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Age of obesity onset affects subcutaneous adipose tissue cellularity differently in the abdominal and femoral region

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Abstract

Objective: We aimed to examine the effect of age of obesity onset, sex, and their interaction on abdominal and femoral subcutaneous adipose tissue (SAT) morphology (degree of adipocyte hyperplasia or hypertrophy).

Methods: In this cross-sectional study, we isolated adipocytes via collagenase digestion from abdominal and femoral SAT biopsies taken from male and female adults with childhood-onset obesity (CO; $n = 8$ males, $n = 16$ females) or adult-onset obesity (AO; $n = 8$ males, $n = 13$ females). Regional body composition was measured with dual-energy x-ray absorptiometry and a single-slice abdominal computed tomography scan. Mean adipocyte size was measured in abdominal and femoral SAT and was used to quantify morphology in android and gynoid subcutaneous fat, respectively.

Results: Abdominal SAT morphology was more hyperplastic in females with CO than females with AO ($p = 0.004$) but did not differ between males with CO and males with AO ($p = 0.996$). Conversely, femoral SAT morphology was more hypertrophic in males and females with CO than those with AO.

Conclusions: Age of obesity onset appears to affect SAT morphology differently in the abdominal and femoral regions of male and female adults. Our findings challenge the notion that SAT is uniformly hyperplastic in CO and hypertrophic in AO.

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INTRODUCTION

In the 1970s, a paradigm arose that equated childhood-onset obesity (CO) with hyperplastic obesity (many small adipocytes) and adult-onset obesity (AO) with hypertrophic obesity (fewer large adipocytes). However, the studies that shaped this paradigm had limitations [1–5]. They measured adipocyte size in one or multiple adipose tissue regions, which often varied among participants, and then divided total fat mass by average adipocyte size to estimate total adipocyte number. Because adipocyte size can vary largely among regions [4], and adipose tissue is not evenly distributed throughout the body, this approach can over- or underestimate total adipocyte number. Moreover, it cannot determine whether the degree of hypertrophy or hyperplasia varies across adipose tissue regions.

Since the 1970s, additional evidence has accumulated questioning the rigidity of the cellularity-based classification of CO and AO. Hyperplastic adipose tissue is considered metabolically protective, and hypertrophic adipose tissue is considered metabolically harmful [6]; however, cardiometabolic risk is greater in CO than AO [7]. Could this paradox mean that hyperplasia is not always benign or that AO is not always hypertrophic? Weight gain studies in lean adults have supported both possibilities. Contrary to the longstanding belief that adipocyte number is established in childhood, adults can accumulate adipose tissue through hyperplasia [8–10], which, in turn, can associate with poor metabolic health [11].

Nevertheless, the labeling of CO as hyperplastic and AO as hypertrophic has only recently been challenged. Overcoming the limitations of earlier studies, Arner et al. measured adipocyte size in abdominal subcutaneous adipose tissue (SAT) and computed adipocyte number in dual-energy x-ray absorptiometry (DXA)-estimated abdominal subcutaneous fat, not total body fat [12]. They concluded that the degree of abdominal SAT hypertrophy or hyperplasia does not differ between people with CO and AO [12]. This novel contribution to the literature stemmed from a secondary analysis that classified CO and AO based on recalled body weight at age 18 years. The groups differed in age, adiposity, and health status, and the group with CO gained more weight per year during adulthood than the group with AO. Also, the generalizability of the findings to other adipose tissue regions remains unknown.

In the present study, we aimed to assess the effect of age of obesity onset (CO vs. AO), sex, and their interaction on abdominal and femoral SAT cellularity. We also explored how the degree of hypertrophy or hyperplasia in abdominal and femoral SAT relates to cardiometabolic risk factors, stratified by age of obesity onset and sex.

Study Importance

What is already known?

- Childhood-onset obesity is often equated with hyperplastic obesity (many small adipocytes) and adult-onset obesity with hypertrophic obesity (fewer large adipocytes).
- Paradoxically, hyperplastic obesity is considered metabolically protective; however, adults with childhood-onset obesity have greater risk of cardiometabolic disease than those with adult-onset obesity.

What does this study add?

- In the abdominal region, only females with childhood-onset obesity had hyperplastic subcutaneous adipose tissue (SAT) compared with females with adult-onset obesity.
- Conversely, in the femoral region, both males and females with childhood-onset obesity had hypertrophic SAT compared with their counterparts with adult-onset obesity.

How might these results change the direction of research or the focus of clinical practice?

- Our results challenge the view that SAT is uniformly hyperplastic in childhood-onset obesity and hypertrophic in adult-onset obesity; both sex and region of the body may play a role in how SAT expands at different life stages.
- Longitudinal studies are necessary to understand when regional SAT hypertrophy and hyperplasia diverge in males and females with different ages of obesity onset. There is a need to study the mechanisms linking regional SAT hyperplasia versus hypertrophy to cardiometabolic risk in obesity.

METHODS

Participants and procedures

Between April 1, 2016, and November 30, 2019, we recruited healthy adults from Montréal, Québec, Canada, to participate in a study investigating adipose tissue characteristics in CO and AO. Eligibility criteria were as follows: obesity onset either pre- or peri-puberty (CO) or after the age of 18 years (AO); age between 25 and 40 years; body mass index (BMI) ≥ 30 kg/m^2 and <40 kg/m^2; sedentary or lightly active lifestyle; weight stability (±2 kg) for at least 2 months; no use of nicotine-containing products; and no medication use (e.g., antidepressants, antihypertensives), surgeries (e.g., gastric bypass), or past or current medical conditions that could affect metabolism or the ability to complete the study. Females who were menopausal, pregnant, or breastfeeding were also ineligible. Participants provided photographic proof of body size around puberty (age ~10–14 years for females, age ~12–15 years for males) and verified their body size at different ages using the Collins Childhood Body Rating Scales [13] and the Stunkard Body Rating Scale [14]. Ethical approval was obtained from the Concordia University Human Research Ethics Committee. All participants provided written informed consent.

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Study procedures occurred after a 12-h fast and included measurements of body composition and arterial stiffness, a blood draw, and an abdominal (lateral periumbilical region) and femoral (lateral upper thigh) SAT biopsy. The biopsy procedure has been previously described [15].

Body composition

Total, android, and gynoid fat mass (detailed elsewhere [16]) were assessed using DXA (Lunar Prodigy Advance, GE HealthCare, Madison, Wisconsin) with Encore Software (version 14.10, GE HealthCare). The android region (~waist) extends upward from the pelvis cut by 20% of the distance between the pelvis and neck cuts [16]. The upper boundary of the gynoid region (~hips/upper thighs) is below the pelvis cut by 1.5 times the height of the android region. The height of the gynoid region is two times the height of the android region.

SAT and visceral adipose tissue (VAT) were quantified from an L2–L3 single-slice (10 mm) computed tomography (Revolution Evo, GE Medical Systems, Inc., Milwaukee, Wisconsin) image using sliceOmatic Software (version 5.0, TomoVision, Montréal, Québec). The ratios of SAT to total adipose tissue and VAT to total adipose tissue were multiplied by the DXA android fat region to compute android SAT and VAT quantities, respectively [17].

Cardiometabolic risk factors

Serum concentrations of glucose, triglycerides, total cholesterol, and high-density lipoprotein (HDL) cholesterol were measured at the McGill University Health Centre central laboratory in Montréal using standard procedures [17]. Low-density lipoprotein (LDL) cholesterol was calculated using the Friedewald equation [18]. Plasma insulin concentration was measured by enzyme-linked immunosorbent assay (ELISA; R&D Systems, Toronto, Ontario), and the homeostatic model assessment for insulin resistance (HOMA-IR) was computed as follows: (glucose in millimoles per liter × insulin in picomoles per liter)/135 [19]. To assess arterial stiffness, we measured carotid-femoral pulse wave velocity using applanation tonometry (SphygmoCor, ATCOR Medical, Sydney, Australia) as previously described [20].

Adipokines

Plasma concentrations of leptin, adiponectin, interleukin (IL)-8 (R&D Systems), and IL-6 (Abcam, Cambridge, UK) were measured by ELISA. Plasminogen activator inhibitor-1 (PAI-1), monocyte chemoattractant protein-1 (MCP-1), and resistin were measured using a Human ProcartaPlex Simplex Kit (Invitrogen, Thermo Fisher Scientific Inc., Waltham, Massachusetts). Adiponectin is an anti-inflammatory, insulin-sensitizing adipokine, whereas the other selected adipokines are proinflammatory and implicated in cardiometabolic risk [21–23].

Regional SAT cellularity

Adipocytes were isolated from approximately 1 g of abdominal and femoral SAT by collagenase digestion and then imaged using phase contrast microscopy (Motic AE2000 TRI, Motic [Xiamen] Electric Group Co., Ltd., Xiamen, China), as previously described [24]. Consistent with the literature, the areas of 100 random adipocytes were measured (FIJI software) [25] and converted to volumes assuming a spherical shape. Mean adipocyte mass was calculated from mean adipocyte volume using a density of 0.915 g/mL (triolein) [26]. Adipocyte number in each region was determined by dividing subcutaneous android and gynoid fat mass by mean abdominal and femoral adipocyte mass, respectively. We computed the abdominal and femoral SAT morphology index developed by Arner et al. [27] based on the relationship between mean adipocyte volume and regional fat mass derived by Spalding et al. [28]: mean adipocyte volume (in picoliters [pL]) = a × regional fat mass (in kilograms)/(1 + [b × regional fat mass (in kilograms)]). To do so, we fit our data to the equation using PROC NLIN in SAS version 9.4 (SAS Institute, Inc., Cary, North Carolina). We then computed the morphology index for each participant as the difference between actual and predicted mean adipocyte volume. Therefore, a positive morphology value indicates hypertrophic SAT, and a negative morphology value indicates hyperplastic SAT, relative to the predicted morphology for a given fat mass.

Statistical analyses

Two-way ANOVA was used to test the effects of obesity onset, sex, and their interaction on participant characteristics, adipokine concentrations, and regional adipose tissue cellularity (adipocyte size, adipocyte number, and morphology). When the interaction was statistically significant, group differences were tested with Tukey post hoc tests. The normality of residuals for each model was assessed using the Shapiro–Wilk test and visual inspection. Dependent variables were natural log-transformed when necessary. When the homogeneity of variances assumption was violated, as per Levene's test and visual inspection, robust standard errors were used. Results are presented as least-squares means and 95% confidence intervals (CI).

Because adiposity can influence adipocyte size and number [26, 29], we considered regional fat mass (android and gynoid subcutaneous fat as appropriate) as a potential covariate in our ANOVA for adipocyte size and number. Of note, the morphology index is independent of regional fat mass. We therefore examined the relationships (Pearson correlation) between regional fat mass and adipocyte size and number. We considered it necessary to adjust for regional fat mass when it differed among our groups and was linearly related to our outcome (i.e., it met the criteria for a confounder) or when it improved the model R^2. Before including the covariate in the model, we verified that regression slopes were similar across groups by testing the interaction between group and the covariate.

Spearman rho (ρ) correlation was used to assess the relationships between the regional SAT morphology indexes and cardiometabolic

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TABLE 1 Demographic and clinical characteristics by sex and obesity onset.

	Females		Males		Effect (p value)		
Characteristic	CO ($n = 16$)	AO ($n = 13$)	CO ($n = 8$)	AO ($n = 8$)	Obesity onset	Sex	Obesity onset × sex
Age (y)	30.5 (28.6 to 32.4)	30.9 (28.8 to 33.1)	30.5 (27.8 to 33.2)	30.3 (27.5 to 33.0)	0.943	0.780	0.780
BMI (kg/m^2)	33.6 (32.2 to 35.1)	34.2 (32.6 to 37.8)	35.9 (33.9 to 37.9)	30.8 (28.8 to 32.8)[d,e]	0.015	0.509	0.003
Lean body mass (kg)[a]	46.6 (44.1 to 49.2)	48.2 (45.5 to 50.9)	62.7 (54.3 to 71.0)	63.4 (57.8 to 69.0)	0.669	<0.001	0.869
Total body fat (kg)	40.4 (37.1 to 43.8)	42.7 (39.0 to 46.3)	43.1 (38.4 to 47.8)	32.9 (28.2 to 37.6)[d,e]	0.062	0.093	0.005
Total body fat (%)	45.0 (43.0 to 47.0)	45.4 (43.3 to 47.6)	39.6 (36.9 to 42.4)[c,d]	33.1 (30.3 to 35.9)[c–e]	0.016	<0.001	0.006
Android visceral fat (kg)	0.75 (0.53 to 0.98)	0.83 (0.57 to 1.07)	1.51 (1.19 to 1.82)	1.66 (1.34 to 1.98)	0.432	<0.001	0.744
Android subcutaneous fat (kg)	2.9 (2.6 to 3.2)	2.8 (2.5 to 3.2)	3.1 (2.7 to 3.5)	1.8 (1.4 to 2.2)[c–e]	<0.001	0.038	0.001
Gynoid fat (kg)	7.3 (6.5 to 8.0)	8.0 (7.2 to 8.8)	6.5 (5.5 to 7.5)	5.0 (4.0 to 6.1)[c,d]	0.392	<0.001	0.019
Log HOMA-IR[a,b]	2.1 (1.5 to 2.8)	1.9 (1.7 to 2.1)	2.2 (1.7 to 2.8)	1.4 (1.1 to 1.7)	0.027	0.415	0.214
Log triglycerides (mmol/L)[b]	0.05 (−0.19 to 0.28)	0.10 (−0.16 to 0.36)	0.38 (0.05 to 0.71)	0.43 (0.10 to 0.76)	0.733	0.027	0.981
HDL cholesterol (mmol/L)	1.3 (1.2 to 1.5)	1.2 (1.1 to 1.4)	1.2 (1.0 to 1.4)	1.1 (0.9 to 1.3)	0.268	0.059	0.893
LDL cholesterol (mmol/L)	2.7 (2.3 to 3.1)	2.6 (2.2 to 3.1)	2.8 (2.3 to 3.4)	2.7 (2.1 to 3.2)	0.684	0.750	0.848
Total/HDL cholesterol	3.5 (3.0 to 4.0)	3.7 (3.2 to 4.3)	4.3 (3.6 to 5.0)	4.2 (3.5 to 4.9)	0.926	0.052	0.628
cfPWV (m/s)	7.2 (6.7 to 7.6)	7.2 (6.7 to 7.8)	7.5 (6.8 to 8.3)	7.6 (6.7 to 7.8)	0.862	0.269	0.896

Note: Results are least-squares means (95% CI). For females with CO, $n = 14$ for HOMA-IR. For males with CO, $n = 7$ for HOMA-IR and cfPWV.
When the obesity onset × sex interaction was statistically significant ($p < 0.05$), groups were compared with Tukey post hoc tests.
Abbreviations: AO, adult-onset obesity; cfPWV, carotid-femoral pulse wave velocity; CO, childhood-onset obesity; HDL, high-density lipoprotein; HOMA-IR, homeostatic model assessment for insulin resistance; LDL, low-density lipoprotein.
[a]Robust standard errors used due to unequal variances.
[b]Natural log-transformed.
[c]Different from females with CO, $p < 0.05$.
[d]Different from females with AO, $p < 0.05$.
[e]Different from males with CO, $p < 0.05$.

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TABLE 2 Adipokine concentrations by sex and obesity onset.

	Females		Males		Effect (p value)		
Adipokine	CO ($n = 16$)	AO ($n = 13$)	CO ($n = 8$)	AO ($n = 8$)	Obesity onset	Sex	Obesity onset × sex
Log leptin (pg/mL)[a,b]	10.9 (10.8 to 11.1)	11.0 (10.8 to 11.1)	10.3 (10.1 to 10.5)[c,d]	9.6 (9.2 to 10.0)[c-e]	0.009	<0.001	0.004
Adiponectin (μg/mL)	4.9 (4.0 to 5.7)	4.3 (3.4 to 5.3)	4.2 (2.9 to 5.5)	3.3 (1.9 to 4.7)	0.208	0.126	0.746
Log IL-6 (pg/mL)[b]	1.5 (1.2 to 1.8)	1.3 (1.0 to 1.6)	1.0 (0.6 to 1.5)	1.3 (0.8 to 1.7)	0.815	0.160	0.279
Log IL-8 (pg/mL)[b]	1.2 (1.0 to 1.4)	1.2 (1.0 to 1.4)	1.5 (1.2 to 1.8)	1.6 (1.3 to 1.8)	0.682	0.007	0.672
Log PAI-1 (pg/mL)[b]	8.9 (8.6 to 9.3)	8.9 (8.5 to 9.3)	9.2 (8.7 to 9.7)	8.9 (8.4 to 9.5)	0.427	0.412	0.606
Log MCP-1 (pg/mL)[b]	4.6 (4.4 to 4.9)	4.8 (4.6 to 5.1)	4.7 (4.4 to 5.0)	5.0 (4.7 to 5.3)	0.062	0.476	0.696
Resistin (ng/mL)	5.7 (3.8 to 7.7)	7.1 (4.9 to 9.2)	4.1 (1.4 to 6.8)	3.4 (0.6 to 6.1)	0.796	0.031	0.393

Note: Results are least-squares means (95% CI). For males with CO, $n = 7$ for leptin, adiponectin, IL-6, and IL-8. For males with AO, $n = 6$ for adiponectin. When the obesity onset × sex interaction was statistically significant ($p < 0.05$), groups were compared with Tukey post hoc tests.
Abbreviations: AO, adult-onset obesity; CO, childhood-onset obesity; MCP-1, monocyte chemoattractant protein-1; PAI-1, plasminogen activator inhibitor-1.
[a]Robust standard errors used due to unequal variances.
[b]Natural log-transformed.
[c]Different from females with CO, $p < 0.05$.
[d]Different from females with AO, $p < 0.05$.
[e]Different from males with CO, $p < 0.05$.

variables by sex and obesity onset. Missing data were dealt with by pairwise deletion. All analyses were conducted using SAS version 9.4. Statistical significance was set at $p < 0.05$.

RESULTS

Participant characteristics

Figure S1 shows the participant flow diagram. Our final sample consisted of 8 males and 16 females with CO and 8 males and 13 females with AO. Body fat percentage was highest in females with CO and AO, intermediate in males with CO, and lowest in males with AO (Table 1). Regardless of obesity onset, males had more visceral fat than females. Compared with the other three groups, males with AO had less total and android subcutaneous fat. Although the four groups were similar in most cardiometabolic risk factors, HOMA-IR was higher in participants with CO than those with AO across sexes.

Group differences in leptin concentrations paralleled those for body fat percentage (Table 2). Regardless of obesity onset, IL-8 was higher and resistin lower in males than females. All other adipokine concentrations were similar among groups.

Regional SAT cellularity

Figure 1 shows the relationships between regional fat mass and mean adipocyte size used to compute the morphology indexes. Of note, because the best fit line was flat in the abdominal region, the morphology index was equivalent to adipocyte volume but on a different scale reflecting relative hypertrophy (positive value) or hyperplasia (negative value).

Because our groups differed in adiposity, we needed to determine whether regional fat mass should be included as a covariate in our models assessing the effects of obesity onset, sex, and their interaction on adipocyte volume and number. To do so, we assessed the linear relationships between regional fat mass and adipocyte volume and number. In both regions, fat mass was not associated with adipocyte volume (Figure S2). Moreover, adding regional fat mass to the models predicting adipocyte volume did not improve the model R^2. Android subcutaneous fat mass associated with abdominal adipocyte number ($r = 0.53$; $p < 0.001$), but gynoid fat mass did not associate with femoral adipocyte number. For models predicting both abdominal and femoral adipocyte number, the R^2 improved when regional fat mass was added as a covariate. For consistency, we displayed the unadjusted and adjusted analyses for abdominal and femoral adipocyte size and number. However, we based our interpretation on the unadjusted models for adipocyte size and adjusted models for adipocyte number. For illustrative purposes, we also correlated all SAT cellularity outcomes with BMI and percent body fat (Figures S3 and S4). Only abdominal adipocyte number correlated with percent body fat ($r = 0.39$; $p = 0.008$).

Table 3 shows the abdominal and femoral SAT cellularity results by sex and obesity onset. Mean abdominal adipocyte volume was lower in females with CO than females with AO ($p = 0.004$) but did not differ between males with CO and males with AO ($p = 0.996$). Abdominal adipocyte number was greater in participants with CO than those with AO across sexes with ($p < 0.001$) and without ($p = 0.034$) adjusting for android subcutaneous fat mass. Abdominal SAT morphology was more hyperplastic (less hypertrophic) in females with CO than females with AO ($p = 0.004$) but did not differ between

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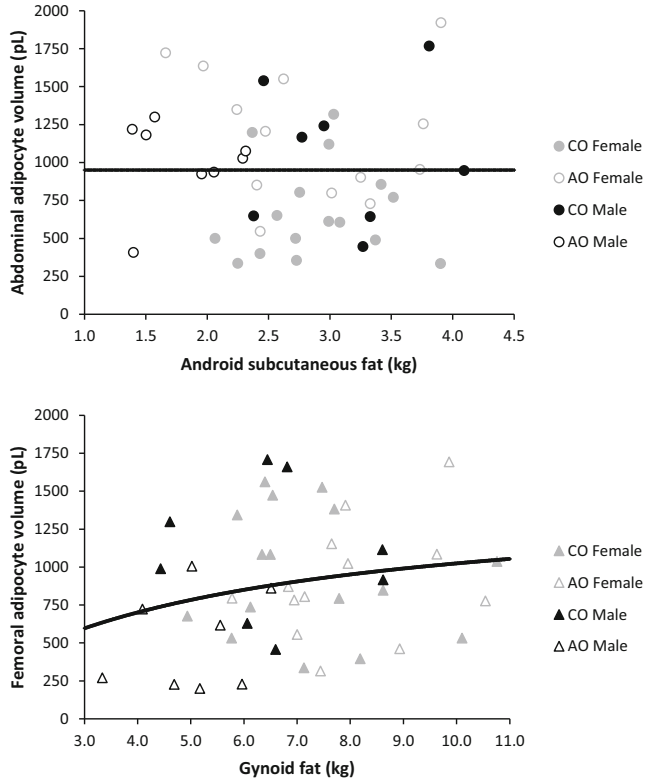


FIGURE 1 The relationships between regional fat mass and mean adipocyte size. AO, adult-onset obesity; CO, childhood-onset obesity.

males with CO and males with AO ($p = 0.996$). Both males with CO and AO had an abdominal SAT morphology that was relatively hypertrophic (morphology index > 0) on average.

Femoral adipocyte volume was lower in males with AO than males with CO ($p = 0.027$) but did not differ between females with CO and females with AO ($p = 0.981$). Femoral adipocyte number was greater in participants with AO than those with CO across sexes ($p = 0.030$), but this difference only persisted in males ($p = 0.027$) when adjusting for gynoid fat mass. Femoral SAT morphology was more hyperplastic (less hypertrophic) in participants with AO than those with CO across sexes ($p = 0.024$).

Relationships between regional SAT cellularity and cardiometabolic variables

Table S1 shows the correlations between regional SAT morphology and cardiometabolic variables by group. In females with CO, abdominal SAT hypertrophy correlated with MCP-1 ($\rho = 0.54$; $p = 0.033$), while femoral SAT morphology did not correlate with any cardiometabolic variables. In females with AO, both abdominal and femoral SAT hyperplasia correlated with resistin ($\rho = 0.62$; $p = 0.025$ and $\rho = 0.78$; $p = 0.002$, respectively). Femoral SAT hyperplasia also correlated with PAI-1 ($\rho = 0.59$; $p = 0.033$) and arterial stiffness ($\rho = 0.59$; $p = 0.033$). Femoral SAT hypertrophy, on the other hand, correlated with triglycerides ($\rho = 0.61$; $p = 0.028$). In males with CO, abdominal SAT morphology did not correlate with any cardiometabolic variables. Femoral SAT hyperplasia correlated with android VAT ($\rho = 0.74$; $p = 0.037$) and the total-to-HDL-cholesterol ratio ($\rho = 0.76$; $p = 0.028$). In males with AO, abdominal SAT morphology did not correlate with any cardiometabolic variables, while femoral SAT hyperplasia correlated negatively with HDL cholesterol ($\rho = -0.81$; $p = 0.015$).

DISCUSSION

We sought to investigate the longstanding notion that hyperplastic SAT is a feature of CO and that hypertrophic SAT is a feature of AO. Our findings were distinct in abdominal and femoral SAT. Abdominal SAT morphology was hyperplastic in females with CO compared with females with AO but did not significantly differ between males with CO and males with AO. Conversely, femoral SAT morphology was hyperplastic in both males and females with AO compared with those with CO.

Our study was, in part, motivated by the methodological limitations of the 1970s studies that shaped the paradigm equating CO with hyperplastic obesity and AO with hypertrophic obesity [1–5]. These studies could not delineate which adipose tissue regions drove their findings because they lacked the technology to measure regional fat mass. The recent study by Arner et al. overcame this limitation using DXA-estimated android SAT and concluded that abdominal SAT morphology does not vary by age of obesity onset [12]. We enhanced their approach by directly measuring abdominal SAT with the gold standard, computed tomography, but concluded the opposite in females. Our studies differed in other important ways, which may explain the conflicting results. The study by Arner et al. classified overweight/obesity onset based on recalled body weight at age 18 years [12]. In contrast, we defined CO as obesity acquired pre- or peri-puberty, a sensitive period for body fat accrual, and we verified the age of obesity onset with photographic evidence and body rating scales. Moreover, we employed narrow inclusion criteria that resulted in groups well-matched for potential confounders, including age and health status.

Collectively, findings from prospective studies align with the greater abdominal SAT hypertrophy in our females with AO and the greater femoral SAT hyperplasia in our males and females with AO compared with their counterparts with CO. A longitudinal study found that children with obesity enter adulthood with greater gluteal adipocyte size and number than lean children [30]. Based on cross-sectional studies comparing lean adults with those with obesity [1, 5, 31], we anticipate this finding to be consistent across SAT regions. To our knowledge, no studies have examined how continued weight gain in adults with CO affects SAT cellularity. However, an overfeeding study showed that lean adults gained SAT primarily through hypertrophy in the abdominal region and hyperplasia in the femoral region [8]. This study also showed that baseline adipocyte size determined how adipose tissue expanded. Femoral SAT hyperplasia

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TABLE 3 Abdominal and femoral SAT cellularity by sex and obesity onset.

	Females		Males		Effect (p value)		
Cellularity	CO ($n = 16$)	AO ($n = 13$)	CO ($n = 8$)	AO ($n = 8$)	Obesity onset	Sex	Obesity onset × sex
Abdominal SAT cellularity							
Mean adipocyte volume (pL)	679 (491 to 868)	1187 (978 to 1396)[d]	1051 (784 to 1317)	1010 (743 to 1276)	0.052	0.409	0.023
Mean adipocyte volume (pL)[a]	682 (488 to 876)	1189 (976 to 1402)[d]	1059 (776 to 1342)	992 (663 to 1321)	0.117	0.476	0.039
Adipocyte number ($\times 10^9$)[b]	5.0 (4.0 to 6.4)	2.7 (2.1 to 3.5)	3.5 (2.5 to 4.9)	2.0 (1.4 to 2.8)	<0.001	0.034	0.832
Adipocyte number ($\times 10^9$)[a,b]	4.7 (3.8 to 5.9)	2.6 (2.0 to 3.3)	3.0 (2.2 to 4.2)	2.8 (1.9 to 4.1)	0.034	0.200	0.094
Morphology index (pL)	−272 (−460 to −83)	236 (27 to 445)[d]	100 (−167 to 367)	59 (−208 to 325)	0.052	0.409	0.023
Femoral SAT cellularity							
Mean adipocyte volume (pL)	959 (759 to 1158)	902 (681 to 1123)	1097 (815 to 1379)	517 (235 to 799)[e]	0.014	0.321	0.040
Mean adipocyte volume (pL)[c]	955 (751 to 1159)	890 (648 to 1131)	1101 (814 to 1389)	539 (209 to 870)	0.017	0.495	0.070
Adipocyte number ($\times 10^9$)[b]	9.0 (6.8 to 11.8)	10.4 (7.7 to 14.1)	6.9 (4.7 to 10.1)	12.7 (8.6 to 18.6)	0.030	0.843	0.177
Adipocyte number ($\times 10^9$)[b,c]	8.6 (6.6 to 11.2)	9.1 (6.7 to 12.5)	7.3 (5.0 to 10.5)	16.1 (10.5 to 24.7)[e]	0.012	0.310	0.038
Morphology index (pL)	50 (−151 to 250)	−42 (−264 to 181)	227 (−56 to 13)	−262 (−546 to 21)	0.024	0.864	0.116

Note: Results are least-squares means (95% CI). When the obesity onset × sex interaction was statistically significant ($p < 0.05$), groups were compared with Tukey post hoc tests.

Abbreviations: AO, adult-onset obesity; CO, childhood-onset obesity; SAT, subcutaneous adipose tissue.

[a]Adjusted for android subcutaneous fat mass.

[b]Natural log-transformed prior to analysis with results presented as back-transformed values.

[c]Adjusted for gynoid fat mass.

[d]Different from females with CO, $p < 0.05$.

[e]Different from male individuals with CO, $p < 0.05$.

occurred at lower baseline femoral adipocyte sizes in males than females, and abdominal SAT hyperplasia occurred only in females with large baseline abdominal adipocytes [8]. A longitudinal study confirmed that, in lean female adults, abdominal adipocytes increase in both size and number after an 18% body weight gain over 10 years [9].

Our study was also spurred by the conflicting concept that hyperplastic SAT is considered both a feature of CO [1–5] and metabolic health [6]; however, CO increases type 2 diabetes risk compared with AO [7]. By design, we studied young adults without any comorbidities, but those with CO still had higher HOMA-IR than those with AO. Given that excess adipose tissue is the first prerequisite for obesity, studying SAT expansion mechanisms via cellularity is a way to capture initial abnormalities that may, in turn, contribute to adipose tissue dysfunction and eventual disease risk. In our study, circulating adipokines and cardiometabolic risk factors did not consistently correlate with SAT hypertrophy or hyperplasia in any group. Because this analysis was exploratory, the correlations should be interpreted with caution. It is possible that studying participants with more variability in cardiometabolic risk factors would have captured more consistent correlations with SAT morphology. Nevertheless, we can draw from the current literature to understand how the distinct SAT cellularity profiles in males and females with CO and AO might impact cardiometabolic health over the long-term.

We found that increased femoral SAT hypertrophy distinguished both males and females with CO from those with AO. Although abdominal SAT hypertrophy has been extensively linked to insulin resistance, high-risk lipid profiles, and systemic inflammation and can even predict type 2 diabetes [6, 32], lower body SAT hypertrophy has been less well-studied. In males with obesity and hypertension, Achimastos et al. showed that gluteal adipocyte size associated with mean arterial pressure [33]. Across a wide adiposity range, Imbeault et al. reported that femoral adipocyte size correlated with fasting plasma insulin in premenopausal females and with high-risk lipid profiles in both males and premenopausal females [34]. Moreover, Espinosa De Ycaza et al. found that femoral adipocyte size correlated as strongly as abdominal subcutaneous adipocyte size with adipose tissue insulin resistance [35].

In our study, abdominal SAT hypertrophy was similar in males with CO and AO but was greater in females with AO than those with CO. This finding ignites the question of why hypertrophic femoral SAT in females with CO may be more harmful than hypertrophic abdominal SAT in females with AO. We hypothesize that the pathological potential of abdominal SAT hypertrophy in females with AO is offset by their hyperplastic femoral SAT, which can still safely accommodate lipids. Conversely, in females with CO, limited lipid storage capacity in metabolically protective femoral SAT could promote lipid storage in more harmful abdominal SAT and VAT depots, as observed after lower body SAT lipectomy [36]. Our previous findings in female bariatric surgery patients (mean BMI = 48 kg/m^2) with CO and AO matched for BMI and diabetes prevalence supports this hypothesis [37]. Although we did not examine lower body SAT, we found that abdominal subcutaneous adipocyte size did not differ between obesity onset groups [37]. Because males have lower gluteofemoral fat storage capacity than females [38], it

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is possible that abdominal SAT turns hypertrophic at a lower obesity severity in males with CO.

It is also plausible that abdominal adipocytes in females with CO become dysfunctional at a lower size threshold. According to the expandability hypothesis, enlarged adipocytes indicate impaired adipogenic potential [39]. Both enlarged adipocytes and reduced adipogenesis have been linked to senescent preadipocytes in abdominal SAT [40]. Correspondingly, we have previously shown that females with CO have more senescent preadipocytes in abdominal and femoral SAT than those with AO [17]. Even though females with CO have hyperplastic abdominal and hypertrophic femoral SAT, their abdominal SAT has more senescent preadipocytes than their femoral SAT [17]. In females with CO, we found that abdominal SAT hypertrophy correlated with MCP-1, a chemokine that attracts monocytes and is linked to macrophage infiltration [41]. A study in children with obesity showed that subcutaneous adipocyte size associated with macrophage infiltration, systemic inflammation, and insulin resistance [42]. Therefore, the pathological nature of enlarged adipocytes, even in predominantly hyperplastic SAT, may begin in childhood.

An alternative view is that hyperplasia is not a benign expansion mechanism. White et al. showed that, in lean males, an increase in proportion of small adipocytes during overfeeding correlated with visceral and ectopic fat accumulation [10]. They also showed that, in females with obesity, in vivo adipogenesis in both abdominal and femoral SAT related to VAT and insulin resistance [11]. In our study, femoral SAT hyperplasia correlated with inflammatory markers and cardiometabolic risk factors in females with AO and males with CO and AO. Another interesting observation was that males with AO had a VAT mass similar to those with CO despite having lower total adiposity. We suspect that the femoral SAT hyperplasia in AO may not be as protective in males as it is in females. We hypothesize that, in males, hyperplasia may reflect failed adipocyte hypertrophy. The hypertrophic femoral SAT in males with CO may be due to the greater capacity for peripheral SAT expansion in childhood. After puberty, central adipose tissue expansion predominates in males. Others have shown that both a high proportion of small adipocytes and an increased peak diameter of large adipocytes associate with cardiometabolic risk [43]. This characteristic adipocyte size distribution has even been seen in insulin-resistant children with a high ratio of visceral to subcutaneous abdominal fat [44]. Therefore, both SAT hypertrophy and hyperplasia may contribute to cardiometabolic risk. Further studies are needed to elucidate the mechanisms.

We used the collagenase digestion method to measure adipocyte size. Although this is a common and well-accepted methodology, it yields one adipocyte population and is limited to a measure of mean adipocyte size. We therefore could not examine the small and large adipocyte populations that are identified with the osmium tetroxide technique. Our study is also limited by its small sample size. Larger studies, especially in males, are required to replicate our findings. We acknowledge that we cannot generalize our findings to adults with severe obesity or comorbidities.

The present study challenges the view that SAT is uniformly hyperplastic in CO and hypertrophic in AO. For the first time, we found that this cellularity-based classification of CO and AO depends on sex and does not apply to all SAT regions. We found that hyperplastic abdominal SAT was characteristic of CO in females only, whereas hyperplastic femoral SAT was characteristic of AO in both males and females. Longitudinal studies are necessary to clarify when regional SAT hypertrophy and hyperplasia diverge in males and females with different ages of obesity onset. Future studies are also required to better understand the cardiometabolic consequences of regional SAT hyperplasia versus hypertrophy in adults with newly acquired versus lifelong obesity.

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CONFLICT OF INTEREST STATEMENT

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