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Anthropometrically-Predicted Visceral Adipose Tissue and Mortality among Men and Women in the Third National Health and Nutrition Examination Survey (NHANES III)

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Abstract

Objective—This study seeks to quantify the relationship between anthropometrically-predicted visceral adipose tissue (apVAT) and all-cause and cause-specific mortality among individuals of European descent in a population-based prospective cohort study of 10,624 participants.

Methods—We predicted apVAT with a validated regression equation that included age, body mass index, and waist and thigh circumferences.

Results—During a median of 18.8 years, 3,531 participants died with 1,153 and 741 deaths attributable to cardiovascular disease and cancer, respectively. In multivariable-adjusted analyses that accounted for demographic, clinical, and behavioral characteristics, higher apVAT was associated with an increased risk of all-cause ($P_{\text{trend}} < 0.001$), cardiovascular-specific ($P_{\text{trend}} < 0.001$), and cancer-specific mortality ($P_{\text{trend}} = 0.007$). Excluding participants with a history of cancer, myocardial infarction, heart failure, or diabetes at baseline did not substantively alter effect estimates. apVAT more accurately predicted all-cause, cardiovascular-specific, and cancer-specific mortality than body mass index ($P < 0.001$), waist circumference ($P < 0.001$), or the combination of body mass index and waist circumference ($P < 0.001$).

Conclusions—These data provide evidence that apVAT is associated with all-cause and cause-specific mortality in a large population-based sample of men and women of European descent. These results support the use of apVAT to risk-stratify individuals for premature mortality when imaging data are not available such as in routine clinical practice or in large clinical trials.

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AUTHOR CONTRIBUTIONS

JCB, MOH, and MNH all contributed to the conception and study design, data analysis and interpretation, manuscript writing, and final approval of manuscript.

CONFLICTS OF INTEREST

The authors report there exist no conflicts of interest.

Keywords

anthropometrics; waist circumference; waist-hip ratio; population-based

INTRODUCTION

Excess visceral adipose tissue (VAT) is one of the most deleterious fat deposits in the body (Despres et al., 2001), with strong links to cardiovascular disease (Despres, 2012; Tchernof and Despres, 2013), and certain types of cancer (Tchernof and Despres, 2013). Computed tomography (CT) and magnetic resonance (MR) imaging techniques are the gold standards to quantify VAT (Shen et al., 2003). However, complexities of access and the cost associated with CT or MR imaging often preclude their use in routine clinical practice and in large interventional and epidemiologic studies. Although waist circumference is often considered an anthropometric proxy for VAT, it cannot differentiate VAT from the less deleterious subcutaneous adipose tissue (SAT) in the abdomen (Despres, 2012; Ibrahim, 2010), and is more closely correlated to total body adipose tissue ($R^2=0.85$) than VAT ($R^2=0.59$) (Bouchard, 2007). Investigators have recently developed equations to predict VAT that simultaneously integrate various anthropometric dimensions such as body mass index (BMI) and circumferences of the waist and thigh to more accurately approximate measured VAT ($R^2=0.80-0.84$) (Eastwood et al., 2013; Neamat-Allah et al., 2014; Samouda et al., 2013). While larger waist circumference is a known predictor of premature mortality (Pischon et al., 2008), the VAT prediction equation has not been studied as a predictor of long-term health outcomes. Therefore, we tested the hypothesis that VAT predicted with a validated anthropometric regression equation (i.e., apVAT) is associated with premature mortality among a large population-based sample of men and women of European descent living in the United States (Samouda et al., 2013). We also explored the discriminative capacity of apVAT versus BMI and waist circumference to prognosticate mortality.

METHODS

Study Design and Participants

The Third National Health and Nutrition Examination Survey, 1988–1994 (NHANES III), was a stratified multistage study designed to provide health information on a nationally-representative sample of 33,994 men and women aged two-months and older. Our sample included men and women of age ≥ 18 years ($n=17,016$), with self-reported Caucasian race ($n=11,603$), who completed the requisite measures necessary to calculate apVAT ($n=10,624$). All study participants provided informed consent.

Anthropometrically-Predicted Visceral Adipose Tissue

apVAT was predicted with sex-specific validated equations that included age, BMI, and circumferences of the waist and thigh (Samouda et al., 2013). The equation for men was: $6 \times \text{waist circumference} - 4.41 \times \text{proximal thigh circumference} + 1.19 \times \text{age} - 213.65$; and the equation for women was: $2.15 \times \text{waist circumference} - 3.63 \times \text{proximal thigh} + 1.46 \times \text{age} + 6.22 \times \text{BMI} - 92.713$.

Mortality Outcome

Vital status and cause of death were identified using the National Death Index publically-released database through December 31, 2011 (National Center for Health Statistics, 2013). Participants were linked to the National Death Index database using a probabilistic matching algorithm that included 12 identifiers including Social Security Number, sex, date of birth, race, state of residence and birth, and marital status (Rogot et al., 1986). The National Center for Health Statistics found that 96.1% of deceased participants and 99.4% of living participants were correctly classified using the probabilistic matching algorithm (National Center for Health Statistics, 2006). In our study, participants who were not matched with a death certificate were categorized as being alive through the end of the follow-up period ($n=7,093$; 66.7%). The publically-released survival data are nearly identical to the restricted-use NHANES III linked mortality file (Wilper et al., 2009). Causes of death were categorized using 113 grouped recodes from the International Classification of Diseases, 10th Edition (ICD-10). Cardiovascular-specific mortality was categorized using ICD-10 codes I00-I079. Cancer-specific mortality was categorized using ICD-10 codes C00-C97.

Covariates

Demographic information including date of birth and sex were self-reported using a standardized questionnaire (National Center for Health Statistics, 1993). Height, body mass, waist circumference, and proximal thigh circumference were measured by study technicians. BMI was calculated as weight divided by the square of height (kg/m^2). Clinical characteristics including smoking history and the presence of comorbid health conditions including cancer, myocardial infarction, heart failure, and diabetes were assessed using standardized questionnaires (National Center for Health Statistics, 1993). Alcohol consumption and the healthy eating index were calculated from 24-hour food recalls (Karvetti and Knuts, 1985). The healthy eating index forms a score than ranges from 0 to 100 to quantify aspects of a healthy diet (Kennedy et al., 1995). Bouts of walking in the past week were self-reported and included any bout of walking that was estimated to be 1 mile in duration, and of moderate or vigorous intensity.

Statistical Analysis

We fit Cox proportional hazards regression models to estimate the hazard ratio [HR] and 95% confidence interval [95% CI] between quintiles of apVAT and mortality. Models were estimated adjusted for age and sex (model 1), fully adjusted for demographic, clinical, and behavioral characteristics (model 2), and fully adjusted but excluding participants with a history of cancer, myocardial infarction, heart failure, or diabetes at baseline (model 3). We confirmed the assumption of proportional hazards using log-log plots (Harrell, 2001). To determine if gender modified the relationship between apVAT and mortality outcomes we incorporated a statistical interaction in the regression models. No statistically significant interactions were identified; consequently all analyses are presented for the overall cohort. Time-dependent receiver operating characteristic (ROC) curves were used to quantify the capacity of apVAT to discriminate participants with respect to each mortality outcome (Heagerty et al., 2000). Time-dependent ROC analyses were conducted to determine if apVAT provided incremental discriminative capacity beyond that of the routinely-collected

anthropometric measures including BMI and waist circumference. Sample weights were incorporated into all statistical analyses to account for nonresponse bias and multistage sampling probabilities (Korn and Graubard, 1991). Stata/SE v.14.1 and R v.3.2.5 statistical software were used for all analyses.

RESULTS

Cohort Characteristics

Among 10,624 men and women, we observed 3,531 deaths during a median of 18.8-years of follow-up; 1,153 and 741 deaths occurred as a result of cardiovascular disease and cancer, respectively. Participant characteristics using the un-weighted sample and the estimated population after applying analytic sample weights are presented in Table 1.

Anthropometrically-Predicted Visceral Adipose Tissue and Mortality

Higher apVAT was associated with an increased risk of all-cause, cardiovascular-specific, and cancer-specific mortality (Figure 1). In multivariable-adjusted analyses that accounted for demographic, clinical, and behavioral characteristics, higher apVAT was associated with an increased risk of all-cause ($P_{\text{trend}} < 0.001$), cardiovascular-specific ($P_{\text{trend}} < 0.001$), and cancer-specific mortality ($P_{\text{trend}} = 0.007$) (Table 2). Excluding participants with a history of cancer, myocardial infarction, heart failure, or diabetes did not substantively alter effect estimates (data not shown).

Discriminative Capacity of Anthropometrically-Predicted Visceral Adipose Tissue

apVAT more accurately predicted all-cause, cardiovascular-specific and cancer-specific mortality compared to BMI, waist circumference, or the combination of BMI and waist circumference (all $P < 0.001$; Table 3).

DISCUSSION

The major finding of this study is that apVAT, predicted from simple and widely used anthropometric measures, is strongly predictive of all-cause and cause-specific mortality in a large population-based cohort. Furthermore, apVAT was a stronger predictor of mortality than BMI and waist circumference or the combination of BMI and waist circumference. Importantly, the observed relationship between apVAT and mortality parallels that of VAT measured by CT or MR, the current gold-standards for measuring VAT (Katzmarzyk et al., 2012).

Commonly used anthropometrics including waist circumference and BMI cannot distinguish VAT from SAT. The presence of SAT in the abdomen serves a non-deleterious purpose, representing a physiologic buffer to store excess energy. When the storage capacity of SAT is exceeded, VAT is accrued. Accordingly, 80–90% of abdominal fat is SAT, and the remaining 10–20% is VAT (Ibrahim, 2010). The adipocytes that constitute VAT are physiologically and pathologically distinct from SAT (Tchernof and Despres, 2013). The adipocytes of VAT secrete bioactive compounds such as adipocytes, cytokines, hormone-like factors, and other metabolites that have negative health effects. VAT adipocytes reside in

close anatomic proximity to vital organs and directly drain secretions into the portal venous vasculature, manifesting a pro-inflammatory and hyperinsulinemic milieu throughout the body. While CT and MR imaging remains a gold-standard to distinguish the burden of VAT from SAT, our study confirms that regression equations developed to incorporate anthropometric measures to estimate VAT can serve as a non-invasive and less expensive proxy to investigate the role of VAT in adverse health outcomes.

Lifestyle behaviors may be efficacious interventions to reduce VAT. Diet-induced (caloric restriction) and exercise-induced (caloric expenditure) weight losses are similar in their efficacy to reduce VAT among men and women (Ross et al., 2000; Ross et al., 2004). However, exercise-induced weight loss additionally yields greater reductions in total body fat than caloric-restriction induced weight loss (Ross et al., 2000; Ross et al., 2004). Prolonged periods of physical inactivity (i.e., 60 days of bed rest) result in a +29% increase in VAT compared to only +7% increase in subcutaneous limb fat, suggesting that excess energy is preferentially stored as VAT during extended periods of inactivity (Belavý et al., 2014). Collectively these data underscore the importance of including exercise or physical activity as a lifestyle intervention to reduce VAT.

There are limitations to this study. Our sample was limited to men and women of European descent because the anthropometric equation to predict VAT was validated in a white population (Samouda et al., 2013). There are several strengths to this study. The population-based sampling framework of NHANES permitted our analyses to represent the national population of men and women of European descent living in the United States. The sample size of our study was relatively large, and our long period of follow-up allowed us to observe a high frequency of mortality outcomes. This provided us with sufficient statistical power to examine cardiovascular- and cancer-specific causes of death.

In conclusion, apVAT is associated with all-cause and cause-specific mortality among a large population of men and women of European descent living in the United States. The newly established prognostic capacity of apVAT provides another complementary tool to assess the health effects of body composition on the population. The development and validation of similar equations in other non-European populations would improve the generalizability of these findings and their use in clinical and research practice. These results support the use of anthropometrically-predicted equations to investigate the deleterious cardio-metabolic and oncologic sequelae of VAT when imaging data are not available, such as in clinical practice or in large scale clinical trials.

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LITERATURE CITED

Belavý D, Möhlig M, Pfeiffer A, Felsenberg D, Armbrrecht G. Preferential deposition of visceral adipose tissue occurs due to physical inactivity. *Int J Obes.* 2014; 38:1478–1480.

- Bouchard C. BMI, fat mass, abdominal adiposity and visceral fat: Where is the 'beef'? *Int J Obes.* 2007; 31:1552–1553.
- Despres JP. Body fat distribution and risk of cardiovascular disease: An update. *Circulation.* 2012; 126:1301–1313. [PubMed: 22949540]
- Despres JP, Lemieux I, Prud'homme D. Treatment of obesity: Need to focus on high risk abdominally obese patients. *BMJ.* 2001; 322:716–720. [PubMed: 11264213]
- Eastwood SV, Tillin T, Wright A, Heasman J, Willis J, Godsland IF, Forouhi N, Whincup P, Hughes AD, Chaturvedi N. Estimation of CT-derived abdominal visceral and subcutaneous adipose tissue depots from anthropometry in europeans, south asians and african caribbeans. 2013
- Harrell, FE. Regression modeling strategies: With applications to linear models, logistic regression, and survival analysis. Springer; 2001.
- Heagerty PJ, Lumley T, Pepe MS. Time-dependent ROC curves for censored survival data and a diagnostic marker. *Biometrics.* 2000; 56:337–344. [PubMed: 10877287]
- Ibrahim MM. Subcutaneous and visceral adipose tissue: Structural and functional differences. *Obesity Reviews.* 2010; 11:11–18. [PubMed: 19656312]
- Karvetti RL, Knuts LR. Validity of the 24-hour dietary recall. *Journal of the American Dietetic Association.* 1985; 85:1437–1442. [PubMed: 4056262]
- Katzmarzyk P, Mire E, Bouchard C. Abdominal obesity and mortality: The pennington center longitudinal study. *Nutrition & Diabetes.* 2012; 2:e42. [PubMed: 23168527]
- Kennedy ET, Ohls J, Carlson S, Fleming K. The healthy eating index: Design and applications. *J Am Diet Assoc.* 1995; 95:1103–1108. [PubMed: 7560680]
- Korn EL, Graubard BI. Epidemiologic studies utilizing surveys: Accounting for the sampling design. *Am J Public Health.* 1991; 81:1166–1173. [PubMed: 1951829]
- National Center for Health Statistics. National Death Index User's Guide. Hayattsville, MD: 2013.
- National Center for Health Statistics. The third national nutrition and health survey linked mortality file: Matching methodology. 2006.
- National Center for Health Statistics. NHANES III questionnaires, datasets and related documentation. 1993.
- Neamat-Allah J, Wald D, Husing A, et al. Validation of anthropometric indices of adiposity against whole-body magnetic resonance imaging--a study within the german european prospective investigation into cancer and nutrition (EPIC) cohorts. *PLoS One.* 2014; 9:e91586. [PubMed: 24626110]
- Pischon T, Boeing H, Hoffmann K, et al. General and abdominal adiposity and risk of death in europe. *N Engl J Med.* 2008; 359:2105–2120. [PubMed: 19005195]
- Rogot E, Sorlie P, Johnson NJ. Probabilistic methods in matching census samples to the national death index. *J Chronic Dis.* 1986; 39:719–734. [PubMed: 3734026]
- Ross R, Dagnone D, Jones PJ, Smith H, Paddags A, Hudson R, Janssen I. Reduction in obesity and related comorbid conditions after diet-induced weight loss or exercise-induced weight loss in men: A randomized, controlled trial. *Ann Intern Med.* 2000; 133:92–103. [PubMed: 10896648]
- Ross R, Janssen I, Dawson J, Kungl A, Kuk JL, Wong SL, Nguyen-Duy T, Lee S, Kilpatrick K, Hudson R. Exercise-induced reduction in obesity and insulin resistance in women: A randomized controlled trial. *Obes Res.* 2004; 12:789–798. [PubMed: 15166299]
- Samouda H, Dutour A, Chaumoitre K, Panuel M, Dutour O, Dadoun F. VAT=TAAT-SAAT: Innovative anthropometric model to predict visceral adipose tissue without resort to CT-Scan or DXA. *Obesity.* 2013; 21:E41–E50. [PubMed: 23404678]
- Shen W, Wang Z, Punyanita M, Lei J, Sinav A, Kral JG, Imielinska C, Ross R, Heymsfield SB. Adipose tissue quantification by imaging methods: A proposed classification. *Obes Res.* 2003; 11:5–16. [PubMed: 12529479]
- Tchernof A, Despres JP. Pathophysiology of human visceral obesity: An update. *Physiol Rev.* 2013; 93:359–404. [PubMed: 23303913]
- Wilper AP, Woolhandler S, Lasser KE, McCormick D, Bor DH, Himmelstein DU. Health insurance and mortality in US adults. *Am J Public Health.* 2009; 99:2289–2295. [PubMed: 19762659]

Figure 1.

Kaplan-Meier survival estimates according to quintile of anthropometrically-predicted visceral adipose tissue for A) all-cause mortality; B) cardiovascular-specific mortality; and C) cancer-specific mortality.

Table 1Characteristics of study participants^a

Characteristic	Sample Size [Un-Weighted] (n=10,624)	Estimated Population [Weighted] (n=149,418,577)
Age, yr	49.6±0.19	44.7±0.21
Sex, %		
Male	47.8%	48.2%
Female	52.2%	51.8%
Body Mass Index, kg/m ²		
Continuous (mean)	26.8±0.05	26.4±0.08
<18.5	2.0%	2.2%
18.5–24.9	37.9%	42.9%
25.0–29.9	36.5%	33.5%
30	23.6%	21.4%
Waist Circumference, cm		
Continuous (mean)	93.5±0.13	91.9±0.21
88 (women), 102 (men)	56.7%	62.8%
>88 (women), >102 (men)	43.3%	37.2%
Predicted Visceral Adipose Tissue, cm ²	180.9±0.73	163.5±1.03
Smoking Status, %		
Never	48.4%	44.2%
Former	28.3%	27.4%
Current	23.3%	28.4%
Comorbid Health Conditions, %		
Cancer	4.4%	4.0%
Myocardial Infarction	5.3%	3.5%
Heart Failure	3.8%	1.9%
Diabetes	7.9%	4.9%
Health Eating Index, 0–100	64.5±0.13	64.2±0.19
Alcohol Consumption, drinks/week	0.95±0.02	1.18±0.03
Bouts of Weekly Walking, %		
0	69.5%	64.8%
1–3	13.1%	16.2%
3	17.4%	19.0%
Length of Follow-Up, yr.	16.8±0.06	18.1±0.06
Mortality Outcome Events, %		
All-Cause	33.2%	22.6%
Cardiovascular-Specific	10.9%	6.7%
Cancer-Specific	7.0%	5.5%

^aValues are means (standard error) or column percentages (%).

Table 2

Association between anthropometrically-predicted visceral adipose tissue and mortality outcomes

Mortality Outcome	Model 1 ^a	Model 2 ^b	Model 3 ^c
All-Cause			
Q1	1.00—Referent	1.00—Referent	1.00—Referent
Q2	1.61 (1.11–2.34)	1.55 (1.06–2.28)	1.51 (0.99–2.30)
Q3	1.60 (1.11–2.30)	1.50 (1.03–2.18)	1.53 (1.02–2.29)
Q4	1.96 (1.36–2.81)	1.78 (1.23–2.59)	1.74 (1.16–2.62)
Q5	2.44 (1.69–3.52)	2.19 (1.50–3.20)	2.20 (1.45–3.33)
<i>P</i> for trend	<0.001	<0.001	<0.001
Cardiovascular-Specific			
Q1	1.00—Referent	1.00—Referent	1.00—Referent
Q2	1.13 (0.43–2.95)	1.03 (0.39–2.71)	0.99 (0.29–3.41)
Q3	1.94 (0.77–4.90)	1.78 (0.70–4.49)	2.09 (0.64–6.82)
Q4	2.14 (0.86–5.37)	1.92 (0.77–4.80)	1.91 (0.59–6.14)
Q5	2.71 (1.08–6.80)	2.39 (0.95–6.00)	2.64 (0.82–8.51)
<i>P</i> for trend	<0.001	<0.001	<0.001
Cancer-Specific			
Q1	1.00—Referent	1.00—Referent	1.00—Referent
Q2	2.88 (1.44–5.76)	2.62 (1.31–5.26)	2.97 (1.40–6.31)
Q3	2.35 (1.18–4.67)	2.02 (1.01–4.04)	2.28 (1.09–4.77)
Q4	2.99 (1.47–6.05)	2.41 (1.19–4.90)	2.91 (1.36–6.23)
Q5	3.37 (1.65–6.89)	2.70 (1.31–5.56)	3.27 (1.48–7.22)
<i>P</i> for trend	0.004	0.007	0.040

^aModel 1 is adjusted for age and sex.^bModel 2 is adjusted for age, sex, smoking status, healthy eating index, alcoholic drink consumption, and weekly bouts of walking.^cModel 3 adjusted for the same covariates as model 3, but excludes participants with a history of cancer, myocardial infarction, heart failure, or diabetes at baseline.

Table 3

Discriminative characteristics for mortality outcomes among anthropometric indices

Mortality Outcome	C-Statistic (95% Confidence Interval)			
	Body Mass Index	Waist Circumference	Body Mass Index + Waist Circumference	Anthropometrically-Predicted Visceral Adipose Tissue
All-Cause	0.542 (0.526–0.558)	0.634 (0.619–0.649) ^a	0.700 (0.686–0.714) ^{a,b}	0.801 (0.789–0.813) ^{a,b,c}
Cardiovascular-Specific	0.549 (0.528–0.569)	0.642 (0.622–0.661) ^a	0.709 (0.689–0.728) ^{a,b}	0.824 (0.801–0.838) ^{a,b,c}
Cancer-Specific	0.559 (0.534–0.583)	0.643 (0.619–0.666) ^a	0.699 (0.675–0.722) ^{a,b}	0.779 (0.760–0.798) ^{a,b,c}

^a $P < 0.001$ versus body mass index.^b $P < 0.001$ versus waist circumference.^c $P < 0.001$ versus body mass index + waist circumference.

Notes: C-statistics calculated using the *timeROC* package in R using the Kaplan-Meier estimator of the censoring distribution with point-wise confidence intervals. *P* values are adjusted to account for the multiplicity of tests (both across time and between anthropometric indices).