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Association of abdominal muscle composition with prediabetes and diabetes: The CARDIA study

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Aim: To evaluate the relationship of abdominal muscle lean tissue and adipose tissue volumes with prediabetes and diabetes.

Research Design and Methods: We measured abdominal muscle composition in 3170 participants in the Coronary Artery Risk Development in Young Adults (CARDIA) study who underwent computed tomography (CT) at Year 25 of follow-up (ages, 43-55 years). Multinomial regression analysis was used to evaluate the associations of CT-measured intermuscular adipose tissue (IMAT), lean muscle tissue (lean) and visceral adipose tissue (VAT) volumes with diabetes at any point during the CARDIA study, newly detected prediabetes, prior history of prediabetes, and normal glucose tolerance. Models were adjusted for potential confounding factors: age, sex, race, height, smoking status, hypertension, hyperlipidaemia, cardiorespiratory fitness and study centre.

Results: Higher IMAT, lean and VAT volumes were all separately associated with a higher prevalence of prediabetes and diabetes. Inclusion of VAT volume in models with both IMAT volume and lean volume attenuated the association of IMAT with both prediabetes and diabetes, but higher lean volume retained its association with prediabetes and diabetes. Individuals in the highest IMAT quartile, coupled with VAT in its lower three quartiles, had a higher prevalence of diabetes, but not of prediabetes, than those with both IMAT and VAT in their respective lower three quartiles. Adjusting for cardiorespiratory fitness did not substantially change the findings.

Conclusion: Higher IMAT volume was associated with a higher prevalence of diabetes even after adjustment for VAT volume. However, further study is warranted to understand the complicated relationship between abdominal muscle and adipose tissues.

KEYWORDS

body composition, glycaemic control, type 2 diabetes

1 | INTRODUCTION

Muscle tissue is the largest insulin-sensitive organ. It accounts for the majority of glucose uptake, playing a crucial role in maintaining systemic glucose homeostasis.[1] Limited attention has been paid to the association between muscle volume and muscle composition (adipose tissue and lean muscle volumes) and the prevalence of type 2 diabetes mellitus (T2DM). The majority of studies have focused on the

relationship between T2DM and adipose tissue (AT).[2] Numerous studies have documented the fact that a high body mass index (BMI) and measures of total intra-abdominal AT, specifically visceral AT (VAT), are associated with a higher risk of T2DM.[3,4]

Another ectopic AT depot is intermuscular adipose tissue (IMAT), which is present between the muscle fiber bundles, resulting in increased muscle volume, in contrast with lean skeletal muscle tissue (lean) volume. Increased IMAT volume is associated with higher fasting glucose and insulin, and a greater prevalence of T2DM.[5–9] One nationally representative US study assessed the ratio of total skeletal muscle mass to total body weight, as measured by bioelectrical impedance, and found that a higher ratio of muscle to body weight was associated with increased insulin sensitivity and lower risk of prediabetes or diabetes after adjusting for BMI and waist circumference.[10] This study may have been limited by the use of dual energy X-ray absorptiometry which fails to discriminate between muscle and IMAT and could lead to overestimation of effective muscle mass in conditions in which there is lipid infiltration such as obesity and aging.[11,12]

Small clinical trials have demonstrated that resistance training in lean individuals or resistance training combined with weight loss in obese individuals is associated with improved insulin sensitivity and improved glucose tolerance.[13,14] A recent report from the Coronary Artery Risk Development in Young Adults (CARDIA) study found that higher cardiorespiratory fitness, based on treadmill performance, was associated with lower risk of developing the composite outcome prediabetes/diabetes, even when adjusting for time-dependent BMI.[15] Another CARDIA study found that treadmill performance was inversely associated with total body fat, assessed by dual energy X-ray absorptiometry, and the inverse association of fitness with fat mass was much stronger than the association of fitness with lean mass.[16]

We therefore sought to further examine the associations of muscle composition with prevalent prediabetes and diabetes, using data from the multicentre community-based CARDIA cohort for whom biochemical and clinical information concerning prediabetes and diabetes, as well as physical fitness data, were available. Participants enrolled in the CARDIA study underwent non-contrast enhanced abdominal computed-tomography (CT) imaging during study Year 25, which provided measurements of lean, IMAT and total muscle volumes for abdominal muscle groups including the psoas, paraspinous, lateral oblique and rectus muscles. Our objective was to investigate the cross-sectional associations of total muscle and lean and IMAT volumes with diabetes and prediabetes at Year 25. We hypothesized that muscle with higher IMAT volume was positively associated with both prediabetes and diabetes, and that this association was independent of physical fitness and VAT volume.

2 | METHODS

2.1 | Study sample

The CARDIA study was initiated in 1985 with recruitment of 5115 participants aged 18 to 30 years at field centres located in Birmingham, Alabama, Chicago, Illinois, Minneapolis, Minnesota and Oakland, California.[17] Black and white adults were recruited from population-based samples that were approximately balanced within centres by sex, age, race and education. After the baseline exam, participants were examined in follow-up visits at 2, 5, 7, 10, 15, 20, 25 and 30 years, with at least 71% of survivors attending an in-person clinical examination at each visit. All participants provided written informed consent, and institutional review boards from each field centre and the coordinating centre approved the study annually (Figure 1).

2.2 | Study measures

With the exception of Year 20 treadmill testing and cumulative (through Year 25) diabetes and hypertension variables, data were

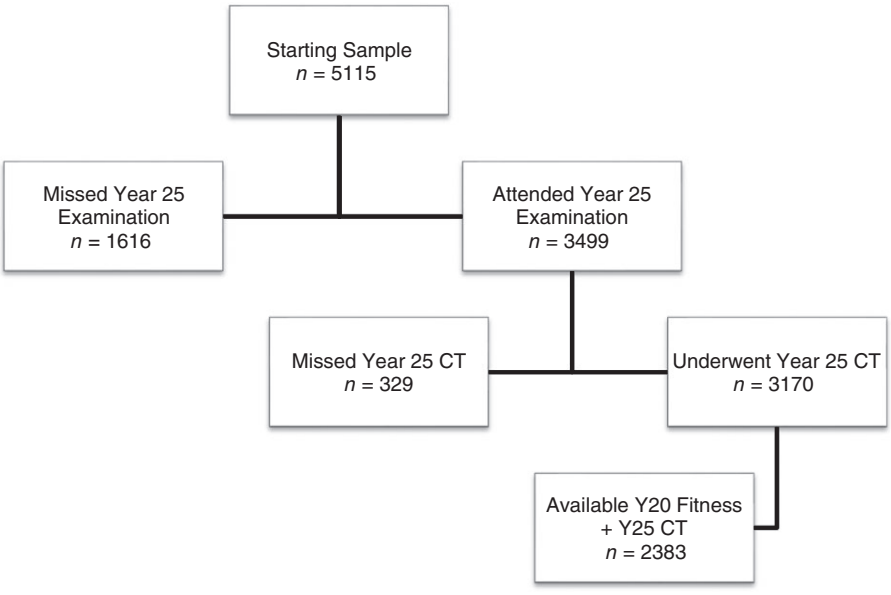

FIGURE 1 Enrolment and follow-up of study participants

drawn from Year 25 of the CARDIA study. Socio-demographic characteristics including sex, race and education were obtained using standard questionnaires and were confirmed at Years 0 and 2. Age was self-reported. Height was measured to the nearest 0.5 cm with the participant standing erect, back against a vertical mounted centimetre ruler without shoes. Weight was measured in light clothing to the nearest 0.5 kg. Cigarette smoking status at Year 25 was classified as never, former or current. Self-reports of high blood cholesterol were obtained through interviewer-administered questionnaires. Cumulative history of hypertension at any point during the CARDIA study was based on seated resting systolic and diastolic blood pressure (≥ 140/90 mm Hg) or on the participant's use of antihypertensive medication.

All 3499 participants at Year 25 were asked to participate in an abdominal CT study at that time. Of these, 3170 participants underwent assessment of adipose tissue distribution in the visceral and subcutaneous compartments[18,19] and measurement of skeletal muscle size (Figure 1).[20] VAT volume was assessed at the L4 to L5 level as previously reported.[18–20] Abdominal muscle composition (lean, IMAT and total) was measured from CT images covering the lower abdomen, obtained without an oral or intravenous contrast agent. MIPAV (Medical Image Processing, Analysis and Visualization) software (http://mipav.cit.nih.gov/index.php), with a custom plug-in, was used to perform quantitative measurements of four paired muscle groups: psoas, paraspinous, lateral oblique and rectus abdominis. Contiguous 1 to 1.25 mm slices constituting 10 mm vertically were loaded into the MIPAV viewer and the axial, coronal and sagittal reformats were used to select the centre of the lumbar disk space at L3 to L4, to avoid artifacts produced by the pelvic bones encountered in some individuals at the lower L4 to L5 level. Each muscle boundary was manually traced. Tissues within muscle with attenuation between −190 and −30 Hounsfield units (HU) were defined as adipose tissue, and those with attenuation between −29 and 160 HU as lean tissue. Because the findings reported here for the average across all eight sites, left and right side for four muscles, were very similar to those for individual muscles (data not shown), the average across the eight sites was used.

Analysis reliability of CT measures was assessed through blinded intra- and inter-reader re-reads of 158 scan pairs (~5%). Overall (intra- and inter-reader) technical error in re-analysis of 158 pairs of scans was 6.6% for CAC, 6.0% for VAT and 7.7% for psoas muscle total volume, with correlations for re-reads >0.95 in each measure.

In Year 20, 2870 participants underwent the CARDIA cardiorespiratory fitness test (Figure 1), which was designed to assess the maximal, symptom-limited performance by using a modified Balke protocol[21] that included up to nine 2-minute stages (≤18 minutes total) of progressively increasing difficulty, with speed increasing from 3.0 mph in stage one to 5.6 mph in stage nine, and grade increasing from 2% in stage one to 25% in stage nine. The first six stages could be performed generally by walking, whereas the final three stages required jogging and running. Estimated metabolic equivalent tasks (METs) ranged from 4.1 in stage one to 19.1 in stage nine. The total seconds of treadmill exercise were recorded for each participant.

2.3 | Main outcome measures: diabetes and prediabetes

Individuals were asked to bring medication bottles and to self-report diabetes medications at every examination. Fasting glucose was measured at Years 0, 7, 10, 15, 20 and 25. The oral glucose tolerance test (OGTT) was measured at Years 10, 20 and 25. HbA1c was measured at Years 20 and 25. Individuals were classified as having diabetes if, at any clinical examination during the CARDIA study, they had fasting blood glucose ≥126 mg/dL, blood glucose 2 hours post OGTT ≥200 mg/dL, HbA1c ≥ 6.5% (48 mmol/mol) or a history of treatment for diabetes. Individuals were classified as having prediabetes if they were not classified as having diabetes and had fasting blood glucose between 100 and 125 mg/dL or blood glucose 2 hours post OGTT between 140 and 200 mg/dL. Duration of diabetes was understood as the number of years before Year 25 that diabetes was first diagnosed during the CARDIA study. Prediabetes was much less consistently observed across examinations. The measure reflecting duration was considered current when prediabetes existed at Year 25 and was considered past when prediabetes was found at any previous examination but was not noted at Year 25.

2.4 | Statistical methods

We described the sample according to sex-specific quartiles of both lean muscle and IMAT volumes and described the same variables according to the four-level outcome variable: (a) diabetes defined by testing or by clinical diagnosis cumulatively through Year 25, (b) prediabetes at Year 25, (c) prediabetes before, but not at, Year 25, and (d) neither diabetes nor prediabetes at any point. Correlations among the muscle and visceral fat variables were examined. The muscle and visceral fat means were computed across cases of diabetes of different durations. We conducted cross-sectional analysis and developed separate multinomial regression models for each independent variable. Covariates included age, sex, race, height, smoking status, hypertension, hyperlipidaemia and study centre.

Odds ratios (OR) and 95% confidence intervals (CI), along with standard errors (SE), were determined. In complementary analyses, a *P* value for trend, treating the predictor variable as continuous, was obtained. Given the complex physiological and statistical relationship between IMAT and VAT volumes, we focused on individuals who were in the highest sex-specific quartile of IMAT, but in a lower sex-specific quartile of VAT; that is, we grouped quartiles 1 to 3 vs quartile 4 of both IMAT and VAT, and crossed these groups to get four categories. Because participants in quartiles 1 to 3 for both IMAT and VAT tended to be thinner, to improve comparison of probabilities of diabetes according to body fatness, we omitted the thinnest individuals in quartile 1 of both IMAT and VAT. Within each of the four categories we computed mean IMAT and VAT volumes. Using multinomial logistic regression, with the four categories as independent variables, we adjusted for covariates and predicted probabilities of prediabetes and diabetes, setting all other predictors constant at their means (age, sex, race, height, smoking status, hypertension, hyperlipidaemia, fitness and study centre) by back-transforming the logit. Possible sex

interaction was examined by adding the product of sex interaction times each of lean, IMAT and VAT volumes as continuous variables.

Missing covariate data in Year 25 for smoking status, height, BMI and self-reported high cholesterol reduced the sample size to 3109, not considering the Y20 treadmill test, and to 2343 in the subset of participants who underwent the treadmill test. In a sensitivity analysis of the participants who underwent measurement of abdominal fat and muscle at Year 25, and who completed the treadmill test at Year 20, further adjustment was made for treadmill duration. The full datasets, without considering treadmill duration at Year 20, of 3170 vs 3109 individuals after removing those for whom covariates were missing yielded similar findings (data not shown). The full dataset, taking treadmill duration at Year 20 into consideration, was also little affected by the loss of 40 individuals for whom covariates were missing. Among the 3170 individuals who underwent muscle and VAT measurement at Year 25, those who completed the treadmill test at Year 20 were a little less likely to be African-American, to smoke, to be hypertensive or obese, or to self-report a history of high cholesterol.

All analyses were performed using SAS version 9.4 or STATA 13. Statistical significance was defined at $P < 0.05$.

3 | RESULTS

Table 1 shows participant characteristics according to quartiles of both abdominal muscle lean volume and IMAT volume. Lean cutpoints were higher for male compared to female participants, but IMAT cutpoints were similar between the sexes. Age was inversely associated with lean volume and directly associated with IMAT volume. Treadmill duration was similar across lean quartiles, but duration was lower with higher IMAT volumes. IMAT, lean and total tissue volumes were each directly associated with lean and fat volumes. IMAT-to-total volume ratio, a measure of muscle composition that is equal to 1 minus lean-to-total volume ratio, was similar across lean quartiles, but increased dramatically in the higher IMAT quartile. VAT, BMI and height increased across both lean and fat quartiles. The percentage of white participants decreased in the higher lean quartile. Hypertension, high cholesterol and current smoking were each more prevalent as IMAT volume increased. The associations of BMI, VAT, treadmill duration, diabetes duration and hypertension appeared to be stronger with IMAT volume than with lean volume.

Age-, race- and sex-adjusted Pearson partial correlation coefficients for the association of abdominal muscle composition with adiposity measures and cardiorespiratory fitness are shown online in Table S1, Supporting Information. BMI and VAT had correlation coefficients over 0.6 with IMAT volume, total muscle volume and IMAT-to-total muscle volume ratio. BMI and VAT correlations with lean volume were 0.3 to 0.4. IMAT volume was tightly correlated with IMAT-to-total muscle ratio ($r = 0.95$); thus, findings involving the ratio or the corresponding lean-to-total volume ratio are effectively the same as those for IMAT volume. Further findings for the ratio are not presented. In the subset of individuals with available data concerning treadmill testing (n = 2383), longer treadmill duration was moderately associated with lower IMAT volume and IMAT-to-total muscle volume ratio and, to a lesser extent, with total muscle volume ratio.

Table 2 presents participant characteristics according to prediabetes and diabetes status. Participants who developed diabetes during the CARDIA study were older, had shorter treadmill duration, higher IMAT, lean and total muscle volumes, higher VAT volume and higher BMI than normoglycaemic participants, while those with prediabetes were intermediate between normoglycaemic and diabetic participants. Participants with prediabetes that was detected during the CARDIA study at Year 25 had higher IMAT, lean and total muscle volumes, higher VAT volume and higher BMI than participants with prediabetes only before Year 25. Interestingly, lean volume was slightly lower in participants with diabetes than in those with prediabetes at Year 25. Approximately two-thirds of the diabetic individuals were black and 55% were female, while the prediabetes groups were more likely to be white and male. Three-quarters of diabetic individuals had hypertension and also hypercholesterolaemia. Current smoking was more prevalent in participants with diabetes compared to those with prediabetes or compared to normoglycaemic individuals.

In those with a diagnosis of diabetes at any point during the CARDIA study, diabetes was first detected at Year 25 in 39%, and duration was 5 or 10 years in 55% of the participants (Table S2, Supporting Information). Diabetes duration was unrelated to any of the muscle or adiposity measures.

Multinomial logistic regression models to evaluate the associations of muscle composition and VAT with prediabetes and diabetes are shown in Table 3. A minimally adjusted model including age, race and sex (Model 1) and another model that includes risk factors (Model 2) are presented. We subsequently added all primary predictor variables, IMAT volume, lean volume and VAT volume to Model 2 simultaneously. As shown, IMAT volume was significantly associated with current prediabetes, detected at Year 25, with prior history of prediabetes and with diabetes in both Models 1 and 2. A 1-SD higher IMAT volume was associated with a 23% higher occurrence of previous history of prediabetes, with a 60% higher risk of newly detected prediabetes and with a 91% higher occurrence of diabetes after adjusting for Model 2 covariates. Although not significantly associated with a previous history of prediabetes, a 1-SD increment in abdominal lean volume was associated with a 1.5-fold higher risk of newly detected prediabetes and with a 1.72-fold higher risk of diabetes in Model 2. Higher VAT volume was apparently more strongly associated with the outcome variable than were either of the muscle-related variables. Inclusion of both lean volume and IMAT volume slightly attenuated findings compared to Model 2. Adjustment for VAT led to greater attenuation compared to Model 2, with IMAT volume losing significance, but with lean volume retaining statistical significance. VAT volume remained strongly associated with both prior prediabetes and diabetes (OR [95% CI] 1.7 [1.49, 1.95] and 2.29 [1.94, 2.7], respectively), but VAT volume was no longer associated with previously detected prediabetes in the full model. Adding terms for sex interaction did not significantly improve any model ($P > 0.15$ in all models; data not shown). All findings in Table S3 (Supporting Information) were slightly attenuated by adding treadmill duration at Year 20 to the model, thus restricting the sample analysed (n = 2343).

TABLE 1 Muscle lean sex-specific quartile (left side) and IMAT sex-specific quartile (right side) (all variables from CARDIA study Year 25, with the exception of treadmill test)

	Muscle lean Q1 N = 782	Muscle lean Q2 N = 773	Muscle lean Q3 N = 779	Muscle lean Q4 N = 775	Muscle fat Q1 N = 782	Muscle fat Q2 N = 782	Muscle fat Q3 N = 778	Muscle fat Q4 N = 767
Male cutpoints	12.0018-19.844	19.8445-21.939	21.9394-24.2463	24.2506-33.9118	0.2055-1.2976	1.3001-1.9126	1.9127-2.9684	2.9786-15.891
Female cutpoints	8.6629-13.1099	13.1116-14.5306	14.5308-16.1186	16.1325-26.6218	0.2081-1.2466	1.2466-1.8972	1.9016-2.9258	2.9279-14.7455
Age (y)	50.9 ± 3.48[a]	50.4 ± 3.62	50.1 ± 3.65	49.3 ± 3.6	49.3 ± 3.63	50.2 ± 3.57	50.5 ± 3.6	50.6 ± 3.61
Height (cm)	167.9 ± 9.7	170 ± 8.92	170.8 ± 9.29	172.5 ± 9.28	169.1 ± 8.83	170.3 ± 9.31	170.6 ± 9.85	171.3 ± 9.63
BMI (kg/m^2)	26.5 ± 5.9	29 ± 6.1	30.9 ± 6.7	34.6 ± 7.1	24.9 ± 4.1	27.9 ± 4.7	31 ± 5.2	37.3 ± 7.4
Diabetes duration (y)	0.7 ± 3.1	0.5 ± 2.15	0.8 ± 2.93	1.2 ± 3.99	0.4 ± 2.32	0.7 ± 3.08	0.7 ± 2.87	1.4 ± 3.93
Lean (cc)	14.67 ± 3.26	16.94 ± 3.53	18.66 ± 3.85	21.67 ± 4.61	16.96 ± 4.37	17.73 ± 4.5	18.26 ± 4.71	18.98 ± 4.65
IMAT (cc)	1.92 ± 1.39	2.19 ± 1.6	2.46 ± 1.7	2.83 ± 1.65	0.93 ± 0.25	1.57 ± 0.19	2.39 ± 0.3	4.56 ± 1.71
Total (cc)	16.67 ± 3.74	19.22 ± 3.97	21.23 ± 4.31	24.64 ± 4.98	17.91 ± 4.41	19.35 ± 4.54	20.73 ± 4.77	23.8 ± 5.06
IMAT/Total (%)	11.3 ± 6.51	11.2 ± 6.56	11.4 ± 6.59	11.5 ± 5.96	5.4 ± 1.8	8.5 ± 2.02	12.1 ± 2.9	19.5 ± 6.29
VAT (cc)	110.9 ± 66.1	124.7 ± 67.9	136.3 ± 76.7	154.8 ± 76.4	75.1 ± 41.7	109.5 ± 49	146.4 ± 59.9	196.8 ± 76.9
Treadmill duration[b] (s)	437 ± 150.6	440 ± 158.6	433 ± 168.6	393 ± 158.1	494 ± 155.9	454 ± 151.7	409 ± 145.7	332 ± 140.5
White race (%)	68.4 (535/782)	58.9 (455/773)	50.6 (394/779)	32 (248/775)	54 (422/781)	53.3 (417/782)	53.8 (419/779)	48.8 (374/767)
Female (%)	56.9 (445/782)	56.5 (437/773)	56.5 (440/779)	56.3 (436/775)	56.7 (443/781)	56.4 (441/782)	56.6 (441/779)	56.5 (433/767)
HTN (%)	30.6 (239/782)	34.9 (270/773)	43.3 (337/779)	50.2 (389/775)	27 (211/781)	35.2 (275/782)	39.7 (309/779)	57.4 (440/767)
High cholesterol (%)	26.6 (208/782)	26.4 (204/773)	29.4 (229/779)	30.1 (233/775)	20.1 (938/157)	27 (993/211)	32.4 (1031/252)	33.1 (1021/254)
Smoking status								
Never (%)	59.7 (467/782)	60.2 (465/773)	61.5 (479/779)	63 (488/775)	67.4 (526/781)	59 (461/782)	61 (475/779)	57 (437/767)
Former (%)	21.7 (170/782)	24.1 (186/773)	21.7 (169/779)	19.4 (150/775)	17.2 (134/781)	24 (188/782)	22.3 (174/779)	23.3 (179/767)
Current (%)	18.5 (145/782)	15.8 (122/773)	16.8 (131/779)	17.7 (137/775)	15.5 (121/781)	17 (133/782)	16.7 (130/779)	19.7 (151/767)

Abbreviations: IMAT, intermuscular adipose tissue; Lean, lean muscle volume; Total, total muscle volume; VAT, visceral adipose tissue; HTN, hypertension cumulative through Year 25.
[a] Mean ± Std or % (n/N). Aside from use of sex-specific quartiles, data are unadjusted.
[b] Treadmill test at Year 20: Lean quartiles N = 589, 596, 603, 555, respectively; IMAT quartiles N = 626, 608, 576, 533, respectively.

Given the high correlation between IMAT volume and VAT volume, the fully adjusted but non-interactive models presented in Table 3 may be misleading. These variables, after being examined in more detail, are presented in Table 4. To understand any independent association of IMAT volume with diabetes prevalence, we focused on the group (N = 302) with IMAT volume in quartile 4 but with VAT volume in quartiles 1 to 3 compared to the group with both IMAT and VAT volumes in quartiles 1 to 3 (N = 1009). Mean VAT volume was comparable between the groups (137.0 and 120.0 cc, respectively), but IMAT volume was very different (4.1 vs 2.0 cc, respectively.) We performed a logistic regression model, adjusted for covariates as presented in Table 3, Model 2, with the four IMAT volume and VAT volume categories shown in Table 4 as the predictors of interest. There was no multiplicative interaction in diabetes prevalence. VAT volume is clearly the stronger predictor of diabetes, but the back-transformed estimated probabilities of having diabetes at or before Year 25 among those with VAT in quartiles 1 to 3 were 0.133 in IMAT volume in quartile 4 vs 0.090 in IMAT volume in quartiles 1 to 3 ($P = 0.008$). Corresponding differences in current or previously detected prediabetes were not significant in these models (data not shown).

4 | DISCUSSION

Our findings suggest that: (a) higher abdominal IMAT volume is associated with a higher risk of prediabetes or diabetes; (b) higher lean volume is also associated with a higher prevalence of current prediabetes and diabetes, a finding that persisted with adjustment for IMAT volume; and (c) the association of IMAT volume, which is highly correlated with muscle composition, with prediabetes and diabetes is tightly associated with VAT volume. Associations of higher IMAT, lean and VAT volumes with prediabetes and diabetes were independent of concomitant risk factors and cardiorespiratory fitness. Although adjusting models for VAT volume attenuated the associations of IMAT and lean volumes with prediabetes and diabetes, participants in the highest sex-specific quartile of IMAT volume had a higher prevalence of diabetes even when VAT volume was not in its highest sex-specific quartile.

Our findings that IMAT and VAT volumes are associated with prediabetes and diabetes are perhaps not surprising, in that a number of clinical and observational epidemiological studies suggest that ectopic adipose deposition is associated with insulin resistance and with prevalent and incident diabetes.[2–6,9,10] In 2011, Srikanthan et al. examined the relationship of total skeletal muscle mass to total body weight as measured by bioelectrical impedance with prediabetes and diabetes using the National Health and Nutrition Examination Survey III (1988-1994) and found that a higher ratio of muscle, ostensibly lean muscle tissue, to body weight was associated with increased insulin sensitivity and a lower risk of prediabetes or diabetes after adjusting for BMI and waist circumference.[10] Measurement by bioelectrical impedance has limitations, including the potential to overestimate muscle mass content in the setting of obesity and the inability of bioelectrical impedance to differentiate among specific contributions of the lean tissue and IMAT components of the total muscle.[11,12]

TABLE 2 Participant characteristics across glycaemia categories

	Normoglycemic at all attended visits N = 1470	Prediabetic before but not at Year 25 N = 474	Prediabetic at Year 25 N = 729	Diabetic at any visit N = 436
Age (y)	49.8 ± 3.68[a]	50.1 ± 3.53	50.5 ± 3.55	50.7 ± 3.6
Height (cm)	168.9 ± 9.21	171.8 ± 9.11	172.4 ± 9.63	170 ± 9.4
Treadmill duration (s)[b]	442 ± 159.4	446 ± 158.9	438 ± 155.3	324 ± 133.4
Diabetes duration (y)	0 ± 0	0 ± 0	0 ± 0	5.7 ± 6.45
IMAT (cc)	1.98 ± 1.29	2.21 ± 1.46	2.65 ± 1.67	3.27 ± 2.17
Lean (cc)	16.75 ± 4.22	18.6 ± 4.51	19.34 ± 4.76	19.18 ± 4.66
Total (cc)	18.79 ± 4.59	20.89 ± 4.85	22.11 ± 5.22	22.67 ± 5.46
IMAT/Total (%)	10.5 ± 5.82	10.6 ± 6.03	11.9 ± 6.47	14.1 ± 7.6
VAT (cc)	106.8 ± 59.9	125.5 ± 64.1	155.9 ± 73.6	181.6 ± 86.6
BMI (kg/m^2)	28.6 ± 6.6	29.2 ± 6.3	31.3 ± 6.6	35 ± 8
White race (%)	55.2 (812/1470)	54 (256/474)	56.8 (414/729)	34.4 (150/436)
Female (%)	67.1 (987/1470)	43.9 (208/474)	44.3 (323/729)	55.1 (240/436)
HTN (%)	28.4 (417/1470)	36.9 (175/474)	42.9 (313/729)	75.7 (330/436)
High cholesterol (%)	21.4 (1785/315)	25.7 (596/122)	28.5 (937/208)	52.5 (665/229)
Smoking status				
Never (%)	62.6 (920/1470)	63.7 (302/474)	57.8 (421/729)	58.7 (256/436)
Former (%)	21.8 (321/1470)	18.4 (87/474)	24.4 (178/729)	20.4 (89/436)
Current (%)	15.6 (229/1470)	17.9 (85/474)	17.8 (130/729)	20.9 (91/436)

Abbreviations: IMAT, intermuscular adipose tissue; Lean, lean muscle volume; Total, total muscle volume; VAT, visceral adipose tissue; HTN, hypertension cumulative through Year 25.

[a] Mean ± Std or % (n/N). Aside from use of sex-specific quartiles, data are unadjusted.

[b] Treadmill test at Year 20, N = 1125, 369, 544, 305, respectively.

TABLE 3 Association of abdominal muscle composition and VAT volume with diabetes and prediabetes

	Model	Past prediabetes (before but not at Year 25)	Current prediabetes (Year 25)	Diabetes (through Year 25)
IMAT	1	1.27 (1.11, 1.45)[a]	1.71 (1.54, 1.90)	2.16 (1.93, 2.42)
	2	1.23 (1.08, 1.41)	1.60 (1.43, 1.78)	1.91 (1.69, 2.15)
	+ Lean	1.20 (1.05, 1.38)	1.48 (1.33, 1.79)	1.77 (1.56, 1.99)
	+ Lean & VAT	1.10 (0.94, 1.28)	1.08 (0.95, 1.23)	1.14 (0.99, 1.32)
Lean	1	1.10 (0.98, 1.23)	1.53 (1.38, 1.69)	1.77 (1.58, 1.98)
	2	1.09 (0.96, 1.23)	1.50 (1.35, 1.67)	1.72 (1.52, 1.96)
	+ IMAT	1.05 (0.93, 1.19)	1.40 (1.26, 1.56)	1.57 (1.38, 1.79)
	+ IMAT & VAT	1.03 (0.91, 1.17)	1.29 (1.16, 1.44)	1.35 (1.18, 1.55)
VAT	1	1.26 (1.12, 1.43)	2.02 (1.82, 2.25)	3.17 (2.80, 3.60)
	2	1.22 (1.07, 1.39)	1.92 (1.72, 2.14)	2.70 (2.36, 3.09)
	+ IMAT & Lean	1.14 (0.96, 1.34)	1.70 (1.49, 1.95)	2.29 (1.94, 2.70)

Abbreviations: IMAT, intermuscular adipose tissue; VAT, visceral adipose tissue; Lean, lean muscle volume.
Model 1: age, race, sex; Model 2: Model 1 + study centre, height, smoking status, hypertension and high cholesterol.
[a] Standardized odds ratio (95% CI).

TABLE 4 Unadjusted IMAT and VAT volumes, and adjusted probability of having diabetes according to the crossing of IMAT with VAT in sex-specific quartiles 1 to 3 (Q1-3) vs quartile 4 (Q4)

	IMAT Q1-3		IMAT Q4	
	N	Mean (SD)	N	Mean (SD)
	IMAT values			
VAT Q1-3	1009	1.97 (0.46)	302	4.09 (1.25)
VAT Q4	301	2.28 (0.45)	471	4.97 (1.96)
	VAT values			
VAT Q1-3	1009	120.02 (31.46)	302	136.98 (30.05)
VAT Q4	301	214.29 (46.6)	471	240.42 (66.18)
	Diabetes probability in multinomial logistic Model 2 (see definitions in Table 3)			
VAT Q1-3	1009	0.090	302	0.133
VAT Q4	301	0.171	471	0.236

The 495 participants in quartile 1 for both IMAT and VAT volumes were much thinner (mean $\pm$ std IMAT 0.87 $\pm$ 0.26 cc and VAT 50.43 $\pm$ 19.61 cc; 4.6% had diabetes) and were omitted to improve comparison of diabetes probabilities according to fatness.

However, studies using CT to specifically assess the role of muscle quality or IMAT volume have shown that lower attenuation in core or peripheral muscles, consistent with higher fat infiltration, is associated with insulin resistance, diabetes and other cardiometabolic abnormalities as well.[6,7,22,23] Using CT, the present study shows that higher IMAT volume and higher lean volume, the major constituent of total muscle volume, independently contribute to the risk of prevalent prediabetes and diabetes.

In our correlational analysis, aerobic physical fitness, as assessed by total treadmill duration 5 years before the abdominal CT scan, was inversely associated with IMAT volume. Although greater aerobic fitness was moderately associated with lower IMAT volume, it was also associated, to a lesser degree, with lower total muscle volume. Including treadmill duration in multivariable models did not explain the associations between muscle composition or VAT volume with prediabetes or diabetes. Prior studies have suggested that interventions such as aerobic exercise, resistance training or dietary weight loss, especially multifaceted interventions including both exercise and diet, may improve insulin sensitivity and may even reduce the incidence of diabetes via an increase in muscle mass, specifically lean muscle tissue.[9,24] Although our study does not directly address these interventions, our findings suggest that it would be difficult to distinguish between metabolic improvements attributable to lean muscle gain from those attributable to loss of either IMAT volume or VAT volume in obese individuals. Thus, the benefit of exercise on the incidence of diabetes may be mediated, in part, by reductions in IMAT volume secondary to fitness. Indeed, any dietary or training intervention that seeks to reduce excess body fat may be expected to reduce VAT volume in proportion to overall weight loss and, in turn, insulin sensitivity may be expected to improve because of its inverse correlation with VAT volume.[25]

The finding that lean volume is positively related to both prediabetes and diabetes seems paradoxical, but it is consistent with the previous finding from the CARDIA study that treadmill duration is only weakly related to DXA-measured lean mass.[16] In a study by Zhu et al, lean mass was positively related to treadmill duration only in the lowest quartile of fat mass, while the relation was inverse in the highest quartile of fat mass.[16] Higher muscle volume may reflect adaptation to obesity, such as lower muscle density (ie, more lipid within adipocytes of the muscle) and the need to support body weight. We

speculate that the quality of lean tissue that results in response to dynamic or isometric activity is higher than the quality of lean tissue that results solely in response to the necessity of supporting a large mass of adipose tissue. Greater IMAT volume has been associated with low-quality lean tissue, inflammation and insulin resistance.[9] Accordingly, IMAT volume may be regarded as one measure of muscle quality, concordant with speculation by Larsen et al[26]

Strengths of this study include the large, well-characterized community-based sample of white and black individuals, the novel and comprehensive measures of muscle mass using CT scan, and the wide array of demographic, lifestyle and chronic disease measures to assess confounding and effect modification, including cardiorespiratory fitness. However, we must also acknowledge limitations to our study. First, the cross-sectional design cannot prove causality, as discussed above. Second, we evaluated abdominal muscle composition and, therefore, our findings may not be applicable to peripheral muscles.

In conclusion, we found that higher abdominal IMAT volume was associated with a higher prevalence of current prediabetes and diabetes. Abdominal IMAT volume is strongly associated with VAT volume and, as such, associations cannot be interpreted without accounting for the larger VAT depot. We also report the novel observation that lean muscle volume is positively associated with diabetes and prediabetes after adjusting for both IMAT volume and VAT volume. This observation requires further study, but it seems probable that lean muscle quality suffers as ectopic adipose depots enlarge, as well as being influenced by other metabolic factors including inflammation and insulin resistance.

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Conflicts of interest

The authors have no conflicts of interest.

Author contributions

The authors were involved in the following ways: study design (S. S. G., J. G. T., J. J. C., J. M. L., A. Gr., A. Ge., D. R. J.), data analysis (A. Ge., D. R. J.), drafting of the manuscript (A. Gr., J. M. L.), review and editing (S. S. G., J. G. T., J. J. C., J. M. L., A. Gr., L. M. S., D. R. J., A. Ge.). J. M. L. had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. All authors have contributed to the manuscript in significant ways and have reviewed and agreed upon the manuscript content.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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