followed by the automated threshold method of Otsu separating adipose from non-adipose tissue, and bone marrow as well as intramuscular fat were removed. The separation of SAT, VAT and CAT using the shape models was done by creating one mask for VAT in the inner abdominal area (within the anatomical muscular borders of abdomen and pelvis, and the pelvic floor and the diaphragm) one for CAT in the thorax, and classifying all remaining AT as SAT. The statistical shape model of the abdomen mask was generated on a training set of 40 whole–body water images. For the validation of the automated approach, the segmentation of SAT and VAT was compared to a manual segmentation by an expert for 52 randomly selected images. This was based on seven image slices per volume including two slices from the thorax, three from the abdomen (one in the upper abdomen at the level of the liver, one at the intervertebral disc between the vertebrae L3-L4, one at the level of the sacral promontory), and one each from the thigh and the lower leg. Further, a complete 3D segmentation of SAT and VAT was performed for evaluation in 6 images.

These validations showed that the automated approach yields very similar measures compared to the manual expert segmentation, for example, the mean of the relative volume differences between the automated approach and the manual expert segmentation were below 6% for both VAT and SAT across all comparisons. Furthermore, the automated segmentation approach showed a high repeatability and reproducibility, based on repeated measures of the same participants (coefficient of variation CV = 0.4% for SAT and TAT, and 3.5% for VAT).

SMT, which constitutes the largest fraction of lean tissue, was quantified by segmenting first all lean tissue parts and then removing all non-SMT including organs and blood by using the abdomen and thorax mask generating for VAT and CAT quantification. It was similarly compared with a manual expert segmentation with equally good validity (relative volumetric differences between automated and manual segmentation <8%).

The technical details of the approach as well as the MRI protocol, sample ascertainment, evaluation, and association with standard anthropometric measures have been described in detail elsewhere [6–9].

## Text S3: Needle aspiration of subcutaneous fat tissue and sample processing

Of 673 participants eligible for AT biopsies, 186 refused the invasive procedure and 209 were excluded (mostly due to reported use of anticoagulant or antiplatelet medication within the last seven days and/or when the goal of 200 biopsies with sufficient material was reached). Further exclusion criteria were any form of prevalent coagulopathy, an allergy against lidocain or plaster, or a disposition for keloids. The biopsy was conducted by a trained study physician, assisted by a study nurse. SAT samples were extracted at a standardized position in the paraumbilical area, by covering the skin with a sterile surgical drape leaving a palm sized area right of the umbilicus blank. Subcutaneous anesthesia was achieved by infiltrating a skin area of approximately 5x5cm with 10ml of 1% lidocaine. Afterwards, a 14G Strauss needle was inserted into the SAT and using a syringe, approx. 4ml of sterile physiological saline solution was injected into the SAT. Afterwards, the plunger was fully retracted to create negative pressure in the syringe and to aspirate tissue. With the plunger in this position, the needle was moved in all directions under the skin two to four times. The syringe was then removed with the plunger pulled back and the aspirate was transferred to a 50ml tube containing 12.5ml of 10% sodium citrate solution. This procedure was repeated ten times. The tube with the fat, blood, saline and sodium citrate solution conglomerate was then transferred to the laboratory and further processed within 30 minutes. Larger blood components were removed manually using a 10ml syringe. Then, sterile physiological saline solution was added and the tube centrifuged at 100g for 2 minutes. The fluid below the AT was then removed with a syringe. This procedure was repeated until no more blood components were visible. The AT was then transferred to a cryotube and centrifuged again for 2 minutes at 100g. After removing the fluid below the AT, saline solution was added again and the tube centrifuged for ten minutes at 100g. Residual fluids were extracted using a syringe and the remaining AT was weighted and then frozen at –80°C. The goal was to extract 0.4g or more of abdominal SAT and of the performed 278 biopsies, 273 yielded material with on average 0.88g aspired AT (min=0.05g, max=3.51g). Sufficient high–quality material was available from 200 participants.

The 273 aspired abdominal SAT samples were first processed using the Qiagen AllPrep DNA/RNA Mini Kit to extract total DNA, RNA, and oil phase for further analysis. The quantity and integrity of purified DNA and RNA was verified using the NanoDrop Photometer (PeqLab) and the Bioanalyzer (Agilent). Then, 2$μ$g RNA were reverse transcribed to cDNA using the High Capacity cDNA Reverse Transcription Kit (Applied Biosystems).

## Text S4: Assessment of biomarker plasma levels

Blood samples were collected during the re–examination of participants, processed, divided into 1ml nunc tubes and stored in ultralow freezers (–80°C). EDTA plasma levels of total, high molecular weight (HMW), and HMW + medium molecular weight (MMW) adiponectin were measured using ELISAs from Alpco (Salem, USA), and concentrations of MMW and low molecular weight (LMW) adiponectin computed by subtraction. Leptin, sOB–R, resistin and FABP4 were measured using ELISAs from BioVendor (Brno, Czech Republic), and IL6 was measured using an ELISA from R&D Systems (Minneapolis, USA). All samples were measured in duplicates according to standard protocol on the TECAN Infinite 200 PRO reader (Männedorf, Switzerland). Concentration estimates adjusted for reference absorption and background noise were obtained using the observed absorption measures and a 4–parameter logistic (4PL) model [10], fitted with the optimx package in the statistical software R version 3.3.1 [11–12]. The duplicate concentration measures were averaged and low concentrations were set to the respective minimum measurable concentration. In total, 3 participants had missing measures for each 1 adipokine. The median intra–assay CV (across the duplicate measures of all sample probes on all 48 plates) was <5% for all biomarkers, except for sOB–R where it was 11%. In order to assess the inter–assay variation, material from 6 external inconspicuous samples was pooled to form an independent control, and the plasma concentrations of this pooled material were measured in duplicate on all plates of all adipokines. The inter–assay CV (of the averaged estimated concentrations of the two measures of pooled material across all 48 plates) was 6% for leptin, 14% for sOB–R, 11% for resistin, 6% for IL6, 8% for FABP4, 4% for total adiponectin, 8% for HMW+MMW adiponectin, and 11% for HMW adiponectin. Hence, all experiments had small inter–assay and intra–assay CVs.

Information regarding fasting status was recorded for blood sampling, and adjusting plasma levels for time to last meal in sensitivity checks had no effect on the results (data not shown). This confirms the results of previous studies, which have shown a good reliability of plasma concentration estimates over time and robustness against fasting status [13–17].

## Text S5: Assessment of SAT gene expression

Quantitative real time polymerase chain reaction (qPCR) was used to evaluate the gene expression in SAT of the target genes adiponectin, leptin, sOB–R, resistin, IL6 and FABP4 in triplicate measures. qPCR was performed using the Applied Biosystems 7500 Fast Real–time PCR system with TaqMan technology (ABI, Darmstadt, Germany). The two–step PCR conditions were 20s at 95°C, 40 cycles with 3s at 95°C, and 30s at 60°C (5μL reaction volume, 4ng template). In each amplification cycle, a cycle threshold (Ct) value was obtained. For each sample and for each gene, gene expression was measured in triplicates and the three Ct values were averaged for each individual. In addition, the expression of the reference rRNA housekeeper gene 18S was measured in triplicate for each sample on four different plates together with the target gene, and the three Ct values were averaged. These four 18S average Ct values were very similar across plates, and further averaged to obtain the reference 18S expression (in form of a grand average Ct value) for each sample. Relative normalized gene expression levels ΔCt in comparison to the reference gene were obtained for each gene and each sample, from the difference between the averaged candidate gene Ct value and the 18S grand averaged Ct value. As measure for gene expression in all analyses, 2–ΔCt values were used, assuming that the number of amplified target molecules at the threshold cycle is identical for the candidate genes and the measured housekeeper gene 18S [18].

There were no missing values for all genes. The inter–assay CV (across the four 18S Ct measures of each sample on the 4 different plates) was on median 1.2%. For all genes, the median intra–assay CV (across the triplicate Ct measures of all sample aliquots on all 84 plates) was smaller than 1.5%. Hence, all experiments had small inter–assay and intra–assay CVs.

Information regarding fasting status was not recorded for AT biopsies, which were conducted after blood sampling. However, time to last meal was recorded for blood sampling, and adjusting SAT gene expression for time to last meal before blood sampling as a proxy variable yielded very similar results (data not shown).

## Text S6: Implicit assumptions of the main analyses and sensitivity analyses

The main analyses of plasma adipokine concentrations and of AT mass are based on the implicit assumptions that (i) plasma concentrations (i.e. the total amount of adipokine molecules present in plasma relative to the blood volume, which depends, among others, on the height and AT mass of a person) are the biologically relevant measure and not the total amount of adipokine molecules, and that (ii) the association of AT with circulating adipokine concentrations does not depend on the relative amount of AT mass (i.e. relative to a person’s height or amount of SMT). To investigate these implicit assumptions, we performed sensitivity analyses by analyzing a crude estimate of the absolute quantity of adipokine molecules in plasma, as well as by analyzing AT/height, AT/height2, AT/height3 and AT/SMT ratios. The crude estimates of plasma adipokine quantities were obtained by multiplying the plasma adipokine concentrations with ${70∙weight}/{\sqrt{\frac{BMI}{22}}}$, see [19]. A further implicit assumption of our analyses was that gene expression is a meaningful predictor of adipokine concentrations and proxy for the metabolic activity of AT – the latter assumption was not testable in our analyses and future studies could also consider the secretion rate and further metabolic differences of the AT compartments [20–21].

Underlying our investigations of the AT/height ratios are the following considerations: The fat mass index FMI=AT/height2 has been proposed in [22] as a relative measure of body fat and has been used in different studies with the argument that it may better reflect nutritional status and therefore be a more relevant measure for chronic disease risk than absolute fat mass [23–24]. However, following the underlying theoretical reasoning regarding which power of height should be used yields different suggestions for different populations, and the powers 1, 3, or others have also been suggested [25]. Also, in our study, the FMI was not independent of height and showed Pearson correlation coefficients of up to r=0.60 for the different AT compartments (data not shown). In our opinion, AT/height ratios are easier to interpret for the goals of our study. Finally, since it is not clear whether any of AT/height, AT/height2, AT/height3 is a more relevant measure to predict adipokine concentrations, we investigated all three measures.

Further, we investigated AT/SMT ratios in order to address the capacity–load model [26–27], which build on the argument that both the metabolic capacity as well as the metabolic load are relevant concepts to study chronic disease. Here, metabolic capacity refers to the organs and tissues that maintain metabolic balance, whereas metabolic load is shaped by the behavior and can change during the course of life. Measures of metabolic capacity and load are the muscle mass and adipose tissue mass, respectively [28]. Regarding our study, it could be hypothesized that in addition to high AT mass, small SMT mass might affect adipokine concentrations. Therefore, we investigated the ratios AT/SMT to assess whether the effect of AT mass on adipokine concentrations is affected by the relative amount of AT with respect to skeletal muscle mass.

In the sensitivity analyses of the primary results, the results were very similar when SAT/height and VAT/height were analyzed (Table S4) instead of absolute SAT and VAT mass (Table 2) – except that the contribution of the interaction of SAT gene expression with SAT/height was much larger compared to with SAT mass for leptin and FABP4 (model 5). The results in Table 2 were also very similar when ratios AT/height2, AT/height3, or AT/SMT were used (data not shown). Furthermore, the partial correlations of the absolute fat measures (SAT, VAT, TAT mass) with adipokine concentrations were very similar compared to the partial correlations of AT/height, AT/height2, AT/height3, and AT/SMT (Table S5). The correlations were also similar to correlations of SAT/TBV, VAT/TBV, TAT/TBV (data not shown). Further, the correlations were similar when a crude estimate of the absolute plasma quantities was used instead of plasma concentrations – slightly higher for leptin, FABP4, IL6 and resistin, and slightly lower for sOB–R and adiponectin (Table S6). In further sensitivity analyses, we calculated Spearman correlation coefficients and found very similar results (data not shown).

In further sensitivity checks, we performed sex–stratified analyses of the main results shown in Table 2. The results (Table S1) showed that while the estimated contribution of some predictors changed slightly (e.g. leptin SAT gene expression explained 32% of circulating leptin’s variance in women and 25% in men, see model 1, Table S1), the main conclusions from Table 2 described in the main manuscript didn’t change. As only exception, substantial differences were observed for leptin and FABP4 explained by VAT as single predictor (model 3).

## Text S7: Additional exploratory analyses of interactions to predict adipokine levels

In addition to the hypothesis-driven analyses described in the main manuscript which investigated specific predictors (mainly MRI-derived AT measures and SAT gene expression, as well as personal, lifestyle and sociodemographic variables) in their ability to predict adipokine levels, we performed exploratory analyses to investigate whether including interactions between MRI-derived measures, SAT gene expression and plasma concentrations of other adipokines allows to explain a higher percentage of the variance of adipokine concentrations.

For this, for each adipokine, we fitted one multiple regression model which included all main effects and all 2-way interaction effects of the MRI-derived measures (SAT, VAT, CAT, TAT, SMT), plasma concentrations of all other adipokines and SAT gene expression of all genes. For example, for leptin, we predicted leptin plasma concentration by all main effects and all 2-way interaction effects between all of the following variables: SAT, VAT, CAT, TAT, SMT, plasma concentrations of sOB-R, total adiponectin, IL6, FABP4 and resistin, and SAT gene expression of leptin, sOB-R, adiponectin, IL6, FABP4 and resistin. In order to fit the model with all 136 predictors and to perform model selection informing about the most important predictors, we computed a regularized multiple linear regression model in form of the least absolute shrinkage and selection operator (LASSO; [29]) by using the *glmnet* R package [30]. Lasso uses an L1 regularization and yields a sparse solution with most regression coefficients set to 0. For this, the optimal tuning parameter lambda was identified through 10-fold cross-validation with respect to smallest mean-squared error using the function *cv.glmnet* with default settings. For the model selection, all variables selected into the final model were extracted as well as the R2 from the *cv.glmnet* object. In order to account for the randomness of the sampling of subsets of the data in the cross-validation, this was performed ten times for each adipokine and the R2 was averaged. The results are shown in Table S12. They indicate that the only mentionable increases in the explained variance compared to the main results in Tables 2-3 are for total adiponectin, where now, 31% of the variance can be explained compared to previously 20%, and for FABP4 where now 61% variance are explained compared to previously 54%. The final model for adiponectin includes 12 predictors with interaction effects between different MRI measures, different adipokine plasma levels, and SAT gene expression of different genes, and can be interesting candidates for relevant biological interactions that can be investigated in future studies.

In further analyses, no further increase of R2 was observed when considering even more complex interactions between predictors by considering all main effects, all 2-way and all 3-way interactions (increase in R2 at most 2%; data not shown). When additionally considering all personal, lifestyle and sociodemographic variables (sex, age, occupational training, physical activity, employment status, partner status, smoking status, socioeconomic status, history of diabetes) and all their 2-way interactions with all other predictors incorporated above, on average, the explained variance was 84% for leptin, 24% for sOB-R, 36% for resistin, 65% for FABP4, 37% for total adiponectin, and 20% for IL6 (data not shown). This presents a slight increase for some adipokines and a doubling of the explained variance for resistin, and might suggest that interactions between lifestyle variables are important determinants for these adipokines. However, these interactions are very hard to interpret from a biological perspective and we think that they predominently describe statistical artifacts caused by the fact that such interactions yield categorical variables with up to 20 levels. As a further note, all the above described estimates of R2 are likely to be liberal and overestimating the explained variance by these predictors, since they are obtained in a data-adaptive approach based on the best prediction model among all prediction models.

# Supplementary Tables

Table S1 shows the results of the same analyses as in Table 2 – predicting plasma adipokine concentrations by AT compartments and gene expression – performed separately in women and men. Tables S2–S3 show sex–stratified partial correlations between adipokine concentrations and AT measures (cf. Table 4) and between adipokine concentrations and gene expression (cf. Table 5). Table S4 shows the explained variance of the plasma adipokine concentrations as in Table 2 but with AT mass standardized by height (AT/height ratios). Table S5 compares the sex–stratified partial correlations between adipokine concentrations and AT measures from Table 4 with the same partial correlations using the AT/height2, AT/height3, AT/SMT ratios. Table S6 shows the partial correlations of circulating adipokines with the anthropometric measures and SAT adipokine gene expression as in Tables 4 and 5, but for crude estimates of the plasma adipokine quantities instead of plasma concentrations.

Table S7 shows the partial correlations between anthropometric measures and SAT adipokine gene expressions. In general, correlations between adipokine gene expressions and AT measures were weaker as compared to the correlations between plasma concentrations and AT measures (Table 4). Leptin expression showed the strongest correlation with SAT; whereas sOB–R, resistin, FABP4, adiponectin, and IL6 showed similar associations with SAT, VAT and TAT. Table S8 shows partial correlations between the plasma adipokine concentrations and SAT gene expression.

Tables S9–S11 show correlations (Pearson correlation coefficient r) between the mRNA expression of the different genes (Table S9), between the concentrations of the plasma adipokine concentrations (Table S10) and between the different MRI and anthropometric measures (Table S11). On the mRNA expression level (Table S9), the highest correlations were observed between adiponectin and FABP4 (r=0.61), adiponectin and leptin (r=0.42), and FABP4 and leptin receptor (r=0.39). Regarding the adipokine plasma concentrations (Table S10), the highest correlations were between leptin and FABP4 (r=0.60) and leptin and leptin receptor (r=–0.43), besides the high correlations between the different adiponectin molecular fractions. Regarding the obesity measures (Table S11), BMI showed a high correlation with overall mass measures (r=0.84 with TBV, r=0.80 with TAT), intermediate correlation with SAT (r=0.69), and only moderate or small correlation with VAT and CAT mass (r≤0.51). WC and WHR had high correlation with internal AT (r=0.79/0.75 with VAT, r=0.74/0.70 with CAT), but very different correlations with overall mass measures (r=0.88/0.49 with TBV; r=0.57/0.02 with TAT; r=0.34/–0.25 with SAT). Regarding the MRI measures (Table S11), the correlation of TAT was high with SAT (r=0.95) but only moderate with TBV (r=0.67) and even smaller with VAT (r=0.40).

Table S12 shows the predictors with non-zero coefficients in a regularized multiple linear regression analysis, where each adipokine is predicted by main and interaction effects between all MRI measures, plasma concentrations and SAT gene expression of all other adipokines.

Table S1. Explained variance (adjusted R2) of the plasma adipokine concentrations, in regression models with predictors as described in Table 2, stratified by sex.\*

|  |
| --- |
| **Women** |
| **Model** | **Leptin** | **sOB–R** | **Resistin** | **FABP4** | **Total Adiponectin** | **HMW Adiponectin** | **MMW Adiponectin** | **LMW Adiponectin** | **IL6** |
| **1** | 0.32 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0.06 |
| **2** | 0.63 | 0.15 | 0 | 0.22 | 0.04 | 0.02 | 0 | 0 | 0.06 |
| **3** | 0.16 | 0.17 | 0 | 0.12 | 0.08 | 0.05 | 0.10 | 0 | 0.14 |
| **4** | 0.72 | 0.16 | 0 | 0.22 | 0.03 | 0.01 | 0 | 0 | 0.11 |
| **5** | 0.17 | 0.08 | 0 | 0.12 | 0.04 | 0.02 | 0 | 0 | 0 |
| **6** | 0.72 | 0.16 | 0 | 0.23 | 0.02 | 0 | 0 | 0 | 0.10 |
| **7** | 0.72 | 0.22 | 0 | 0.25 | 0.06 | 0.03 | 0.09 | 0 | 0.17 |
| **Men** |
| **Model** | **Leptin** | **sOB–R** | **Resistin** | **FABP4** | **Total Adiponectin** | **HMW Adiponectin** | **MMW Adiponectin** | **LMW Adiponectin** | **IL6** |
| **1** | 0.25 | 0 | 0 | 0.03 | 0.02 | 0 | 0.03 | 0 | 0 |
| **2** | 0.68 | 0.12 | 0.01 | 0.35 | 0.03 | 0.07 | 0 | 0 | 0.02 |
| **3** | 0.45 | 0.05 | 0 | 0.34 | 0.05 | 0.05 | 0.01 | 0.02 | 0.06 |
| **4** | 0.71 | 0.13 | 0.01 | 0.41 | 0.04 | 0.06 | 0.02 | 0 | 0.01 |
| **5** | 0.39 | 0.14 | 0.03 | 0.13 | 0.05 | 0.07 | 0.01 | 0 | 0.02 |
| **6** | 0.71 | 0.16 | 0 | 0.42 | 0.05 | 0.05 | 0.06 | 0 | 0.01 |
| **7** | 0.74 | 0.12 | 0 | 0.47 | 0.04 | 0.05 | 0.01 | 0 | 0.03 |

\*Plasma adipokine concentrations, SAT adipokine gene expression, VAT and SAT were log-transformed for analysis.

HMW, high molecular weight; MMW, medium molecular weight; LMW, low molecular weight.Table S2. Partial Pearson correlation coefficients (adjusted for age, physical activity, occupational training) and 95% confidence intervals between anthropometric measures and plasma adipokine concentrations, stratified by sex.\*

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Women** | **Leptin** | **sOB-R** | **Resistin** | **FABP4** | **Total Adipoq**  | **HMW Adipoq** | **MMW Adipoq** | **LMW Adipoq** | **IL6** |
| **r** | **95% CI** | **r** | **95% CI** | **r** | **95% CI** | **r** | **95% CI** | **r** | **95% CI** | **r** | **95% CI** | **r** | **95% CI** | **r** | **95% CI** | **r** | **95% CI** |
| **Weight** | 0.62 | (0.47; 0.74) | -0.35 | (-0.53; -0.15) | -0.02 | (-0.24; 0.19) | 0.40 | (0.20; 0.56) | -0.29 | (-0.48; -0.09) | -0.10 | (-0.31; 0.11) | -0.03 | (-0.25; 0.18) | -0.08 | (-0.29; 0.14) | 0.34 | (0.13; 0.51) |
| **BMI** | 0.67 | (0.53; 0.77) | -0.37 | (-0.54; -0.17) | 0.05 | (-0.16; 0.26) | 0.49 | (0.31; 0.64) | -0.28 | (-0.47; -0.07) | -0.13 | (-0.33; 0.09) | -0.02 | (-0.23; 0.20) | -0.05 | (-0.26; 0.17) | 0.32 | (0.11; 0.50) |
| **WC** | 0.62 | (0.46; 0.73) | -0.45 | (-0.61; -0.26) | 0.08 | (-0.14; 0.29) | 0.49 | (0.31; 0.64) | -0.27 | (-0.46; -0.06) | -0.16 | (-0.36; 0.05) | -0.12 | (-0.33; 0.10) | -0.12 | (-0.33; 0.10) | 0.34 | (0.13; 0.51) |
| **HC** | 0.66 | (0.52; 0.77) | -0.38 | (-0.55; -0.18) | 0.01 | (-0.21; 0.22) | 0.39 | (0.19; 0.56) | -0.16 | (-0.36; 0.06) | -0.03 | (-0.24; 0.19) |  0.05 | (-0.17; 0.26) | -0.12 | (-0.33; 0.10) | 0.29 | (0.08; 0.48) |
| **WHR** | 0.14 | (-0.08; 0.34) | -0.24 | (-0.43; -0.02) | 0.13 | (-0.09; 0.33) | 0.31 | (0.11; 0.49) | -0.24 | (-0.43; -0.03) | -0.24 | (-0.43; -0.02) | -0.27 | (-0.46; -0.06) | -0.05 | (-0.26; 0.17) | 0.17 | (-0.04; 0.37) |
| **VAT** | 0.48 | (0.29; 0.63) | -0.47 | (-0.62; -0.29) | 0 | (-0.21; 0.21) | 0.35 | (0.15; 0.53) | -0.33 | (-0.51; -0.12) | -0.31 | (-0.49; -0.10) | -0.38 | (-0.55; -0.18) | -0.06 | (-0.27; 0.16) | 0.36 | (0.16; 0.53) |
| **CAT** | 0.31 | (0.11; 0.50) | -0.34 | (-0.52; -0.14) | 0.03 | (-0.18; 0.25) | 0.39 | (0.19; 0.56) | -0.29 | (-0.47; -0.08) | -0.36 | (-0.53; -0.16) | -0.30 | (-0.48; -0.09) | -0.05 | (-0.26; 0.17) | 0.35 | (0.14; 0.52) |
| **SAT** | 0.79 | (0.69; 0.86) | -0.38 | (-0.55; -0.18) | 0.07 | (-0.14; 0.28) | 0.50 | (0.32; 0.64) | -0.22 | (-0.42; -0.01) | -0.14 | (-0.34; -0.07) | -0.01 | (-0.22; 0.21) | -0.12 | (-0.33; 0.10) | 0.29 | (0.08; 0.47) |
| **TAT** | 0.78 | (0.69; 0.85) | -0.43 | (-0.59; -0.23) | 0.07 | (-0.15; 0.28) | 0.52 | (0.34; 0.66) | -0.27 | (-0.46; -0.06) | -0.19 | (-0.39; 0.02) | -0.09 | (-0.30; 0.13) | -0.12 | (-0.33; 0.10) | 0.34 | (0.14; 0.52) |
| **Men**  | **Leptin** | **sOB-R** | **Resistin** | **FABP4** | **Total Adipoq** | **HMW Adipoq** | **MMW Adipoq** | **LMW Adipoq** | **IL6** |
| **r** | **95% CI** | **r** | **95% CI** | **r** | **95% CI** | **r** | **95% CI** | **r** | **95% CI** | **r** | **95% CI** | **r** | **95% CI** | **r** | **95% CI** | **r** | **95% CI** |
| **Weight** | 0.64 | (0.48; 0.76) | -0.29 | (-0.49; -0.05) | -0.21 | (-0.43; 0.02) | 0.51 | (0.31; 0.66) | -0.34 | (-0.53; -0.12) | -0.38 | (-0.56; -0.16) | -0.26 | (-0.47; -0.02) | -0.06 | (-0.29; 0.18) | 0.24 | (0.01; 0.45) |
| **BMI** | 0.70 | (0.56; 0.81) | -0.43 | (-0.60; -0.21) | -0.21 | (-0.42; 0.03) | 0.60 | (0.42; 0.71) | -0.37 | (-0.56; -0.15) | -0.41 | (-0.58; -0.19) | -0.19 | (-0.41; 0.05) | -0.17 | (-0.39; 0.07) | 0.26 | (0.03; 0.47) |
| **WC** | 0.73 | (0.60; 0.82) | -0.36 | (-0.55; -0.13) | -0.18 | (-0.40; 0.06) | 0.54 | (0.35; 0.69) | -0.32 | (-0.51; -0.09) | -0.35 | (-0.54; -0.12) | -0.20 | (-0.42; 0.04) | -0.14 | (-0.36; 0.10) | 0.30 | (0.07; 0.50) |
| **HC** | 0.68 | (0.52; 0.79) | -0.38 | (-0.57; -0.16) | -0.08 | (-0.31; 0.16) | 0.56 | (0.37; 0.70) | -0.37 | (-0.55; -0.14) | -0.45 | (-0.62; -0.24) | -0.26 | (-0.47; -0.02) | -0.07 | (-0.30; 0.17) | 0.19 | (-0.04; 0.41) |
| **WHR** | 0.54 | (0.34; 0.68) | -0.21 | (-0.42; 0.03) | -0.23 | (-0.44; 0.01) | 0.33 | (0.10; 0.52) | -0.14 | (-0.37; 0.09) | -0.10 | (-0.33; 0.14) | -0.06 | (-0.29; 0.18) | -0.16 | (-0.38; 0.08) | 0.30 | (0.07; 0.50) |
| **VAT** | 0.71 | (0.57; 0.81) | -0.28 | (-0.48; -0.05) | -0.12 | (-0.35; 0.12) | 0.60 | (0.43; 0.74) | -0.30 | (-0.50; -0.06) | -0.30 | (-0.50; -0.06) | -0.20 | (-0.42; 0.04) | -0.17 | (-0.39; 0.07) | 0.26 | (0.03; 0.47) |
| **CAT** | 0.67 | (0.52; 0.78) | -0.27 | (-0.48; -0.04) | -0.08 | (-0.31; 0.16) | 0.60 | (0.43; 0.74) | -0.21 | (-0.43; 0.02) | -0.26 | (-0.47; -0.03) | -0.18 | (-0.40; 0.06) | -0.09 | (-0.32; 0.15) | 0.32 | (0.10; 0.52) |
| **SAT** | 0.83 | (0.73; 0.89) | -0.38 | (-0.57; -0.16) | -0.12 | (-0.35; 0.12) | 0.62 | (0.45; 0.75) | -0.23 | (-0.44; 0) | -0.32 | (-0.52; -0.09) | -0.14 | (-0.37; 0.10) | -0.06 | (-0.29; 0.18) | 0.29 | (0.06; 0.49) |
| **TAT** | 0.84 | (0.73; 0.90) | -0.38 | (-0.56; -0.16) | -0.13 | (-0.35; 0.11) | 0.66 | (0.50; 0.77) | -0.27 | (-0.47; -0.04) | -0.33 | (-0.53; -0.11) | -0.18 | (-0.40; 0.06) | -0.10 | (-0.33; 0.14) | 0.30 | (0.07; 0.50) |

\*Plasma adipokine concentrations, VAT, CAT, SAT and TAT were log-transformed for analysis.

BMI, body mass index; WC, waist circumference; HC, hip circumference; WHR, waist-hip-ratio; AT, adipose tissue; VAT, visceral AT; CAT, coronary AT; SAT, subcutaneous AT; TAT, total AT; HMW, high molecular weight; MMW, medium molecular weight; LMW, low molecular weight.

Table S3. Partial Pearson correlation coefficients (adjusted for age, physical activity, occupational training) and 95% confidence intervals between SAT adipokine gene expressions and plasma adipokine concentrations of the same gene, stratified by sex.\*

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Women** | **Leptin** | **sOB-R** | **Resistin** | **FABP4** | **Total Adipoq**  | **HMW Adipoq** | **MMW Adipoq** | **LMW Adipoq** | **IL6** |
| **r** | **95% CI** | **r** | **95% CI** | **r** | **95% CI** | **r** | **95% CI** | **r** | **95% CI** | **r** | **95% CI** | **r** | **95% CI** | **r** | **95% CI** | **r** | **95% CI** |
| **GE** | 0.56 | (0.39; 0.69) | -0.11 | (-0.31; 0.11) | 0.11 | (-0.10; 0.32) | -0.14 | (-0.34; 0.08) | 0.13 | (-0.09; 0.33) | 0.12 | (0.09; 0.33) | 0.10 | (-0.11; 0.31) | -0.09 | (-0.30; 0.13) | 0.27 | (0.06; 0.46) |
| **Men**  | **Leptin** | **sOB-R** | **Resistin** | **FABP4** | **Total Adipoq** | **HMW Adipoq** | **MMW Adipoq** | **LMW Adipoq** | **IL6** |
| **r** | **95% CI** | **r** | **95% CI** | **r** | **95% CI** | **r** | **95% CI** | **r** | **95% CI** | **r** | **95% CI** | **r** | **95% CI** | **r** | **95% CI** | **r** | **95% CI** |
| **GE** | 0.47 | (0.26; 0.64) | 0.03 | (-0.20; 0.27) | 0.08 | (-0.16; 0.31) | 0.21 | (-0.03; 0.43) | 0.22 | (-0.02; 0.43) | 0.16 | (-0.08; 0.38) | 0.24 | (0; 0.45) | 0.06 | (-0.18; 0.29) | 0.12 | (-0.12; 0.35) |

\*Plasma adipokine concentrations and GE were log-transformed for analysis.

GE, gene expression of the corresponding gene; HMW, high molecular weight; MMW, medium molecular weight; LMW, low molecular weight.

Table S4. Explained variance (adjusted R2) of the plasma adipokine concentrations in regression models with predictors as described in Table 2, by replacing the AT measures by the respective AT/height ratios.\*

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Model** | **Variables** | **Leptin** | **sOB–R** | **Resistin** | **FABP4** | **Total Adiponectin** | **HMW Adiponectin** | **MMW Adiponectin** | **LMW Adiponectin** | **IL6** |
| **1** | **GEsame** | 0.48 | 0 | 0 | 0 | 0.04 | 0.03 | 0.03 | 0 | 0.02 |
| **2** | **SAT/height** | 0.78 | 0.12 | 0.01 | 0.46 | 0 | 0 | 0 | 0 | 0 |
| **3** | **VAT/height** | 0 | 0.07 | 0 | 0.01 | 0.14 | 0.14 | 0.09 | 0.02 | 0.12 |
| **4** | **GEsame, SAT/height** | 0.81 | 0.12 | 0.01 | 0.48 | 0.03 | 0.03 | 0.03 | 0 | 0.02 |
| **5** | **GEsame × SAT/height** | 0.81 | 0.11 | 0 | 0.45 | 0.01 | 0.01 | 0.01 | 0 | 0.01 |
| **6** | **GEsame, SAT/height, GEsame × SAT/height** | 0.81 | 0.12 | 0 | 0.48 | 0.03 | 0.02 | 0.05 | 0 | 0.04 |
| **7** | **GEsame, SAT/height, VAT/height** | 0.82 | 0.17 | 0.01 | 0.49 | 0.14 | 0.14 | 0.10 | 0.02 | 0.12 |

\*Plasma adipokine concentrations, SAT adipokine gene expression, SAT/heightand VAT/heightwere log–transformed for analysis.

GE, gene expression of the corresponding gene; AT, adipose tissue; SAT, subcutaneous AT; VAT, visceral AT; HMW, high molecular weight; MMW, medium molecular weight; LMW, low molecular weight.

Table S5. Partial Pearson correlation coefficients (adjusted for sex, age, physical activity, occupational training) between anthropometric measures and plasma adipokine concentrations.\*

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | **Leptin** | **sOB–R** | **Resistin** | **FABP4** | **Total Adiponectin** | **HMW Adiponectin** | **MMW Adiponectin** | **LMW Adiponectin** | **IL6** |
| **VAT** | 0.58 | -0.40 | -0.06 | 0.45 | -0.32 | -0.30 | -0.32 | -0.10 | 0.31 |
| **CAT** | 0.51 | -0.30 | -0.01 | 0.50 | -0.24 | -0.30 | -0.24 | -0.06 | 0.33 |
| **SAT** | 0.81 | -0.37 | -0.04 | 0.57 | -0.23 | -0.24 | -0.08 | -0.10 | 0.27 |
| **TAT** | 0.82 | -0.40 | -0.05 | 0.59 | -0.26 | -0.27 | -0.14 | -0.12 | 0.31 |
| **VAT/ height** | 0.59 | -0.41 | -0.06 | 0.47 | -0.32 | -0.30 | -0.31 | -0.11 | 0.30 |
| **CAT/ height** | 0.51 | -0.31 | 0 | 0.51 | -0.24 | -0.30 | -0.23 | -0.07 | 0.33 |
| **SAT/ height** | 0.82 | -0.38 | -0.03 | 0.59 | -0.23 | -0.24 | -0.07 | -0.11 | 0.27 |
| **TAT/ height** | 0.82 | -0.41 | -0.04 | 0.61 | -0.27 | -0.28 | -0.13 | -0.13 | 0.30 |
| **VAT/ height2** | 0.59 | -0.42 | -0.05 | 0.48 | -0.32 | -0.30 | -0.31 | -0.12 | 0.30 |
| **CAT/ height2** | 0.51 | -0.31 | 0 | 0.52 | -0.24 | -0.30 | -0.22 | -0.08 | 0.32 |
| **SAT/ height2** | 0.81 | -0.39 | -0.02 | 0.60 | -0.23 | -0.25 | -0.06 | -0.12 | 0.26 |
| **TAT/ height2** | 0.82 | -0.41 | -0.03 | 0.62 | -0.26 | -0.28 | -0.12 | -0.13 | 0.29 |
| **VAT/ height3** | 0.60 | -0.42 | -0.05 | 0.49 | -0.31 | -0.31 | -0.30 | -0.12 | 0.29 |
| **CAT/ height3** | 0.51 | -0.32 |  0.01 | 0.53 | -0.24 | -0.30 | -0.21 | -0.08 | 0.31 |
| **SAT/ height3** | 0.80 | -0.39 | -0.02 | 0.60 | -0.22 | -0.25 | -0.05 | -0.12 | 0.24 |
| **TAT/ height3** | 0.81 | -0.41 | -0.02 | 0.62 | -0.26 | -0.28 | -0.11 | -0.14 | 0.28 |
| **VAT/ SMT** | 0.57 | -0.39 | -0.01 | 0.45 | -0.28 | -0.28 | -0.31 | -0.10 | 0.30 |
| **CAT/ SMT** | 0.46 | -0.27 |  0.05 | 0.48 | -0.19 | -0.27 | -0.20 | -0.06 | 0.32 |
| **SAT/ SMT** | 0.77 | -0.33 |  0.05 | 0.54 | -0.15 | -0.19 | -0.02 | -0.09 | 0.25 |
| **TAT/ SMT** | 0.80 | -0.36 |  0.04 | 0.58 | -0.20 | -0.23 | -0.09 | -0.11 | 0.29 |

\* Plasma adipokine concentrations and all AT measures and ratios were log-transformed for analysis

AT, adipose tissue; VAT, visceral AT; CAT, coronary AT; SAT, subcutaneous AT; TAT, total AT; SMT skeletal muscle tissue; HMW, high molecular weight; MMW, medium molecular weight; LMW, low molecular weight.

Table S6. Partial Pearson correlation coefficients (adjusted for sex, age, physical activity, occupational training) between anthropometric measures, SAT adipokine gene expressions of the same gene, and estimates of plasma adipokine quantities.\*,†

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | **Leptin** | **sOB–R** | **Resistin** | **FABP4** | **Total Adiponectin** | **HMW Adiponectin** | **MMW Adiponectin** | **LMW Adiponectin** | **IL6** |
| **VAT** | 0.61 | -0.31 | 0.08 | 0.53 | -0.23 | -0.23 | -0.25 | -0.01 | 0.38 |
| **CAT** | 0.52 | -0.23 | 0.10 | 0.55 | -0.17 | -0.24 | -0.18 |  0.01 | 0.39 |
| **SAT** | 0.84 | -0.25 | 0.14 | 0.66 | -0.11 | -0.15 |  0.02 |  0.01 | 0.38 |
| **TAT** | 0.85 | -0.27 | 0.14 | 0.68 | -0.15 | -0.18 | -0.04 | 0 | 0.41 |
| **GE** | 0.51 | -0.03 | 0.08 |  -0.03 |  0.12 |  0.10 |  0.13 |  -0.06 | 0.19 |

\*Plasma adipokine quantities, VAT, CAT, SAT, TAT, and gene expression were log–transformed for analysis.

†Crude estimates of plasma adipokine quantities were obtained by multiplying the plasma adipokine concentrations with $\frac{70∙weight}{\sqrt{\frac{BMI}{22}}}$, see [19].

AT, adipose tissue; VAT, visceral AT; CAT, coronary AT; SAT, subcutaneous AT; TAT, total AT; HMW, high molecular weight; MMW, medium molecular weight; LMW, low molecular weight; GE, gene expression of the corresponding gene.

Table S7. Partial Pearson correlation coefficients r (adjusted for sex, age, physical activity, occupational training) and 95% confidence intervals between anthropometric measures and SAT gene expressions.\*,†

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|   | **Leptin** | **sOB–R** | **Resistin** | **FABP4** | **Adiponectin** | **IL6** |
| **r** | **95% CI** | **r** | **95% CI** | **r** | **95% CI** | **r** | **95% CI** | **r** | **95% CI** | **r** | **95% CI** |
| **Weight** | 0.22 | (0.06; 0.37) | 0.08 | (-0.08; 0.23) | 0.07 | (-0.09; 0.22) | -0.27 | (-0.41; -0.11) | -0.26 | (-0.40; -0.11) | 0.13 | (-0.03; 0.28) |
| **BMI** | 0.27 | (0.11; 0.41) | 0.03 | (-0.12; 0.19) | 0.09 | (-0.07; 0.25) | -0.21 | (-0.35; -0.05) | -0.25 | (-0.40; -0.10) | 0.16 | (0; 0.31) |
| **WC** | 0.26 | (0.10; 0.40) | 0.03 | (-0.13; 0.19) | 0.10 | (-0.06; 0.26) | -0.27 | (-0.41; -0.11) | -0.27 | (-0.41; -0.11) | 0.14 | (-0.02; 0.29) |
| **HC** | 0.29 | (0.14; 0.43) | -0.01 | (-0.17; 0.15) | 0.05 | (-0.11; 0.21) | -0.26 | (-0.40; -0.11) | -0.24 | (-0.38; -0.08) | 0.12 | (-0.04; 0.28) |
| **WHR** | 0.07 | (-0.09; 0.22) | 0.06 | (-0.10; 0.21) | 0.10 | (-0.06; 0.25) | -0.14 | (-0.29; 0.02) | -0.15 | (-0.30; 0) | 0.08 | (-0.08; 0.24) |
| **VAT** | 0.24 | (0.09; 0.39) | 0.15 | (0; 0.30) | 0.24 | (0.08; 0.38) | -0.25 | (-0.39; -0.09) | -0.29 | (-0.43; -0.14) | 0.26 | (0.11; 0.41) |
| **CAT** | 0.21 | (0.05; 0.36) | 0.11 | (-0.05; 0.27) | 0.13 | (-0.03; 0.28) | -0.12 | (-0.28; 0.03) | -0.20 | (-0.35; -0.04) | 0.18 | (0.02; 0.33) |
| **SAT** | 0.36 | (0.22; 0.49) | 0.04 | (-0.12; 0.20) | 0.18 | (0.02; 0.33) | -0.23 | (-0.37; -0.07) | -0.25 | (-0.39; -0.10) | 0.20 | (0.05; 0.35) |
| **TAT** | 0.34 | (0.20; 0.48) | 0.06 | (-0.10; 0.22) | 0.20 | (0.04; 0.35) | -0.25 | (-0.39; -0.09) | -0.28 | (-0.42; -0.13) | 0.22 | (0.07; 0.37) |
| **VAT/height** | 0.25 | (0.10; 0.39) | 0.15 | (-0.01; 0.30) | 0.24 | (0.08; 0.39) | -0.23 | (-0.38; -0.08) | -0.29 | (-0.43; -0.14) | 0.27 | (0.12; 0.41) |
| **CAT/height** | 0.22 | (0.06; 0.36) | 0.11 | (-0.05; 0.26) | 0.13 | (-0.03; 0.28) | -0.11 | (-0.26; 0.05) | -0.19 | (-0.34; -0.04) | 0.19 | (0.03; 0.34) |
| **SAT/height** | 0.37 | (0.23; 0.50) | 0.03 | (-0.13; 0.19) | 0.19 | (0.03; 0.34) | -0.21 | (-0.35; -0.05) | -0.25 | (-0.39; -0.09) | 0.21 | (0.06; 0.36) |
| **TAT/height** | 0.35 | (0.21; 0.49) | 0.06 | (-0.10; 0.21) | 0.21 | (0.05; 0.36) | -0.23 | (-0.37; -0.07) | -0.28 | (-0.42; -0.12) | 0.23 | (0.08; 0.38) |

\*Gene expression, VAT, CAT, SAT, TAT, VAT/height, CAT/height, SAT/height and TAT/height were log–transformed for analysis.

†Correlations of gene expression with the traditional anthropometric measures and MRI–based measures with r>|0.26| correspond to Bonferroni–adjusted p–values<0.05 adjusted for 78 comparisons.

BMI, body mass index; WC, waist circumference; HC, hip circumference; WHR, waist–hip–ratio; AT, adipose tissue; VAT, visceral AT; CAT, coronary AT; SAT, subcutaneous AT; TAT, total AT.

Table S8. Partial Pearson correlation coefficients (adjusted for sex, age, physical activity, occupational training) and 95% confidence intervals between plasma adipokine concentrations and SAT gene expressions.\*

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | **Leptin** | **sOB–R** | **Resistin** | **FABP4** | **Adiponectin** | **IL6** |
| **r** | **95% CI** | **r** | **95% CI** | **r** | **95% CI** | **r** | **95% CI** | **r** | **95% CI** | **r** | **95% CI** |
| **Leptin** |  0.52 | (0.40; 0.63) |  0.08 | (-0.08; 0.24) |  0.21 | (0.06; 0.36) | -0.23 | (-0.37; -0.07) | -0.23 | (-0.38; -0.08) |  0.24 | (0.08; 0.38) |
| **sOB-R** | -0.33 | (-0.46; -0.18) | -0.05 | (-0.20; 0.11) | -0.07 | (-0.23; 0.09) |  0.17 | (0.01; 0.32) |  0.17 | (0.01; 0.32) | -0.18 | (-0.33; -0.03) |
| **Resistin** |  0.14 | (-0.02; 0.29) |  0.02 | (-0.14; 0.18) |  0.08 | (-0.08; 0.24) |  0.03 | (-0.13; 0.19) |  0.11 | (-0.05; 0.26) |  0.04 | (-0.12; 0.20) |
| **FABP4** |  0.15 | (-0.01; 0.30) |  0.12 | (-0.04; 0.27) |  0.18 | (0.02; 0.33) |  0.02 | (-0.13; 0.18) | -0.13 | (-0.28; 0.03) |  0.18 | (0.02; 0.33) |
| **Total Adiponectin** | -0.23 | (-0.38; -0.08) | -0.18 | (-0.33; -0.02) |  0.01 | (-0.15; 0.17) |  0.10 | (-0.06; 0.25) |  0.15 | (-0.01; 0.30) | -0.12 | (-0.27; 0.04) |
| **HMW Adiponectin** | -0.22 | (-0.37; -0.07) | -0.19 | (-0.33; -0.03) | -0.05 | (-0.21; 0.11) |  0.04 | (-0.12; 0.20) |  0.13 | (-0.03; 0.28) | -0.14 | (-0.29; 0.02) |
| **MMW Adiponectin** | -0.21 | (-0.35; -0.05) | -0.11 | (-0.27; 0.05) |  0.04 | (-0.13; 0.20) |  0.07 | (-0.09; 0.23) |  0.16 | (0; 0.31) |  0.01 | (-0.15; 0.17) |
| **LMW Adiponectin** | -0.16 | (-0.31; 0) | -0.17 | (-0.32; -0.01) | -0.02 | (-0.19; 0.14) |  0 | (-0.16; 0.16) | -0.03 | (-0.19; 0.13) | -0.17 | (-0.32; -0.01) |
| **IL6** |  0.14 | (-0.02; 0.29) | -0.01 | (-0.15; 0.17) |  0.09 | (-0.07; 0.25) |  0.05 | (-0.10; 0.21) | -0.04 | (-0.20; 0.12) |  0.19 | (0.03; 0.34) |

\*Plasma concentrations and gene expressions were log–transformed for analysis.

HMW, high molecular weight; MMW, medium molecular weight; LMW, low molecular weight.

Table S9. Pearson correlation coefficients between the different SAT gene expressions.\*

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | **Leptin** | **sOB–R** | **Resistin** | **FABP4** | **Adiponectin** | **IL6** |
| **Leptin** | 1 |  |  |  |  |  |
| **sOB–R** |  0.26 | 1 |  |  |  |  |
| **Resistin** |  0.07 | 0.15 | 1 |  |  |  |
| **FABP4** |  0.22 | 0.39 |  0.08 | 1 |  |  |
| **Adiponectin** |  0.42 | 0.26 | -0.21 |  0.61 | 1 |  |
| **IL6** |  0.29 | 0.27 |  0.35 |  0.13 | 0.05 | 1 |

\*Gene expressions are shown relative to the housekeeping gene expression in the unit 2–ΔCt and were log–transformed for analysis.

Table S10. Pearson correlation coefficients between the different plasma adipokine concentrations.\*

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | **Leptin** | **sOB-R** | **Resistin** | **FABP4** | **IL6** | **Total Adiponectin** | **HMW Adiponectin** | **MMW Adiponectin** | **LMW Adiponectin** |
| **Leptin** | 1 |  |  |  |  |  |  |  |  |
| **sOB-R** | -0.43 | 1 |  |  |  |  |  |  |  |
| **Resistin** | -0.09 | 0 | 1 |  |  |  |  |  |  |
| **FABP4** |  0.60 | -0.22 |  0.16 | 1 |  |  |  |  |  |
| **IL6** |  0.05 |  0.02 |  0.14 |  0.15 | 1 |  |  |  |  |
| **Total Adiponectin** |  0.06 |  0.19 | -0.13 | -0.03 | -0.13 | 1 |  |  |  |
| **HMW Adiponectin** |  0.02 |  0.20 | -0.14 | -0.11 | -0.16 | 0.92 | 1 |  |  |
| **MMW Adiponectin** |  0.02 |  0.18 | 0 |  0.06 | -0.19 | 0.68 | 0.60 | 1 |  |
| **LMW Adiponectin** |  0.02 |  0.03 | -0.02 | -0.02 |  0.07 | 0.47 | 0.26 | -0.07 | 1 |

\*Plasma concentrations were log-transformed for analysis.

HMW, high molecular weight; MMW, medium molecular weight; LMW, low molecular weight.

Table S11. Pearson correlation coefficients between the different anthropometric and MRI measures.\*

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | **BMI** | **WC** | **WHR** | **TBV\*** | **VAT\*** | **CAT\*** | **SAT\*** | **TAT\*** |
| **BMI** | 1 |  |  |  |  |  |  |  |
| **WC** | 0.77 | 1 |  |  |  |  |  |  |
| **WHR** | 0.26 | 0.75 | 1 |  |  |  |  |  |
| **TBV\*** | 0.84 | 0.88 | 0.49 | 1 |  |  |  |  |
| **VAT\*** | 0.51 | 0.79 | 0.75 | 0.68 | 1 |  |  |  |
| **CAT\*** | 0.47 | 0.74 | 0.70 | 0.62 | 0.83 | 1 |  |  |
| **SAT\*** | 0.69 | 0.34 |  -0.25 | 0.49 | 0.10 | 0.09 | 1 |  |
| **TAT\*** | 0.80 | 0.57 | 0.02 | 0.67 | 0.40 | 0.36 | 0.95 | 1 |

\*TBV, VAT, CAT, SAT and TAT are log–transformed for analysis.

BMI, body mass index; WC, waist circumference; WHR, waist–hip–ratio; TBV, total body volume; AT, adipose tissue; VAT, visceral AT; CAT, coronary AT; SAT, subcutaneous AT; TAT, total AT.

Table S12. Selected predictors (with non-zero regression coefficients) in the exploratory model-selection analyses using lasso and the explained variance (R2) of the regression model based on these predictors.\*

|  |  |  |
| --- | --- | --- |
| **Adipokine** | **Selected predictors** | **R2** |
| **Leptin** | TATVAT × CATCAT × SMT Leptin\_GESAT × Resistin\_PLVAT × IL6\_PLCAT × SOB-R\_PLTAT × total\_Adiponectin\_PLTAT × SOB-R\_GETAT × FABP4\_GETAT × Adiponectin\_GETAT × IL6\_GESOB-R\_PL **×** Resistin\_PLSOB-R\_PL × Leptin\_GEFABP4\_PL × FABP4\_GE Leptin\_GE × Resistin\_GE | 0.86 |
| **sOB-R** | VAT × Leptin\_PL CAT × IL6\_PLSMT × Leptin\_PLLeptin\_PL × FABP4\_GELeptin\_PL × Adiponectin\_GEtotal\_Adiponectin\_PL × Leptin\_GEtotal\_Adiponectin\_PL × IL6\_GELeptin\_GE × IL6\_GE | 0.28 |
| **Resistin** | SAT × CATSAT × total\_Adiponectin\_PLSAT × Leptin\_GESAT × Resistin\_GE FABP4\_PL × IL6\_PLFABP4\_PL × Leptin\_GEFABP4\_PL × FABP4\_GE | 0.14 |
| **FABP4** | SAT × TATCAT × SMTSAT × Resistin\_PLTAT × Resistin\_PLSMT × total\_Adiponectin\_PLSAT × Leptin\_GESMT × FABP4\_GELeptin\_PL × Resistin\_PLLeptin\_PL × IL6\_PLLeptin\_PL × Leptin\_GEtotal\_Adiponectin\_PL × SOB-R\_GEtotal\_Adiponectin\_PL × FABP4\_GE | 0.61 |
| **IL6** | CAT × SMTVAT × FABP4\_PLTAT × SOB-R\_PLTAT × Resistin\_PLSOB-R\_PL × Resistin\_PL | 0.18 |
| **Total Adiponectin** | Adiponectin\_GEVAT × CATSAT × SOB-R\_PLVAT × FABP4\_PLSMT × Resistin\_PLSMT × FABP4\_PLSAT × Leptin\_GESMT × FABP4\_GESMT × Adiponectin\_GE" Leptin\_GE × SOB-R\_GEResistin\_GE × Adiponectin\_GEFABP4\_GE × Adiponectin\_GE | 0.31 |

\*All AT, plasma concentrations, and SAT gene expression measures are log–transformed for analysis.

AT, adipose tissue; VAT, visceral AT; CAT, coronary AT; SAT, subcutaneous AT; TAT, total AT; GE, SAT gene expression; PL, adipokine plasma levels.

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