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Original Contribution

Evaluation of the Value of Waist Circumference and Metabolomics in the Estimation of Visceral Adipose Tissue

Sebastiaan C. Boone*, Maarten van Smeden, Frits R. Rosendaal, Saskia le Cessie, Rolf H. H. Groenwold, J. Wouter Jukema, Ko Willems van Dijk, Hildo J. Lamb, Philip Greenland, Ian J. Neeland, Matthew A. Allison, Michael H. Criqui, Matthew J. Budoff, Lars L. Lind, Joel Kullberg, Håkan Ahlström, Dennis O. Mook-Kanamori, and Renée de Mutsert

* Correspondence to Sebastiaan Boone, Leiden University Medical Center, Department of Clinical Epidemiology, Postal Zone C7-P, P.O. Box 9600, 2300 RC Leiden, the Netherlands (e-mail: s.c.boone@lumc.nl).

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Visceral adipose tissue (VAT) is a strong prognostic factor for cardiovascular disease and a potential target for cardiovascular risk stratification. Because VAT is difficult to measure in clinical practice, we estimated prediction models with predictors routinely measured in general practice and VAT as outcome using ridge regression in 2,501 middle-aged participants from the Netherlands Epidemiology of Obesity study, 2008–2012. Adding waist circumference and other anthropometric measurements on top of the routinely measured variables improved the optimism-adjusted R^2 from 0.50 to 0.58 with a decrease in the root-mean-square error (RMSE) from 45.6 to 41.5 cm^2 and with overall good calibration. Further addition of predominantly lipoprotein-related metabolites from the Nightingale platform did not improve the optimism-corrected R^2 and RMSE. The models were externally validated in 370 participants from the Prospective Investigation of Vasculature in Uppsala Seniors (PIVUS, 2006–2009) and 1,901 participants from the Multi-Ethnic Study of Atherosclerosis (MESA, 2000–2007). Performance was comparable to the development setting in PIVUS ($R^2 = 0.63$, RMSE = 42.4 cm^2, calibration slope = 0.94) but lower in MESA ($R^2 = 0.44$, RMSE = 60.7 cm^2, calibration slope = 0.75). Our findings indicate that the estimation of VAT with routine clinical measurements can be substantially improved by incorporating waist circumference but not by metabolite measurements.

added value; development; external validation; metabolomics; prediction; visceral adipose tissue

Abbreviations: BMI, body mass index; CI, confidence interval; HDL-C, high-density lipoprotein cholesterol; LASSO, least absolute shrinkage and selection operator; MAE, mean absolute error; MESA, Multi-Ethnic Study of Atherosclerosis; MRI, magnetic resonance imaging; NEO, Netherlands Epidemiology of Obesity; PIVUS, Prospective Investigation of Vasculature in Uppsala Seniors; RMSE, root-mean-square error; TBF, total body fat percentage; VAT, visceral adipose tissue.

Abdominal obesity has been firmly established as an important prognostic factor for cardiometabolic changes (1) such as type 2 diabetes (2) and cardiovascular disease (3, 4). Visceral adipose tissue (VAT) is a major contributor to the increased cardiometabolic risk in individuals with abdominal obesity as it is causally associated with cardiovascular risk factors, coronary heart disease, and type 2 diabetes as was demonstrated in several recent Mendelian randomization studies (5, 6). These associations make VAT a potentially interesting target to measure for cardiometabolic risk stratification in addition to existing cardiovascular risk models or to identify and motivate individuals that could benefit from preventive treatments such as lifestyle changes. However, direct measurements of VAT are possible only through imaging methods such as magnetic resonance imaging (MRI) or computed tomography. These measurements are expensive and time-consuming compared with conventional clinical assessments such as a physical examination or blood sampling and therefore not well suited for large epidemiologic studies or clinical practice.

Several studies have developed alternatives to direct measurements of VAT, including the hypertriglyceridemic waist

phenotype (7), the visceral adiposity index (8) and the lipid accumulation product (9), or models that estimate cross-sectional VAT surface area (10, 11). Most of these indices include waist circumference along with variables such as triglyceride concentrations and age (7–13). Although waist circumference is generally considered the best single predictor of VAT (14), it is not measured routinely in clinical settings (15). One reason that waist circumference is not measured more frequently may be that its added value for the prediction of VAT and other cardiometabolic outcomes on top of more routine measurements has not been established yet.

A potential source of new candidate predictors for VAT is the field of metabolomics, which concerns the measurement and analysis of metabolites, small molecular compounds that are involved in metabolism. Contemporary technical developments enable the quantification of large numbers of metabolites at steadily decreasing costs, making the clinical use of metabolomics increasingly feasible. Although several studies have evaluated the associations of metabolites with VAT (16–19), there are no well-described attempts to use metabolite measurements in prediction models for VAT.

In this study, using 3 cohorts from the Netherlands, Sweden, and the United States, we developed and externally validated a prediction model for VAT containing routinely measured clinical predictors. We then investigated whether including waist circumference and measurements from a well-established lipid-focused metabolomics platform improved this model.

METHODS

Throughout the entire study, we adhered to the Transparent Reporting of a Multivariable Prediction Model for Individual Prognosis or Diagnosis (TRIPOD) guidelines for the reporting of prediction studies (20).

Development study design and study population

The Netherlands Epidemiology of Obesity (NEO) study is a prospective, population-based cohort study aimed at investigating pathways leading to obesity-related conditions (21). Between 2008 and 2012 a total of 6,671 men and women aged 45–65 years were included, with an oversampling of persons with overweight or obesity. The study was approved by the medical ethics committee of the Leiden University Medical Center, and all participants gave written informed consent.

Participants were invited for a baseline visit at the NEO study center at the Leiden University Medical Center after an overnight fast of at least 10 hours. Participants came to the research site in the morning and underwent a physical examination, including anthropometry and blood sampling. The Nightingale metabolomics platform was used to measure 224 metabolites, of which 144 were used in this study (details provided in Web Appendix 1, available at https://doi.org/10.1093/aje/kwab298). Approximately 35% of the participants (n = 2,580) without contraindications for MRI were randomly selected to undergo direct assessment of the amount of VAT by MRI. For this study, we excluded participants with incomplete or poor-quality VAT measurements (n = 11), who were nonfasting during blood sampling at the baseline visit (n = 3), who were missing any of the predictors for the clinical models (n = 32), or who were missing all metabolomics measurements (n = 17), and those with metabolite concentrations >10 standard deviations from the mean (n = 16), as they were deemed to be biologically implausible, leaving a study population of 2,501 participants (Web Figure 1).

External validation study designs and study populations

For external validation, we used 2 separate data sets from Sweden and the United States. First, the Prospective Investigation of Vasculature in Uppsala Seniors (PIVUS) is a population-based prospective cohort study that started in 2001 and included a random sample of 1,016 individuals aged 70 years from the city of Uppsala in Sweden (22). All living participants were invited back for a second measurement at age 75; 370 of these individuals had valid abdominal MRI measurements with quantification of VAT, metabolomics measurements with the Nightingale platform, and no missing values in the clinical predictors.

Second, the Multi-Ethnic Study of Atherosclerosis (MESA) is a population-based prospective cohort study that included 6,814 participants from different ethnicities (White, Black, Chinese, and Hispanic) across the United States (23). Starting in July 2000, the participants underwent a baseline visit and a series of follow-up exams. During exams 2 and 3, a subset of the MESA cohort underwent abdominal computed tomography scans, from which VAT area was quantified. Data from a total of 1,901 participants with valid VAT measurements and no missing values in the clinical predictors were available for analysis (Web Figure 1). In MESA, metabolomics measurements were performed using an untargeted nuclear magnetic resonance approach. Because only half of the metabolomics measurements from the Nightingale platform used in the NEO study overlapped with the MESA metabolomics data, we could not validate the metabolite-containing models and only validated the clinical models in the MESA cohort.

Data collection

Fasting blood samples were obtained in all 3 cohorts. A detailed description of the data collection of both predictors and outcomes in all participating cohorts is included in the Web Material.

Statistical analyses

Model development. Because of substantial heteroscedasticity when using the original cross-sectional VAT area, we used the natural logarithm of VAT area as the outcome and back-transformed all predicted values. To create the prediction models for VAT, all models were estimated using linear ridge regression, while we also used least absolute

shrinkage and selection operator (LASSO) regression for models containing metabolomics measurements. As a tuning parameter, we used the mean tuning parameter that minimized the mean squared error across 10 repeats of 10-fold cross-validation.

Based on knowledge from previously published studies, we considered the following variables for our core model: age, sex, height, body weight, body mass index (BMI), selected laboratory results (total cholesterol, triglycerides, high-density lipoprotein cholesterol (HDL-C), and glucose), and the total cholesterol/HDL-C ratio (7–11, 24, 25). All these variables are measured routinely during a standard cardiovascular risk assessment by general practitioners in the Netherlands (26). We then sequentially added the following variables that are not routinely measured yet clinically measurable and have been associated with VAT, starting with the least expensive or time-consuming to measure: waist circumference (WC), hip circumference (HC), waist-to-hip ratio (WHR), serum insulin concentration, and total body fat percentage (TBF). We selected an extended clinical model based on improvements in model performance, hereafter referred to as the extended clinical model. We then fitted ridge and LASSO regression models forcing in the predictors from this extended clinical model, so they could not be dropped from the models, while further adding 144 metabolite variables from the Nightingale metabolomics platform but allowing shrinkage on all variables. All models were developed in the total sample as well as stratified by sex because men are known to have more VAT than women (25).

As performance measures we calculated the explained variance (R^2), root-mean-square error (RMSE), mean absolute error (MAE), calibration slope, and calibration-in-the-large, as well as the mean predicted versus observed values and C statistics at VAT cutoffs of 70 cm^2 (27, 28), 100 cm^2 (27, 28), and 130 cm^2 (29, 30) from the predicted values on the logarithmic development scale as well as after back-transforming the values to the original scale in cm^2. More detailed descriptions of these performance measures are included in the Web Material. Additionally, we created calibration plots with locally weighted scatterplot smoothing (LOWESS) curves and assessed the added predictive value of metabolites with back-to-back histograms and scatterplots of the predicted VAT of the metabolite-containing versus the extended clinical models. We internally validated all models using bootstrapping with 1,000 repeats for the models with only clinical predictors and 500 repeats for the metabolite-containing models, repeating all modeling steps, including the estimation of the tuning parameters for the ridge and LASSO models, and calculated bootstrap optimism-corrected estimates of the performance measures (31).

External validation. We externally validated the core and extended clinical models in both PIVUS and MESA, and we validated the metabolite-containing model in PIVUS. External validation was performed by calculating the expected amount of VAT with the regression equations developed in the NEO study and evaluating the same performance metrics as in the development study. Additionally, we evaluated model performance after recalibration by updating the model intercepts to account for differences in VAT distribution between the development and validation cohorts. All validations were performed in the total available study populations as well as stratified by sex, and additionally by ethnicity in MESA.

RESULTS

The development population in the NEO study consisted of 2,501 individuals, mostly of White ethnicity (96%), and 1,311 (52.4%) were men (Table 1). Men had a larger waist circumference and more VAT but less total body fat than women. Compared with PIVUS and MESA, NEO study participants were younger and had a higher BMI, higher waist and hip circumference, and a poorer cardiometabolic profile, with higher fasting glucose, cholesterol, and total cholesterol/HDL-C ratio (Table 1 and Web Table 1). The amount of VAT was similar in the NEO study and PIVUS but substantially higher in MESA.

Clinical model development and validation

The optimism-corrected performance measures for all models developed in the total population are summarized in Table 2 and Web Table 2. We observed a similar pattern on the logarithmic development scale as well as after back-transforming the predicted values to the original scale. Adding waist circumference increased the R^2 from 0.50 (95% confidence interval (CI): 0.46, 0.53) to 0.55 (95% CI: 0.52, 0.58) on the original scale, while the RMSE decreased from 45.6 (95% CI: 43.6, 47.3) to 42.9 (95% CI: 41.1, 44.5) cm^2 and MAE from 33.3 (95% CI: 32.0, 34.4) to 31.5 (95% CI: 30.3, 32.6) cm^2. C statistics increased from 0.91 (95% CI: 0.90, 0.93) to 0.92 (95% CI: 0.91, 0.93) for >70 cm^2, 0.87 (95% CI: 0.86, 0.88) to 0.88 (95% CI: 0.87, 0.90) for >100 cm^2, and 0.84 (95% CI: 0.83, 0.86) to 0.86 (0.85, 0.88) for >130 cm^2. Further adding hip circumference and waist-to-hip ratio increased the R^2 to 0.58 (95% CI: 0.55, 0.61), while RMSE decreased to 41.5 (95% CI: 39.7, 42.8) cm^2 and MAE to 30.6 (95% CI: 29.4, 31.5) cm^2. Calibration slopes increased from 0.88 (95% CI: 0.84, 0.91) for the core model to 0.95 (95% CI: 0.92, 0.97) in the model that included the waist and hip circumference and the waist-to-hip ratio. We observed some overestimation of the amount of VAT for individuals at the upper end of the observed VAT distribution, which improved when adding waist and hip circumference (Figure 1). The errors of the predicted values increased at higher predicted VAT amounts.

In the models developed in men and women separately, including waist and hip circumference and the waist-to-hip ratio also improved model performance, while further including total body fat or insulin did not. In men the R^2 was lower at 0.46 (95% CI: 0.43, 0.51) on the original scale for the model that included waist and hip circumference and the waist-to-hip ratio, with a higher RMSE of 47.1 (95% CI: 44.6, 49.3) and MAE of 35.3 (95% CI: 33.5, 36.8) cm^2, while in women the R^2 was 0.58 (95% CI: 0.55, 0.63) with a RMSE of 34.4 (95% CI: 32.2, 36.2) and MAE of 25.3 (95% CI: 23.8, 26.5) cm^2 (Web Tables 3–4, Web Figures 2–3).

Table 1. Characteristics of the Model Development Population (n = 2,501) of the Netherlands Epidemiology of Obesity Study, the Netherlands, 2008–2012

Characteristic	Total (n = 2,501)		Men (n = 1,311)		Women (n = 1,190)	
	Mean (SD)	Median (IQR)	Mean (SD)	Median (IQR)	Mean (SD)	Median (IQR)
Age, years		56 (51–61)		56 (51–61)		56 (51–61)
Male sex[a]	1,311	52.4				
White ethnicity[a]	2,394	95.9	1,265	96.7	1,129	95.0
Body fat and distribution						
Height, m	1.74 (0.10)		1.81 (0.07)		1.66 (0.06)	
Weight, kg	89.2 (15.2)		96.0 (12.7)		81.7 (14.2)	
Body mass index[b]	29.5 (4.2)		29.4 (3.4)		29.5 (4.8)	
Waist circumference, cm	101 (12)		105 (10)		96 (13)	
Hip circumference, cm	109 (9)		108 (7)		110 (10)	
Waist-to-hip ratio	0.92 (0.08)		0.97 (0.06)		0.87 (0.07)	
Body fat percentage		33.8 (27.8–42.2)		28.5 (25.1–31.9)		42.3 (38.1–45.4)
Visceral adipose tissue, cm^2		114 (76–157)		134 (100–176)		89 (59–128)
>100 cm^2[a]	1,478	59.1	978	74.6	500	42.0
Laboratory measurements						
Glucose, mmol/L		5.5 (5.1–6.0)		5.6 (5.2–6.1)		5.4 (5.0–5.9)
Insulin, IU		10.5 (6.8–15.4)		11.5 (7.4–16.7)		9.7 (6.3–14.3)
Triglycerides, mmol/L		1.3 (0.9–1.8)		1.4 (1.0–2.0)		1.1 (0.8–1.5)
HDL-C, mmol/L	1.4 (0.4)		1.3 (0.3)		1.6 (0.4)	
Total cholesterol, mmol/L	5.7 (1.1)		5.6 (1.1)		5.8 (1.1)	
Total cholesterol/HDL-C ratio		4.1 (3.3–5.0)		4.5 (3.8–5.5)		3.6 (3.0–4.4)

Abbreviations: HDL-C, high-density lipoprotein cholesterol; IQR, interquartile range; IU, international units; SD, standard deviation.
[a] Values are expressed as numbers and percentages.
[b] Weight (kg)/height $(m)^2$.

Overall, adding waist circumference resulted in the largest increase in model performance, with minor improvement from further addition of hip circumference and the waist-to-hip ratio. As all 3 can be easily measured together, we decided to use this model with the core predictors, waist and hip circumference, and the waist-to-hip ratio as our extended clinical model on top of which to assess the added predictive value of metabolomics.

Metabolite-extended model development and validation

The optimism-corrected performance measures of the models in which the 144 metabolite predictors were added to the extended clinical model in the total development population are summarized in Table 2. The R^2 on the original scale increased from 0.58 (95% CI: 0.55, 0.61) to 0.60 (95% CI: 0.58, 0.63), RMSE decreased from 41.5 (95% CI: 39.7, 42.8) to 40.5 (95% CI: 38.4, 41.4) cm^2, and MAE decreased from 30.6 (95% CI: 29.4, 31.5) to 29.9 (95% CI: 28.4, 30.5) cm^2 for the ridge and LASSO models. Calibration characteristics were similar to the extended clinical model (Figure 2). The difference between the predictions from the extended clinical model and metabolite-extended models was small, with no substantial differences in the size or distribution of the predicted values (Figure 3). The number of metabolites selected in the LASSO models varied by bootstrap sample from 25 to 62 with a median of 46, and no combination of metabolites was selected more than once. The most consistently selected metabolites included the amino acids and other nonlipoprotein compounds, especially tyrosine, acetate, and acetyl glycoprotein concentrations, which were selected in all 500 bootstrap samples (Web Table 5). In men and women separately, we also observed small improvements after including metabolites (Web Tables 3–4, Web Figures 4–5).

The regression equations for the models developed in the complete population are summarized in Web Table 6.

External validation

Because the models that were developed in the complete NEO study population with sex included as a predictor performed similarly to the models developed in men and women separately (Web Tables 3–4, 7–8), we decided to externally validate only the models developed in the complete NEO study population with sex included as a predictor.

Table 2. Bootstrap-Optimism Corrected Estimates[a] of Model Performance for Development and Internal Validation, the Netherlands Epidemiology of Obesity Study (n = 2,501), the Netherlands, 2008–2012

Model	Predictors	Logarithmic Scale					Original Scale					*C* Statistic		
		R^2	RMSE	MAE	Calibration		R^2	RMSE	MAE	Calibration		VAT > 70 cm^2	VAT > 100 cm^2	VAT > 130 cm^2
					CITL	Slope				CITL	Slope			
1	Core[b]	0.60	0.37	0.29	0.00	1.00	0.50	45.6	33.3	6.1	0.88	0.91	0.87	0.84
2	Core + WC	0.64	0.35	0.28	0.00	1.00	0.55	42.9	31.5	5.5	0.90	0.92	0.88	0.86
3	Core + WC + HC	0.65	0.35	0.27	0.00	1.00	0.57	42.1	30.9	5.4	0.90	0.92	0.89	0.86
4	Core + WC + HC + WHR	0.66	0.34	0.27	0.00	1.00	0.58	41.5	30.6	5.5	0.95	0.92	0.89	0.86
5	Core + WC + HC + WHR + insulin	0.66	0.34	0.27	0.00	1.00	0.57	42.2	30.5	5.4	0.91	0.92	0.89	0.87
6	Core + WC + HC + WHR + TBF	0.66	0.34	0.27	0.00	1.00	0.58	41.2	30.4	5.4	0.94	0.92	0.89	0.86
7	Core + WC + HC + WHR + insulin + TBF	0.66	0.34	0.27	0.00	1.00	0.57	41.8	30.4	5.3	0.91	0.92	0.89	0.87
Ridge	Core + WC + HC + WHR + metabolites	0.68	0.33	0.26	0.00	0.99	0.60	40.5	29.9	5.0	0.93	0.93	0.89	0.87
LASSO	Core + WC + HC + WHR + metabolites	0.68	0.33	0.26	0.00	0.99	0.60	40.5	29.9	5.1	0.95	0.93	0.89	0.87

Abbreviations: CITL, calibration-in-the-large; HC, hip circumference; LASSO, least absolute shrinkage and selection operator; MAE, mean absolute error; RMSE, root-mean-square error; TBF, total body fat percentage; VAT, visceral adipose tissue; WC, waist circumference; WHR, waist-to-hip ratio.

[a] The estimates are reported for the development scale (natural logarithm of VAT) and the original scale (in cm^2) after back transforming the predicted values.

[b] The core predictors include age, sex, height, body weight, body mass index, concentrations of total cholesterol, triglycerides, high-density lipoprotein cholesterol and glucose, and the total cholesterol/high-density lipoprotein cholesterol ratio.

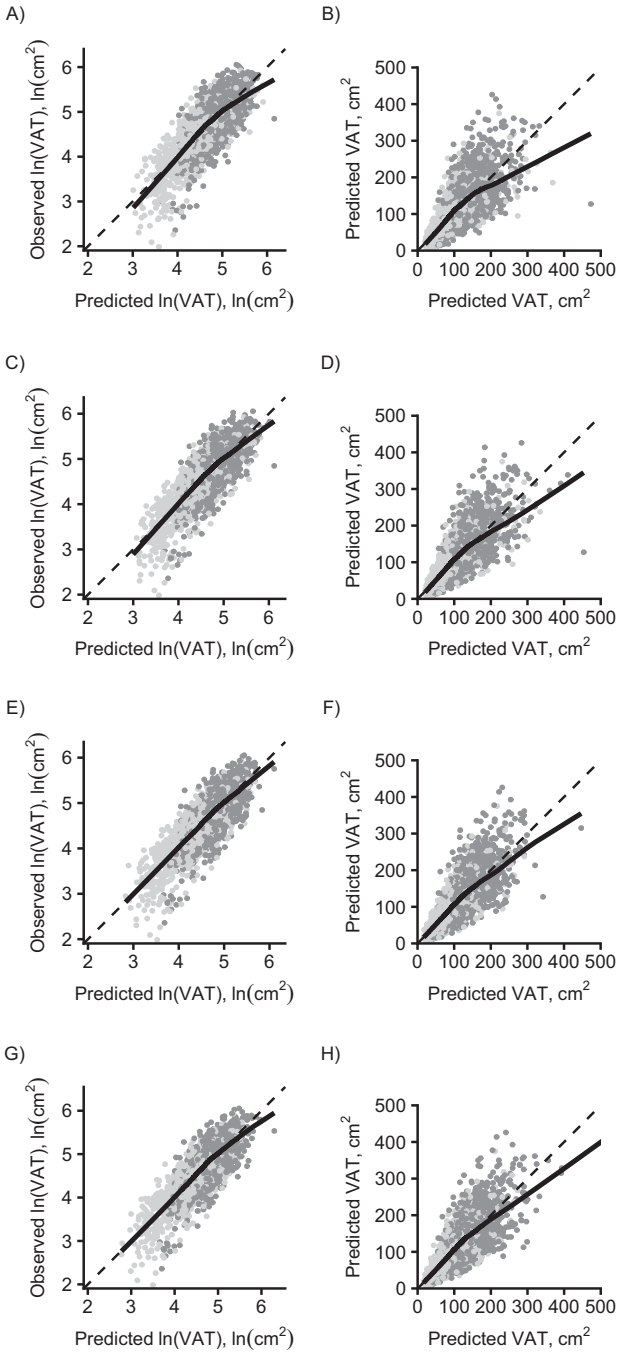

Figure 1. Calibration plots of models with clinical predictors developed in the Netherlands Epidemiology of Obesity Study (n = 2,501), the Netherlands, 2008–2012. Left column, calibration plots on the natural logarithm scale (development scale): A) core; C) core + waist circumference (WC); E) core + WC + hip circumference (HC) + waist-to-hip ratio (WHR); G) core + WC + HC + WHR + insulin + total body fat percentage (TBF). Right column, calibration plots after back transforming the predicted values to the original scale (in cm^2). B) core; D) core + WC; F) core + WC + HC + WHR; H) core + WC + HC + WHR + insulin + TBF. The black dashed line indicates unity ($x = y$); the black continuous line is a locally weighted scatterplot smoothing curve fitted to the data points. Women, light gray dots; men, dark gray dots. VAT, visceral adipose tissue.

The performance of the models with only clinical predictors was similar to the development setting in the total population of the PIVUS study with an R^2 of 0.65 (95% CI: 0.57, 0.71) on the logarithmic scale and 0.62 (95% CI: 0.50, 0.70) on the original scale for the extended clinical model that included waist, hip and waist-to-hip ratio (Table 3, Web Tables 9–10). RMSE and MAE were slightly higher at 42.9 (95% CI: 37.7, 48.0) and 31.0 (28.1, 43.2) cm^2 while C statistics were practically identical to the NEO study. In MESA, the R^2 of both clinical models was lower while the extended clinical model still performed better with an R^2 of 0.40 (95% CI: 0.35, 0.45) on the logarithmic scale and 0.24 (95% CI: 0.19, 0.29) on the original scale compared with 0.28 (95% CI: 0.21, 0.34) and 0.07 (95% CI: −0.05, 0.16) for the core model. RMSE and MAE were substantially higher at 70.8 (95% CI: 68.1, 73.7) cm^2 and 53.8 (95% CI: 51.7, 55.9) cm^2 for the extended clinical model, while C statistics were similar to the NEO study. Recalibration of the model intercept in MESA improved performance although the R^2 on the original scale remained lower at 0.44 (95% CI: 0.36, 0.51) and the RMSE and MAE remained higher at 60.7 (95% CI: 57.0, 65.0) and 43.6 (95% CI: 41.6, 45.6) cm^2. Calibration plots of both external cohorts show a similar pattern with a good calibration in PIVUS but an overall underestimation in MESA, which improved with recalibration of the model intercept (Figures 4–5).

The results in men and women were similar to those for the total population in MESA after recalibration of the intercept, although the RMSE and MAE were lower in women than in men at 50.1 (95% CI: 45.4, 54.9) and 35.8 (95% CI: 33.6, 38.3) cm^2 for the extended clinical model in women versus 63.0 (95% CI: 56.5, 70.4) and 45.4 (95% CI: 42.7, 48.2) cm^2 in men (Web Tables 11–14, Web Figures 6–9). Conversely, in PIVUS the extended clinical model seemed to perform better in men (R^2 of 0.68 (95% CI: 0.55, 0.76), RMSE of 42.3 (95% CI: 36.9, 48.4), and MAE of 31.1 (95% CI: 27.2, 35.4) cm^2) than in women (R^2 of 0.43 (95% CI: 0.20, 0.59), RMSE of 43.5 (95% CI: 35.8, 51.0), and MAE of 31.0 (26.8, 35.6) cm^2).

Within the separate ethnicities in MESA, the clinical models performed best in White and Chinese participants but only after intercept recalibration (Table 4, Web Tables 15–16). For White participants, we observed an R^2 of 0.58 (95% CI: 0.52, 0.63), RMSE of 58.1 (95% CI: 54.4, 61.8), and MAE of 43.6 (95% CI: 40.9, 46.2) cm^2, while the R^2 in Chinese participants was 0.56 (95% CI: 0.44, 0.64) with a RMSE of 38.6 (95% CI: 34.0, 43.1) and MAE of 29.1 (95% CI: 25.8, 32.1) cm^2 on the original scale for the recalibrated extended clinical model. In Black and Hispanic participants, R^2 was lower even after recalibration (0.19 (95% CI: −0.08, 0.40) for Black and 0.31 (95% CI: 0.11, 0.47) for Hispanic participants), with higher values for the RMSE and MAE. The clinical models strongly overestimated VAT for 3–6 individuals in the Black, Hispanic, and White groups (estimated VAT for these individuals ranged from 484 to 1,010 cm^2), and these were removed from the calibration plots to improve the plots' interpretability (Web Figures 10–13).

The metabolite-extended models, which were validated only in PIVUS, had a lower R^2, higher RMSE and MAE, and poorer calibration than the extended clinical model (Table 3,

Table 3. Estimates of Model Performance of the Core, Extended Clinical, and Metabolite-Extended Models[a] in the Prospective Investigation of the Vasculature in Uppsala Seniors (n = 370), Uppsala, Sweden, 2006–2009, and the Multi-Ethnic Study of Atherosclerosis (n = 1,901), United States, 2000–2007

Outcome Measure	MESA				PIVUS							
	Clinical Models				Clinical Models				Metabolite-Extended Models			
	Core[b]		Extended[c]		Core[b]		Extended[c]		Ridge		LASSO	
	Initial	Recalibrated	Initial	Recalibrated	Initial	Recalibrated	Initial	Recalibrated	Initial	Recalibrated	Initial	Recalibrated
Logarithmic scale												
Mean observed	4.94	4.94	4.94	4.94	4.70	4.70	4.70	4.70	4.70	4.70	4.70	4.70
Mean predicted	4.64	4.94	4.68	4.94	4.74	4.70	4.77	4.70	3.89	4.70	4.47	4.70
R^2	0.28	0.55	0.40	0.62	0.54	0.55	0.65	0.66	−8.10	−5.94	0.34	0.51
RMSE	0.49	0.38	0.44	0.35	0.38	0.37	0.33	0.32	1.67	1.46	0.45	0.39
MAE	0.41	0.30	0.37	0.28	0.30	0.30	0.26	0.25	1.31	1.22	0.36	0.30
CITL	0.30	0.00	0.27	0.00	−0.04	0.00	−0.07	0.00	0.81	0.00	0.23	0.00
Slope	0.87	0.87	0.92	0.92	0.93	0.93	0.97	0.97	−0.03	−0.03	0.96	0.96
Original scale												
Mean observed	162.2	162.2	162.2	162.2	127.2	127.2	127.2	127.2	127.2	127.2	127.2	127.2
Mean predicted	117.9	159.3	120.6	157.8	126.7	121.7	131.1	122.4	99.4	224.5	95.4	119.7
R^2	0.07	0.17	0.24	0.44	0.51	0.51	0.62	0.63	−3.32	−17.43	0.22	0.42
RMSE	78.4	74.0	70.8	60.7	49.0	48.8	42.9	42.4	144.8	298.8	61.6	53.0
MAE	58.5	47.9	53.8	43.6	36.3	35.7	31.0	30.1	106.3	193.0	42.6	37.3
CITL	44.2	2.8	41.6	4.3	0.5	5.6	−3.9	4.8	27.9	−97.2	31.8	7.6
Slope	0.77	0.57	0.98	0.75	0.82	0.85	0.88	0.94	−0.04	−0.02	1.17	0.93
C statistic per VAT cutoff												
>70 cm^2	0.93	0.93	0.94	0.94	0.88	0.88	0.91	0.91	0.51	0.51	0.89	0.89
>100 cm^2	0.90	0.90	0.91	0.91	0.86	0.86	0.90	0.90	0.49	0.49	0.86	0.86
>130 cm^2	0.88	0.88	0.90	0.90	0.81	0.81	0.86	0.86	0.46	0.46	0.80	0.80

Abbreviations: CITL, calibration-in-the-large; LASSO, least absolute shrinkage and selection operator; MAE, mean absolute error; MESA, Multi-Ethnic Study of Atherosclerosis; PIVUS, Prospective Investigation of the Vasculature in Uppsala Seniors; RMSE, root-mean-square error; VAT, visceral adipose tissue.

[a] Estimates are reported for the development scale (natural logarithm of VAT) and the original scale (in cm^2) after back transforming the predicted values. We report the initial results and the performance after intercept recalibration.

[b] Core predictors include age, sex, height, body weight, body mass index, total cholesterol, triglycerides, high-density lipoprotein cholesterol, glucose and the total cholesterol/high-density lipoprotein cholesterol ratio.

[c] The extended clinical model includes the core predictors, waist circumference, hip circumference, and the waist-to-hip ratio.

Table 4. Estimates of Model Performance of the Core and Extended Clinical Models Before and After Recalibration[a] Among White (n = 764), Chinese (n = 249), Black (n = 397), and Hispanic (n = 491) Participants of the Multi-Ethnic Study of Atherosclerosis Cohort (n = 1,901), United States, 2000–2007

Outcome Measure	White				Chinese				Black				Hispanic			
	Core[b]		Extended[c]		Core[b]		Extended[c]		Core[b]		Extended[c]		Core[b]		Extended[c]	
	Initial	Recalibrated	Initial	Recalibrated	Initial	Recalibrated	Initial	Recalibrated	Initial	Recalibrated	Initial	Recalibrated	Initial	Recalibrated	Initial	Recalibrated
Logarithmic scale																
Mean observed	5.00	5.00	5.00	5.00	4.71	4.71	4.71	4.71	4.78	4.78	4.78	4.78	5.11	5.11	5.11	5.11
Mean predicted	4.63	5.00	4.67	5.00	4.36	4.71	4.40	4.71	4.70	4.78	4.69	4.78	4.76	5.11	4.82	5.11
R^2	0.30	0.65	0.40	0.69	0.11	0.58	0.27	0.64	0.41	0.43	0.47	0.50	−0.03	0.48	0.21	0.57
RMSE	0.51	0.36	0.47	0.34	0.49	0.34	0.44	0.31	0.41	0.40	0.39	0.38	0.50	0.36	0.44	0.33
MAE	0.44	0.28	0.41	0.27	0.42	0.26	0.37	0.25	0.32	0.31	0.32	0.30	0.43	0.28	0.37	0.26
CITL	0.37	0.00	0.33	0.00	0.35	0.00	0.32	0.00	0.07	0.00	0.09	0.00	0.36	0.00	0.30	0.00
Calibration slope	0.98	0.98	1.01	1.01	0.96	0.96	0.95	0.95	0.75	0.75	0.79	0.79	0.76	0.76	0.84	0.84
Original scale																
Mean observed	174.1	174.1	174.1	174.1	125.6	125.6	125.6	125.6	134.9	134.9	134.9	134.9	184.2	184.2	184.2	184.2
Mean predicted	116.6	168.0	120.0	166.7	85.2	121.4	89.5	122.8	125.0	134.8	122.2	133.9	130.9	186.8	136.0	182.7
R^2	0.12	0.46	0.22	0.58	0.07	0.53	0.20	0.56	−0.05	−0.14	0.23	0.19	−0.28	−0.27	0.05	0.31
RMSE	84.6	66.6	79.5	58.1	56.1	39.7	51.8	38.6	67.1	69.9	57.5	58.8	86.2	85.9	74.4	63.1
MAE	65.5	46.4	61.7	43.6	44.6	29.7	40.0	29.1	42.5	42.7	40.7	40.4	67.5	52.7	59.0	46.5
CITL	57.5	6.1	54.1	7.4	40.4	4.1	36.1	2.8	9.8	0.1	12.7	1.0	53.3	−2.6	48.2	1.5
Calibration slope	1.06	0.74	1.22	0.88	1.18	0.83	1.10	0.80	0.49	0.45	0.64	0.58	0.61	0.43	0.86	0.64
C statistic per VAT cutoff																
>70 cm^2	0.93	0.93	0.94	0.94	0.86	0.86	0.92	0.92	0.93	0.93	0.94	0.94	0.95	0.95	0.94	0.94
>100 cm^2	0.93	0.93	0.92	0.92	0.88	0.88	0.89	0.89	0.85	0.85	0.86	0.86	0.94	0.94	0.95	0.95
>130 cm^2	0.92	0.92	0.92	0.92	0.87	0.87	0.88	0.88	0.85	0.85	0.86	0.86	0.91	0.91	0.91	0.91

Abbreviations: CITL, calibration-in-the-large; MAE, mean absolute error; RMSE, root-mean-square error; VAT, visceral adipose tissue.

[a] Estimates are reported for the development scale (natural logarithm of VAT) and the original scale (in cm^2) after back transforming the predicted values. We report the initial results and the performance after intercept recalibration.

[b] Core predictors include age, sex, height, body weight, body mass index, total cholesterol, triglycerides, high-density lipoprotein cholesterol, glucose, and the total cholesterol/high-density lipoprotein cholesterol ratio.

[c] The extended clinical model includes the core predictors, waist circumference, hip circumference and the waist-to-hip ratio.

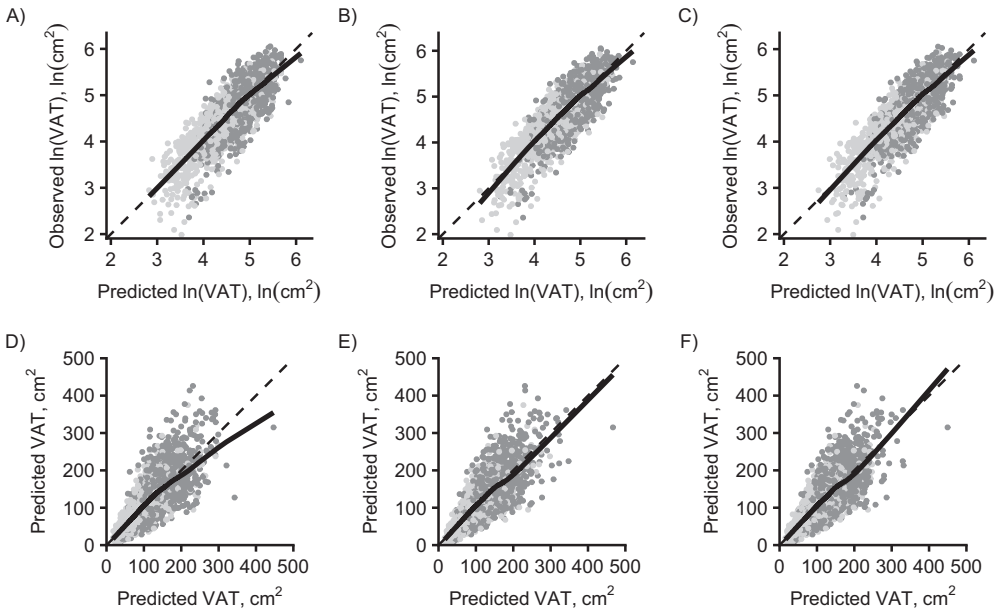

Figure 2. Calibration plots of the extended clinical and metabolite-extended models developed in the Netherlands Epidemiology of Obesity Study (n = 2,501), the Netherlands, 2008–2012. A–C) Calibration plots on the natural logarithm scale (development scale): A) Extended clinical model with core predictors, waist circumference (WC), hip circumference (HC), and waist-to-hip ratio (WHR); B) metabolite-extended, ridge; C) metabolite-extended, least absolute shrinkage and selection operator (LASSO). D–F) calibration plots after back transforming the predicted values to the original scale (in cm^2): D) extended clinical model with core predictors, WC, HC, and WHR; E) metabolite-extended, ridge; F) metabolite-extended, LASSO. The black dashed line indicates unity ($x = y$); the black continuous line is a locally weighted scatterplot smoothing curve fitted to the data points. Women, light gray dots; men, dark gray dots. VAT, visceral adipose tissue.

Figure 4, Web Tables 17–19). The ridge model in particular performed poorly, with an R^2 of −3.32 (95% CI: −4.58, −2.41) and C statistics around 0.5, indicating nonuseful predictions.

DISCUSSION

We developed prediction models to estimate VAT area in a middle-aged, ethnically White cohort and externally validated these models in a Swedish cohort with an older population and a multi-ethnic cohort from the United States. We showed that adding waist circumference to measurements routinely performed at a general practitioner's office improved VAT prediction, while further adding insulin concentrations, total body fat, or Nightingale metabolomics measurements did not. Models that included waist circumference also performed consistently better in the external validation with performances similar to the development setting in PIVUS and White and Chinese participants from the MESA cohort. The overall performance in the MESA cohort was lower, likely due to the poorer performance in Black and Hispanic participants.

Several previous studies have created prediction models for VAT, often incorporating similar predictors as such as age, waist circumference, and cholesterol concentrations, with the earliest attempts dating back over 30 years (10, 11, 32–34). In a review of VAT prediction models that used anthropometric measurements up to 2014, waist measurements were used in 25 out of 27 equations, and the explained variance of these models ranged between 30% and 80%, with comparatively large prediction errors (13), which is in line with our own findings. A direct comparison with these and more recent studies is difficult as most of the models were tested only in their development cohorts, internal validation was not or only partially performed, and reporting of recommended information for prediction studies was often incomplete (20). We found only 1 study that performed an external validation, but information on measures such calibration or the RMSE in the external data set were not reported (11). In contrast, we were able to demonstrate our models' efficacy in 2 geographically separated and demographically diverse cohorts. Another important difference from previous studies is our focus on the added value of predictors as criteria for inclusion in our models. In previous studies, waist circumference was included in models on statistical grounds such as by stepwise regression (11, 32, 33) or because it was considered to be the best single predictor of VAT (10). With our study we now clearly demonstrate that waist circumference improves VAT prediction on top of more routine clinical measurements such as BMI.

Given the strong association of VAT with cardiometabolic disorders such as atherosclerosis, type 2 diabetes, and cardiovascular disease (2, 24, 35), measurements of VAT could be useful for the identification of individuals with an elevated cardiometabolic risk, or to motivate preventive

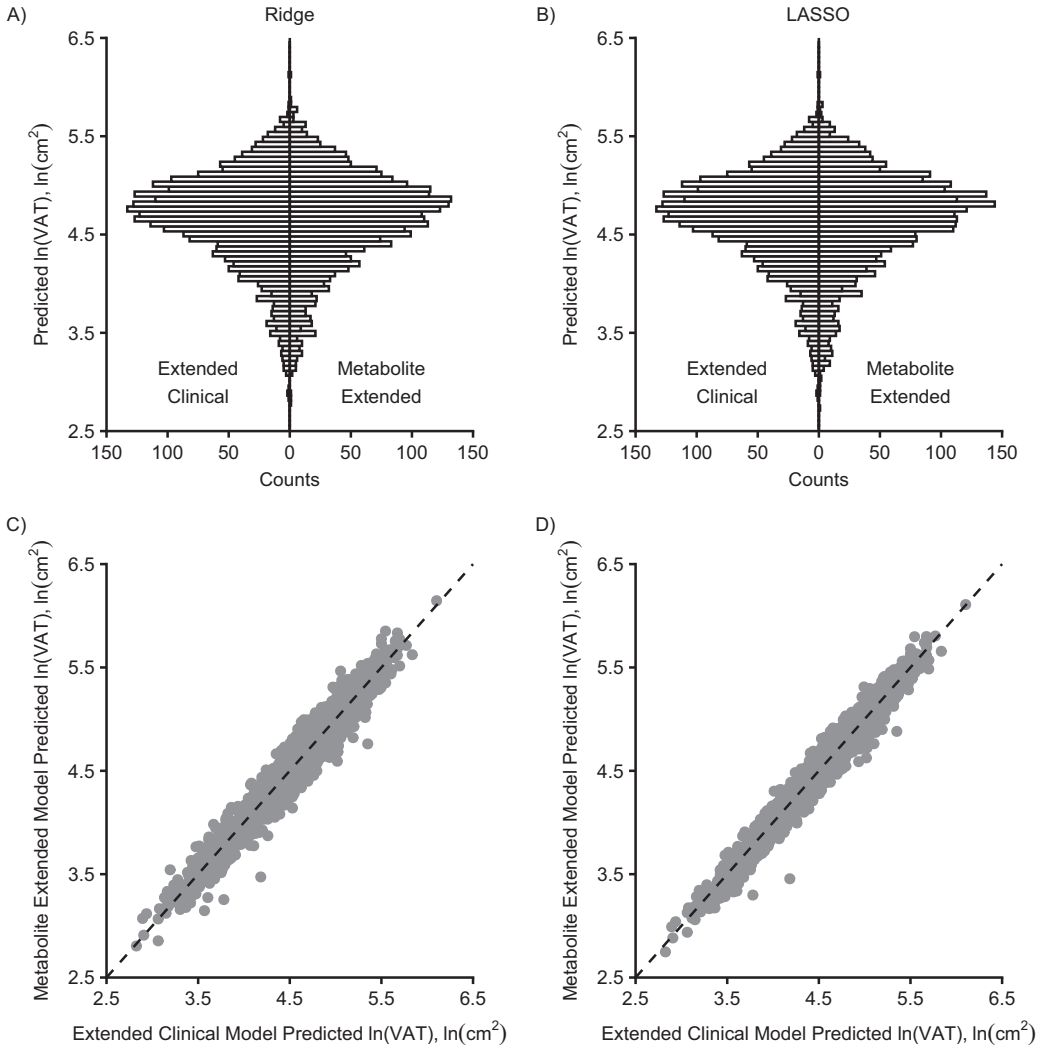

Figure 3. Back-to-back histograms and scatterplots of predicted values of ln(VAT) of the extended clinical model (core + waist circumference (WC) + hip circumference (HC) + waist-to-hip ratio (WHR)) versus the metabolite-extended models in the Netherlands Epidemiology of Obesity Study (n = 2,501), the Netherlands, 2008–2012. A–B) back-to-back histograms with predictions from the extended clinical model on the left-hand side and the metabolite extended models on the right-hand side: A) metabolite-extended, ridge; B) metabolite-extended, least absolute shrinkage and selection operator (LASSO). C–D) scatterplots with values predicted by the extended clinical model on the x-axis and values predicted by the extended models on the y-axis: C) metabolite-extended, ridge; D) metabolite-extended, LASSO. The dashed line is the $x = y$ line. VAT, visceral adipose tissue.

measures such as lifestyle changes, in addition to traditional measures such as BMI or risk predictions from cardiovascular risk prediction models. Measurements of VAT could also help in identifying individuals with a normal BMI at risk of metabolic dysfunction as even in these individuals a higher VAT is associated with cardiometabolic changes (36). Because computed tomography and MRI imaging are practically unfeasible, the International Atherosclerosis Society and the International Chair on Cardiometabolic Risk Working Group on Visceral Obesity recently emphasized the need for more research into "simple, clinically applicable tools" to identify individuals with excess VAT (37). Together, the results from previous studies and our own suggest that waist circumference is an important predictor for VAT, which strengthens the call to measure waist circumference routinely in clinical practice (15).

Although we previously showed that measurements from the Nightingale metabolomics platform, including acetyl glycoproteins, branched-chain amino acids, and lipoprotein measures, were associated with VAT after adjusting for many of the variables that we included in our models here (16), adding these measurements did not improve predictive performance. The high correlations between the predominantly lipid metabolism–related measurements in the Nightingale platform and the standard laboratory measures in our clinical models, indicative of a high collinearity

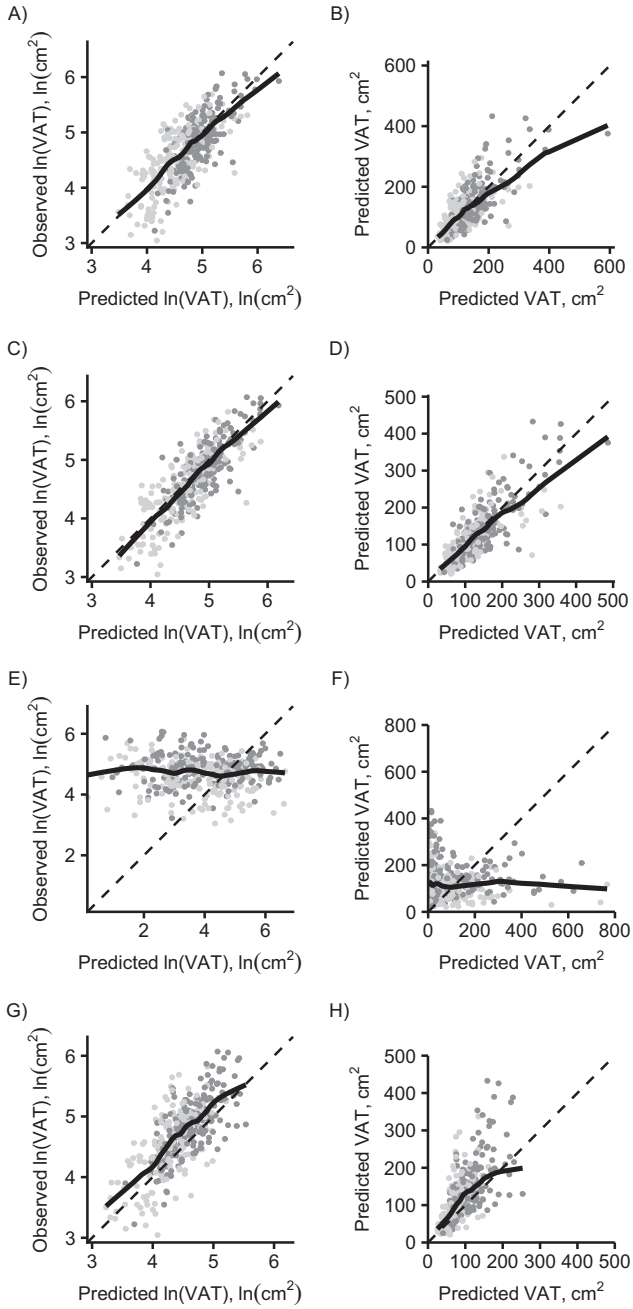

Figure 4. Calibration plots of the external validation of the core and extended clinical models and the metabolite extended models in the Prospective Investigation of the Vasculature in Uppsala Seniors (n = 370), Uppsala, Sweden, 2006–2009. Left column, calibration plots on the natural logarithm scale (development scale): A) core; C) extended; E) metabolite-extended, ridge, G) metabolite-extended, least absolute shrinkage and selection operator (LASSO). Right column, calibration plots of the predicted values back transformed to the original scale (in cm^2): B) core; D) extended; F) metabolite-extended, ridge; H) metabolite-extended, LASSO. The black dashed line indicates unity ($x = y$); the black continuous line is a locally weighted scatterplot smoothing curve fitted to the data points. Light gray dots are women; dark gray dots are men. VAT, visceral adipose tissue.

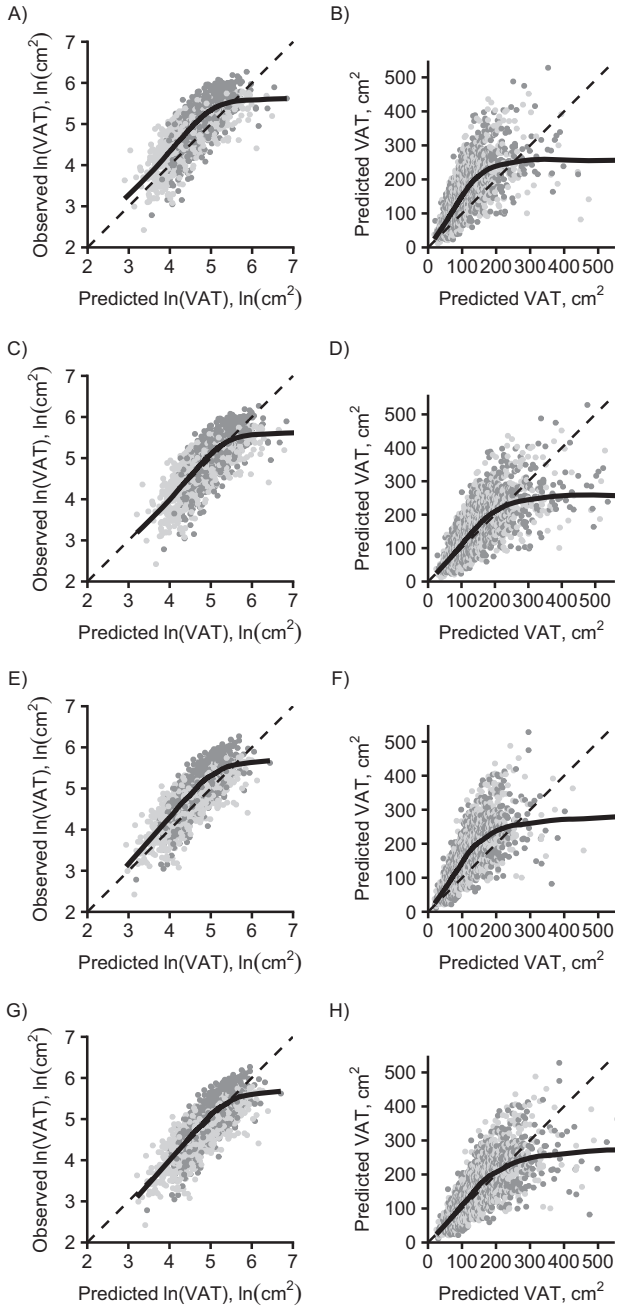

Figure 5. Calibration plots of the external validation of the core and extended clinical models before and after intercept recalibration in the Multi-Ethnic Study of Atherosclerosis (n = 1,901), United States, 2000–2007. Left column, calibration plots on the natural logarithm scale (development scale): A) core; C) core, recalibrated; E) extended; G) extended, recalibrated. Right column, calibration plots after back transforming the predicted values to the original scale (in cm^2): B) core; D) core, recalibrated; F) extended; H) extended, recalibrated. To improve plot interpretability, we restricted the axis range in E–H, excluding from 1 to 9 individuals with large overestimations of VAT. The black dashed line indicates unity ($x = y$); the black continuous line is a locally weighted scatterplot smoothing curve fitted to the data points. Light gray dots are women; dark gray dots are men. VAT, visceral adipose tissue.

between the metabolites and clinical predictors, likely explain why the metabolomics measurements did not have a clear added value on top of the clinical measurements (Web Table 5). Our findings should therefore not discourage further attempts to improve VAT prediction models. There are several other potential predictors, such as inflammatory markers other than acetyl glycoproteins (38), adipokines (39), sex hormones (40), and phosphatidylcholines and sphingomyelins, that can be measured with other metabolomics platforms (18, 19, 41) and that have been associated with VAT but whose role in VAT prediction has not yet been evaluated. As the costs of metabolomics measurements decrease, improvements in VAT prediction from other metabolomics platforms could result in a favorable cost-benefit ratio when weighed against the costs of performing imaging such as MRI. While older age (42) and BMI (43) are associated with increases in VAT, our models seemed to generalize well to the validation cohorts whose participants were older and had a lower body weight than the participants from the NEO study. Further exploration of the role of ethnicity and sex in VAT prediction seems warranted given the heterogeneity in outcomes we observed within these subgroups. Similar differences in model performance were also observed in previous studies, such as one of 622 middle-aged Japanese-Americans (11), where the explained variance was higher and mean-squared error was lower among women than among men. We found only 2 previous studies that examined the role of ethnicity in VAT prediction, one that estimated prediction formulas containing anthropometric variables separately in different ethnicities (10) and another that included race as a predictor (34). Both studies reported high R^2 values ranging from 0.43 to 0.78; however, the sample size in both studies was limited, especially within the non-White subgroups, and only (partial) internal validation was performed. Several descriptive studies have delineated ethnic differences in the distribution of VAT, such as a higher average VAT in White compared with Black individuals and differences in the association between BMI and VAT in different ethnic subgroups (44–46), which could partially explain why our models, which were developed in an ethnically White cohort, performed more poorly in Black and Hispanic participants in MESA.

Our study has several limitations, including the use of cross-sectional VAT areas rather than total VAT volume as the outcome. As a result, it is possible that our models do not accurately estimate the VAT burden in an individual, although abdominal cross-sectional areas have been shown to correlate well (ρ: 0.70–0.99) with total VAT volume (47–49). In addition, VAT was measured using different imaging techniques and protocols in the NEO study, PIVUS, and MESA, which, together with measurement heterogeneity of the predictors, could explain some of the differences in performance between the cohorts (50). Strengths include our access to a large development cohort in which we performed a thorough development and internal validation. We also used a modeling approach that focuses on the added value of predictors on top of routinely measured ones instead of using purely statistical grounds for variable selection. Such statistical approaches can lead to models whose predictions transport poorly to a new setting (51) or that contain expensive or otherwise nonpractically measurable predictors. Last, we were able to validate and demonstrate the efficacy of both the models with currently measurable predictors as well as those with metabolomics measurements in 2 cohorts that were demographically, ethnically, and geographically distinct from the development cohort.

In conclusion, our study demonstrated that the prediction of VAT using routinely measured clinical variables can be improved by measuring and including waist circumference in the estimations but not by including metabolomics measurements from the Nightingale platform. We therefore encourage the routine measurement of waist circumference in clinical practice, for example, during cardiovascular risk assessment.

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Author affiliations: Department of Clinical Epidemiology, Leiden University Medical Center, Leiden, the Netherlands (Sebastiaan C. Boone, Maarten van Smeden, Frits R. Rosendaal, Saskia le Cessie, Rolf H. H. Groenwold, Dennis O. Mook-Kanamori, Renée de Mutsert); Department of Biomedical Data Sciences, Medical Statistics and Bioinformatics Section, Leiden University Medical Center, Leiden, the Netherlands (Maarten van Smeden, Saskia le Cessie); Department of Cardiology, Leiden University Medical Center, Leiden, the Netherlands (J. Wouter Jukema); Netherlands Heart Institute, Utrecht, the Netherlands (J. Wouter Jukema); Department of Human Genetics, Leiden University Medical Center, Leiden, the Netherlands (Ko Willems van Dijk); Einthoven Laboratory for Experimental Vascular Medicine, Leiden University Medical Center, Leiden, the Netherlands (Ko Willems van Dijk); Department of Medicine, Division of Endocrinology, Leiden University Medical Center, Leiden, the Netherlands (Ko Willems van Dijk); Department of Radiology, Leiden University Medical Center, Leiden, the Netherlands (Hildo J. Lamb); Department of Preventive Medicine, Northwestern University, Chicago, Illinois, United States (Philip Greenland); Division of Cardiovascular Disease, University Hospitals Harrington Heart and Vascular Institute, Cleveland, Ohio, United States (Ian J. Neeland); Division of Cardiovascular Disease, Case Western Reserve University School of Medicine, Cleveland, Ohio, United States (Ian J. Neeland); Department of Family Medicine and Public Health, Division of Preventive Medicine, University of California San Diego, San Diego, California, United States (Matthew A. Allison, Michael H. Criqui); Department of Medicine, Lundquist Institute at Harbor-UCLA Medical Center, Torrance, California, United States (Matthew J. Budoff); Department of Medical Sciences, Uppsala University, Uppsala, Sweden (Lars L. Lind); Department of Surgical Sciences, Section of Radiology, Uppsala University, Uppsala, Sweden (Joel Kullberg, Håkan Ahlström); Antaros Medical AB, Mölndal, Sweden (Joel Kullberg, Håkan Ahlström); and

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