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Visceral and intrahepatic fat are associated with cardiometabolic risk factors above other ectopic fat depots: The Framingham Heart Study

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Abstract

Background—Obesity is a heterogeneous condition and specific patterns of body fat distribution are differentially associated with cardiometabolic risk factors. It is not currently known which fat depots contribute most to individual cardiometabolic risk factors. We examined the associations among eight different fat depots accumulated in various anatomical regions and the relationship between these fat depots and multiple cardiometabolic risk factors.

Methods—Participants were from the Framingham Heart Study Offspring (seventh examination) and Third Generation (first examination) who also participated in the multi-detector computed tomography sub-study between 2002 and 2005. Exposures were multi-detector computed tomography-derived fat depots, including abdominal subcutaneous adipose tissue, abdominal visceral adipose tissue, intramuscular fat, intrathoracic fat, pericardial fat, thoracic periaortic fat, intrahepatic fat, and renal sinus fat. Multivariable-adjusted regression analyses with a forward selection procedure were performed to identify the most predictive fat depots.

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Results—Of 2,529 participants, 51.9% were women (mean age 51.1 years). Visceral adipose tissue had the strongest correlations with each of the other fat measures (ranging from 0.26 to 0.77), as well as with various cardiometabolic risk factors (ranging from -0.34 to 0.39). As determined by the selection models, visceral adipose tissue was the only fat depot that was associated with all cardiometabolic risk factors evaluated in this study (all $p < 0.05$). Selection models also showed that subcutaneous adipose tissue and intrahepatic fat were associated with cardiometabolic risk factors related to the traits of dysglycemia, dyslipidemia, and hypertension (all $p < 0.05$). However, only associations with visceral adipose tissue and intrahepatic fat persisted after further adjustment for BMI and waist circumference.

Conclusions—Visceral adipose tissue and intrahepatic fat were consistent correlates of cardiometabolic risk factors, above and beyond standard anthropometric indices. Our data provide important insights for understanding the associations between variations in fat distribution and cardiometabolic abnormalities.

Keywords

Ectopic fat; cardiometabolic risk factors; epidemiology; computed tomography

Introduction

Obesity affects more than one-third¹ of U.S. adults and is a primary risk factor for cardiovascular morbidity² and mortality.^{3, 4} The body mass index (BMI) is the most commonly used measure to assess the risk involved with adiposity-related metabolic derangements. However, individuals with similar BMIs have different cardiometabolic risk, suggesting that obesity is a heterogeneous condition.^{5, 6} Accordingly, specific patterns of body fat distribution may be differentially associated with cardiometabolic abnormalities.^{6, 7}

Weight gain induces expansion of fat in ectopic sites, such as the heart, liver, kidney, muscles, vasculature, and viscera, which systemically or locally contributes to manifestations of cardiometabolic disease.⁶ These fat depots can be quantified on advanced imaging techniques, such as multi-detector computed tomography (MDCT) and magnetic resonance imaging (MRI).^{6, 7} A large set of participants in the Framingham Heart Study were assessed by MDCT to characterize various adipose tissue depots. Using that data, we have previously shown that higher region-specific fat measures, including abdominal subcutaneous, abdominal visceral adipose tissue,⁸⁻¹⁰ intramuscular fat,¹¹ intrathoracic fat,^{12, 13} pericardial fat,^{12, 13} thoracic periaortic fat,^{14, 15} intrahepatic fat,¹⁶ and renal sinus fat,¹⁷ are individually associated with more adverse cardiometabolic risk factors.^{8, 9, 11-16} Importantly, the magnitude of the association between each fat measure and cardiometabolic related traits varied by fat depot type, suggesting that the potential adverse contribution of fat measure on cardiometabolic health are not the same. Yet, current literature lacks studies that systemically explored the associations between various fat depots accumulated in different anatomical regions and a broad array of cardiometabolic risk factors simultaneously. Accordingly, it is not currently known which fat depots contribute most to individual cardiometabolic risk factors. Thus, we examined the associations of eight different fat depots and the associations between these fat depots and a comprehensive list of cardiometabolic risk factors by leveraging our rich data sources. This study is the first to

compare the relative importance of eight distinct MDCT-derived fat depots in relation to multiple cardiometabolic risk factors among participants in a large and well-characterized community-dwelling epidemiological study.

Methods

Methods are available in the Supplemental Materials.

Results

Study sample characteristics

Descriptive statistics given in Table 1 describe the demographic, physical, clinical, and lifestyle characteristics of the study participants. The mean age was 51.1 years and 51.9% were women. Hypertriglyceridemia showed the highest prevalence rate (33%), followed by metabolic syndrome (29.8%), hypertension (28.1%), and low HDL cholesterol (26.9%). Diabetes mellitus was least prevalent (5.8%), followed by high LDL cholesterol (9.4%).

Associations among the fat measures

A heat map depicting the age- and sex- adjusted Pearson correlation coefficients between fat measures is given in Figure 1a. All fat measures, including MDCT-acquired fat depots, BMI, and waist circumference were correlated with each other (all $p < 0.05$). However, the strength of these associations varied greatly. In particular, visceral adipose tissue had the strongest correlations (highest magnitudes) with each of the MDCT-derived fat depot. Both subcutaneous and visceral adipose tissue were highly correlated with BMI and waist circumference (r-values ranging from 0.72 to 0.88). Intramuscular fat, intrahepatic fat, and renal sinus fat were only weakly to moderately correlated with all the other fat measures evaluated. Similar patterns of the associations were observed in both women and men (Supplemental Figure 1a).

Associations between the fat measures and cardiometabolic risk factors

The associations between fat measures and continuous cardiometabolic risk factors are visually presented in a heat map (Figure 1b). Higher fat measures were associated with higher systolic blood pressure, diastolic blood pressure, fasting plasma glucose, total cholesterol, LDL cholesterol, triglycerides and lower HDL cholesterol. Among the MDCT-derived fat depots, visceral adipose tissue showed the strongest correlations with each of the cardiometabolic risk factors. Among the cardiometabolic risk factors, the strongest correlations were observed with triglycerides. Total cholesterol and LDL cholesterol were only weakly associated with the fat measures (strongest correlation, $r = 0.12$).

In the sex-stratified analyses, most of the fat measures were significantly associated with total and LDL cholesterol in women; whereas, in men, a majority of the associations between fat measures with total and LDL cholesterol were statistically non-significant (Supplemental Figure 1b). In the BMI-stratified analyses, a majority of the associations between MDCT-derived fat depots and cardiometabolic risk factors shown by correlation coefficients were stronger among participants with BMI ≥ 25 kg/m² or higher (Supplemental

Figure 2b), as compared to the participants with BMI less than 25kg/m². (Supplemental Figure 2a).

Fat measures as risk factor correlates of cardiometabolic risk profile

Stepwise forward selection regression analyses identified the subset of MDCT-acquired fat depots that were associated with continuous (Table 2) and categorical (Table 3) cardiometabolic risk factors. Visceral adipose tissue was identified via the selection procedure in each of the cardiometabolic risk factor models. After further adjustment for BMI, visceral adipose tissue remained associated with all cardiometabolic risk factors, with the exception of diabetes mellitus. Similar results were obtained for models that were additionally adjusted for waist circumference instead of BMI (data not shown).

The stepwise forward selection regression analysis identified subcutaneous adipose tissue in half of the risk factor models including those predicting: BMI, systolic blood pressure, diastolic blood pressure, LDL cholesterol, obesity, hypertension, diabetes mellitus, and metabolic syndrome. However, additional adjustment for BMI or waist circumference substantially attenuated these associations (all $p>0.05$). Additional adjustment for BMI changed the direction of some of the associations between subcutaneous adipose tissue and cardiometabolic risk factors (i.e., subcutaneous adipose tissue with systolic blood pressure, hypertension, diabetes mellitus, and metabolic syndrome in Tables 2 and 3), however none of these associations were statistically significant (all $p>0.05$).

Similarly, intrahepatic fat was selected in more than half of the cardiometabolic risk factor models, including those predicting systolic blood pressure, diastolic blood pressure, fasting plasma glucose, log triglycerides, hypertension, diabetes, low HDL, hypertriglyceridemia, and metabolic syndrome. Intrahepatic fat remained associated with all of these cardiometabolic risk factors even after further adjustment for BMI or waist circumference (separately).

When we used lower cutoff points for defining hypercholesterolemia (>200 mg/dL) and high LDL cholesterol (>100 mg/dL), visceral adipose tissue and renal sinus fat were selected as significant predictors of hypercholesterolemia; however, for high LDL cholesterol, only renal sinus fat was selected as a predictor (Supplemental Table 1).

Sex-stratified analysis

The trends of the associations identified in the sex-pooled analysis were generally consistent with the results of the sex-stratified analysis (Supplemental Tables 2 and 3). In particular, the direction of the associations was generally consistent between women and men. In women, visceral adipose tissue was consistently associated with all the cardiometabolic risk factors evaluated regardless of the additional adjustment for BMI or waist circumference. In contrast, several exceptions were noted in men.

Discussion

Principal findings

Our investigation explored associations among a broad list of region-specific fat measures, including radiographic measures of fat depots and traditional anthropometric measures of adiposity. Our principal findings are three-fold. First, visceral adipose tissue generally showed the highest correlations with all of the other fat measures. While subcutaneous and visceral adipose tissue were both strongly correlated with BMI and waist circumference, intrahepatic fat was not, which may indicate that BMI and waist circumference are poor surrogates for intrahepatic fat. Second, visceral adipose tissue was the only fat depot that was consistently associated with each cardiometabolic risk factor evaluated, and these associations were attenuated, but generally remained, after additional adjustment for BMI or waist circumference. While subcutaneous adipose tissue was included in the selection models for many cardiometabolic risk factors, these associations were attenuated and no longer statistically significant after BMI or waist circumference was added to the multivariable-adjusted model indicating that subcutaneous adipose tissue does not contribute to cardiometabolic risk factors beyond a measure of generalized or central adiposity. Intrahepatic fat was also associated with multiple cardiometabolic risk factors related to glucose and lipid metabolism, as well as measures of hypertension, and these associations remained even after adjustment for the standard anthropometric indices. Finally, in addition to visceral adipose tissue, subcutaneous adipose tissue and intrahepatic fat, we identified differential associations between various fat depots (i.e., intramuscular fat, intrathoracic fat, pericardial fat, thoracic periaortic fat, and renal sinus) and cardiometabolic risk factors.

Potential mechanisms

The most compelling finding of this investigation was that among the eight MDCT-acquired fat depots, only visceral adipose tissue was consistently associated with each of the cardiometabolic risk factors. Although subcutaneous adipose tissue was also associated with multiple cardiometabolic risk factors, the association did not persist after adjustment of BMI or waist circumference. More specifically, additional adjustment of BMI attenuated the associations or changed the direction of the associations (all $p < 0.05$) that were observed between subcutaneous adipose tissue and cardiometabolic risk factors based on the multivariable-adjusted models. These findings are mainly due to the high correlation between subcutaneous adipose tissue and BMI ($r = 0.86$, $p < 0.05$), and suggesting that subcutaneous adipose tissue does not contribute to cardiometabolic risk factors beyond a measure of generalized or central adiposity.

Multiple lines of evidence support that abdominal subcutaneous and visceral adipose tissue are associated with different cardiometabolic consequences; in particular, a more adverse effect may be attributed to visceral adipose tissue.¹⁸ In the state of positive energy balance, expansion of visceral adipose tissue reflects an inability to expand fat depot subcutaneously due to the decreased capacity of subcutaneous adipose tissue hypertrophy, hyperplasia, and angiogenesis.¹⁸ As an active endocrine organ, the expansion of visceral adipose tissue is associated with overproduction of metabolically active substances, such as pro-inflammatory,^{18, 19} hemostasis, and fibrinolysis biomarkers²⁰ that mediate the relations with

cardiometabolic risk factors. As compared to subcutaneous adipose tissue, hypertrophy of visceral adipocytes was related to measures of insulin resistance²¹ where adipocyte size is an important determinant of cellular functionality.²² Taken together, visceral and subcutaneous adipose tissue may differentially contribute to cardiometabolic risk factors owing to their distinctive functions.

In this study, intrahepatic fat was associated with a number of cardiometabolic risk factors related to dysglycemia and dyslipidemia traits, as well as measures of blood pressure. This may be explained by the joint role of visceral adipose tissue and intrahepatic fat in glucose and lipid metabolism.²³ Expansion of visceral adipose tissue volume with concomitant enlargement of the adipocyte size has been associated with increased visceral adipose tissue lipolytic activity, substantially increasing the free fatty acids released from visceral adipose tissue to the liver via the portal vein by approximately 20%.²⁴ In response to the elevated hepatic fatty acids presented to the liver, the liver must store the non-esterified free acids in the form of triglycerides.²⁵ In addition, increased hepatic fatty acids may be responsible for hepatic insulin resistance and an increase in the production and release of very-low-density lipoprotein cholesterol.²⁵ Our findings support that both visceral and intrahepatic fat may be contributing fat depots for lipid regulation and metabolism. Yet, the precise mechanisms are still unclear.

In addition to our primary findings, we found no correlation or only weak correlations with total and LDL cholesterol and the MDCT-derived fat depots. Of note, metabolic syndrome is determined by the combination of physiological, biochemical, clinical, and metabolic factors.²⁶ Among the measures of lipid metabolism, only HDL cholesterol and triglycerides levels are used to define metabolic syndrome. In particular, total cholesterol and LDL cholesterol are risk factors of atherosclerotic cardiovascular disease, which does not directly fit into the category of metabolic disease traits. Collectively, we have shown that ectopic fat depots are more strongly associated metabolic risk factors, rather than clustering risk factors for atherosclerotic heart disease.

It is well-established that risk of cardiometabolic disease increases with both increasing age and fat accumulation, while accumulation of fat also increases with advanced age.^{10, 27-30} In a similar context, demographic and lifestyle factors, such as sex, smoking status, alcohol use, physical activity, postmenopausal status, and hormone replacement therapy, are also considered as traditional risk factors for cardiometabolic disease, that are also related to accumulation of fat.³¹⁻³⁷ Accordingly, the relationships between fat measures and cardiometabolic risk factors are not uniform across individuals with various demographic and lifestyle factors. This suggests that there are potential effects of measuring fat distributions at different ages and depending on various factors (e.g., alcohol intake, smoking status) in an individual's lifetime. And whether the effects of fat deposits are constant over time or only correlated with specific cardiometabolic risk factors will vary. Although adjusting for traditional risk factors (e.g., age and sex) statistically ruled out their contributions in a pooled analysis, the important issue of how adiposity affects disease risk in younger vs. older adults and in different factors would be obscured. The lack of association between fat measures and LDL cholesterol may be a measurement issue. Further studies that include more specific fat profiles, such as LDL particles, LDL size,

apolipoprotein B would be useful to confirm the associations between fat depots and lipid profiles.

Implications

This study adds an important facet to the obesity research spectrum in which, within the heterogeneity of fat distribution, visceral adipose tissue and, to a lesser degree, intrahepatic fat, are the fat depots most closely associated with multiple cardiometabolic risk factors, above and beyond generalized and central adiposity. BMI is the most cost effective method to determine overall obesity status that can predict cardiometabolic disease risk. Accordingly, BMI is ideal for preliminary screening in clinical and field settings. However, the sensitivity involved with screening populations by this method is relatively crude because the index does not provide information on body fat distribution, such as visceral and subcutaneous fat. Our findings add to evidence that imaging fat volume provides important clues to cardiometabolic risk that BMI may not explain. In regards to the preventive implications of the present study, our findings support that making recommendations solely by BMI may result in misclassifying individuals at high risk for those who are “metabolically healthy obese”. And those who are “metabolically unhealthy non-obese” and “metabolically unhealthy normal weight” will be misclassified as being at lower risk.^{38, 39} To date, CT and MRI are the gold standard for noninvasively measuring abdominal visceral fat. More cost-effective methods for assessing abdominal visceral fat are needed before screening at risk populations can be recommended.

Our work also demonstrated associations between intramuscular fat, intrathoracic fat, pericardial fat, thoracic periaortic fat, and renal sinus fat with several different cardiometabolic risk factors, supporting that these fat depots should not be overlooked as pathologic fat depots contributing to cardiometabolic disease. Future studies are warranted to explore the biology of ectopic adipose tissue storage to precisely decipher the pathogenicity of excess adiposity.

In the context of the current literature, strengths, and limitations

Additional discussions on our findings in the context of current literature, strengths and limitations are described in Supplemental Materials.

Conclusions

On the basis of a community-based epidemiologic study, visceral adipose tissue was consistently associated with all cardiometabolic risk factors evaluated in this study. subcutaneous adipose tissue and intrahepatic fat were associated with multiple cardiometabolic traits related to glucose and lipid metabolism, as well as measures of blood pressure. However, these associations only remained significant for visceral and intrahepatic fat above and beyond the contribution of generalized obesity and central adiposity. Our findings highlight the importance of the role of ectopic fat distribution for a better understanding of the metabolic complications of obesity.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Clinical Significance

- Relation of eight fat measurements and cardiometabolic risk factors were assessed.
- Eight different fat depots accumulated in various anatomical regions were evaluated.
- Visceral adipose tissue was consistently associated with cardiometabolic risk factors.
- Intrahepatic fat was also associated with multiple cardiometabolic risk factors.
- These associations were independent of standard anthropometric indices.

Figure 1.

Heat map of the association a) among fat measures; b) between fat measures and cardiometabolic risk factors based on age and sex-adjusted partial Pearson correlation coefficients (r). The color depth of each cell represents the magnitude of the absolute values of the correlation coefficients from low ($|r|=0$ for **Figure 1a and 1b**; yellow) to high ($|r|=1$

for **Figure 1a** and $|r|=0.5$ for **Figure 1b**; red). Unless otherwise specified, all results were significant at $p<0.05$. ^a $p>0.05$. For **Figure 1b**, correlation coefficients associated with higher abdominal subcutaneous adipose tissue and visceral adipose tissue, intrathoracic fat, pericardial fat, thoracic periaortic fat, and renal sinus fat; and lower intramuscular fat and intrahepatic fat are presented. Abbreviations: HDL, high-density lipoprotein; LDL, low-density lipoprotein; MDCT, multi-detector computed tomography.

Table 1

Characteristics of the study sample.

Characteristics	Women (n=1313)	Men (n=1216)	Overall Participants (n=2529)
Demographics			
Age, ^a years	51.9 (9.8)	50.2 (10.8)	51.1 (10.3)
Adiposity Measures			
Body Mass Index, kg/m ²	26.8 (5.8)	28.0 (4.5)	27.4 (5.2)
Waist Circumference, cm	92.5 (15.6)	99.7 (11.6)	96.0 (14.3)
Subcutaneous Adipose Tissue, cm ³	3082 (1503)	2503 (1152)	2804 (1377)
Visceral Adipose Tissue, cm ³	1325 (820)	2172 (1042)	1733 (1025)
Intramuscular Fat, HU	54.4 (6.4)	57.6 (6.5)	56.0 (6.6)
Intrathoracic Fat, cm ³	65.6 (40.2)	123.4 (63.0)	93.4 (59.8)
Pericardial Fat, cm ³	99.7 (38.1)	122.6 (45.4)	110.7 (43.3)
Thoracic Periaortic Fat, cm ³	9.7 (5.3)	16.8 (8.6)	13.1 (7.9)
Intrahepatic Fat, liver phantom ratio	0.36 (0.05)	0.36 (0.06)	0.36 (0.05)
Renal Sinus Fat, ^b cm ²	0.19 (0.05-0.43)	0.43 (0.19-0.89)	0.28 (0.10-0.63)
Cardiometabolic Risk Factors			
Systolic Blood Pressure, mmHg	119.8 (17.6)	123.1 (14.8)	121.4 (16.4)
Diastolic Blood Pressure, mmHg	73.4 (9.2)	77.4 (9.1)	75.3 (9.3)
Fasting Plasma Glucose, mg/dL	95.5 (17.9)	101.7 (23.8)	98.5 (21.1)
Total Cholesterol, mg/dL	197.7 (35.7)	194.4 (33.8)	196.1 (34.8)
LDL Cholesterol, mg/dL	113.9 (32.7)	121.8 (30.4)	117.7 (31.9)
HDL Cholesterol, mg/dL	61.5 (16.4)	47.1 (12.4)	54.6 (16.3)
Triglycerides, ^b mg/dL	94.0 (66-139)	108.5 (73-162)	101.0 (70-150)
Overweight, ^c %	55.0 (722)	74.3 (903)	64.3 (1625)
Obesity, ^c %	23.8 (313)	26.2 (319)	25.0 (632)
Hypertension, %	26.2 (344)	30.1 (366)	28.1 (710)
Diabetes Mellitus, %	5.2 (68)	6.5 (79)	5.8 (147)
Hypercholesterolemia, %	19.8 (260)	25.6 (311)	22.6 (571)
High LDL Cholesterol, %	8.2 (108)	10.6 (129)	9.4 (237)

Characteristics	Women (n=1313)	Men (n=1216)	Overall Participants (n=2529)
Low HDL Cholesterol, %	24.8 (326)	29.2 (355)	26.9 (681)
Hypertriglyceridemia, %	26.1 (343)	40.4 (491)	33.0 (834)
Metabolic Syndrome, %	26.4 (346)	33.6 (408)	29.8 (754)
Lifestyle Factors			
Current Smoking, %	12.0 (158)	13.4 (163)	12.7 (321)
Moderate to Heavy Alcohol Use, %	15.0 (197)	16.7 (203)	15.8 (400)
Diabetes Treatment, %	2.8 (37)	3.2 (39)	3.0 (76)
Antihypertensive Treatment, %	18.8 (247)	18.2 (221)	18.5 (468)
Lipid-Lowering Treatment, %	9.4 (124)	17.2 (209)	13.2 (333)
Postmenopausal Status, %	50.9 (668)	-	-
Hormone Replacement Therapy, %	19.9 (261)	-	-

Unless otherwise indicated, data are shown as means (standard deviations) for continuous variables or percentages (counts) for dichotomous variables.

^aMedian (25th-75th percentile) age of our participants was 50.0 (44.0-58.0) years for women; 49.0 (42.0-57.0) for men; and 49.0 (43.0-58.0) for overall participants.

^bValues were shown as median (25th-75th percentile) due to their skewed distribution.

^cOverweight was defined as BMI 25 kg/m² or higher and less than 30 kg/m²; obesity was defined as BMI 30 kg/m² or higher.

Percentages (counts) for hypercholesterolemia defined based on the cutoff point of >200 mg/dL was 49.5% (650) for women; 53.9% (655) for men; and 51.6% (1305) for overall participants. Percentages (counts) for high LDL defined based on the cutoff point of >100 mg/dL was 64.1% (841) for women; 75.2% (914) for men; and 69.4% (1755) for overall participants.

Abbreviations: BMI, body mass index; HDL, high-density lipoprotein; HU, Hounsfield unit; LDL, low-density lipoprotein.

Table 2

Associations between continuous cardiometabolic risk factors and MDCT-acquired fat depots (as determined by stepwise forward selection).

Cardio-metabolic Risk Factors	Model Type ^a	Effect Size	MDCT-Acquired Fat Depots							
			Subcutaneous Adipose Tissue	Visceral Adipose Tissue	Intramuscular Fat	Intrathoracic Fat	Pericardial Fat	Thoracic Periaortic Fat	Intrahepatic Fat	Renal Sinus Fat
BMI	MV	β (95% CI)	3.60 (3.48,3.73)	1.75 (1.61,1.90)	0.14 (0.03,0.26)					
		<i>P</i> Value	<.001	<.001	0.02					
Systolic Blood Pressure ^b	MV	β (95% CI)	1.75 (0.99,2.51)	1.95 (1.02,2.87)					0.99 (0.37,1.61)	
		<i>P</i> Value	<.001	<.001					0.002	
	MV+ BMI	β (95% CI)	-0.07 (-1.21,1.07)	1.12 (0.12,2.12)					0.95 (0.34,1.57)	
		<i>P</i> Value	0.91	0.03					0.002	
Diastolic Blood Pressure ^b	MV	β (95% CI)	1.03 (0.56,1.49)	1.71 (1.05,2.36)			-0.57 (-1.05,-0.09)		0.49 (0.11,0.86)	0.53 (0.08,0.97)
		<i>P</i> Value	<.001	<.001			0.02		0.01	0.02
	MV+ BMI	β (95% CI)	0.27 (-0.43,0.96)	1.35 (0.66,2.05)			-0.56 (-1.03,-		0.47 (0.10,0.84)	0.52 (0.08,0.97)
		<i>P</i> Value	0.45	<.001			0.02		0.01	0.02
Fasting Plasma Glucose ^c	MV	β (95% CI)		6.45 (5.15,7.75)		-2.26 (-3.57,-0.95)			0.95 (0.20,1.69)	
		<i>P</i> Value		<.001		<.001			0.01	
	MV+ BMI	β (95% CI)		4.18 (2.62,5.74)		-2.07 (-3.37,-0.77)			0.92 (0.18,1.66)	
		<i>P</i> Value		<.001		.002			0.01	
Total Cholesterol ^d	MV	β (95% CI)		5.05 (2.52,7.58)				-2.91 (-5.49,-0.32)		2.98 (1.29,4.68)
		<i>P</i> Value		<.001				0.03		<.001
	MV+ BMI	β (95% CI)		4.86 (1.92,7.80)				-2.91 (-5.50,-		2.97 (1.27,4.67)
		<i>P</i> Value		0.001				0.03		<.001
LDL Cholesterol ^d	MV	β (95% CI)	1.70 (0.12,3.29)	5.55 (3.05,8.04)				-2.91 (-5.26,-0.56)		
		<i>P</i> Value	0.04	<.001				0.02		
	MV+ BMI	β (95% CI)	1.53 (-0.86,3.92)	5.47 (2.85,8.09)				-2.92 (-5.27,-		
		<i>P</i> Value	0.21	<.001				0.02		
HDL Cholesterol ^d	MV	β (95% CI)		-5.99 (-6.63,-5.36)	-1.08 (-1.74,-0.42)					
		<i>P</i> Value		<.001	0.001					
	MV+ BMI	β (95% CI)		-4.41 (-5.30,-	-1.08 (-1.73,-0.43)					
		<i>P</i> Value								

Cardio-metabolic Risk Factors	Model Type ^a	Effect Size	MDCT-Acquired Fat Depots							
			Subcutaneous Adipose Tissue	Visceral Adipose Tissue	Intramuscular Fat	Intrathoracic Fat	Pericardial Fat	Thoracic Periaortic Fat	Intrahepatic Fat	Renal Sinus Fat
Log Triglycerides ^d		<i>P</i> Value		<.001	0.001					
		β (95% CI)		0.22 (0.18,0.25)	0.03 (0.01,0.06)	-0.04 (-0.08,-0.01)			0.06 (0.04,0.08)	0.06 (0.04,0.08)
	MV	<i>P</i> Value		<.001	0.004	0.01			<.001	<.001
		β (95% CI)		0.18 (0.14,0.23)	0.03 (0.01,0.06)	-0.04 (-0.08,-0.01)			0.06 (0.04,0.08)	0.06 (0.03,0.08)
		<i>P</i> Value		<.001	0.004	0.02			<.001	<.001
		MV + BM								

Data are shown as β coefficients (95% CIs) and *P*-values. The β coefficients describe the association with continuous cardiometabolic risk factor per 1 standard deviation decrement in intramuscular fat and intrahepatic fat; and per 1 standard deviation increment in other MDCT-acquired fat depots. Shaded cells indicate that the fat measures were not selected via the stepwise forward selection regression procedure.

^aMV model included following covariates: age, sex, current smoking, alcohol use, physical activity index, postmenopausal status (women only), and hormone replacement therapy (women only). BMI was additionally adjusted for in the models labelled ‘‘MV+BMI model.’’

^bAntihypertensive treatment was included as a covariate for systolic and diastolic blood pressure models.

^cDiabetes treatment was included as a covariate for fasting plasma glucose model.

^dLipid-lowering treatment was included as a covariate for total cholesterol, LDL cholesterol, HDL cholesterol, and triglycerides models. Abbreviations: BMI, body mass index; CI, confidence interval; HDL, high-density lipoprotein; LDL, low-density lipoprotein; MDCT, multi-detector computed tomography; MV, multivariable model.

Table 3

Associations between dichotomous cardiometabolic risk factors and MDCT-acquired fat depots (as determined by stepwise forward selection).

Cardiometabolic Risk Factors	Model Type ^a	Effect Size	MDCT-Acquired Fat Depots				
			Subcutaneous Adipose Tissue	Visceral Adipose Tissue	Intramuscular Fat	Intrahepatic Fat	Renal Sinus Fat
Obesity	MV	OR (95% CI)	14.20 (10.72, 18.79)	4.69 (3.71, 5.92)			
		<i>p</i>	<.001	<.001			
Hypertension	MV	OR (95% CI)	1.15 (1.01, 1.31)	1.55 (1.32, 1.82)		1.27 (1.15, 1.40)	1.22 (1.05, 1.41)
		<i>p</i>	0.03	<.001		<.001	0.008
	MV+BMI	OR (95% CI)	0.82 (0.68, 1.00)	1.32 (1.11, 1.57)		1.26 (1.15, 1.40)	1.21 (1.05, 1.40)
		<i>p</i>	0.05	0.002		<.001	0.009
Diabetes Mellitus	MV	OR (95% CI)	1.36 (1.10, 1.68)	1.51 (1.21, 1.89)		1.28 (1.11, 1.48)	
		<i>p</i>	0.005	<.001		<.001	
	MV+BMI	OR (95% CI)	0.69 (0.50, 0.95)	1.13 (0.89, 1.45)		1.27 (1.10, 1.48)	
		<i>p</i>	0.02	0.32		0.001	
Hyper-cholesterolemia	MV	OR (95% CI)		1.50 (1.34, 1.67)			
		<i>p</i>		<.001			
	MV+BMI	OR (95% CI)		1.46 (1.25, 1.71)			
		<i>p</i>		<.001			
High LDL Cholesterol	MV	OR (95% CI)		1.25 (1.08, 1.45)			
		<i>p</i>		0.003			
	MV+BMI	OR (95% CI)		1.31 (1.06, 1.62)			
		<i>p</i>		0.01			
Low HDL Cholesterol	MV	OR (95% CI)		2.02 (1.78, 2.29)	0.81 (0.71, 0.92)	1.17 (1.06, 1.29)	
		<i>p</i>		<.001	0.001	0.001	
	MV+BMI	OR (95% CI)		1.72 (1.46, 2.04)	0.81 (0.71, 0.92)	1.17 (1.06, 1.29)	
		<i>p</i>		<.001	0.001	0.002	
Hyper-triglyceridemia	MV	OR (95% CI)		1.79 (1.57, 2.04)		1.22 (1.10, 1.34)	1.23 (1.08, 1.40)
		<i>p</i>		<.001		<.001	0.003
	MV+BMI	OR (95% CI)		1.69 (1.43, 1.99)		1.21 (1.10, 1.34)	1.22 (1.07, 1.40)
		<i>p</i>		<.001		<.001	0.003

Cardiomatabolic Risk Factors	Model Type ^a	Effect Size	MDCT-Acquired Fat Depots			
			Subcutaneous Adipose Tissue	Visceral Adipose Tissue	Intramuscular Fat	Intrahepatic Fat
Metabolic Syndrome	MV	OR (95% CI)	1.46 (1.27, 1.68)	3.35 (2.79, 4.01)		1.33 (1.19, 1.49)
		<i>p</i>	<.001	<.001		<.001
	MV+BMI	OR (95% CI)	0.85 (0.69, 1.05)	2.62 (2.15, 3.18)		1.33 (1.19, 1.48)
		<i>p</i>	0.13	<.001		<.001

Data are shown as ORs (95% CIs) and *p*-values. Intrathoracic fat, pericardial fat, and thoracic periaortic fat are not included in the table as those fat depots were not selected for any of the outcomes (cardiomatabolic risk factors) via the stepwise forward selection regression procedure. The ORs describe the association with dichotomous cardiomatabolic risk factors per 1 standard deviation decrement in intramuscular fat and intrahepatic fat; and per 1 standard deviation increment in other MDCT-acquired fat depots. Shaded cells indicate that the fat measures were not selected via the stepwise forward selection regression procedure.

^aMV model was adjusted for following covariates: age, sex, current smoking, alcohol use, physical activity index, postmenopausal status (women only), and hormone replacement therapy (women only). BMI was additionally adjusted for in the models labeled "MV+BMI model."

Abbreviations: BMI, body mass index; CI, confidence interval; HDL, high-density lipoprotein; LDL, low-density lipoprotein; MDCT, multi-detector computed tomography; MV, multivariable model; OR, odds ratio.