



# Design and validation of a novel estimator of visceral adipose tissue area and comparison to existing adiposity surrogates

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## ABSTRACT

**Aims:** Visceral adiposity measured by computed tomography (CT) as intra-abdominal fat area (IAFA) predicts metabolic diseases. Existing adiposity surrogates have not been systematically compared to a regression-based model derived in individuals of Japanese ancestry. We developed and validated a method to estimate IAFA in individuals of Japanese ancestry and compared it to existing adiposity surrogates.

**Methods:** We assessed age, BMI, waist circumference (WC), fasting lipids, glucose, smoking status, grip strength, mid-thigh circumference (MTC), humeral length, leg length, and IAFA by single-slice CT at the umbilicus for 622 Japanese Americans. We used stepwise linear regression to predict IAFA and termed the predicted value the Estimate of Visceral Adipose Tissue Area (EVA). For men, the final model included age, BMI, WC, high-density lipoprotein cholesterol (HDLc), glucose, and MTC; for women, age, BMI, WC, HDLc, low-density lipoprotein cholesterol, glucose, and MTC. We compared goodness-of-fit ( $R^2$ ) from linear regression models and mean-squared errors (MSE) from k-fold cross-validation to compare the ability of EVA to estimate IAFA compared to an estimate by Després et al., waist-to-height ratio, WC, deep abdominal adipose tissue index, BMI, lipid accumulation product, and visceral adiposity index (VAI). We classified low/high IAFA using area under receiver-operating characteristic curves (AUROC) for IAFA dichotomized at the 75th percentile.

**Results:** EVA gave the least MSE and greatest  $R^2$  (men: 1244, 0.61; women: 581, 0.72). VAI gave the greatest MSE and smallest  $R^2$  (mean 2888, 0.08; women 1734, 0.14).

**Conclusions:** EVA better predicts IAFA in Japanese-American men and women compared to existing surrogates for adiposity.

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## 1. Introduction

Excess visceral adipose tissue, quantified as intra-abdominal fat area (IAFA), is a major risk factor for metabolic disease in Japanese Americans.<sup>1–6</sup> Surrogate measures of visceral adiposity derived from anthropometric measures including body mass index (BMI) and waist circumference (WC) are routinely used<sup>7</sup> in both clinical practice and epidemiologic research, as direct measurement of IAFA is often prohibitively expensive or logistically difficult to obtain. Measures incorporating

blood-based biomarkers have also been used to estimate IAFA, including the Lipid Accumulation Product<sup>8</sup> and the Visceral Adiposity Index.<sup>9</sup>

When compared to White populations, Asians have more visceral fat<sup>10,11</sup> and a higher body fat percentage for a given BMI.<sup>12</sup> Adiposity surrogates derived in non-Asian populations might therefore perform poorly when applied to Japanese, Japanese-American, and other Asian populations.<sup>10</sup> We therefore examined whether an alternate adiposity surrogate might more closely parallel the quantity of IAFA among individuals of Japanese ancestry. We hypothesized that an adiposity surrogate incorporating widely available demographic information, anthropometric data, and blood-based biomarkers could predict computed tomography (CT)-measured IAFA better in Japanese Americans than existing visceral adiposity surrogates. These include anthropometric measures such as BMI, WC, and WHtR; indices experimentally derived from clinical and anthropometric measurements such as the Deep Abdominal Adipose-Tissue index<sup>13</sup> and an index calculated by

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Després<sup>14</sup>; and indices derived from clinical, anthropometric and blood-based measurements such as the Visceral Adiposity Index<sup>9</sup> and the Lipid Accumulation Product.<sup>8</sup>

## 2. Materials/subjects & methods

### 2.1. Study design and setting

We measured demographic, metabolic and body composition variables in 622 Japanese-American men and women from the Japanese-American Community Diabetes Study (JACDS), a community-based cohort of second- and third-generation Japanese Americans of 100% Japanese ancestry who lived in King County, Washington State. These individuals were representative of Japanese-American residents of the county in age, residential distribution and parental immigration pattern. JACDS was initially designed to investigate risk factors for and prevalence of type 2 diabetes among Japanese Americans. Individuals were recruited between 1983 and 1991. Selection and recruitment have been described previously.<sup>15</sup> Of an initial sample of 658 individuals, 36 were missing data on covariates, leaving an analytic sample of 622 participants. The study was approved by the University of Washington Human Subjects Division, and all participants provided written informed consent.

### 2.2. Data collection

Evaluations were done at the General Clinical Research Center at the University of Washington, Seattle. Information on age, sex, and current and former tobacco use was obtained by interview. Trained staff measured height, weight and WC. Weight was measured using a digital scale after shoes and outer clothing were removed. BMI was defined as weight in kg divided by height in meters squared. WC was measured twice using a flexible but non-stretchable tape measure and averaged. In male participants, the measurement was obtained at the midpoint between the iliac crest and the inferior border of the lowest rib. In female participants, the minimal circumference between iliac crest and lowest rib was used. WHtR was defined as waist circumference in cm divided by height in cm. Serum glucose, triglycerides (TG), high-density lipoprotein cholesterol (HDLc) and low-density lipoprotein cholesterol (LDLc) were measured in specimens taken after at least a 10-h fast.

For comparison to our new index, we chose seven existing measures that have been used as IAFA surrogates. Measures included BMI, WC, and WHtR; indices experimentally derived from clinical and anthropometric measurements such as the Deep-Abdominal Adipose Tissue index<sup>13</sup> and an index calculated by Després<sup>14</sup>; and indices derived from clinical, anthropometric and blood-based measurements such as the Visceral Adiposity Index<sup>9</sup> and the Lipid Accumulation Product.<sup>8</sup> We calculated sex-specific values of each index for all participants. The Deep-Abdominal Adipose Tissue index was defined as  $-382.9 + [1.09 \times \text{weight (kg)}] + [6.04 \times \text{WC (cm)}] + (-2.29 \times \text{BMI})$  for men, and  $-278 + [-0.86 \times \text{weight (kg)}] + [5.19 \times \text{WC (cm)}]$  for women.<sup>13</sup> The Després index was defined as  $-225.39 + 2.125 \times \text{age (years)} + 2.843 \times \text{WC (cm)}$ .<sup>14</sup> Because the Després index was derived in a male cohort, we restricted the analysis of this index to the men in our dataset. The Visceral Adiposity Index was defined as  $\{\text{WC (cm)} / (39.68 + [1.88 \times \text{BMI (kg/m}^2)])\} \times (\text{triglycerides}/1.03) \times (1.31/\text{HDL})$  for men, and  $\{\text{WC (cm)} / (36.58 + [1.89 \times \text{BMI (kg/m}^2)])\} \times (\text{triglycerides}/0.81) \times (1.52/\text{HDL})$  for women,<sup>9</sup> with both triglycerides and HDL specified in mmol/L. The Lipid Accumulation Product was defined as  $[(\text{WC (cm)} - 65) \times \text{TG (mmol/L)}]$  in men, and  $[(\text{WC (cm)} - 58) \times \text{TG (mmol/L)}]$  in women.<sup>8</sup>

To estimate IAFA, single (1 cm) CT-scan slices were obtained at the level of the umbilicus. Scans were analyzed for cross-sectional area of fat using automated density contour software. Areas corresponding to a density of  $-250$  to  $-50$  Hounsfield units were classified as adipose tissue.<sup>16</sup> IAFA was defined as fat within the confines of the transversalis fascia and

reported in  $\text{cm}^2$ . Intra-observer variability for multiple measurements by a single observer of a single CT scan ranged from 0.2% to 1.4%.

### 2.3. Statistical analysis

We used number (%) and mean (standard deviation) for categorical and normally distributed continuous variables, respectively, to describe study population characteristics, both overall and stratified by sex. For TG, we reported median (inter-quartile range), as the distribution was skewed. To derive a novel adiposity estimate, we used backward stepwise linear regression to fit models using easy-to-obtain demographic, anthropometric, and blood-based measurements (age, BMI, WC, HDLc, LDLc, TG, fasting glucose, and smoking status) to predict IAFA. A  $p$ -value  $\leq 0.05$  allowed entry into the model, while a  $p$ -value of 0.1 or greater prompted removal. Because there was evidence of a multiplicative first-order interaction of sex with WC, we chose to perform analyses stratified by sex. We fit linear regression models looking for evidence of nonlinearity in associations of metabolic variables and body composition with IAFA using the Stata command *mfp*. We also performed model diagnostics to identify influential outliers and for evidence of violations of model assumptions.<sup>17</sup> We termed the new index the Estimate of Visceral Adipose Tissue Area (EVA). We dichotomized IAFA at the 75th percentile values and plotted receiver-operating characteristic (ROC) curves to estimate ability of EVA to categorize IAFA as below or above the 75th percentile.

We compared performance of EVA to the seven previously described adiposity surrogates. Because mid-thigh circumference may be assessed less frequently than the other anthropometric measures that were collected, we also compared performance of EVA to a version of our model that did not include mid-thigh circumference, which we called EVA-R (reduced). We regressed IAFA on each adiposity surrogate in a univariate linear regression model. We compared  $R^2$  values among the models and identified the model with the lowest Akaike Information Criterion (AIC). We validated results internally using k-fold cross-validation to compare mean-squared errors (MSE).<sup>18</sup> For these analyses, data were partitioned into five sub-samples repeatedly. Four sub-samples were combined as the training dataset and the last was left out as a validation dataset. Prediction errors (mean squared errors) were obtained on the left-out group. For each round this was repeated with each of the sub-samples used as the validation dataset. This was repeated 500 times. Errors were averaged, and 95% confidence intervals were calculated. Lastly, we compared performance of the seven visceral adiposity surrogates to EVA in discriminating low vs. high categories of IAFA. We used sex-specific 75th percentile cutpoints taken from the training dataset for all analyses ( $140 \text{ cm}^2$  [men] and  $100 \text{ cm}^2$  [women]). We compared the area under the ROC curves (AUROC) using chi-squared tests.<sup>19</sup>

For AUROC comparisons, a  $p$ -value of  $<0.05$  was considered statistically significant. MSE with non-overlapping 95% confidence intervals were considered statistically significantly different. Analyses were performed with Stata (version 15.0; StataCorp, College Station, TX).

## 3. Results

Table 1 shows participant characteristics overall and stratified by sex. Coefficients and  $p$ -values from sex-specific linear regression models testing associations of metabolic risk factors with IAFA in the derivation cohort are shown in Table 2. All the variables shown in Table 1 with the exception of IAFA and diabetes status were considered in the multivariable models described in Table 2. Using the stepwise methods described above, LDLc, triglycerides, smoking status, grip strength, humeral length and leg length were dropped from the model in men, leaving age, BMI, WC, HDLc, fasting glucose and mid-thigh circumference. In the model for women, triglycerides, smoking status, grip strength, humeral length, and leg length were dropped from the

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