Imaging of the cardiorenal syndrome and visceral fat

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Chapter 3

Novel Artificial Neural Network and Linear Regression Based Equation for Estimating Visceral Adipose Tissue Volume

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ABSTRACT

Objectives: There is a growing interest in fast and reliable assessment of abdominal visceral adipose tissue (VAT) volume for risk stratification of metabolic disorders. However, imaging based measurement of VAT is costly and limited by scanner availability. Therefore, we aimed to develop equations to estimate abdominal VAT volume from simple anthropometric parameters and to assess whether linear regression based equations differed in performance from artificial neural network (ANN) based equations.

Methods: MRI-measured abdominal VAT volumes and anthropometric parameters of 5772 subjects (White ethnicity, age 45-76 years, 52.7% females) were obtained from the UK Biobank. Subjects were divided into the derivation sample (n=5195) and the validation sample (n=577). Basic models (age, sex, height, weight) and expanded models (basic model + waist circumference and hip circumference) were constructed from the derivation sample by linear regression and ANN respectively. Performance of the linear regression and ANN based equations in the validation sample were compared and estimating accuracies were evaluated by receiver-operating characteristic curves (ROC).

Results: The basic and expanded equations based on linear regression and ANN demonstrated the adjusted coefficient of determination (R^2) ranging from 0.71 to 0.78, with bias ranging from less than 0.001L to 0.07L in comparison with MRI-measured VAT. Both basic and expanded ANN based equations demonstrated slightly higher adjusted R^2 and lower error measurements than linear regression equations. However, no statistical difference was found between linear regression equations and their ANN based counterparts in ROC analysis. Both linear regression and ANN based expanded equations presented higher estimating accuracies (76.9%-90.1%) than the basic equations (74.5%-87.5%) in ROC analysis.

Conclusions: We present equations based on linear regression and artificial neural networks to estimate abdominal VAT volume by simple anthropometric parameters for middle-aged and elderly White population. These equations can be used to estimate VAT volume in general practice as well as population-based studies.

INTRODUCTION

The disease burden related to obesity has increased significantly over the last decades, making excess body weight one of the most challenging public health problems of our time (1). Body mass index (BMI) is the most widely used tool to estimate obesity-related risks. However, previous studies suggested that people with similar BMI may have heterogeneous obese status, with remarkably different comorbidities and health risks (2, 3). It has been reported that relying on BMI as a measure of obesity could lead to misclassification of cardiometabolic health risks (4, 5).

Several studies have shown that abdominal or central obesity, measured by visceral adipose tissue (VAT) is a superior marker of cardio-metabolic risk and mortality than anthropometric indices of obesity such as BMI and waist-to-hip ratio (WHR) (6). There is a growing interest in fast and reliable assessment of VAT volume for improved risk stratification in obese individuals (7). Volumetric VAT derived from magnetic resonance imaging (MRI) or computer tomography (CT) is generally accepted as a gold standard for VAT estimation (8). Cross-sectional VAT area measured in a single CT or MRI slice at a predefined lumbar level (e.g. L3-L4 or L4-L5) is widely used as the proxy of volumetric VAT in a number of studies. However, CT or MRI quantifications of VAT are costly, and dependent on scanner availability, limiting their application in clinical and epidemiologic settings. The need for a simple and clinically applicable tool to monitor visceral fat is emphasized in the latest position statement (7).

Previous studies have developed a number of equations consisting of several anthropometric variables to predict VAT area based on linear regression models (**Supplementary Table S3.1**). However, population-based utility of these equations were limited by small sample size (up to N=1410), and the lack of internal or external validation. In addition, the VAT estimation was based on cross-sectional VAT area rather than whole abdominal VAT volume (9, 10), which could lead to estimation errors up to 14% (10). Also, the need for information on diverse combinations of anthropometric parameters such as skinfold, thigh circumference and sagittal diameter limited the use of these equations in clinical practice. Moreover, predictive capacity varied among previous equations, explaining 50% to 80% of the variance in VAT areas in both sex (**Supplementary Table S3.1**).

While linear regression equation is simple and interpretable, its estimation capacity could be compromised by potential nonlinear association between volumetric VAT and anthropometric parameters. Deep learning by artificial neural network (ANN) has been widely used in medical fields and is theoretically advantageous over traditional linear regression for complex medical problems. An ANN is an emulation of biological neural

network, which contains input, hidden and output layers, with each layer consisting of multiple neurons. The neurons are computing nodes that operate as nonlinear summing devices (11). Each neuron is connected by weighted lines to all the neurons in adjacent layers. An ANN gains functions by "training" process, during which multiple densely connected layers and neurons are activated by input variables and the activations are propagated in a non-linear way through multiple computational stages, to make the ANN exhibit desired behaviour (12). ANN has been increasingly applied to various medical fields, performing a wide range of tasks, such as clinical classification and prediction, image analysis and postprocessing, biochemical analysis and drug development (13). ANN based estimation equations have been developed for other medical interests (14, 15), and can yield higher accuracy than the linear regression equation when applied to estimate maximal oxygen uptake in adolescents (15). No ANN based equation for estimation of VAT has been reported yet.

The aim of this study was to develop equations to estimate abdominal VAT volume (eVAT) based on simple anthropometric parameters using large dataset of individuals with MRI-based measurements of VAT volume. Linear regression and ANN were utilized respectively in equation derivation and the performance of the estimating equations were compared. We intended to involve a basic and an expanded combination of anthropometric parameters that adapt to different circumstances in clinical and epidemiologic settings.

METHODS

Subjects

The UK Biobank Study (see www.ukbiobank.ac.uk for more information) is a large population-based prospective cohort that includes 503,325 individuals aged 40 to 69 years old (16). The participants were recruited across the United Kingdom for participation in the UK Biobank over a 5-year period beginning in 2006. The study protocol was approved by the National Health Service Research Ethics Service (reference 16/NW/0274). All participants gave informed consent for data provision and linkage. Access to the UK Biobank data was provided by the UK Biobank under application number 20666. For the current study, we only included individuals with MRI-measured VAT volume (n=5995) available at the release date of 30th January 2018. We selected the subjects with White background including "White", "British", "Irish" and "Any other White background". Then 90% of the female and male subjects were randomly selected to form the derivation sample, while the rest 10% subjects consisted

of the validation sample. The process of subjects selection and sampling is shown in the flow chart. (**Figure 3.1**)

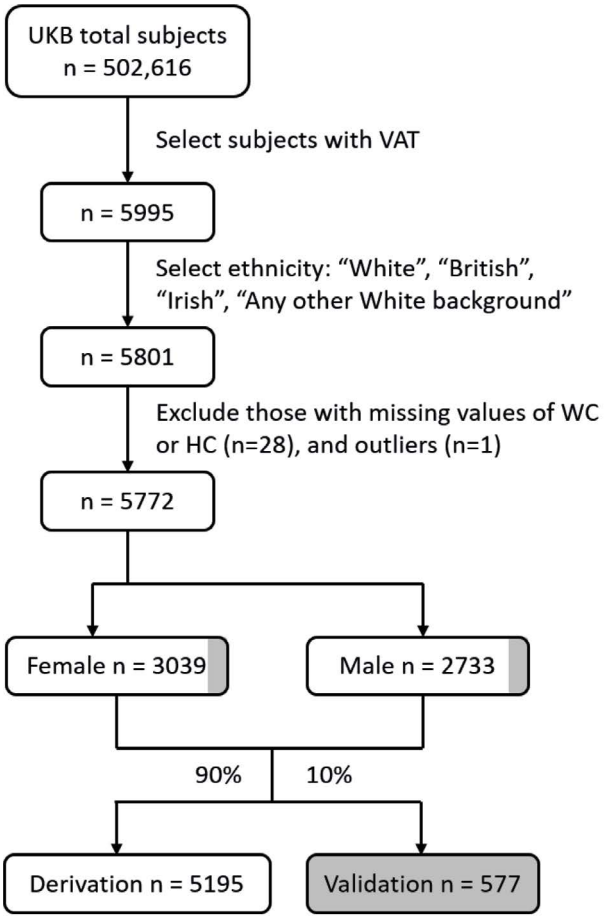

Figure 3.1 Flow chart of subjects selection and random selection of the derivation and validation sample using the UK biobank.

Anthropometric Measurements

Anthropometric measurements were obtained by trained research clinic staff. Weight (without shoes and outdoor clothing) was measured using the Tanita BC 418 body composition analyzer, and height (without shoes) was measured using the wall-mounted SECA 240 height measure. Waist circumference (WC) was measured at a midway between the lowest rib margin and the iliac crest, and hip circumference (HC) was measured just over the hips at the maximum circumference. Waist-hip ratio (WHR) was calculated by dividing the WC by the HC.

Volumetric VAT based on MRI

The body composition scan was made according to a protocol described previously (17, 18). During the imaging visit participants underwent a dual-echo Dixon Vibe protocol on a clinical wide bore 1.5 Tesla scanner (MAGNETOM Aera, Syngo Platform VD13A, Siemens Healthcare, Erlangen, Germany). The six minute protocol covered neck to knees by six 3D axial slabs. Using the integrated scanner software, fusion of the axial slabs provided a volumetric dataset containing isolated water and fat images. VAT volume was calculated by automatic segmentation using AMRA Profiler (AMRA Medical AB, Linköping, Sweden) (18). All images were inspected and if required corrected by an analysis engineer.

Analysis in the derivation sample

Considering that the expediency and simplicity of the equation is crucial for clinical application, we developed a basic model that can estimate VAT with the knowledge of age, sex, height and weight, and an expanded model requiring WC and HC in addition to the four basic parameters. Both linear regression and artificial neural network (ANN) were used to develop the basic model and the expanded model.

Derivation of linear regression equation

Multivariable linear regression models were built using anthropometric parameters as the predictor variables, and MRI-measured VAT volume as the response variable, within the derivation sample. Age, sex, height, weight, BMI and BSA were involved in the stepwise procedure for the basic model, while WC, HC and WHR were involved additionally for the expanded model. Stepwise Akaike information criterion was adopted to select variables for the final models (19). Coefficients in the final models were used to construct the equations. The goodness-of-fit between estimated VAT (eVAT) and MRI-measured VAT volumes was evaluated by Bland-Altman plot, mean difference (bias), adjusted coefficient of determination (R^2), root mean squared errors (RMSE) and mean absolute error (MAE) for each model. All the analyses were carried out by RStudio (20), version 1.1.463.

ANN modelling procedure

The ANN modelling was performed in RStudio using the keras package (21). The estimation models for VAT were built and trained by several steps: 1. Data pre-processing. The derivation sample was used to train the neural network. All the variables for the construction of ANN were recorded in their original units. VAT was coded as the training target, and the anthropometric variables formed the input dataset.

2. Neural network design. In construction of the neural network, we used a sequential model with several densely connected hidden layers. The input layer contained four neurons (age, sex, height and weight) for the basic model, and six neurons (age, sex, height, weight, WC and HC) for the expanded model. The output layer returned a single continuous value of VAT volume. Each hidden layer could be activated by different activation function, which was decided in training process. 3. Learning algorithm. The loss function for learning algorithm was "MSE" (mean squared error), and the metrics as "MAE" (mean absolute error), which were in concordance with the goodness-of-fit evaluation for the regression models. The optimizer and learning rate for each model were decided in training process. 4. Training of the network. Tuning of each model was based on the shape of the learning curve and the value of adjusted R^2, RMSE and MAE. The numbers of hidden layers and neurons, the activation functions, the learning algorithms, and several parameters of the training process, including epochs, batch size and validation split, were tuned to achieve the highest possible adjusted R^2 as well as the lowest possible RMSE and MAE.

The neural network model with the highest adjusted R^2 and the lowest RMSE and MAE in the derivation sample was selected as the final model. Bland-Altman plot and mean difference (bias) were also evaluated for the final ANN models. We developed an interactive webpage based on the final ANN models for the estimation of VAT, using the shiny package in RStudio.

Analysis in the validation dataset

The linear regression equations and the ANN models were applied in the validation sample. Bland-Altman plots, bias, adjusted R^2, RMSE and MAE were demonstrated to evaluate the performances. The eVATs by different models were compared using the paired Student t test.

Receiver-operating characteristics (ROC) curves were computed for measured-VAT volume less than 2 L, 2 L ≤ VAT < 5 L, and VAT ≥ 5 L. Sensitivity, specificity and accuracy (percentage of the concordance of eVAT and measured-VAT) were calculated to present how well each model can predict eVAT that falls in the same interval of the measured-VAT. Accuracy was calculated by the following formula: Accuracy = (number of correct estimations/number of cases) × 100%. The area under the ROC (AUC) were compared among all the equations using the DeLong's test.

The characteristics of the derivation sample and the validation sample were presented as mean ± standard deviation with ranges in parentheses. Correlations between VAT volume and anthropometric parameters were assessed by Pearson's correlation coefficient. Overview of the methods in this study is shown **Figure 3.2**.

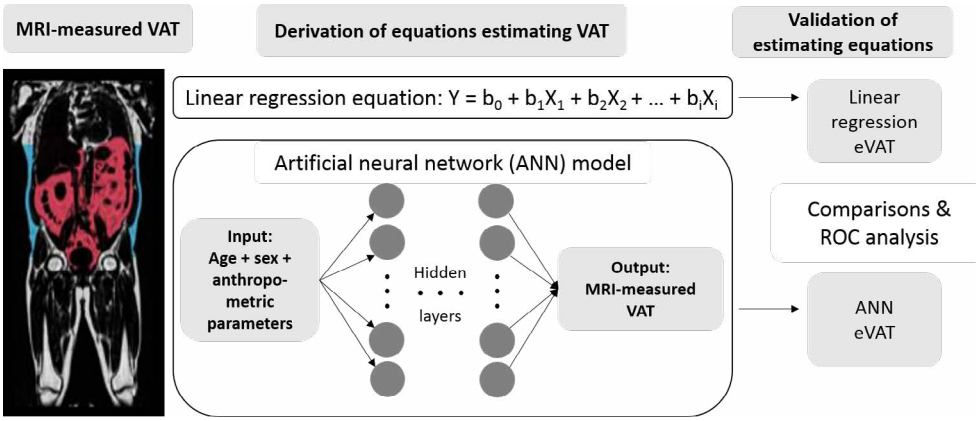

Figure 3.2 Overview of the methods in this study. The image with colored overlay is adopted from an open access publication (17), and shows the central coronal MRI slice of a subject from UK Biobank. Both linear regression and ANN were utilized to estimate abdominal VAT volume from anthropometric parameters, based on MRI-measured VAT. The eVATs generated by regression equations and ANN models were then compared and evaluated in the validation sample.

RESULTS

The demographic and anthropometric characteristics and MRI-measured VAT volumes for the whole dataset were shown in **Table 3.1**. There was no statistic difference between the derivation sample and the validation sample in age, height, weight, BMI, BSA, WC, HC, WHR and VAT. The total study population had a mean age of 61.9 years (range 45 to 76), mean VAT of 3.73 L (ranging from 0.12 to 14.41) and 52.7% (n=3039) was female.

Pearson's correlation coefficients between VAT and main anthropometric parameters were: weight (r=0.80), BMI (r=0.68), WC (r=0.83), HC (r=0.53), and WHR (r=0.73), all with $p<0.001$.

Description of the estimation models

The final basic linear regression model of the stepwise analysis included all the tested variables, which were age, sex, height, weight, BMI and BSA ($F=2152$, $p<0.001$). The final expanded linear regression model of the stepwise analysis also included all the tested variables, which were age, sex, height, weight, BMI, BSA, WC, HC and WHR ($F=1872$, $p<0.001$). **Table 3.2** shows the equations generated from the final models.

Table 3.1 Characteristics of the included participants of the UK biobank, all values are presented as mean ± standard deviation

Characteristics	Total (n=5772)	Derivation sample (n=5195)	Validation sample (n=577)
Age (year)	61.9 ± 7.4	62.0 ± 7.4	61.2 ± 7.2
Height (cm)	163.5 ± 6.5	169.9 ± 9.4	170.1 ± 9.8
Weight (kg)	68.6 ± 12.7	75.7 ± 15.0	76.7 ± 15.6
BMI (kg/m^2)	26.2 ± 4.3	26.1 ± 4.3	26.4 ± 4.4
Females	25.7 ± 4.6	25.7 ± 4.6	25.7 ± 4.6
Males	26.7 ± 3.8	26.6 ± 3.8	27.2 ± 3.9
BSA (m^2)	1.88 ± 0.22	1.88 ± 0.22	1.90 ± 0.23
Females	1.76 ± 0.17	1.76 ± 0.17	1.75 ± 0.17
Males	2.03 ± 0.18	2.02 ± 0.18	2.06 ± 0.17
WC (cm)	87.5 ± 12.1	87.4 ± 12.0	88.4 ± 12.4
Females	82.1 ± 11.4	82.1 ± 11.3	82.4 ± 11.6
Males	93.6 ± 9.8	93.4 ± 9.8	95.0 ± 9.7
HC (cm)	101.4 ± 8.5	101.3 ± 8.5	102.2 ± 8.8
Females	101.1 ± 9.7	101.1 ± 9.7	101.6 ± 9.7
Males	101.7 ± 7.1	101.6 ± 7.0	102.9 ± 7.7
WHR	0.86 ± 0.08	0.86 ± 0.08	0.86 ± 0.08
Females	0.81 ± 0.07	0.81 ± 0.07	0.81 ± 0.06
Males	0.92 ± 0.06	0.92 ± 0.06	0.92 ± 0.05
VAT (L)	3.73 ± 2.25	3.72 ± 2.25	3.76 ± 2.26
Females	2.63 ± 1.50	2.63 ± 1.50	2.61 ± 1.52
Males	4.95 ± 2.31	4.94 ± 2.32	5.04 ± 2.26

BMI: body mass index; BSA: body surface area; WC: waist circumference; HC: hip circumference; WHR: waist-hip ratio; VAT: visceral adipose tissue.

Similar to linear regression models, we also developed a basic model and an expanded model by ANN. The final basic ANN model was constructed by six hidden layers containing 120, 80, 50, 24, 12, 6 neurons respectively. The final expanded ANN model was constructed by five hidden layers containing 100, 50, 24, 12, 6 neurons respectively. The activation function for each hidden layer and the output layer was rectified linear unit (ReLU) in both two models. The optimizer and learning rate was "optimizer_adm (lr=0.001)" for the basic model and "optimizer_rmsprop (lr=0.001)"

for the expanded model. The final basic model was trained with epochs = 100, batch size = 32, and validation split = 0.1, while the final expanded model was trained with epochs = 200, batch size = 32, and validation split = 0.1. Based on the ANN models trained in our study, we built an webpage, in which the estimation volume of VAT can be obtained interactively (**Table 3.2**).

Table 3.2 The regression equations and the webpage based on ANN models for estimating VAT (L)

Linear Regression	Equation
Basic	$0.04 \cdot age + 1.22 \cdot sex - 0.32 \cdot height + 0.17 \cdot weight - 5846 \cdot weight/height^2 + 0.21 \cdot (height \cdot weight)^{0.5} + 33.15$
Expanded	$0.03 \cdot age + 0.40 \cdot sex - 0.26 \cdot height + 0.09 \cdot weight - 4518 \cdot weight/height^2 + 0.22 \cdot (height \cdot weight)^{0.5} + 0.24 \cdot WC - 0.20 \cdot HC - 15.16 \cdot WC/HC + 37.74$
ANN	See webpage for automatic estimation using the basic and expanded models **https://radi-evat.lumc.nl**

Units for the variables: age (year), sex (female=0, male=1), height (cm), weight (kg), WC (cm), HC (cm)
ANN: artificial neural network; VAT: visceral adipose tissue

The performance parameters including adjusted R^2, RMSE, MAE and bias are presented in **Table 3.3**. The scatter plots and Bland-Altman plots of the eVAT and measured-VAT are shown in **Figure 3.3, 3.4**.

Model performance in the validation sample

The performance parameters of the four equations in the validation sample were also demonstrated in **Table 3.3**. There was no statistical difference between basic and expanded linear regression eVATs. The basic and expanded ANN based eVATs were statistically different with mean difference = −0.17 L ($p<0.001$). The basic linear regression eVAT was different from basic ANN based eVAT with mean difference = 0.04 L ($p=0.003$). The expanded linear regression eVAT was different from expanded ANN based eVAT with mean difference = −0.12 L ($p=0.003$).

The AUCs and accuracies of each equation in estimating VAT < 2 L, 2 L ≤ VAT < 5 L and VAT ≥ 5 L were presented in **Table 3.4**. The ROC curves of the basic ANN based equation to estimate 2 L ≤ VAT < 5 L and VAT ≥ 5 L were statistically different from those of the expanded ANN equation ($p=0.01$, $P<0.001$), while the ROC curves to VAT less

Table 3.3 Performance of the linear regression and ANN based equations in the derivation sample and the validation sample

	Derivation sample				Validation sample			
	Regression		ANN		Regression		ANN	
	Basic	Expanded	Basic	Expanded	Basic	Expanded	Basic	Expanded
Adjusted R^2	0.71	0.76	0.73	0.78	0.72	0.76	0.73	0.78
RSME (L)	1.20	1.09	1.16	1.05	1.20	1.10	1.18	1.04
MAE (L)	0.92	0.83	0.88	0.78	0.94	0.84	0.90	0.79
Bias (L)	<0.001	<0.001	-0.07	-0.05	0.05	0.07	0.01	0.04

ANN: artificial neural network; RMSE: root mean sum of squared errors; MAE: mean absolute error

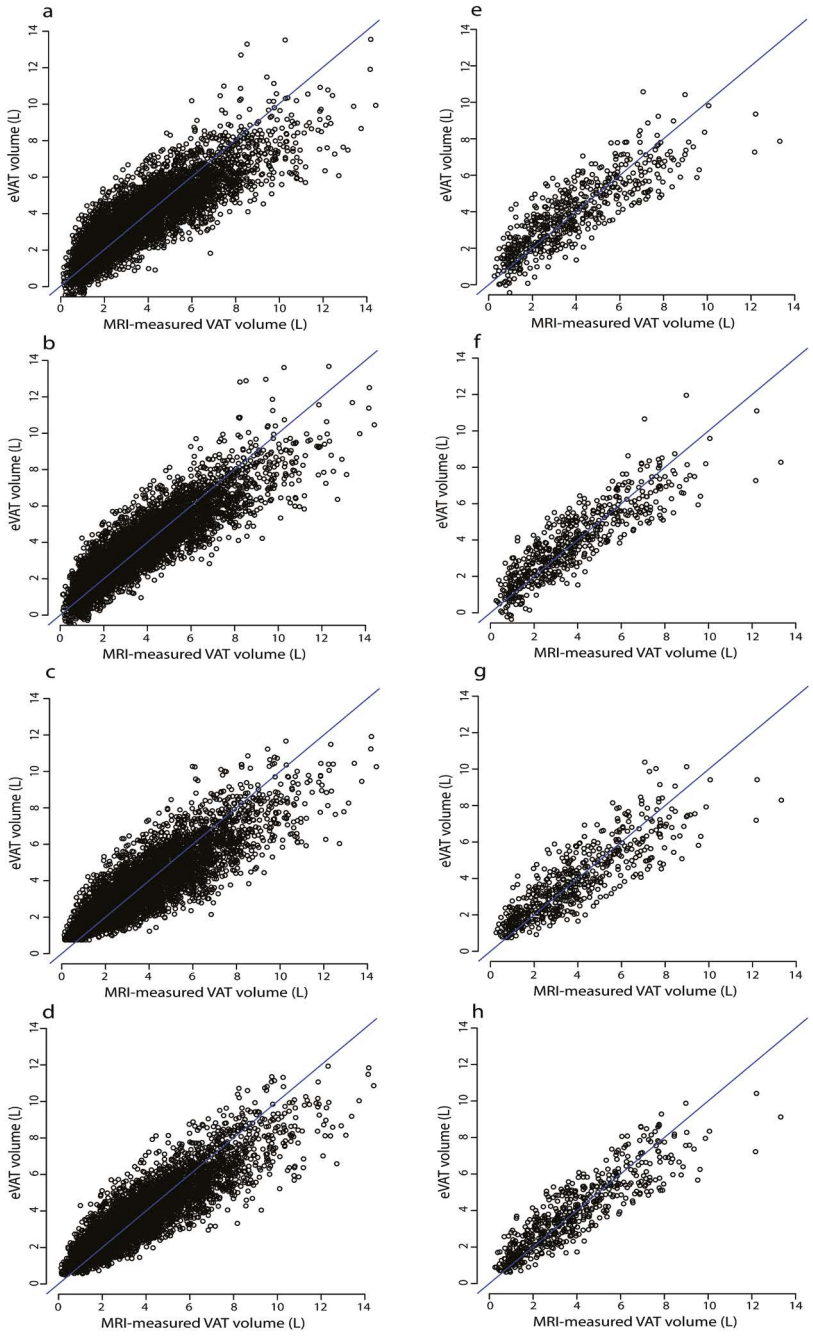

Figure 3.3 Scatter plots of the MRI-measured VAT and estimated VAT (eVAT) by different equations. (a-d) Scatter plots for the derivation sample. (e-h) Scatter plots for the validation sample. (a, e) The basic linear regression equation. (b, f) The expanded linear regression equation. (c, g) The basic ANN equation. (d, h) The expanded ANN equation.

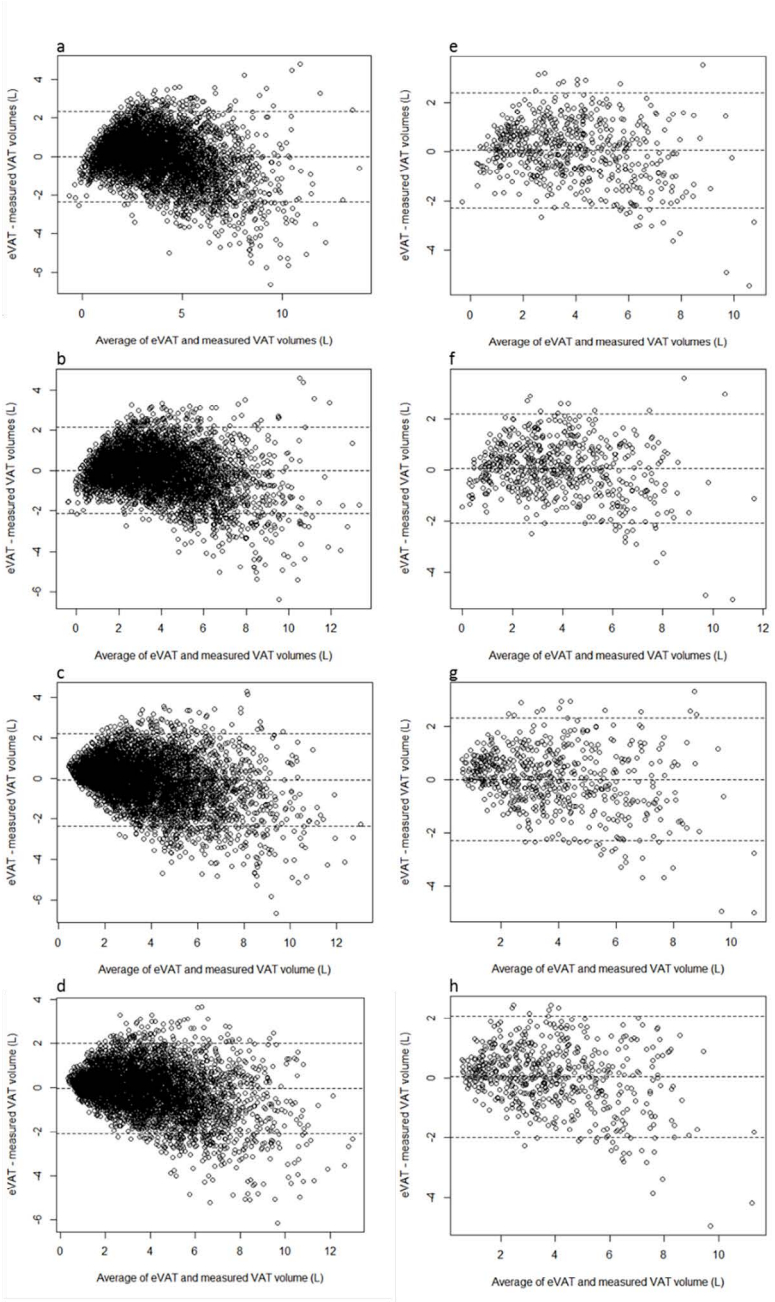

Figure 3.4 Bland-Altman plots of the MRI-measured VAT and estimated VAT (eVAT) by different equations. (a-d) Bland-Altman plots for the derivation sample. (e-h) Bland-Altman plots for the validation sample. (a, e) The basic linear regression equation. (b, f) The expanded linear regression equation. (c, g) The basic ANN equation. (d, h) The expanded ANN equation.

than 2 L did not differ between the two ANN based equations (p=0.464). The ROC curves to estimate VAT ≥ 5 L were also different between the basic and the expanded linear regression equations (p=0.04). There was no statistical difference in the ROC curves to estimate VAT less than 2 L and 2 L < VAT < 5 L between the two linear regression equations (p=0.883, p=0.57). Comparisons between linear regression equations and their ANN based counterparts did not reveal statistical significance.

Table 3.4 Areas under the ROC curves (AUC), sensitivities, specificities and accuracies of the four equations in the validation sample

VAT < 2 L (n=147)		AUC	Sensitivity (%)	Specificity (%)	Accuracy (%)
Linear Regression	Basic	0.80	64.6	95.1	87.3
	Expanded	0.80	64.6	95.6	87.7
ANN	Basic	0.80	66.0	94.4	87.2
	Expanded	0.84	70.7	96.7	90.1
2 L ≤ VAT < 5 L (n=277)					
Linear Regression	Basic	0.75	78.3	71.7	74.9
	Expanded	0.77	79.8	74.3	76.9
ANN	Basic	0.75	79.1	70.3	74.5
	Expanded	0.80	83.4	76.3	79.7
VAT ≥ 5 L (n=153)					
Linear Regression	Basic	0.85	78.4	90.8	87.5
	Expanded	0.87	83.7	91.3	89.3
ANN	Basic	0.83	74.5	92.0	87.3
	Expanded	0.87	81.7	92.5	89.6

ROC: receiver-operating characteristic; AUC: area under ROC curve; VAT: visceral adipose tissue; ANN: artificial neural network

DISCUSSION

In the current study, we developed and validated new equations to estimate abdominal visceral adipose tissue from simple anthropometric parameters in 5772 of the UK Biobank. We compared the performances of linear regression with artificial neural network based equations for estimating abdominal VAT volume.

Both the basic and the expanded linear regression and ANN based equations in this

study yielded favourable performances in both the derivation sample and the validation sample. Although the eVATs generated by ANN based equations were statistically different from those based on linear regression, the mean differences were minor. Considering the adjusted R^2 and error measurements, ANN based equations exhibited moderately improved performances over the linear regression equations, with higher adjusted R^2, lower RMSE and MAE. However, the moderately superior performance of the ANN models over regression equations were not evident enough to demonstrate statistical significance in comparisons of ROC curves. ANN models demonstrated limited increases in estimating accuracies with similar AUCs compared with linear regression equations. Similar phenomenon was reported in a recently published systematic review showing no performance benefit of machine learning over logistic regression for clinical prediction models (22). Therefore, based on adjusted R^2 and error measurements, the ANN based equations might provide the theoretically best estimation of VAT, whereas regression equations could yield competent estimation according to ROC analysis. Taken this into account, we suppose either equation can be adopted in clinical practice.

Although ANN-based equations did not demonstrate substantial improvement in accuracy when compared with linear regression in this study, this does not undermine the potential value of applying ANN to other medical purposes. An ANN-based equation developed in a previous study to estimate maximal oxygen uptake demonstrated higher accuracy than the conventional linear regression equation (15). The extent of improvements generated by ANN model in comparison with linear regression is largely determined by the proportion of non-linearity in the association between the dependent and independent variables, as well as the characteristics of the training data. For clinical parameters that lack sufficient estimation accuracy by linear regression, ANN might serve as a promising alternative.

As presented above, the basic linear regression and ANN based equations showed slightly less favourable performance than the expanded ones. However, the addition of WC and HC to the expanded equations did not substantially improve the performance of the equations. Although WC and WHR were strongly correlated with VAT (r=0.83, r=0.73), there were substantial differences in WC, WHR and VAT between females and males. Therefore, the variance of VAT related to WC and WHR was mostly explained by the larger coefficient of “sex” in the basic equation. Meanwhile, it is possible that the performance of the expanded equations could be compromised by intra- and inter-observer variability of WC and HC. Previous studies suggested that circumference measurements are less reliable than weight and height indexes (23), due to tissue composition (e.g. amount of subcutaneous fat, intestines, etc.) (24), measurement site (25) and abdominal wall tension (26).

Nevertheless, within ANN based equations in this study, the expanded equation demonstrated higher accuracies than the basic one in estimating VAT ≥ 5 L and 2 L ≤ VAT < 5 L, which accounted for 75% of the validation sample. Within linear regression equations, the expanded equation was superior to the basic one in estimating VAT ≥ 5 L with statistical difference in ROC curves, which is potentially more important for clinical application in obesity. Thus the expanded equation is recommended whenever WC and HC can be obtained without disproportionate burden.

Several equations for estimation of VAT have been developed previously (**Supplementary Table S3.1**), of which only one equation predicted abdominal VAT volume based on volumetric MRI of the abdomen (adjusted R^2 = 0.47) (9). However, this equation was derived from a population of 200 middle-aged Japanese obese men, which limits the use of this equation in other populations. The majority of previous equations were based on cross-sectional VAT areas of various measurement sites (e.g. lumbar vertebra L3-L5). Although cross-sectional VAT area is widely used as the proxy of volumetric VAT in a number of studies, single-slice image may not accurately represent individual's VAT (27, 28), and VAT volume is more strongly associated with the risk factors of metabolic syndrome than VAT area at L4-L5 level (29, 30). Moreover, none of the previous studies evaluated the performance of the estimation equation by ROC analysis.

It has been revealed that the determination coefficient (R^2) of cross-sectional VAT area in estimation of whole abdominal VAT volume varies with anatomy sites, and no concordance has been reached upon the best reference site. The R^2 was 0.31 for VAT area at the level of L2-L3, and 0.58 for L4-L5 in a study of 59 healthy female volunteers(27). In a study of 200 participants from the Framingham Heart study, R^2 ranged from 0.76 to 0.98 for VAT areas measured at multiple vertebral levels from L1 to S1(31). Another study reported R^2 from 0.78 to 0.97 for VAT areas measured at multiple lumbar vertebral levels from L1 to L5 in 142 healthy Caucasians(32). A study of 197 overweight to severely obese patients reported R^2 from 0.58 to 0.95 for single-slice VAT volumes and 0.63 to 0.92 for five-slice VAT volumes at multiple lumbar intervertebral levels from L1 to S1(33). It is worth noticing that all four equations in this study demonstrated the adjusted R^2 >0.71, in which 0.78 was the best, indicating that our equations might achieve similar estimation of VAT volume with that from suboptimal cross-sectional VAT areas measured in single CT/MRI slice. Thus for studies in which CT/MR examinations are only for the measurement of cross-sectional VAT area, our equation could be a cost-efficient alternative.

Our study has several limitations. Considering the age distribution and ethnicity of the UK Biobank participants, our estimation equations are developed using data from participants aged 45-76 years and white participants only, which compromises

the application of our equations in other age groups and ethnicities. Due to inter- and intra-variability of the anthropometric parameters, as well as inter-study disagreement of MRI/CT-derived VAT volumes, it is also possible that the estimation capacity of our equations varies in external samples, which remains area for future research. Another limitation is that eVATs calculated by linear regression equations were below zero in 16.7% of very lean females (BMI < 20kg/m^2) in the validation sample. This is inevitable due to the nature of linear regression, and no such defect is observed in ANN based equations. Finally, several parameters (e.g. dual-energy X-ray absorptiometry android per cent fat, bioelectrical impedance analysis, skinfold and sagittal diameter) that might improve the accuracy of the estimation according to previous studies were not used in this study, due to controversial estimating capacity for VAT(34, 35), concerns regarding their accuracies (36, 37), and requirement of dedicated equipment for measurement.

CONCLUSION

In this study, linear regression and artificial neural network-based equations were built to estimate abdominal VAT volume by simple anthropometric parameters. The presented equations can be used in general practice as well as population-based studies, especially worth considering when imaging modalities are applied only for the measurement of cross-sectional VAT area. Further investigations are required to assess the association between eVAT and clinical outcomes, and to determine the cut-off values of eVAT for metabolic risk.

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SUPPLEMENTARY

Table S3.1 Summary of previous VAT estimation equations based on CT/MR measurements and anthropometric variables

Publication year and authors	Reference imaging	Number of participants (N), age (years ± SD and/or range) and % male	Ethnicity	Outcome	Variables involved in the Equations	Adjusted R^2	Validation
2018 Lee et al. (1)	Four MR intervertebral slices ((L1/L2 + L2/L3 + L3/L4 + L4/L5)	N=32, age 9-13 years, 0% male,	Not specified	VAT mass (sum of 4 slices) (g)	Age, DXA APF, WC	0.74	No
2017 Pinho, et al. (2)	Single CT slice at the level of L4	N=109, age 20-75 years, 25.7% male	38.5% white, 10.1% black and 51.4% brown	VAT area (cm^2)	Abdominal circumference, WHR, conicity index (male) Age, sagittal diameter, conicity index, neck circumference (female)	0.64 (male) 0.40 (female)	No
2017 So et al. (3)	MRI slices from T9 to S1	N=260 (200 for derivation, 60 for validation), age 30-59 years, 100% male	Asian (Japanese)	VAT volume (cm^3)	Age, BMI, WC	0.47	Yes
2017 Pinter et al. (4)	Multiple CT slices at the level of L4-L5	N=198 (98 for derivation, 100 for validation), age 20-81 years, 50% male	Not specified	VAT area (mm^2)	HC, calf circumference, WHR (male) Sagittal diameter, thigh circumference, triceps skinfold (female)	0.713 (male) 0.845 (female)	Yes
2014 Chen et al. (5)	Multiple CT slices at the level of L4-L5	227: 152 for derivation (age 28.56±11.20 years for males, 33.28±16.23 years for females); 75 for validation (age 26.13±12.63 years for male; 27.07±8.11 years for female), 57% male	Asian (Taiwanese)	VAT area (cm^2)	Age, WC, abdominal skinfold	0.92	Yes

2013 Eastwood et al. (6)	Single CT slice at the level of L4	N=1410 (~66% for derivation, ~33% for validation), age 70±7 years, range 58-85 years, 76% male	669 white European, 514 South Asian and 227 African-Caribbean	VAT area (cm^2)	age, weight, height, WC, HC, thigh circumference	0.55-0.73	Yes
2008 Goel et al. (7)@¯Ţ	Single MR slice at L3-4 intervertebral level	N=100 (70 for derivation, 30 for validation), age 15-50 years, 56% male	Indian	VAT area (mm^2)	Age, gender, BMI, WC, HC	0.52	Yes
2006 Brundavani et al. (8)	Single CT slice at the level of L4-5	N=120, age 40-79 years, 50% male	Indian	VAT area (cm^2)	Weight, BMI, WC (male) Weight, WC (female)	0.74 0.63	No
2004 Stanforth et al. (9)	Single CT slice between L4 and L5 vertebral level	N=692, age 17-65 years, 46% male	228 Black 464 White	VAT area (cm^2)	Age, race, BMI, WHR	0.78 (male) 0.73 (female)	Yes
1996 Kekes-Szaboo et al. (10)ª¨z	Single CT slice between L4 and L5 vertebral level	N=204 (153 for derivation, 51 for validation), age 17-76, years	Caucasian	VAT area (cm^2)	Age, umbilicus circumference, suprailiac skinfold	0.75	Yes
1995 Bonora et al. (11)	Single MR slice at the level of L4	N=73 (49 for derivation, 24 for validation), age 22-70 years, 39% male	Not specified	VAT area (cm^2)	WC (male) Age, WC (female)	0.56 0.68	Yes
1994 Kekes-Szaboo et al. (12)	Single CT slice between L4 and L5 vertebral level	N=202 (151 for derivation, 51 for validation), age 18-71 years, 100% male	White	VAT area (cm^2)	Age, WC, abdominal skinfold, leg circumferences	0.73	Yes
1992 Koester et al. (13)	Single CT slice between L4 and L5 vertebral level	N=61 (40 for derivation, 21 for validation), age 18-30 years, 100% male	Caucasian	VAT area (cm^2)	WC, log chest ratio	0.67	Yes
1991 Despres et al. (14)	Single CT slice at the level of L4-5	N=110, age 18-42 years, 100% male	Not specified	VAT area (cm^2)	Age, WC	0.74	No
1989 Ferland et al. (15)	Single CT slice between L4 and L5 vertebral level	N=51, age 23-50 years, 0% male	Not specified	VAT area (cm^2)	Age, weight, WHR, abdominal skinfold, subscapular skinfold	0.74	No

1988 Weits et al. (16)	Single CT slice at the umbilical level	N=130, age16-81 years, 52% male	Not specified	VAT area (cm^2)	WC, HC	0.74 (male) 0.56 (female)	No
1988 Kvist et al. (17)	Multiple CT slices from T8-L5	N=43 (27 for derivation, 16 for validation), age 24-64 years, 56% male	Not specified	VAT volume (L)	Sagittal diameter	0.81 (male) 0.80 (female)	Yes
1987 Seidell et al. (18)	Single CT slice at the L4 level	N=105, age 19-85 years, 68% male	Not specified	VAT area (cm^2)	Age, BMI, WHR, umbilical skinfold, suprailiac skinfold (male) Menopausal state, BMI, WHR (female)	0.82 (male) 0.80 (female)	No

SEE, standard error of the estimate; DXA APF, dual-energy X-ray absorptiometry android per cent fat; WC, waist circumference; AC: Abdominal Circumference; WHR: Waist-to-hip ratio; CI: Conicity Index; HC: hip circumference.

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