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Higher pericardial adiposity is associated with prevalent diabetes: The Coronary Artery Risk Development in Young Adults study

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Abstract

Background and Aims—Pericardial adipose tissue (PAT) is located on both sides of the pericardium. We tested whether PAT was associated with prevalent diabetes at the year 25 exam of the Coronary Artery Risk Development in Young Adults (CARDIA) study.

Methods and Results—The CARDIA Year 25 exam (2010–2011) included complete data for all covariates on 3107 participants. Prevalent diabetes ($n=436$) was defined as high fasting (≥ 126 mg/dl) or 2-hour postload glucose (≥ 200 mg/dl) or HbA_{1c} ($\geq 6.5\%$) or use of diabetes medications. Volume of PAT was measured from computed tomographic scans. Logistic regression was performed to examine the relationship between quartiles of PAT and diabetes. In regression models adjusted for field center, sex, race, age, systolic blood pressure, total cholesterol, log triglycerides,

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and treatment with blood pressure and cholesterol lowering medication, PAT volume in the 4th quartile was significantly associated with diabetes status after adjustment for BMI (OR 2.57, 95% CI 1.66, 3.98) or visceral adipose tissue (OR 2.08, 95% CI 1.32, 3.29). PAT volume in the 2nd and 3rd quartiles was not significantly associated with diabetes status relative to the first quartile.

Conclusions—Metabolically active pericardial adipose tissue is associated with prevalent diabetes only at higher volumes independent of overall obesity.

Introduction

Obesity, particularly abdominal obesity, leads to insulin resistance, metabolic derangements, and often diabetes [1-5]. However, adipose tissue surrounding the heart has also been associated with insulin resistance [6-8] and diabetes [9-11]. Pericardial adipose tissue (PAT) is an ectopic fat depot consisting of adipose tissues contained within the pericardium [epicardial, (EAT)] and surrounding the pericardium (paracardial) [12, 13]. The pericardium restricts excessive EAT accumulation, therefore, increasing fat deposition with obesity primarily occurs external to the pericardium [6, 14].

PAT volumes have been shown to be higher in those with diabetes, but many of the available investigations did not study whether these associations are independent of BMI or other anthropometric measures and were performed in relatively small subject populations [9, 15]. A few studies have investigated whether the relationship is independent of BMI or abdominal visceral adipose tissue (VAT), but have had conflicting results [10, 11]. As PAT is correlated with BMI and measures of adiposity [12], increased deposition could reflect a general increase in body adiposity with increasing obesity, or preferential deposition of PAT, so it is important to distinguish whether PAT effects are independent of overall obesity.

We hypothesized that PAT is associated with diabetes independent of other measures of adiposity (BMI, VAT, and waist circumference). The purpose of this report is to investigate this hypothesis in cross-sectional data from a large cohort study with computed tomographic (CT)-based measures of PAT and performance of robust adjustment for VAT, BMI, and waist circumference. As previous studies have shown that the association between BMI and diabetes varies by race and gender [16, 17], we evaluated whether differences existed for the association between PAT and diabetes.

Methods

Study Population

We utilized data on PAT and diabetes from the Year 25 exam (2010-2011) of the CARDIA study. CARDIA is a bi-racial population-based cohort study of the development of cardiovascular risk factors [18]. The initial study population consisted of 5115 randomly selected healthy, young adults between the ages of 18 and 30 with a permanent residence in one of the 4 field centers (Birmingham, Chicago, Minneapolis, and Oakland). Exclusion criteria included those who were chronically ill, disabled, institutionalized, pregnant at the time of the exam, or who could not complete the exam components.

From 3499 Year 25 participants, we excluded those with missing CT (no PAT or VAT data, n=325), diabetes status (n=16), BMI (n=8), waist circumference (n=9), or any of the other covariates for the multivariable models (n=51), leaving 3107 participants. Study participants that were excluded due to missing data were similar to included study participants by age, sex, field center, diabetes status, systolic blood pressure, total cholesterol, triglycerides, treatment with blood pressure and cholesterol lowering medication, and VAT and PAT volume. Those excluded had lower diastolic blood pressure (72.8 mmHg vs. 74.1 mmHg; $p=0.032$) and BMI (29.4 m/kg² vs. 30.3 m/kg²; $p=0.032$), and a higher percentage were white (58.3% vs. 52.5%, $p=0.029$). The study was reviewed and approved by institutional review boards at each study site. All participants provided written informed consent.

Exam Measurements

Standard protocols were used at each study site for collection of all exam components. Age, race, sex, and medication use were determined by standardized questionnaire. BMI was calculated from height, measured with a vertical ruler, and weight, assessed with a calibrated scale. Waist circumference was measured to the nearest centimeter using an anthropometric tape. Systolic and diastolic blood pressure were measured using an automated, calibrated monitor and averaged from the second and third readings. Fasting blood samples were drawn and processed at central laboratories (Molecular Epidemiology and Biomarker Research Laboratory, University of Minnesota, Minneapolis, MN and Northwest Lipid Research Center, Seattle, WA) for measurement of glucose, cholesterol, and triglyceride values. Glucose was assayed using the Roche Modular P hexokinase method (Roche, Basel, Switzerland). Plasma concentrations of total cholesterol and triglycerides were determined enzymatically using a Hitachi 917 analyzer. Prevalent diabetes was defined as a high fasting glucose (≥ 126 mg/dl), 2-hour postload glucose levels (≥ 200 mg/dl) or HbA_{1c} ($\geq 6.5\%$), or the use of diabetes medications.

PAT Measurement

PAT was measured on cardiac CT scans using the same images used to measure coronary artery calcium. All cardiac CT scans were performed using 64 channel multi-detector CT scanners [GE Healthcare, Milwaukee, WI (Birmingham and Oakland centers) or Siemens, Erlangen, Germany (Chicago and Minneapolis centers)]. Three experienced CT analysts measured PAT volume using the same structured reading protocol validated and described in NHLBI's Multi-Ethnic Study of Atherosclerosis (MESA) [19]. In brief, slices within 15 mm above and 30 mm below the superior extent of the left main coronary artery were selected for PAT measurement using an image processing workstation (OsiriX, Pixmeo, Geneva, Switzerland). The analysts manually segmented the images and then applied a threshold of -190 to -30 Hounsfield units to isolate adipose tissue. The volume (mL) of PAT was determined by summing the adipose tissue containing pixels and accounting for the slice thickness. Reader reproducibility of PAT was estimated in 156 randomly selected rereads (intra-reader - 49 pairs; inter-reader - 107 pairs). Intra-reader variability was 2.0% and inter-reader variability was 4.2%.

VAT Measurement

Noncontrast abdominal CT scans were performed to quantify VAT volume. A semiautomatic segmentation technique was used to define the different compartments (including VAT) using a structured reading protocol and a dedicated software for the Medical Image Processing, Analysis, and Visualization (MIPAV) application developed by Center for Information Technology (CIT), National Institutes of Health (NIH). Tissue attenuation thresholds of -190 to -30 HU were used to distinguish adipose tissue voxels in the selected regions. The VAT volume was calculated as the sum of voxels across a 10 mm slice centered at L4-5 disk. Intra- and inter-reader variability in the 156 rereads (mentioned above) were 2.4% and 6.7%, respectively.

Statistical analyses

Participant characteristics were calculated as means ($\pm$ SD) for normally distributed continuous variables, medians (25th-75th percentiles) for skewed continuous variables, and n (%) for categorical variables. Comparisons by diabetes status, gender and race were performed using the t-test, Wilcoxon rank sum, or chi-square tests. PAT was not normally distributed and was categorized into quartiles because the apparent trend in the relationship between PAT quartiles and diabetes was not linear. Triglycerides were not normally distributed, so this variable was log transformed.

The primary interest was in multivariable logistic regression used to model the relationship between PAT and diabetes while controlling for other covariates. Initial models adjusted for field center, age, sex, race, systolic blood pressure, total cholesterol, log triglycerides, and treatment with blood pressure and cholesterol lowering medication. Additional models adjusted for BMI, VAT, and waist circumference. However, a complication in these primary analyses is that PAT was moderately to highly correlated with other measures of adiposity (VAT $r=0.74$, BMI $r=0.44$, and waist circumference $r=0.63$). Categories which jointly represent high PAT but low general adiposity or low PAT but high general adiposity therefore have low sample size, which could invalidate the overall adjusted model. We therefore characterized the relationships between PAT, BMI and diabetes in more detail to better understand what the adjusted numbers in the main regression analysis meant (not with the perspective that we would see an interaction). We used 3D column plots of the estimated prevalence of diabetes by quartiles of PAT and categories of BMI: underweight and normal (BMI <25), overweight (BMI 25-29.9), and obese (BMI ≥ 30). As expected, one category (PAT quartile 4 and BMI <25) had small sample size ($n=36$). A similar analysis was performed to estimate the prevalence of diabetes by quartiles of PAT within tertiles of VAT. Tertiles of VAT were chosen to minimize small sample size in most categories; nevertheless, as expected, sample sizes for categories of PAT quartile 4 in VAT tertile 1 ($n=16$) and PAT quartile 1 in VAT tertile 3 ($n=22$) were small. Estimated values were constructed using Poisson regression at the stratum-specific means of the covariates in the given model. Additionally, we performed statistical testing within each BMI stratum, and similarly for VAT strata. Analyses were repeated treating PAT as a log-transformed continuous variable and in strata by race and sex (supplementary tables).

Multiplicative interaction terms in the primary models were tested for sex and race. All analyses were conducted using SAS version 9.4 (SAS Institute, Cary, NC). Statistical significance was considered as $p < 0.05$.

Results

Participants with diabetes ($n=436$) were older, fewer were white, and more reported taking blood pressure and cholesterol lowering medications (Table 1). Systolic and diastolic blood pressure, total cholesterol, and triglycerides were higher in participants with diabetes compared to those without. BMI, VAT, and PAT were significantly higher in participants with diabetes compared to those without. PAT volume was higher in both male and female white participants compared to black participants, despite whites having lower BMI (Table 2). VAT volume was higher in white males compared to black males, but lower in white females compared to black females.

Compared to the first quartile of PAT, quartiles 2, 3, and 4 were significantly associated with diabetes status in the unadjusted model and after adjustment for demographic factors (field center, sex, race, and age; Table 3, Model 1). For quartile 2, this association was attenuated after additional adjustment for systolic blood pressure, total cholesterol, log triglycerides, and treatment with blood pressure and cholesterol lowering medication (Model 2). After adjustment for BMI, VAT, and waist circumference (Models 3-5), quartile 3 was no longer significantly associated with diabetes. Quartile 4 was significantly associated with diabetes status in all models. We did not find any significant effect modification by race or sex. Stratified analyses by race and sex are presented in Supplementary Tables 1 and 2, respectively.

Figure 1 panel A presents the estimated prevalence of diabetes by PAT quartiles and BMI categories. Panel B presents the estimated prevalence of diabetes by PAT quartiles and VAT tertiles. PAT in the 4th quartile was consistently associated with a higher prevalence of diabetes, across all categories of BMI and VAT. Higher prevalence of diabetes was observed generally as BMI or VAT increased within PAT category, or as PAT increased with BMI or VAT category. Given the high correlation between PAT and VAT, 77% (595/774) of participants with PAT in the 4th quartile had VAT in the highest tertile.

Detailed statistical testing related to Figure 1A and Figure 1B leads to similar conclusions (Table 4), although confidence intervals are often wide given small sample sizes in some cells. In general the detailed examination of categories supports the primary regression presented in Table 3, at the same time emphasizing both the overlap between PAT and BMI or PAT and VAT and the findings for the less usual situation in which different fat beds were dissimilar in their relative sizes. Results modeling PAT as a log-transformed continuous variable are presented in Supplementary Table 1, and show similar associations.

Discussion

We observed a significant association between high pericardial adiposity and diabetes status in a large, biracial cohort of adults. Prevalence of diabetes was consistently higher at high levels of PAT (quartile 4) within obesity and VAT strata. There was an apparent threshold

effect since lower levels of PAT (quartiles 2 and 3) were not associated with diabetes prevalence in a fully adjusted model. These results suggest that the association between PAT and diabetes is similar to other fat measures at lower levels, but adds additional information at high levels. Moreover, these findings were consistent by race and gender. Due to the small sample size of groups with excess PAT but low BMI or VAT, we have limited power to test statistically whether there is interaction by BMI or VAT category, and therefore only note the finding.

Relatively few studies have examined the relationship between cardiac adipose tissue and diabetes status. Iozzo et al. [20] found that pericardial fat mass (g/ml) measured by MRI was significantly higher in those with type 2 diabetes (n=12) compared with BMI-matched obese controls without diabetes (n=25; $p<0.001$) [20]. Gaborit et al. [15] found that EAT volume was higher in obese adults with diabetes (n=13) than in obese adults without diabetes (n=17), however, their study population did not include any lean individuals with diabetes and they did not perform any additional multivariable modeling to adjust for other confounders. Yang et al. [9] reported on a study of 562 participants (50 with type 2 diabetes, 155 with pre-diabetes, and 357 without diabetes) that purportedly measured PAT from multi-detector CT scans, although the definition of PAT used would be more consistent with EAT, since the fat measured was contained within the pericardium. They found that PAT was significantly higher in those with diabetes compared to those without, however, they did not do any multivariable analysis of this association, and so it is not possible to say whether the differences they observed were independent of overall obesity.

In a study of 49 patients with type 2 diabetes and 78 subjects without diabetes, Wang et al. [10] found the highest tertile of EAT to be significantly associated with diabetes status relative to the first tertile (OR 4.82, 95% CI 1.55-16.58), after adjustment for age, gender, waist circumference, and smoking status. In contrast, Liu et al. [11] found that PAT (per 1 sd) was significantly associated with diabetes in a multivariable model adjusted for age, sex, smoking, alcohol, and treatment of hypertension, diabetes, or dyslipidemia (OR 1.40, 95% CI 1.01-1.94), but this was attenuated after adjustment for BMI or VAT. Our study has demonstrated a threshold effect in which the association between PAT and diabetes was attenuated in quartiles 2 and 3 after adjustment for BMI or VAT, but persisted in quartile 4. This observed threshold may explain why these two studies had conflicting results as use of a continuous measure of PAT could dilute the stronger associations seen at high PAT with the weaker associations in lower categories of PAT.

Despite having lower BMI, white participants had higher volume of PAT compared to black participants. The difference was more striking for males, but was still significant for females. Our results confirm reports from other studies of higher PAT and EAT in white compared to black participants [21, 22]. However, despite the differences that were observed in PAT volume, we did not find a difference in the relationship between PAT and diabetes by race or gender.

As obesity is known to be associated with diabetes [1], the relationship between PAT and diabetes may be mediated by insulin resistance and altered production of adipocytokines and inflammatory mediators. EAT has been shown to produce higher levels of inflammatory

mediators, such as IL-6, IL-1 β , and TNF- α , and free fatty acids than subcutaneous adipose tissue [23, 24]. In addition, EAT production of adiponectin is suppressed in those with obesity and coronary artery disease [25, 26]. In the MESA study, PAT and liver attenuation were found to be significantly associated with HOMA-IR, independent of BMI and waist circumference [8]. EAT has also been associated with impaired fasting glucose and insulin resistance [15, 27, 28]. More research is needed, particularly to investigate whether a temporal relationship exists between PAT and insulin resistance.

There are several important limitations in this work. First, we used cross-sectional data, and so are unable to characterize the temporal relationships between PAT deposition and diabetes. Our measure of PAT was a single measure at one point in time. Future work will use longitudinal data, but VAT is only available at year 25 in CARDIA. Second, we have chosen to measure PAT which includes both epicardial and paracardial adipose tissue as a measure of adipose tissue around the heart and these two depots may have different associations. We have previously shown Spearman correlation between PAT and EAT to be 0.92 (P, 0.0001) when performed with careful identification of the pericardium [19]. Unfortunately, with traditional 2.5-3 mm slice CT scans used for coronary artery calcification measurement as well as standard echocardiography images neither can consistently identify the normal pericardium. Note that this problem is also true for cardiac MRI using 6 mm slice thickness [15]. The inability to consistently identify the pericardium, especially in lean individuals makes determination of the true location of the adipose tissue, epicardial or paracardial impossible in some cases and could lead to significant bias in attributing effect to one depot or the other. Therefore, the choice to measure PAT results in a decreased risk of inaccurately identifying the pericardium and misclassifying PAT as EAT. There is the potential for misclassification of diabetes status for individuals taking diabetes medications but that do not have diabetes. Our analysis accounted for many but not all ectopic adipose tissue depots, however, we performed a robust adjustment for VAT and overall obesity, in addition to other risk factors to demonstrate that the association of PAT with diabetes was independent of overall obesity and VAT. There is a paucity of published studies on the association between PAT and diabetes, and this report from a large, well-characterized cohort adds a novel and solid foundation to this area of research from which future studies can build.

Our results suggest that metabolically active pericardial adipose tissue is associated with prevalent diabetes only at higher volumes of PAT independent of BMI, VAT, and waist circumference for both black and white men and women. This work is significant in highlighting that an individual's propensity to store fat ectopically could be an important determinant of metabolic derangement and disease. Future work will explore the longitudinal relationships between PAT and diabetes to further characterize the temporal relationships.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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- PAT volume is higher in those with diabetes compared to those without
- High PAT was associated with diabetes independent of BMI and visceral adipose tissue
- The relationship between PAT and diabetes did not differ by sex or race

Figure 1.

Panel A. Estimated prevalence of diabetes by PAT quartiles and BMI categories. Sample sizes across quartiles of PAT were as follows: 418, 216, 84, 36 for normal BMI; 224, 282, 288, 184 for overweight; and 135, 282, 404, 554 for obese; respectively. Panel B. Estimated prevalence of diabetes by PAT quartiles and VAT tertiles. Sample sizes across quartiles of PAT were as follows: 586, 319, 99, 16 for VAT tertile 1; 169, 348, 351, 163 for VAT tertile 2; 22, 113, 326, 595 for VAT tertile 3.

Table 1

Participant characteristics by diabetes status

Variable	Diabetes (n=436)	No Diabetes (n=2671)	p-value
Age (years) ^a	51 (±4)	50 (±4)	0.001
Sex (% male) ^b	194 (44.5)	1156 (43.3)	0.63
Race (% white) ^b	149 (34.2)	1481 (55.5)	<0.001
Field center ^b			<0.001
Birmingham, AL	138 (31.7)	587 (22.0)	
Chicago, IL	103 (23.6)	635 (23.8)	
Minneapolis, MN	81 (18.6)	692 (25.9)	
Oakland, CA	114 (26.2)	757 (28.3)	
On BP-lowering meds ^b	268 (61.5)	583 (21.8)	<0.001
On Cholesterol-lowering meds ^b	186 (42.7)	304 (11.4)	<0.001
Systolic blood pressure (mmHg) ^a	124.2 (±17.2)	117.9 (±14.9)	<0.001
Diastolic blood pressure (mmHg) ^a	77.4 (±10.8)	73.6 (±10.8)	<0.001
Total cholesterol (mg/dL) ^a	185 (±42)	194 (±36)	<0.001
Triglycerides (mg/dL) ^c	118 (84-176)	90 (66-128)	<0.001
BMI (kg/m ²) ^a	35.0 (±8.0)	29.5 (±6.7)	<0.001
BMI category ^b			<0.001
Underweight (<18.5 kg/m ²)	1 (0.23)	20 (0.75)	
Normal (18.5-<25 kg/m ²)	32 (7.3)	701 (26.2)	
Overweight (25-<30 kg/m ²)	90 (20.6)	888 (33.3)	
Obese (≥30 kg/m ²)	313 (71.8)	1062 (39.8)	
Waist circumference (cm) ^a	106.5 (±16.5)	92.6 (±14.9)	<0.001
VAT (mL) ^c	164.9 (117.8-226.1)	112.1 (72.5-162.1)	<0.001
PAT (mL) ^c	66.6 (44.3-93.5)	46.4 (32.1-68.1)	<0.001
PAT quartiles ^b			<0.001
<33.5 mL	51 (11.7)	726 (27.2)	
33.5-<48.7 mL	76 (17.4)	704 (26.4)	
48.7-<71.7 mL	106 (24.3)	670 (25.1)	
≥71.7 mL	203 (46.6)	571 (21.4)	

^aData presented as mean ±SD, p-value from t-test^bData presented as number (%), p-value from chi-square or Fisher's exact^cData presented as median (interquartile range), p-value from Wilcoxon rank sum test

Table 2

PAT, body mass, and adiposity measures by gender and race

Variable	Males		Females		p-value
	White (n=764)	Black (n=586)	White (n=866)	Black (n=891)	
PAT (mL) ^a	69.5 (49.3-98.9)	47.4 (32.9-69.9)	43.3 (30.5-65.1)	41.5 (29.0-57.1)	0.002
BMI (kg/m ²) ^b	28.9 (±5.0)	30.2 (±6.4)	28.3 (±7.2)	33.4 (±8.0)	<0.001
VAT (mL) ^a	160.2 (111.3-219.5)	120.1 (80.5-166.7)	99.3 (61.3-150.9)	108.4 (72.0-147.3)	0.06
Waist circumference (cm) ^b	98.8 (±13.0)	98.7 (±14.7)	86.7 (±15.6)	95.8 (±16.4)	<0.001

^aData presented as median (interquartile range), p-value from Wilcoxon rank sum test^bData presented as mean ±SD, p-value from t-test

Table 3

Logistic regression of PAT on diabetes status

Variable	Unadjusted OR (95% CI)	Model 1 ^a OR (95% CI)	Model 2 ^b OR (95% CI)	Model 3 ^c OR (95% CI)	Model 4 ^d OR (95% CI)	Model 5 ^e OR (95% CI)
PAT volume						
<33.5 mL ^f	ref	ref	ref	Ref	ref	ref
33.5 - <48.7 mL	1.54 (1.06, 2.22)	1.60 (1.10, 2.33)	1.30 (0.87, 1.95)	1.12 (0.74, 1.68)	1.10 (0.73, 1.66)	1.03 (0.68, 1.56)
48.7 - <71.7 mL	2.25 (1.59, 3.20)	2.62 (1.82, 3.75)	1.70 (1.15, 2.52)	1.28 (0.85, 1.94)	1.20 (0.80, 1.82)	1.07 (0.70, 1.63)
71.7 mL	5.06 (3.65, 7.01)	7.67 (5.38, 10.94)	3.86 (2.60, 5.74)	2.57 (1.66, 3.98)	2.08 (1.32, 3.29)	1.92 (1.21, 3.02)

gP-values for interactions terms in Model 3: PAT quartile × race (p=0.65, 0.69, 0.20; respectively); PAT quartile × sex (p=0.47, 0.25, 0.35; respectively)

^a Adjusted for field center, sex, race, age

^b Adjusted for variables in Model 1 + systolic blood pressure, total cholesterol, log triglycerides, treatment with blood pressure and cholesterol lowering medication

^c Adjusted for variables in Model 2 + BMI

^d Adjusted for variables in Model 2 + VAT

^e Adjusted for variables in Model 2 + waist circumference

^f Referent category

Table 4

Logistic regression of PAT (independent) on diabetes (dependent) stratified by BMI or VAT category

PAT volume ^a	Normal (BMI<25; N=754)		Overweight (BMI<30; N=978)		Obese (BMI ≥30; N=1375)	
	N with diabetes/Total N	OR (95% CI)	N with diabetes/Total N	OR (95% CI)	N with diabetes/Total N	OR (95% CI)
<33.5 mL ^b	9/418	Ref	20/224	Ref	22/135	Ref
33.5 - <48.7 mL	13/216	3.36 (1.28, 8.83)	23/282	1.11 (0.55, 2.25)	40/282	0.76 (0.41, 1.41)
48.7 - <71.7 mL	4/84	1.91 (0.50, 7.32)	18/288	0.71 (0.32, 1.57)	84/404	1.37 (0.77, 2.46)
71.7 mL	7/36	10.45 (2.80, 38.95)	29/184	2.00 (0.87, 4.58)	167/554	2.45 (1.36, 4.45)

PAT volume ^a	VAT Tertile 1 (N=1020)		VAT Tertile 2 (N=1031)		VAT Tertile 3 (N=1056)	
	N with diabetes/Total N	OR (95% CI)	N with diabetes/Total N	OR (95% CI)	N with diabetes/Total N	OR (95% CI)
<33.5 mL ^b	21/586	Ref	26/169	Ref	4/22	Ref
33.5 - <48.7 mL	19/319	1.60 (0.76, 3.37)	34/348	0.69 (0.38, 1.27)	23/113	1.72 (0.48, 6.19)
48.7 - <71.7 mL	8/99	2.11 (0.78, 5.75)	40/351	0.84 (0.46, 1.53)	58/326	1.71 (0.51, 5.78)
71.7 mL	3/16	6.81 (1.30, 35.64)	36/163	1.76 (0.91, 3.41)	164/595	3.42 (1.02, 11.48)

^a Adjusted for field center, sex, race, age, systolic blood pressure, total cholesterol, log triglycerides, and treatment with blood pressure and cholesterol lowering medication^b Referent category