Implications of Abdominal Adipose Tissue Distribution on Nonalcoholic Fatty Liver Disease and Metabolic Syndrome: A Chinese General Population Study

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INTRODUCTION: **Visceral adipose tissue (VAT) has been found to play a critical role in the development of metabolic syndrome and nonalcoholic fatty liver disease (NAFLD) independent of generalized obesity.**

METHODS: **In this secondary study of prospectively acquired data, 625 participants underwent magnetic resonance spectroscopy and chemical shift fat–water separation MRI (2-point Dixon) of the liver and whole abdomen, respectively, in a 3 Tesla magnet. Whole abdominal VAT and subcutaneous adipose tissue (SAT) were extracted from the 2-point Dixon image series using an automated method. Clinical/anthropometric/blood biochemistry parameters were measured. Using region-specific body mass index, participants were classified into 3 paired subgroups (lean, overweight, and obese) and presence of NAFLD (liver fat content ≥ 5.5%).**

RESULTS: **All relevant clinical/anthropometric/blood biochemistry characteristics and liver enzymes were statistically significant between groups ($P < 0.001$). NAFLD was found in 12.1%, 43.8%, and 68.3% and metabolic syndrome in 51.1%, 61.9%, and 65% of the lean, overweight, and obese, respectively. Odds ratio for metabolic syndrome and NAFLD was increased by 2.73 (95% confidence interval [CI] 2.18–3.40) and 2.53 (95% CI 2.04–3.12), respectively, for 1SD increase in VAT volume while prevalence of metabolic syndrome was increased by 2.26 (95% CI 1.83–2.79) for 1SD increase in liver fat content (%). VAT/SAT ratio in the lean with fatty liver showed the highest ratio (0.54) among all the subgroups, without a significant difference between the lean and obese with NAFLD ($P = 0.127$).**

DISCUSSION: **Increased VAT volume/disproportional distribution of VAT/SAT may be vital drivers to the development of metabolic syndrome and NAFLD irrespective of body mass index category.**

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INTRODUCTION

Obesity defined as "a state of increased body weight, especially adipose tissue of sufficient magnitude to provide health consequences (1)" is a result of chronic caloric intake exceeding energy expenditure. It is linked to an increased risk of metabolic syndrome and emerging as one of the main causes limiting life expectancy in developed countries (2). Among the common complications of obesity is nonalcoholic fatty liver disease (NAFLD) (3), defined as liver fat content ≥5% of hepatocytes by histology or intrahepatic triglyceride content ≥5.5% by MRI in nonalcoholics (4). NAFLD is a chronic liver disease and a predominant marker for type 2 diabetes mellitus, cardiovascular disease, metabolic syndrome, and liver-related deaths (5).

Notwithstanding obesity being a risk factor for NAFLD, a proportion of 30% of obese individuals do not develop NAFLD and other metabolic aberrations; meanwhile, a proportion of 20%–30% of lean individuals develop these conditions (6), suggesting that the development of such complications might be related to adipose tissue distribution, different fat tissue types and functions. Adipose tissue especially visceral adipose tissue (VAT) is a highly metabolic ectopic fat depot and has been found to play a critical role in the development of metabolic diseases and

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NAFLD independent of generalized obesity (7). Although VAT is a principal cause of high prevalence of NAFLD globally and is strongly associated with metabolic syndrome (8), population studies on the connection among lean/overweight/obese populations with NAFLD especially those that used chemical shift–encoded MRI as an accurate quantitative measure of both liver fat and visceral fat are not numerous. Most studies either used ultrasound or computed tomography to determine NAFLD and VAT measured as either visceral fat area or volume with computed tomography or dual-energy x-ray absorptiometry.

In this study, we sought to evaluate the association of abdominal adipose distribution (VAT/subcutaneous adipose tissue [SAT]) with fatty liver infiltration and metabolic syndrome development in the lean, overweight, and obese adult populations using a chemical shift–encoded MRI method.

METHODS

Study participants

This study was a secondary analysis of a prospective trial by Wong et al. (9) reported previously, that determined the prevalence of NAFLD and advanced fibrosis in the general Chinese population in Hong Kong involving 922 participants, from which 625 are reported in this substudy. Our institutional review board approved the study, and written informed consent was obtained from all the participants. From May 2008 to September 2010, 625 participants who had undergone both liver magnetic resonance spectroscopy (MRS) and supplementary chemical shift encoding-based water–fat separation imaging (2-point Dixon) technique were enrolled in this substudy after excluding 297 of the initial 922 (Figure 1). The study included participants aged 18–70 years with an alcohol consumption limit of 30 g/d for men and 20 g/d for women. Exclusion criteria included any active malignancy, hepatitis B surface antigen positive or positive antibody against hepatitis C virus, being on medication known to affect liver fat, decompensated liver disease, and all known MRI contraindications.

Clinical assessment

During the medical clinic visit, medical history, drug history, alcohol intake, and smoking were recorded using a standardized questionnaire. The body weight, height, waist circumference, and systolic and diastolic blood pressures were measured and recorded accordingly. Body mass index (BMI) was used to categorize BMI status of the participants using the ethnic specific cutoff values (10): BMI < 23 kg/m^2, 23–24.9 kg/m^2, and ≥ 25 kg/m^2 for lean, overweight, and obese status, respectively. Blood tests (liver biochemistry, glucose, and lipids) were performed for participants after at least 8 hours of fasting.

The modified ethnic specific International Diabetes Federation criteria were used to define metabolic syndrome as any 3 of the following: central obesity (waist circumference ≥ 90 cm in men and ≥ 80 cm in women), triglycerides > 1.7 mmol/L, high-density lipoprotein-cholesterol < 1.03 mmol/L in men and < 1.29 mmol/L in women, blood pressure $\geq 130/80$ mm Hg and fasting plasma glucose ≥ 5.6 mmol/L, or on treatment for the above metabolic aberrations (11).

Magnetic resonance image acquisition and reconstruction

MRI was performed in all participants within 8 weeks from baseline using a 3.0 T scanner (Achieva; Philips Medical Systems, Best, the Netherlands). Chemical shift water–fat 2-point Dixon sequence was used to obtain fat-only, water-only, in-phase, and out-of-phase image series of the whole abdomen. VAT and SAT volumes were automatically extracted and quantified from the abdominal MRI series using an in-house method, developed using insight segmentation and registration toolkit (12). Briefly, this method is based on the application of K-means ($K = 2$) clustering and gradient-vector-field–driven deformable model algorithms.

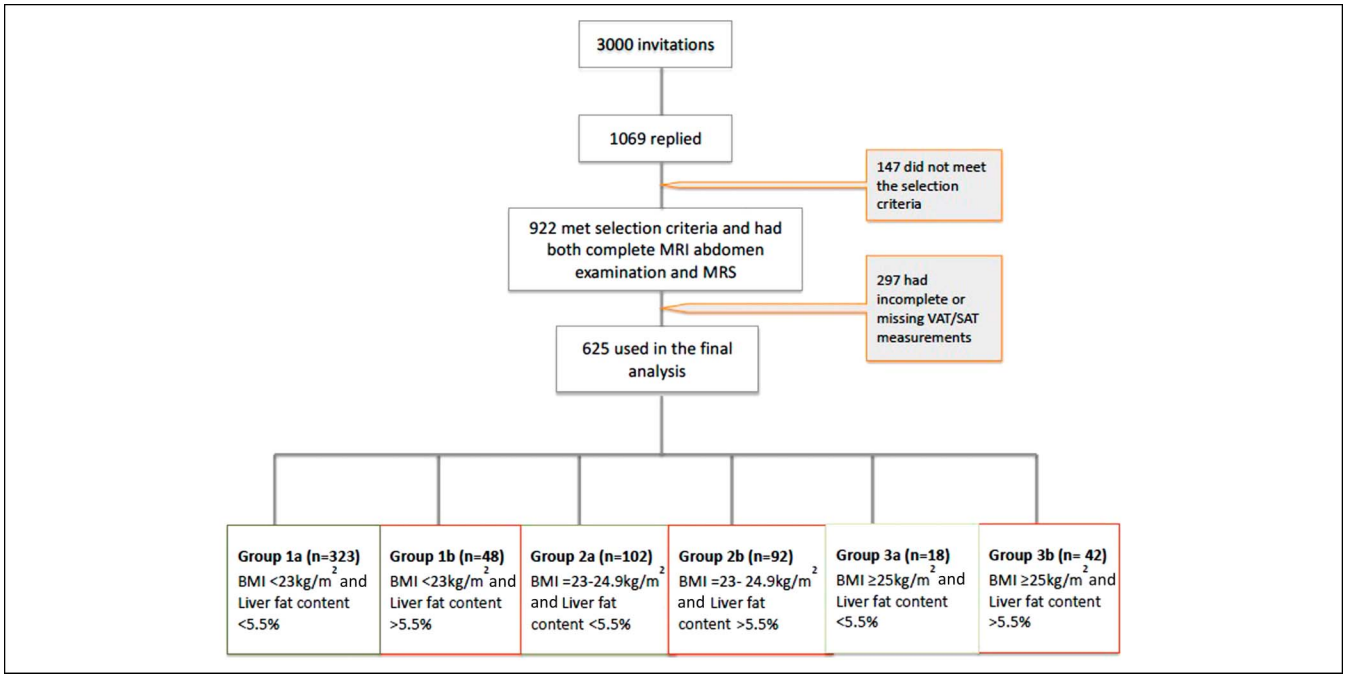

Figure 1. Flow chart of the study population. BMI, body mass index; MRS, magnetic resonance spectroscopy; SAT, subcutaneous adipose tissue; VAT, visceral adipose tissue.

Table 1. Clinical and anthropometric characteristics of participants according to weight and fatty liver status

Variable	All participants, N = 625	Lean without fatty liver, N = 326	Lean with fatty liver, N = 45	Overweight without fatty liver, N = 109	Overweight with fatty liver, N = 85	Obese without fatty liver, N = 19	Obese with fatty liver, N = 41	*P* value
Age (y)	48 ± 10	47 ± 11	50 ± 10	49 ± 10	53 ± 8	45 ± 8	50 ± 9	<0.001[b]
Men	49 ± 11	47 ± 13	50 ± 10	47 ± 12	53 ± 8	50 ± 2	48 ± 9	0.085
Women	48 ± 10	47 ± 10	50 ± 9	50 ± 8	54 ± 9	44 ± 8	51 ± 9	<0.001
Male, n (%)	38	27	52	49	58.7	22.2	40.5	0.046
Female, n (%)	62	73	48	51	41.3	77.2	59.5	
BMI (kg/m^2)	22.9 ± 3.5	20.5 ± 1.7	21.7 ± 1.3	24.9 ± 1.2	25.1 ± 1.2	30.2 ± 3.6	30.0 ± 3.2	<0.001[a]
Men	23.7 ± 2.9	21.1 ± 1.4	21.9 ± 1.3	25.0 ± 1.2	25.1 ± 1.2	28.7 ± 0.8	29.5 ± 1.9	<0.001
Women	22.5 ± 3.8	20.3 ± 1.7	21.6 ± 1.4	24.8 ± 1.3	25.2 ± 1.3	30.6 ± 4.0	30.3 ± 3.9	<0.001
Waist circumference (cm)	81.2 ± 9.9	75.1 ± 7.4	84.2 ± 7.3	85.6 ± 7.0	89.0 ± 5.0	90.8 ± 9.5	95.2 ± 9.6	<0.001[a]
Men	86.1 ± 7.9	79.7 ± 5.1	86.2 ± 6.6	88.7 ± 5.9	89.4 ± 4.4	96.0 ± 6.7	98.9 ± 8.4	<0.001
Women	78.3 ± 9.9	73.5 ± 7.5	82.2 ± 7.9	82.6 ± 6.7	85.9 ± 5.1	89.3 ± 9.9	92.9 ± 9.8	<0.001
Waist-to-hip ratio	0.86 ± 0.08	0.82 ± 0.08	0.91 ± 0.06	0.88 ± 0.06	0.91 ± 0.05	0.88 ± 0.05	0.91 ± 0.08	<0.001[a]
Men	0.90 ± 0.06	0.86 ± 0.05	0.92 ± 0.06	0.90 ± 0.05	0.92 ± 0.04	0.91 ± 0.08	0.94 ± 0.06	<0.001
Women	0.84 ± 0.08	0.81 ± 0.08	0.90 ± 0.06	0.85 ± 0.06	0.88 ± 0.05	0.87 ± 0.04	0.89 ± 0.08	<0.001
Diastolic blood pressure (mm Hg)	81 ± 13	78 ± 11	82 ± 11	82 ± 11	89 ± 12	81 ± 10	91 ± 15	<0.001[b]
Systolic blood pressure (mm Hg)	129 ± 20	124 ± 18	131 ± 18	132 ± 20	140 ± 20	127 ± 10	141 ± 22	<0.001[a]
Liver fat content (%)	4.75 ± 6.1	1.51 ± 1.1	11.16 ± 7.6	2.53 ± 1.4	11.5 ± 6.2	2.50 ± 1.4	13.91 ± 8.1	<0.001[a]
Men	6.25 ± 6.84	1.79 ± 1.1	10.2 ± 6.2	2.56 ± 1.3	12.10 ± 6.5	2.81 ± 1.8	16.7 ± 8.3	<0.001
Women	3.83 ± 5.39	1.40 ± 1.1	12.15 ± 8.8	2.50 ± 1.5	10.64 ± 5.6	2.41 ± 1.3	12.0 ± 7.6	<0.001
VAT volume (L)	1.92 ± 1.43	1.31 ± 0.89	2.72 ± 1.84	2.21 ± 1.35	2.77 ± 1.57	2.26 ± 1.24	2.93 ± 1.75	<0.001[a]
Men	2.48 ± 1.74	1.60 ± 1.12	3.13 ± 1.98	2.61 ± 1.62	3.08 ± 1.82	2.43 ± 1.92	3.51 ± 2.05	<0.001
Women	1.58 ± 1.06	1.19 ± 0.76	2.30 ± 1.60	1.84 ± 0.91	2.33 ± 0.99	2.21 ± 1.07	2.54 ± 1.42	<0.001
SAT volume (L)	5.81 ± 2.30	5.04 ± 1.69	5.17 ± 1.77	6.71 ± 2.09	5.91 ± 2.08	8.59 ± 3.03	8.67 ± 3.39	<0.001[a]
Men	4.69 ± 1.82	3.58 ± 1.17	4.42 ± 1.23	5.60 ± 1.67	4.86 ± 1.54	6.19 ± 1.87	6.84 ± 2.50	<0.001
Women	6.49 ± 2.30	5.57 ± 1.52	5.95 ± 1.93	7.78 ± 1.90	7.40 ± 1.84	9.28 ± 2.98	9.92 ± 3.39	<0.001
VAT/SAT ratio	0.35 ± 0.25	0.27 ± 0.19	0.54 ± 0.33	0.35 ± 0.21	0.50 ± 0.29	0.31 ± 0.27	0.38 ± 0.27	<0.001[a]
Men	0.52 ± 0.28	0.43 ± 0.23	0.69 ± 0.35	0.46 ± 0.23	0.62 ± 0.29	0.39 ± 0.23	0.55 ± 0.33	<0.001
Women	0.25 ± 0.16	0.21 ± 0.13	0.38 ± 0.20	0.24 ± 0.12	0.34 ± 0.21	0.28 ± 0.28	0.26 ± 0.13	<0.001
Metabolic syndrome, n (%)	32.4	12	51.1	47.7	61.9	50	65	<0.001[a]
Men	41.9	11.5	52	48	66	50	93.8	<0.001
Women	26.5	12	50	50	50	53.8	44	<0.001
Hypertension, n (%)	50.6	40	51.1	56.5	74.1	47.4	70.7	<0.001[a]
Men	67.2	54	68	64	81.5	50	100	0.001
Women	40.4	34.5	37.5	49	60.5	42.9	52	0.024

BMI, body mass index; VAT, visceral adipose tissue; SAT, subcutaneous adipose tissue.
[a]Indicates at least 1 group of significant differences using the Welch test, and *post hoc* analysis was performed.
[b]Indicates at least 1 group of significant differences using ANOVA, and *post hoc* analysis was performed.

Proton MRS

During the same MRI scan, a single voxel PRESS sequence was performed using the body coil without water suppression to acquire a spectrum of intrahepatic triglycerides. A 20 × 15 × 40-mm^3 voxel was placed in the right liver lobe, avoiding major vessels. Selecting short echo time and long repetition time,

respectively, minimized T2 and T1 effects. A noncommercially available jMRUI software package (13) was used for spectral analysis. Liver fat fraction was obtained from the main methylene peak and calculated using equation (1).

$$\mathrm{FF}(\%)\frac{\text{Signal intensity of fat}}{\text{Sum of signal intensity of fat and water}}\times 100 \qquad (1)$$

Statistical analysis

Normally distributed data were expressed as mean ± SD, unless stated otherwise. Analysis of variance (ANOVA) and Welch ANOVA were used as necessary. *Post hoc* analyses were performed by using Scheffe or Dunnett T3 methods accordingly. The Mann-Whitney U test was used for testing differences between 2 groups. Linear trends were tested using the χ^2 test. Associations were tested using Pearson correlation coefficients. Multiple linear and binary logistic regression analyses with correction for multiple comparisons were used to evaluate causation relationships. All tests were 2-sided and P values <0.05 were considered statistically significant. Statistical analyses were performed with SPSS software, version 25.0 (IBM, Chicago, IL).

RESULTS

Participant characteristics

Six hundred twenty-five participants (38% men, 62% women, 48 ± 10 years; age range 19–70 years, BMI 22.9 ± 3.5 kg/m^2, BMI range 15.8–42.7 kg/m^2) were analyzed. Men had a higher VAT volume than women ($P < 0.001$) while women had higher SAT volume than men ($P < 0.001$). VAT volume, liver fat content, and prevalence of metabolic syndrome increased exponentially with age ($P < 0.001$). The prevalence of metabolic syndrome and fatty liver disease in men was 41.9% and 37.4%, respectively, while in women, it was 26.5% and 21%, respectively, with a significant difference between them ($P < 0.001$).

The study cohort was classified into 3 paired subgroups according to their BMI and presence of fatty liver as follows: group 1a—lean without fatty liver (n = 326); group 1b—lean with fatty liver (n = 45 or 12.1%); group 2a—overweight without fatty liver (n = 109); group 2b—overweight with fatty liver (n = 85 or 43.8%); group 3a—obese without fatty liver (n = 19); and group 3b—obese with fatty liver (n = 41 or 68.3%).

Clinical, anthropometric, and blood biochemistry characteristics

All clinical, anthropometric, and blood biochemistry characteristics were significantly different between groups ($P < 0.001$) except for aspartate aminotransferase ($P < 0.261$), total bilirubin ($P < 0.651$), and albumin ($P < 0.786$) (Tables 1 and 2). In addition, there were significant differences in biochemistry and liver enzymes between sex ($P < 0.001$) except for cholesterol ($P = 0.469$), low-density lipoprotein-cholesterol ($P = 0.106$), and HbA1c ($P = 0.064$).

Adipose tissue and metabolic syndrome

Metabolic syndrome was diagnosed in 202 or 32.4% of the entire study cohort with a significant difference between those with and without fatty liver disease ($P < 0.001$). The distribution of metabolic syndrome in those with fatty liver was 51.1%, 61.9%, and 65% in the lean, overweight, and obese, respectively. The incidence of metabolic syndrome showed an increasing linear trend with an increase in VAT volume ($P < 0.001$), but a higher prevalence was observed in the fatty liver subgroups.

Interestingly, *post hoc* analysis showed no significant difference in the prevalence of metabolic syndrome between the lean with fatty liver subgroup and in all overweight/obese subgroups ($P = 1.000$, 0.994, 1.000, and 0.963), indicating that lean participants with fatty liver were as metabolically unhealthy as the overweight/obese participants with fatty liver.

Table 3 summarizes the pairwise subgroup comparisons in those with and without metabolic syndrome. The results indicated that VAT volume in the lean and obese groups added a risk to the development of metabolic syndrome. Notably, a trend of increased VAT volume was observed in the overweight subgroups with metabolic syndrome except that this difference was not statistically significant ($P > 0.05$). Meanwhile, comparison by sex showed that VAT, SAT, VAT/SAT ratio, and liver fat content in those with and without metabolic syndrome were significantly different between them ($P < 0.001$).

Multiple linear regression analysis showed age ($P < 0.001$), waist circumference ($P = 0.003$), VAT volume ($P < 0.001$), and VAT/SAT ratio ($P = 0.012$) as predictors of metabolic syndrome after controlling for sex, SAT, waist-to-hip ratio, BMI and liver fat content ($R^2 = 0.352$). The odds ratio (OR) of metabolic syndrome was increased by 2.73 (95% confidence interval [CI] 2.18–3.40) for 1SD increase in VAT volume while it was increased by 2.26 (95% CI 1.83–2.79) for 1SD increase in liver fat content (%). Moreover, VAT, SAT, and VAT/SAT ratio all showed significant association with metabolic syndrome ($P < 0.001$) (Table 4).

Adipose tissue and NAFLD

In the entire cohort, VAT volume, SAT volume, and VAT/SAT ratio were significantly higher in those with fatty liver disease than in those without ($P < 0.001$, 0.004, and <0.001, respectively). Intriguingly, *post hoc* analyses showed that VAT volume was not significantly different between 1b and 2a/b ($P = 1.000$, 0.683), 1b and 3a/b ($P = 1.000$, 0.966), suggesting that VAT volume in the lean with NAFLD was as high and similar to VAT volume in both the overweight and obese participants regardless of the presence of NAFLD.

SAT volume was not significantly different between the lean subgroups ($P = 1.000$), overweight subgroups ($P = 0.398$), and obese subgroups ($P = 0.119$), indicating that SAT volumes in those with and without NAFLD in each BMI category were similar.

VAT/SAT ratio was not significantly different between 1b and 2b/3a and b ($P = 1.000$, 0.065, 0.127). VAT/SAT ratio in the lean with fatty liver subgroup showed the highest ratio (0.54) among all the subgroups, suggesting a disproportional distribution of fat in this subgroup, with an increased fat deposition in the viscera as opposed to the subcutaneous region.

Liver fat content was not significantly different between subgroups 1a and 3a, 1b and 2b, 1b and 3b, 2a and 3a, and 2b and 3b ($P = 0.105$, 1.000, 0.861, 1.000, and 0.738), suggesting that there could be another mechanism responsible for ectopic fat infiltration in the liver other than general and central obesity. The incidence of fatty liver disease showed an increasing linear trend with an increase in VAT volume ($P < 0.001$). The OR of fatty liver was increased by 2.53-fold (95% CI 2.04–3.12) for 1SD increase in VAT volume.

Binary logistic regression analysis showed male gender ($P < 0.001$), BMI ($P < 0.001$), waist circumference ($P < 0.001$), alanine

Table 2. Blood biochemistry characteristics of the study population by weight and fatty liver status

Variables	All participants, N = 629	Lean/no fatty liver, N = 323	lean/with fatty liver, N = 48	overweight/no fatty liver, N = 102	Overweight/with fatty liver, N = 92	Obese/no fatty liver, N = 18	Obese/with fatty liver, N = 42	*P* value
ALT (IU/L)	25.6 ± 16.5	21.0 ± 10.7	33.2 ± 17.1	26.3 ± 22.8	32.4 ± 15.3	22.6 ± 9.4	37.4 ± 24.2	<0.001[a]
AST (IU/L)	21.5 ± 16.5	21.1 ± 17.3	23.8 ± 13.1	20.1 ± 5.9	23.3 ± 7.9	18.4 ± 4.6	24.0 ± 10.0	0.261
ALP (IU/L)	64.3 ± 18.7	61.3 ± 19.8	69.2 ± 16.8	64.7 ± 16.8	72.4 ± 17.3	58.3 ± 11.2	66.1 ± 15.7	<0.001 [b]
Total bilirubin (mmol/L)	13.1 ± 5.7	13.2 ± 5.9	12.5 ± 4.7	12.6 ± 4.9	13.0 ± 6.3	14.9 ± 8.2	13.0 ± 4.7	0.651
HbA1c (%)	5.4 ± 0.7	5.3 ± 0.4	5.8 ± 1.2	5.5 ± 0.5	5.6 ± 0.7	5.2 ± 0.4	5.9 ± 1.1	<0.001[a]
Hemoglobin (g/dL)	13.8 ± 1.5	13.5 ± 1.4	14.2 ± 1.2	13.9 ± 1.5	14.4 ± 1.7	13.3 ± 1.1	14.4 ± 1.4	<0.001[b]
Ferritin	467.9 ± 482.1	355.1 ± 392.4	611.6 ± 466.9	455.1 ± 414.3	740.8 ± 609.8	298.9 ± 361.9	683.8 ± 672.2	<0.001[a]
AST/ALT ratio	0.97 ± 0.74	1.12 ± 0.97	0.77 ± 0.29	0.91 ± 0.32	0.79 ± 0.26	0.86 ± 0.19	0.72 ± 0.20	<0.001[b]
Fasting glucose (IU/L)	5.12 ± 1.02	4.86 ± 0.44	5.67 ± 1.64	5.25 ± 0.77	5.36 ± 0.87	4.96 ± 0.53	5.70 ± 1.59	<0.001[a]
Albumin (mmol/L)	45.1 ± 2.7	45.1 ± 2.9	45.2 ± 3.00	44.8 ± 2.21	43.4 ± 2.3	44.7 ± 2.8	45.1 ± 2.2	0.786
Total cholesterol (mmol/L)	5.2 ± 1.0	5.08 ± 0.92	5.38 ± 1.16	5.24 ± 1.13	5.48 ± 1.1	5.53 ± 1.5	5.17 ± 0.81	0.012[b]
HDL-cholesterol (mmol/L)	1.6 ± 0.4	1.71 ± 0.40	1.36 ± 0.27	1.48 ± 0.36	1.28 ± 0.31	1.56 ± 0.4	1.28 ± 0.24	<0.001[a]
LDL-cholesterol (mmol/L)	3.1 ± 0.9	2.92 ± 0.81	3.11 ± 1.05	3.13 ± 0.88	3.28 ± 0.91	3.39 ± 1.57	3.12 ± 0.67	0.004[a]
Triglycerides (mmol/L)	1.4 ± 1.3	1.00 ± 0.60	2.17 ± 1.66	1.37 ± 1.01	2.24 ± 2.52	1.22 ± 0.76	1.68 ± 1.06	<0.001[a]

ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; HDL, high-density lipoprotein; LDL, low-density lipoprotein.
[a]Indicates at least 1 group of significant differences using the Welch test, and *post hoc* analysis was performed.
[b]Indicates at least 1 group of significant differences using ANOVA, and *post hoc* analysis was performed.

aminotransferase ($P = 0.030$), total cholesterol ($P = 0.045$), high-density lipoprotein-cholesterol ($P = 0.001$), and low-density lipoprotein-cholesterol ($P = 0.035$) as independent predictors of fatty liver after controlling for age, waist to hip ratio, VAT, SAT, VAT/SAT ratio, triglycerides, ferritin, hemoglobin, aspartate aminotransferase, alkaline phosphatase, and hypertension ($R^2 = 0.538$). Moreover, VAT, SAT, and VAT/SAT ratio all showed significant association with fatty liver disease ($P < 0.001$). Liver fat content also showed a significant association with metabolic syndrome ($P < 0.001$) (Table 4).

DISCUSSION

VAT is associated with metabolic syndrome (14) and fatty liver disease (15). In this present population substudy involving asymptomatic general adult Hong Kong Chinese population, MRS and fat–water separation MRI methods were used. Prevalence of NAFLD was 12.1%, 43.8%, and 68.3% in the lean, overweight, and obese, respectively, while the prevalence of metabolic syndrome in participants with fatty liver was 51.1%, 61.9%, and 65% in the lean, overweight, and obese, respectively.

In agreement with previous studies, the global occurrence of fatty liver in the lean population ranges from 7% to 20% (16,17) and 50%–90% in the obese (18–20). Previously reported global prevalence of metabolic syndrome in the lean population with fatty liver disease ranges from 14% to 37.8% (16) and 46.6% in overweight/obese Chinese (21). Metabolic syndrome prevalence in our cohort seems to be higher, and this discrepancy could be attributed to different methods used to diagnose fatty liver disease, criteria to diagnose metabolic syndrome and the varying/ethnic specific BMI cutoff values to categorize BMI status. The BMI cutoff in the Asian population is 2–5 BMI units lower than the international classification (10).

It has been shown that the mean VAT volumes are significantly higher in the fatty liver subgroups than in those without. In fact, the VAT/SAT ratios are significantly higher in all fatty liver subgroups, with the lean with fatty liver subgroup showing the highest VAT/SAT ratio among them, suggesting that there is a limited subcutaneous mass relative to expanding visceral mass (an indication of the thin on the outside, fat on the inside phenotype) in this subgroup. These outcomes are in agreement with the hypothesis that increased VAT mass (representing adipocytes hyperplasia or hypertrophy) plays a significant mediatory role in the development of fatty liver disease either by direct delivery of free fat acids into the liver through the portal circulation or as a secondary effect from the dysfunctional adipocytes that produce more inflammatory adipokines and cytokines (interleukin 6 and tumor necrosis factor—alpha) (22), with dysfunctional adipocytes in particular, affecting the lean.

Despite VAT volume not being an independent predictor of fatty liver disease in this current study, increased VAT volume has nearly 3-fold greater risk of the development of fatty liver disease in our cohort. Previous Australian and Korean cohorts showed VAT volume/area had an OR 2.1, 95% CI 1.1–4.2 (23) and OR 2.21 (per 1SD), 95% CI 1.25–3.89 (24), respectively, for the development of fatty liver disease.

One of the interesting and reassuring findings from the current study is that BMI and waist circumference (among others) are independent predictors of fatty liver disease in agreement with previous studies (25,26). In fact, Mansour et al. (27) further found that waist circumference was independently associated with liver

Table 3. Association of VAT, nonalcoholic fatty liver disease, and metabolic syndrome

	Lean without fatty liver		Lean with fatty liver		Overweight without fatty liver		Overweight with fatty liver		Obese without fatty liver		Obese fatty liver	
Variable	With vs without METS	*P* value	With vs without METS	*P* value	With vs without METS	*P* value	With vs without METS	*P* value	With vs without METS	*P* value	With vs without METS	*P* value
VAT (L)	1.77 vs 1.24	<0.001[a]	3.28 vs 2.14	0.028[a]	2.24 vs 1.97	0.065	3.02 vs 2.41	0.070	2.89 vs 1.64	0.035[a]	3.50 vs 1.90	0.004[a]
SAT (L)	5.62 vs 4.95	0.038[a]	5.54 vs 4.79	0.119	6.75 vs 6.67	0.835	5.99 vs 5.87	0.787	10.29 vs 6.50	0.007[a]	8.65 vs 8.84	0.870
VAT/SAT ratio	0.35 vs 0.26	0.003[a]	0.60 vs 0.48	0.234	0.39 vs 0.31	0.077	0.53 vs 0.45	0.165	0.31 vs 0.32	0.923	0.45 vs 0.24	0.017[a]
BMI (kg/m^2)	21.6 vs 20.4	<0.001[a]	21.9 vs 21.5	0.183	25.3 vs 24.5	0.002[a]	25.6 vs 24.5	<0.001[a]	29.6 vs 31.2	0.379	29.7 vs 30.5	0.413
Liver fat content (%)	2.05 vs 1.42	<0.001[a]	10.70 vs 11.65	0.889	2.62 vs 2.45	0.554	12.33 vs 10.18	0.103	3.37 vs 1.44	0.002[a]	15.51 vs 11.07	0.096

Table 3 shows differences between variables in each subgroup in those with and without metabolic syndrome.
BMI, body mass index; METS, metabolic syndrome; SAT, subcutaneous adipose tissue; VAT, visceral adipose tissue.
[a]Indicates significant level $P < 0.05$ using the Mann-Whitney *U* test.

fibrosis with OR 1.15, 95% CI 1.05–1.25. These tools are relatively inexpensive, simple to use, and appear to be sensitive and reliable markers in predicting fatty liver disease and its progression. However, in a more scientific point of view, waist circumference although more or less reflecting the amount of abdominal adipose tissue, it does not discriminate between VAT and SAT. Similarly, BMI does not differentiate between fat and muscle mass. In fact, as opposed to the causal role VAT volume seems to play in the development of fatty liver disease, SAT seems to have a protective effect as can be seen in the reduced prevalence of fatty liver disease in the females who have significantly increased SAT volume compared to males. Of course, we are not oblivious to the fact that this outcome could in part be explained by sex differences and related physiology. In support with this assertion, Kim et al. (28) concluded that increased SAT volume was associated with regression or decreased risk of fatty liver disease. This renders the use of waist circumference and BMI unreliable methods to infer the presence of fatty liver disease.

The incidence of metabolic syndrome is higher in the fatty liver subgroups and increases exponentially with increase in VAT volume in all groups. *Post hoc* analysis shows that the incidence of metabolic syndrome is not statistically different between the lean with fatty liver disease subgroup and the overweight/obese subgroups. Interestingly, VAT volume in all paired subgroups with metabolic syndrome is higher than in those without. In agreement with previous studies (29–31), metabolic syndrome has a significant linear relationship with VAT volume. Moreover, VAT volume, waist circumference, and VAT/SAT ratio are independent predictors of metabolic syndrome. In agreement with our findings, Bi et al. (32) and Nakao et al. (33) showed that VAT area was an independent predictor of metabolic syndrome.

In addition, the odds of metabolic syndrome are shown to increase by nearly 3-fold greater for 1SD increase in VAT volume. This outcome is in agreement with Fox et al. (34) who showed a 4.7-fold risk of metabolic syndrome per 1SD increase in VAT of women. Similarly, Kwon et al. (31) showed that the OR of

Table 4. Correlations between variables

		Metabolic syndrome components				
Variable	Fatty liver	Hypertension	Glucose	HDL	Triglycerides	Metabolic syndrome
Waist circumference (cm)	0.486,[a] $P < 0.001$	0.329,[a] $P < 0.001$	0.290,[a] $P < 0.001$	−0.413,[a] $P < 0.001$	0.257,[a] $P < 0.001$	0.548,[a] $P < 0.001$
Waist-to-hip ratio	0.401,[a] $P < 0.001$	0.298,[a] $P < 0.001$	0.291,[a] $P < 0.001$	−0.362,[a] $P < 0.001$	0.278,[a] $P < 0.001$	0.716,[a] $P < 0.001$
BMI	0.426,[a] $P < 0.001$	0.235,[a] $P < 0.001$	0.213,[a] $P < 0.001$	−0.391,[a] $P < 0.001$	0.261,[a] $P < 0.001$	0.407,[a] $P < 0.001$
VAT (L)	0.391,[a] $P < 0.001$	0.274,[a] $P < 0.001$	0.254,[a] $P < 0.001$	−0.211,[a] $P < 0.001$	0.226,[a] $P < 0.001$	0.410,[a] $P < 0.001$
SAT (L)	0.173,[a] $P < 0.001$	0.048, $P = 0.231$	0.021, $P = 0.598$	−0.041, $P = 0.304$	−0.019, $P = 0.633$	0.242,[a] $P < 0.001$
VAT/SAT ratio	0.342,[a] $P < 0.001$	0.255,[a] $P < 0.001$	0.245,[a] $P < 0.001$	−0.317,[a] $P < 0.001$	0.276,[a] $P < 0.001$	0.289,[a] $P < 0.001$
Liver fat content (%)	—	0.212,[a] $P < 0.001$	0.318,[a] $P < 0.001$	−0.412,[a] $P < 0.001$	0.368,[a] $P < 0.001$	0.351,[a] $P < 0.001$

Table 4 shows the correlation between selected variables with fatty liver and metabolic syndrome.
BMI, body mass index; HDL, high-density lipoprotein; SAT, subcutaneous adipose tissue; VAT, visceral adipose tissue; VAT/SAT ratio, visceral adipose tissue to subcutaneous adipose tissue ratio.
[a]R^2 correlation coefficient significant at 0.01 level.

metabolic syndrome per 1SD of VAT area was 1.50 (95% CI 1.29–1.74). These results seem to support the hypothesis that increased VAT mass may have a causal effect in the development of metabolic syndrome.

Concerning the link between fatty liver and metabolic syndrome, we have shown that metabolic syndrome increases by 2.26-fold for 1SD increase in liver fat content. These findings are in concordance with Faria et al. study (29), which showed fatty liver infiltration had a 5.3-fold risk of metabolic syndrome. The prevalence of metabolic syndrome is significantly higher in the fatty liver disease subgroups than in those without. Similarly, fasting glucose/triglycerides (components of metabolic syndrome) are overly produced in NAFLD (35), a finding observed in our study. These outcomes demonstrate that fatty liver infiltration maybe a cause and consequence of a worsening metabolic condition regardless of the BMI category.

This study is not without limitations. Insulin resistance was not assessed despite its close association with VAT and NAFLD. There was a time gap of around 8 weeks between MRI/MRS and blood biochemistry/lipid profile/glucose tests, of which the metabolic profile could have changed. However, given that this was a study in asymptomatic population, the significance of time lapse is probably minimal and would be unlikely to affect the major observations in this study. Two-point Dixon technique and MRS were used as opposed to multiecho chemical shift–encoded MRI method, as the former was the available method at a time the main study was conducted. Finally, our study participants were Chinese with a relatively small sample size and using region-specific BMI cutoff; thus, caution must be taken in the generalizability of these results.

In conclusion, increased VAT volume (representing adipocytes hypertrophy or hyperplasia) and a disproportional distribution of VAT/SAT may be vital drivers to the development of metabolic syndrome and NAFLD irrespective of BMI category. Further studies on adipose tissue-liver cross-talk would be useful to understand the mechanism why some participants within the same BMI develop fatty liver disease and metabolic syndrome while others are spared despite having a comparable VAT volume. To date, multiecho chemical shift–encoded MRI technique can concurrently assess liver fat and adipose tissue while the application of segmentation program can readily calculate VAT and SAT volumes. These technical advances might shed light to personalized medicine assessment for understanding why some lean individuals over accumulate visceral abdominal fat while at the same time some obese individuals seem not to over accumulate visceral abdominal fat.

CONFLICTS OF INTEREST

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Specific author contributions: C.C. and W.C.W.C. conceptualized the study. S.C.N.H. and D.K.W.Y. performed the technical aspect of the experiments. C.C., V.W.-S.W., G.L.-H.W., and H.L.-Y.C. were involved in investigation and analysis. V.W.-S.W. sourced the project funding. C.C. wrote the initial draft of the manuscript. All authors revised the manuscript, approved the final manuscript as submitted, and agreed to be accountable for all aspects of the work.

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Study Highlights

WHAT IS KNOWN

- ✓ Nonalcoholic fatty liver disease (NAFLD) and metabolic syndrome are common manifestation of obesity.
- ✓ Adipose tissue especially visceral adipose tissue (VAT) is a highly metabolic ectopic fat depot.
- ✓ Chemical shift endoding (CSE) MRI is an established method to quantify fat in the human body.

WHAT IS NEW HERE

- ✓ The OR for metabolic syndrome and NAFLD increased by 2.73 and 2.53, respectively, for 1SD increase in VAT volume.
- ✓ There was no difference in VAT volume and VAT/SAT ratio between the lean with and obese with NAFLD, suggesting a "thin on the outside, fat on the inside phenotype" in the lean participants with NAFLD who also were as metabolically unhealthy as the overweight/obese participants with fatty liver.
- ✓ The incidence of both metabolic syndrome and NAFLD increased linearly with an increase in VAT volume.

TRANSLATIONAL IMPACT

- ✓ CSE MRI can accurately quantify liver fat and adipose tissue without the need for extra hardware while segmentation software programs can automatically quantity VAT and SAT volumes.
- ✓ These technical advances might shed light to personalized medicine assessment for understanding why some lean individuals over accumulate visceral abdominal fat while at the same time, some obese individuals seem not to over accumulate visceral abdominal fat.

OUTCOMES

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