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Abdominal visceral and subcutaneous adipose tissue and associations with cardiometabolic risk in Inuit, Africans and Europeans: a cross-sectional study

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ABSTRACT

Objectives Abdominal fat has been identified as a risk marker of cardiometabolic disease independent of overall adiposity. However, it is not clear whether there are ethnic disparities in this risk. We investigated the associations of visceral adipose tissue (VAT) and abdominal subcutaneous adipose tissue (SAT) with cardiometabolic risk factors in three ethnic diverse populations of Inuit, Africans and Europeans.

Design Cross-sectional pooled study.

Setting Greenland, Kenya and Denmark.

Methods A total of 5113 participants (2933 Inuit, 1397 Africans and 783 Europeans) from three studies in Greenland, Kenya and Denmark were included. Measurements included abdominal fat distribution assessed by ultrasound, oral glucose tolerance test, hepatic insulin resistance, blood pressure and lipids. The associations were analysed using multiple linear regressions.

Results Across ethnic group and gender, an increase in VAT of 1 SD was associated with higher levels of hepatic insulin resistance (ranging from 14% to 28%), triglycerides (8% to 16%) and lower high-density lipoprotein cholesterol (HDL-C, −1.0 to −0.05 mmol/L) independent of body mass index. VAT showed positive associations with most of the other cardiometabolic risk factors in Inuit and Europeans, but not in Africans. In contrast, SAT was mainly associated with the outcomes in Inuit and Africans. Of notice was that higher SAT was associated with higher HDL-C in African men (0.11 mmol/L, 95% CI: 0.03 to 0.18) and with lower HDL-C in Inuit (−0.07 mmol/L, 95% CI: -0.12 to −0.02), but not in European men (−0.02 mmol/L, 95% CI: −0.09 to 0.05). Generally weaker associations were observed for women. Furthermore, the absolute levels of several of the cardiometabolic outcomes differed between the ethnic groups.

Conclusions VAT and SAT were associated with several of the cardiometabolic risk factors beyond overall adiposity. Some of these associations were specific to ethnicity, suggesting that ethnicity plays a role in the pathway from abdominal fat to selected cardiometabolic risk factors.

Strengths and limitations of this study

► This study analysed the cardiometabolic risk related to visceral and subcutaneous abdominal fat in indigenous populations in Greenland and Kenya where the knowledge is scarce.
► We assessed abdominal fat using ultrasound, which is a low cost and accessible field method to be used on a large scale in logistic challenging settings.
► Missing data was handled using multiple imputation reducing the likelihood of bias.
► The cross-sectional design means that we cannot draw causal conclusions about the associations of abdominal fat and cardiometabolic risk.
► We did not have comparable information on dietary factors across the studies.

INTRODUCTION

The last few decades of research have established abdominal adipose tissue as a key factor and driver of the health risk related to overweight and obesity.[1] Visceral adipose tissue (VAT) has been identified as the more pathogenic depot contributing to the metabolic consequences of obesity both in cross-sectional and longitudinal studies,[2–4] whereas abdominal subcutaneous adipose tissue (SAT) has been linked with detrimental effects less consistently,[2 5] and may even be protective.[6] In addition, studies have found that the relative distribution of VAT and SAT varies across ethnic groups and suggested that this might explain differences in cardiometabolic disease between populations.[7 8] Studies suggest that African ancestry populations have less VAT than Europeans[8 9] whereas Asians have been found to be more prone to VAT accumulation at lower body mass index (BMI) values.[10] The impact of VAT and SAT on cardiometabolic health has been examined in several ethnic populations

including Chinese, Hispanics, South Asians, Canadian Aboriginals and African ancestry populations,[3 4 7 9 11 12] with some studies showing ethnic differences in the trend of the associations,[9 11 12] and others showing similar trends across ethnic groups.[3 4 7] Thus, it is not clear whether abdominal fat is associated differently with cardiometabolic risk factors beyond ethnic differences in absolute values of VAT and SAT. Neither is the effect of abdominal fat on cardiometabolic risk fully understood in all ethnic groups. However, considering the global burden of diabetes and cardiovascular disease (CVD) and rapidly changing countries with economic growth and changing life conditions in some parts of the world, this knowledge becomes increasingly important.

We recently showed ethnic differences in VAT and SAT in relation to simple anthropometric measures such as BMI and waist circumference in a population of Inuit, Africans and Europeans.[13] Inuit and Africans had lower levels of VAT and SAT for a given level of the anthropometric measures compared with Europeans, with most considerable differences in VAT at higher levels of the anthropometric measures. Inuit and European women, however, had similar SAT levels for a given BMI. Whether these results suggest that Inuit and Africans are less affected by VAT and/or SAT than Europeans, and to which extent this accounts for differences in cardiometabolic health between these populations needs to be clarified. Based on these findings, we aimed to examine whether VAT and SAT were associated differently with cardiometabolic risk factors in Inuit, Africans and Europeans.

MATERIALS AND METHODS
Study population
This study was based on pooled data from three cross-sectional studies (the Inuit Health in Transition Study, the Kenya Diabetes Study and Health2008) as described in our previous study.[13] In brief, the Inuit Health in Transition Study was a geographically representative, population-based study among Inuit (18+ years) in Greenland conducted in the period 2005 to 2010.[14] We included 3083 participants with clinical examinations and Inuit ethnicity based on self-identification and the participant's language. The Kenya Diabetes Study was carried out as an opportunistic sample among three rural populations (Luo, Kamba and Maasai) and an urban population in Nairobi of mixed ethnicity from 2005 to 2006.[15] A total of 1397 participants (17+ years) completed the clinical examination. The Health2008 study was a population-based study among 795 healthy Danes (30 to 60 years old) living in the western part of Copenhagen from 2008 to 2009.[16] Participants who showed up non-fasting for examination were excluded (n=162) in the current analyses resulting in a final sample of 5113 individuals (see online supplementary figure 1). All participants provided written informed consent or oral in case of illiteracy in the Kenya Diabetes Study. The studies were performed according to the Helsinki Declaration.

Measurements
Anthropometrics and ultrasonography
Height and weight were measured with the participants in light clothing and without shoes. Waist circumference was measured midway between the iliac crest and the rib cage on the standing participant. Ultrasonography was used to measure VAT and SAT based on a validated protocol.[15 17–19] The measures were carried out with a portable ultrasound scanner (Pie Medical) using a 3.5 MHz transducer with the participant lying on their back. VAT was the distance in centimetre from the peritoneum to the front of the lumbar spine and SAT was the depth in centimetre from the skin to the linea alba.

Glucose homoeostasis markers
A 75 g oral glucose tolerance test (OGTT) was performed after a minimum of 8 hours of fasting in participants without medical treatment for diabetes. Blood samples were collected at fasting and 2 hours after the test for the measurement of glucose and insulin. In Inuit Health in Transition and Health2008 plasma glucose were analysed by the hexokinase/G6P-DH method.[14 16] In Kenya Diabetes Study whole blood glucose was analysed by the glucose dehydrogenase method on a HemoCue B-Glucose 201+ device.[20] The measures were converted to fasting plasma glucose (×1.12) to be comparable with the other studies. Serum insulin was measured by an AutoDELFIA using fluoro-immunoassay in all three studies. Plasma glucose and serum insulin were in all three studies analysed in the same laboratories at Steno Diabetes Center in Gentofte, Denmark. Homoeostasis model assessment for insulin resistance (HOMA-IR) was calculated as (fasting plasma glucose (mmol/L) × fasting plasma insulin (pmol)/6.945)/22.5.[21]

Cardiovascular risk factors
Blood pressure (BP) was measured at the right arm of the sitting participant after at least 5 min of initial rest using an automatic mercury sphygmomanometer (Kivex UA-779 in the Inuit Health in Transition Study, Mercuro 300, Speidel & Keller in Health2008 and Omron M6, HEM-7001-E, Kyoto, Japan in the Kenya Diabetes Study). BP was read three times in the Inuit Health in Transition Study with the two last measures averaged.[14] Two readings were done in Health2008 and if systolic BP ≥140 mm Hg or diastolic BP ≥90 mm Hg, the measurements were repeated twice at the same visit. The two lowest values were used and averaged.[18] In the Kenya Diabetes Study two measures were performed and a third, if systolic or diastolic BP differed by more than 5 mm Hg. Mean BP was calculated from the two lowest measurements.[22] Plasma total cholesterol, high-density lipoprotein cholesterol (HDL-C) and triglycerides were analysed from fasting blood samples by enzymatic tests using a Hitachi 912 system. Low-density lipoprotein cholesterol (LDL-C) was calculated from these.[14 16 22] Lipid concentrations were analysed at Steno Diabetes Center in Gentofte, Denmark, for all three studies.

Covariates

Demographic and behavioural factors were obtained from questionnaires. Smoking was coded as current smoker or non-smoker. Current medical treatment for diabetes, hypertension and dyslipidaemia was reported. Classification as Inuit, African or European was done according to Bhopal using the concept ethnicity defined as "the group a person belongs to as a result of a mix of cultural factors including language, diet, religion and ancestry".[23] Physical activity was measured objectively using a combined accelerometer and heart rate monitor (Actiheart, CamNTech, Cambridge, UK) following the same protocol as previously described.[24–26] Physical activity energy expenditure (PAEE) was calculated as kJ/kg/day, and only valid recordings >24 hours were included. The blood samples in the Inuit Health in Transition Study were genotyped and the Inuit-specific *TBC1D4* variant (Arg684Ter) associated with insulin resistance was identified.[27] Participants were coded as either non-carrier, heterozygous or homozygous carriers, and non-carrier status was assumed for participants in the Kenya Diabetes Study and the Health2008.

Statistical analyses

Missing data was imputed using Multivariate Imputations by Chained Equations (MICE) in R software with missing-at-random assumptions.[28] Data were imputed from as many variables as possible to increase the probability that missing values depend on observed data only.[29] The ultrasound measures had together 4% missing values and PAEE 36% missing. Fifty data sets were imputed to get sufficiently precise estimates of imputation variability and thus valid inference.[29] A mean estimate of the relevant parameters was averaged across the 50 copies, and SEs and p values were computed after Rubin's rules.[30]

Multiple linear regression analyses were performed with the continuous cardiometabolic variables as functions of VAT and SAT. VAT and SAT were standardised to a mean of 0 and a SD of 1 for the pooled sample to be able to compare the effects. Outcomes with skewed residuals were log-transformed (HOMA-IR and triglycerides) and results presented as percentwise change. All models were adjusted for age, age^2, smoking, PAEE and BMI. SAT was included in the models with VAT and vice versa. Age^2 was included to improve model fit because changes in body fat increase rapidly with age. Models with glucose homoeostasis outcomes were additionally adjusted for the *TBC1D4* Arg684Ter variant in Inuit. Non-linearity was tested and examined graphically, and linearity was assumed for all models. Test for interactions between ethnicity and VAT and SAT were done in the pooled study sample using the likelihood ratio test.

The associations were examined graphically stratified by sex and ethnicity and predicted for median values of the covariates (43 years, PAEE of 54 kg/kJ/day, smoker, *TBC1D4* non-carrier, BMI of 25 kg/m² and VAT or SAT of 0 SD). Participants on glucose-lowering (n=57),

blood pressure-lowering (n=501) or lipid-lowering drugs (n=171) were excluded in the analyses with the corresponding outcomes. Thus, the sample sizes vary for the outcomes. Data management was performed in SAS V.9.4 (SAS Institute, Cary, North Carolina, USA), and statistical analyses and graphics in R V.3.2.3 (The R Foundation for Statistical Computing, www.r-project.org).

RESULTS

Characteristics of the population are shown in table 1. The highest median values of VAT and SAT were observed in Europeans among men and in Inuit among women. Overall, the Africans were younger, more physically active and correspondingly had a better cardiometabolic profile than the Inuit and Europeans.

Among men, higher VAT was associated with higher levels of HOMA-IR, triglycerides and lower HDL-C across all ethnic groups after adjustment for confounders and independently of BMI (table 2). For example, 1 SD increase in VAT was associated with a 28% (95% CI: 19 to 37) higher HOMA-IR in European men versus 15% (95% CI: 10 to 20) in Inuit men versus 25% (95% CI: 15 to 35) in African men. Positive associations were found between VAT and most of the other cardiometabolic risk factors in Inuit and Europeans, but weak and statistically insignificant associations were observed in Africans. The same pattern was seen in women although with weaker associations. Adjustment for BMI generally attenuated the associations; however, the directions remained the same (see online supplementary table 1 - table 1 without adjustment for BMI).

An increase in SAT of 1 SD was associated with higher levels of all the cardiometabolic risk factors in African men, except fasting glucose, and several in Inuit men (diastolic BP, LDL-C and lower HDL-C and fasting glucose) (table 2). Similar but weaker associations were found in Inuit and African women. SAT only showed significant positive associations with HOMA-IR in European men and HOMA-IR, LDL-C and triglycerides in European women. Removing the *TBC1D4* Arg684Ter variant from the analyses showed similar estimates for the associations of VAT and SAT with glucose homoeostasis outcomes (results not shown).

For VAT, only the association with HDL-C had a significant ethnicity interaction (figure 1), while several significant interactions between ethnicity and SAT were found with generally steeper associations in African men. For example, per 1 SD increment in SAT, systolic BP increased with 5.9 mm Hg (CI 95%: 2.49 to 9.32) in African men, while no significant associations were found for Inuit (1.68 mm Hg, CI 95%: −0.11 to 3.46) and European men (−0.42 mm Hg, CI 95%: −2.92 to 2.09). Furthermore, of notice was that higher SAT was associated with higher HDL-C in Africans and with lower HDL-C in Inuit but not significantly in Europeans (figure 1).

Besides differences in the slopes, ethnic differences were found for the adjusted absolute levels of several of the outcomes for a given VAT and SAT level (see online

Table 1 Population characteristics for each sex and ethnic group (n=5113)

	N	Men				Women			
		Inuit	African	European	P	Inuit	African	European	P
n	5113	1272	579	340		1661	818	443	
Age (years)	5113	45.0 (35.0 to 55.0)	37.0 (28.0 to 47.0)	47.0 (40.0 to 54.0)	<0.001	43.0 (34.0 to 53.0)	38.0 (30.0 to 46.0)	47.0 (41.0 to 53.0)	<0.001
Height (cm)	5092	168.5 (163.0 to 173.3)	172.9 (167.4 to 177.1)	180.7 (176.5 to 185.0)	<0.001	157.0 (152.5 to 161.4)	160.1 (155.4 to 164.4)	167.5 (163.5 to 171.0)	<0.001
Weight (kg)	5079	71.3 (61.8 to 82.2)	60.6 (54.7 to 67.4)	84.5 (76.8 to 95.5)	<0.001	64.0 (55.1 to 75.3)	56.4 (49.8 to 64.7)	68.1 (61.2 to 76.7)	<0.001
BMI (kg/m^2)	5079	25.1 (22.3 to 28.7)	20.3 (18.8 to 22.4)	26.0 (23.9 to 28.9)	<0.001	26.0 (22.7 to 30.2)	21.7 (19.5 to 24.9)	24.3 (22.0 to 27.5)	<0.001
Waist circumference (cm)	5052	90.5 (82.5 to 101.6)	76.4 (72.5 to 82.3)	94.0 (87.4 to 101.6)	<0.001	90.0 (81.0 to 101.0)	76.5 (70.9 to 84.0)	83.0 (76.0 to 90.8)	<0.001
Visceral adipose tissue (cm)	5015	7.1 (5.9 to 8.9)	5.9 (5.1 to 6.9)	8.2 (6.8 to 9.9)	<0.001	6.3 (5.2 to 7.7)	5.4 (4.5 to 6.5)	5.9 (5.1 to 7.4)	<0.001
Subcutaneous adipose tissue (cm)	5012	2.2 (1.4 to 3.0)	0.7 (0.4 to 1.3)	2.7 (2.1 to 3.4)	<0.001	3.7 (2.6 to 4.7)	1.5 (0.9 to 2.5)	3.3 (2.4 to 4.2)	<0.001
Fasting glucose (mmol/L)	5105	5.7 (5.3 to 6.1)	4.8 (4.5 to 5.3)	5.6 (5.3 to 6.0)	<0.001	5.5 (5.2 to 5.9)	4.9 (4.6 to 5.4)	5.4 (5.1 to 5.7)	<0.001
2 hour glucose (mmol/L)	4964	5.0 (4.0 to 6.4)	5.4 (4.4 to 6.5)	5.2 (4.4 to 6.3)	0.561	5.7 (4.7 to 7.0)	5.9 (5.0 to 6.9)	5.1 (4.4 to 6.1)	<0.001
Fasting insulin (pmol/L)	5049	33.0 (22.0 to 49.8)	19.0 (13.0 to 30.8)	29.5 (21.0 to 46.0)	<0.001	42.0 (29.0 to 61.0)	25.0 (17.0 to 38.0)	27.5 (18.2 to 39.0)	<0.001
2 hour insulin (pmol/L)	3573	64.0 (31.0 to 142.0)	NA	125.0 (66.0 to 225.0)	<0.001	148.0 (81.0 to 251.0)	NA	162.0 (105.0 to 245.0)	0.868
HOMA-IR	5048	1.2 (0.8 to 1.9)	0.6 (0.4 to 1.0)	1.1 (0.7 to 1.7)	<0.001	1.5 (1.0 to 2.2)	0.8 (0.5 to 1.2)	0.9 (0.6 to 1.4)	<0.001
Diastolic blood pressure (mm Hg)	5083	80.0 (71.5 to 89.0)	74.0 (68.0 to 80.0)	80.0 (74.0 to 86.0)	<0.001	76.5 (69.0 to 84.0)	73.0 (67.0 to 80.0)	75.0 (69.0 to 81.0)	<0.001
Systolic blood pressure (mm Hg)	5084	131.5 (122.0 to 145.0)	120.0 (112.0 to 131.0)	125.0 (117.0 to 135.0)	<0.001	122.5 (112.5 to 136.0)	116.0 (108.0 to 126.0)	116.0 (107.0 to 127.0)	<0.001
Total cholesterol (mmol/L)	5057	5.8 (5.0 to 6.6)	3.9 (3.2 to 4.5)	5.4 (4.7 to 6.1)	<0.001	5.8 (5.0 to 6.6)	3.8 (3.2 to 4.4)	5.2 (4.5 to 6.0)	<0.001
HDL-cholesterol (mmol/L)	5035	1.5 (1.2 to 1.9)	1.1 (0.9 to 1.3)	1.3 (1.0 to 1.5)	<0.001	1.7 (1.4 to 2.0)	1.1 (0.9 to 1.3)	1.5 (1.3 to 1.8)	<0.001
LDL-cholesterol (mmol/L)	4997	3.6 (2.9 to 4.3)	2.3 (1.8 to 2.8)	3.4 (2.8 to 4.1)	<0.001	3.5 (2.8 to 4.2)	2.2 (1.7 to 2.8)	3.1 (2.5 to 3.7)	<0.001
Triglycerides (mmol/L)	5057	1.0 (0.7 to 1.4)	0.9 (0.7 to 1.2)	1.4 (1.0 to 1.9)	<0.001	1.0 (0.8 to 1.4)	0.8 (0.7 to 1.1)	0.9 (0.7 to 1.3)	<0.001
Glucose-lowering drugs, n (%)	5113	20 (1.6)	4 (0.7)	0 (0.0)	0.026	31 (1.9)	2 (0.2)	0 (0.0)	<0.001
Blood pressure-lowering drugs, n (%)	5113	152 (11.9)	3 (0.5)	26 (7.6)	<0.001	258 (15.5)	13 (1.6)	49 (11.1)	<0.001

Continued

Table 1 Continued

	N	Men				Women			
		Inuit	African	European	P	Inuit	African	European	P
Lipid-lowering drugs, n (%)	5113	60 (4.7)	0 (0.0)	19 (5.6)	<0.001	78 (4.7)	0 (0.0)	14 (3.2)	<0.001
TBC1D4 variant, n (%)	4795				<0.001				<0.001
Non-carrier		801 (70.3)	579 (100.0)	340 (100.0)		1019 (69.0)	818 (100.0)	443 (100.0)	
Heterozygous carrier		294 (25.8)	0 (0.0)	0 (0.0)		403 (27.3)	0 (0.0)	0 (0.0)	
Homozygous carrier		44 (3.9)	0 (0.0)	0 (0.0)		54 (3.7)	0 (0.0)	0 (0.0)	
Current smoker, n (%)	5031	839 (66.1)	101 (18.5)	80 (23.6)	<0.001	1151 (69.5)	41 (5.3)	90 (20.3)	<0.001
PAEE (kJ/kg/day)	3266	55.6 (39.5 to 73.1)	76.0 (55.8 to 92.9)	42.4 (32.2 to 53.9)	<0.001	45.2 (33.4 to 59.8)	64.4 (50.4 to 80.8)	39.4 (30.6 to 46.3)	<0.001

Values are median (IQR) or n (%). P values are from analysis of variance or χ^2 tests.
BMI, body mass index; HDL, high-density lipoprotein; HOMA-IR, homoeostasis model assessment for insulin resistance; LDL, low-density lipoprotein; PAEE, physical activity energy expenditure.

supplementary figures 2–5). Inuit generally had higher absolute levels of total cholesterol, LDL-C and HDL-C and Africans the lowest levels. Africans also had lower fasting glucose compared with the other groups, but markedly higher 2 hour glucose levels were found in African men.

DISCUSSION
Summary of findings
The main findings of this study of Inuit, Africans and Europeans are that VAT and SAT were associated with several cardiometabolic risk factors across the ethnic groups independently of each other and BMI. Ethnic differences were found in the absolute values of several of the cardiometabolic outcomes for a given VAT or SAT, but the trends in the associations of VAT were similar in Inuit and Europeans, and less consistent in Africans. In contrast, several ethnic differences in the trends were found for SAT, with steeper slopes among African men. Weaker associations were generally observed for women.

In context of current literature
Although both VAT and SAT have been associated with cardiometabolic risk factors in some studies, the evidence on associations of VAT remain more robust.[2–5] In the present study, VAT was generally stronger associated with cardiometabolic risk than SAT in Europeans and slightly more in Inuit. We included VAT and SAT simultaneously in models to adjust for the concomitant variation of the other adipose tissue and thus to get the independent effect of VAT and SAT as suggested by Tchernof.[1] This approach was chosen because in a heterogeneous population even simple adiposity measures are almost as strongly correlated to cardiometabolic abnormalities as VAT.

VAT was positively associated with several of the cardiometabolic risk factors in Inuit and Europeans with similar trends, but less consistently so for Africans. In contrast, ethnic differences existed for several of the associations with SAT, showing steeper associations for Africans. In line with our results, a study reported stronger associations of SAT than VAT with HOMA-IR and the metabolic syndrome in young South African men with no effect in women.[31] The South African study used dual-energy x-ray absorptiometry to measure abdominal tissue and adjusted for VAT, SAT and total body fat similarly to ours. The adverse effects of SAT were proposed to explain the high prevalence of insulin resistance and type 2 diabetes mellitus in African ancestry populations despite relatively low VAT levels. Other studies have demonstrated similar stronger correlations with insulin resistance for SAT than VAT in African ancestry populations.[32 33] In addition, we observed high absolute levels of 2 hour glucose in the African men and a strong effect of SAT suggesting reduced peripheral insulin sensitivity despite markedly higher levels of physical activity. The underlying mechanism and whether it is specific

Table 2 Multiple adjusted regression coefficients for cardiometabolic risk factors for 1 SD increase in VAT or SAT stratified on sex and ethnic group

	Men				Women			
	Inuit	African	European	$P_{interaction}$*	Inuit	African	European	$P_{interaction}$*
Fasting glucose†, mmol/L								
VAT	0.11 (0.04 to 0.18)	0.11 (−0.02 to 0.23)	0.13 (0.06 to 0.2)	0.336	0.09 (0.04 to 0.14)	0.14 (−0.02 to 0.3)	0.16 (0.09 to 0.24)	0.197
SAT	−0.12 (−0.2 to −0.04)	0.21 (−0.02 to 0.43)	−0.08 (−0.17 to 0.02)	0.681	−0.05 (−0.12 to 0.01)	0.15 (−0.11 to 0.41)	0.02 (−0.05 to 0.09)	0.425
2 hour glucose†, mmol/L								
VAT	0.2 (0.02 to 0.38)	0.1 (−0.25 to 0.45)	0.42 (0.19 to 0.65)	0.795	0.19 (0.03 to 0.34)	0.03 (−0.26 to 0.32)	0.26 (0.05 to 0.47)	0.367
SAT	−0.04 (−0.25 to 0.17)	0.82 (0.22 to 1.42)	0.08 (−0.22 to 0.38)	**0.026**	0.11 (−0.08 to 0.29)	0.44 (−0.01 to 0.89)	0.05 (−0.16 to 0.26)	0.26
HOMA-IR, % change								
VAT	1.15 (1.1 to 1.2)	1.25 (1.15 to 1.35)	1.28 (1.19 to 1.37)	0.082	1.14 (1.1 to 1.18)	1.17 (1.09 to 1.26)	1.21 (1.12 to 1.31)	0.077
SAT	1.05 (1.0 to 1.11)	1.53 (1.32 to 1.77)	1.14 (1.03 to 1.25)	**<0.000**	1.09 (1.04 to 1.14)	1.17 (1.07 to 1.28)	1.1 (1.02 to 1.19)	0.289
Diastolic BP, mm Hg								
VAT	0.57 (−0.55 to 1.7)	0.96 (−0.22 to 2.15)	1.36 (0.13 to 2.59)	0.886	0.9 (0.03 to 1.76)	0.74 (−0.34 to 1.82)	1.6 (0.25 to 2.95)	0.839
SAT	2.48 (1.14 to 3.81)	4.63 (2.46 to 6.79)	1.02 (−0.61 to 2.65)	0.258	1.95 (0.95 to 2.95)	1.21 (−0.17 to 2.58)	1.17 (−0.18 to 2.52)	0.862
Systolic BP, mm Hg								
VAT	0.98 (−0.52 to 2.48)	0.5 (−1.37 to 2.36)	1.24 (−0.65 to 3.12)	0.462	0.74 (−0.51 to 1.99)	1.32 (−0.31 to 2.96)	2.31 (0.18 to 4.44)	0.98
SAT	1.68 (−0.11 to 3.46)	5.9 (2.49 to 9.32)	−0.42 (−2.92 to 2.09)	**0.004**	1.32 (−0.12 to 2.76)	2.03 (−0.05 to 4.11)	1.1 (−1.02 to 3.22)	0.614
Total cholesterol, mmol/L								
VAT	0.18 (0.09 to 0.28)	0.05 (−0.06 to 0.16)	0.18 (0.03 to 0.32)	0.605	0.05 (−0.04 to 0.13)	−0.01 (−0.11 to 0.09)	−0.09 (−0.24 to 0.05)	0.261
SAT	0.11 (1.0 to 0.22)	0.55 (0.34 to 0.75)	0.08 (−0.11 to 0.27)	**<0.000**	0.06 (−0.04 to 0.16)	0.28 (0.15 to 0.41)	0.12 (−0.02 to 0.26)	**<0.000**
HDL-cholesterol, mmol/L								
VAT	−0.06 (−0.1 to −0.02)	−0.05 (−0.09 to −0.01)	−0.09 (−0.14 to −0.03)	**0.029**	−0.05 (−0.08 to −0.01)	−0.07 (−0.11 to −0.03)	−0.1 (−0.16 to −0.04)	**0.049**
SAT	−0.07 (−0.12 to −0.02)	0.11 (0.03 to 0.18)	−0.02 (−0.09 to 0.05)	**<0.000**	−0.11 (−0.15 to −0.07)	0.04 (0 to 0.09)	−0.05 (−0.11 to 0)	**<0.000**
LDL-cholesterol, mmol/L								
VAT	0.14 (0.05 to 0.22)	0.05 (−0.05 to 0.14)	0.14 (0.01 to 0.27)	0.546	0.01 (−0.06 to 0.09)	0.01 (−0.07 to 0.1)	−0.05 (−0.18 to 0.08)	0.289
SAT	0.17 (0.07 to 0.27)	0.36 (0.19 to 0.53)	0.07 (−0.1 to 0.24)	**0.002**	0.14 (0.05 to 0.23)	0.21 (0.11 to 0.32)	0.13 (0.01 to 0.26)	0.118
Triglycerides, % change								
VAT	1.14 (1.1 to 1.19)	1.1 (1.05 to 1.15)	1.16 (1.08 to 1.24)	0.999	1.13 (1.04 to 1.14)	1.09 (1.04 to 1.14)	1.08 (1.01 to 1.15)	0.076
SAT	1.04 (1 to 1.09)	1.15 (1.06 to 1.25)	1.05 (0.96 to 1.15)	**0.048**	1.07 (1.03 to 1.1)	1.04 (0.98 to 1.1)	1.1 (1.03 to 1.17)	**0.009**

Values are β-coefficients or % change (95% CI) for 1 SD increase in VAT or SAT. All models are adjusted for age, age², smoking, PAEE, BMI and VAT or SAT. VAT: 1 SD=2.21 cm, SAT: 1 SD=1.58 cm. Bold illustrates significant associations.

*P value for ethnic interaction with VAT or SAT.

†Additionally adjusted for the TBC1D4 variant.

BMI, body mass index; BP, blood pressure; HDL, high-density lipoprotein; LDL, low-density lipoprotein; PAEE, physical activity energy expenditure; SAT, subcutaneous adipose tissue; VAT, visceral adipose tissue.
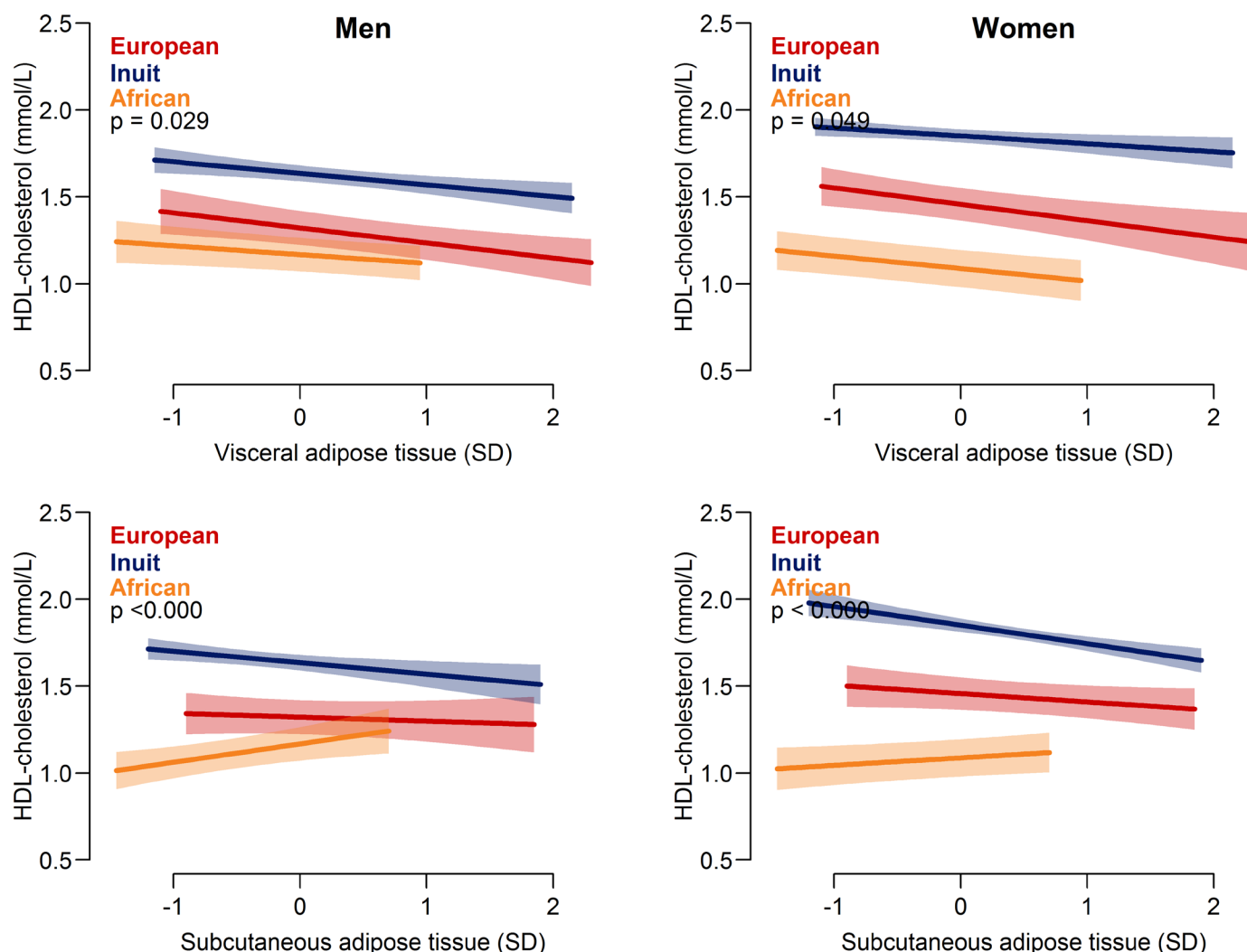
Figure 1 Mean values of HDL cholesterol as a function of VAT (upper) and SAT (lower) for each ethnic group in men (left) and women (right). The regression lines are predicted for a person with the following values: 43 years, smoker, PAEE level of 54 kJ/kg/day, BMI of 25 kg /m², *TBC1D4* non-carrier and VAT or SAT of 0 SD. The predictions are shown for the quantile range 5% to 95% of VAT or SAT for each ethnic group. P values are for the interaction between ethnicity and VAT or SAT testing the hypothesis of parallel lines. BMI,body mass index; HDL, high-density lipoprotein; LDL,low-density lipoprotein; PAEE, physical activityenergy expenditure; SAT, subcutaneous adipose tissue; VAT, visceral adipose tissue.

for this African population remains to be determined. A possible biological explanation for the associations of SAT with several of the cardiometabolic risk factors in Africans and in Inuit could be found in morphological differences between deep and superficial SAT layers, which may have distinct metabolic characteristics.[7] For instance, deep SAT has been found to be equally correlated to the metabolic syndrome as VAT.[34] Measuring the distinctive SAT layers in future studies could contribute to the understanding of the differences in the metabolic effect of abdominal adiposity in these populations.

We generally observed weaker associations for women. Sex-related dimorphism in body fat distribution is well-known[35] and it has been suggested that the amount of VAT accelerates after menopause in women independently of age.[36] Thus, it is possible that menopause affects the associations for women and could

explain the weaker associations. Since information on menopause was not collected in all three studies, menopause status was not included in our analyses. However, when repeating the predictions for women aged 55 years assumed to be postmenopausal, the absolute levels of 2 hour glucose, total cholesterol and LDL-C were similar for European and Inuit women for a given VAT and SAT, while no changes were seen for Africans and the other outcomes (results not shown). This could indicate that menopause plays a role, but to adequately assess the impact of menopause on the strength of the associations, a longitudinal study with comparable information on menopause is required.

Some studies have suggested that populations of African ancestry are less prone to accumulate VAT and more prone to SAT accumulation.[9 37] The African population in our study had lower absolute levels of both VAT and SAT than the Inuit and Europeans as well as

a smaller variation. The low values may be caused by the fact that it was predominantly a rural population with lower VAT and SAT than the urban group reported on in a previous study.[15] Furthermore, it was a generally lean population with a high physical activity level. Of special notice was that higher SAT was associated with higher HDL-C in the Africans and lower HDL-C in the two other populations. We cannot rule out that this may be a result of the small variation of SAT as well as the high positive correlation with BMI, which may have reversed the estimated effect of SAT, because of the consequently negative correlation of estimates. However, the association remained after adjustment for BMI. We adjusted for BMI because we wanted to examine the effect independently of overall adiposity. Waist circumference could have been used as another measure of overall adiposity, but since waist circumference is highly correlated with VAT and SAT such adjustment yielded multicollinearity in the models. Other studies have either adjusted for BMI,[11 12] waist circumference[12] or both.[2] Although similar results are reported from analyses where BMI and waist circumferences have replaced one another, the various approaches may contribute to differences in results between studies. It is also likely that HDL-C subclass and/or function, rather than the actual concentration of adipose tissue plays a role. A recent study from South Africa has shown that weight gain and centralisation of fat, in particular VAT in black women was associated with no change in HDL-C concentrations, but a decrease in large HDL-C subtypes.[38]

African ancestry populations are thought to have a healthier lipid profile characterised by lower triglycerides and higher HDL-C, which could anticipate a lower cardiometabolic disease burden.[39] However, a higher prevalence of CVD has been found in African-Americans compared with Europeans. In this study, the Africans had a more beneficial lipid profile and worse risk profile for hypertension in line with the current evidence, except for low HDL-C. The combination of a low HDL-C and normal triglycerides has been reported in African populations with insulin resistance,[40] suggesting that isolated low HDL-C could be a major factor in the development of cardiometabolic disease in Africans.[41] However, a study in South African women found lower HDL-C levels and triglycerides in black compared with white women, which could not be explained by lower VAT or lower insulin sensitivity in black women.[42] Hence, there may be distinct pathways whereby lipids contribute to cardiometabolic risk, which varies between African ancestry populations. Moreover, no one in the African population were treated for dyslipidaemia and very few for hypertension, which is often seen in sub-Saharan African populations[43] indicating that either these conditions are undiagnosed, untreated or occur less frequently in this African population than in migrated African populations. Migrated populations may differ from the population of origin on several aspects like lifestyle and admixture, which could have influenced their cardiometabolic profile.[44] More research that compare African populations living in their country of origin with similar ethnic migrated populations is needed to better understand the interplay between lifestyle, environment and genes in the context of urbanisation and changing lifestyles.[45]

In the Inuit population we found higher absolute levels of total cholesterol, HDL-C, LDL-C, blood pressure and lower/similar triglycerides for a given VAT or SAT compared with the Europeans. In a previous study lower absolute levels of blood pressure, triglyceride, 2 hour glucose, insulin and higher HDL-C for a given BMI and waist circumference level were identified in Inuit compared with Europeans, but the trends in the associations were the same.[46] We extend these findings by showing that also VAT had similar trends in the associations with cardiometabolic risk factors in Inuit as in Europeans even after adjustment for BMI. The differences in the absolute values were overall consistent with the former study but in contrast we found higher blood pressure, LDL-C and total cholesterol, pointing in the opposite direction. Studies in Arctic Inuit have generally demonstrated a favourable lipid profile, but the evidence on LDL-C and total cholesterol as well as blood pressure is not clear.[47] Differences in the results may partly be due to differences in the European populations, methods and time trends. For instance, it is possible that lifestyle changes over time since our first studies in Greenland explain the different lipid and blood pressure levels. A diet high on n-3 fatty acids and a unique genetic background have been associated with a beneficial lipid profile among Inuit,[48] and although the intake of n-3 fatty acids has decreased the intake is still high.[49] Taken together this indicates that both abdominal and overall adiposity influence cardiometabolic risk in Inuit and Europeans, but differences in the absolute levels of the risk factors suggest that other factors than adiposity may explain the different cardiometabolic profile in Inuit.

Strengths and limitations

Major strengths of the study are the use of standardised ultrasound to assess VAT and SAT, the OGTT to give a more detailed picture of glucose metabolism and objectively measured physical activity in such a large population and in settings with logistic challenges. Also, comparing the three culturally heterogeneous populations with extreme differences in lifestyle makes it easier to identity associations between obesity and cardiometabolic health and elucidate ethnic differences. Furthermore, multiple imputation of missing values was used instead of complete case analyses reducing the likelihood of biassed estimates.[29]

The main limitation of the study is the cross-sectional design, not allowing causal relationships to be established. The studies were designed and carried out using similar protocols; however, some differences in design and data collection may still be present. Blood pressure

was not measured identically but repeat measurements were carried out in all studies minimising the white coat effect. VAT and SAT could have been measured more detailed with two-dimensional or three-dimensional MRI and CT. Although ultrasound is not a guideline-based method, the protocol used has been validated against MRI and CT in different populations, and was the most feasible method in the current large-scale epidemiological study.[17 50 51] Measures of liver fat could provide more insight into the biological mechanisms of the cardiometabolic risk associated with VAT but was not performed in all three studies included. Some studies have shown that intrahepatic lipid accumulation including non-alcoholic fatty liver disease is more detrimental and plays a greater role in type 2 diabetes development than VAT,[52] and may also vary according to ethnicity.[8]

Furthermore, intra-ethnic and rural/urban differences in abdominal fat distribution, insulin resistance and beta-cell function has been shown in the African population as the Kenya Diabetes Study recruited different ethnic groups from rural and urban areas.[15 53] These differences may be reflected in our results.

Lastly, ethnic differences are a result of an interplay between biological mechanisms, genetic and environmental mechanisms. Despite an effort to adjust for important confounding factors there will be known and unknown factors which we could not take into account, for example, we lacked comparable measures of diet and alcohol. Especially diet is complex to measure and compare across populations, and thus is missing in many studies. More studies should elucidate the complexity of ethnicity with comparable measures ideally by studying populations in the country of origin with migrated populations.

CONCLUSION

We showed clinically relevant associations of VAT and SAT with several cardiometabolic risk factors in Inuit, African and Europeans with ethnic differences. Thus, the results support the adverse effect of VAT and SAT beyond the effect of overall adiposity. However, the magnitude of the effects is not large and significantly different enough to propose that VAT (and SAT) is the key driver of differences in cardiometabolic disease between the included populations. The absolute differences in several of the cardiometabolic risk factors do, however, imply that the groups differ in their underlying adverse or protective cardiometabolic profile.

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Competing interests MEJ, GSA, BC and PFR was until 31 December 2016 employed by Steno Diabetes Center A/S, a research hospital working in the Danish National Health Service and owned by Novo Nordisk A/S. MEJ, GSA and BC hold shares in Novo Nordisk A/S. MEJ received grants and lecture fees from AstraZeneca. DLC participated in evaluation meetings in Mexico paid by Novo Nordisk A/S. TL, MA and NG have no disclosures.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not required.

Ethics approval Ethical approval was obtained from the Ethical Review Committee for Greenland for the Inuit Health in Transition Study, the National Ethical Review Committee in Kenya and the Danish National Committee on Biomedical Research Ethics in Denmark for the Kenya Diabetes Study and from the Ethics Committee of the Copenhagen Region for Health2008 (KA-20060011).

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Data availability statement Data are available in a public, open access repository. Data are available upon reasonable request. Data may be obtained from a third party and are not publicly available. Due to ethical and legal restrictions, some access restrictions apply to the data underlying the findings. Data from the Inuit Health in Transition study are made freely available in the Danish public repository, the Danish Data Archive ('Befolkningsundersøgelsen i Grønland (IHIT), 2005-2010', accession number 2002-38/13132). The Greenlandic exome sequencing and RNA sequencing data have been deposited at the European Genome-phenome Archive (https://www.ebi.ac.uk/ega/home) under accession EGAS00001002727, EGAD00010001427 and EGAD00010001428. Data from Health2008 cannot be made publicly available for ethical and legal reasons. Public availability may compromise participant privacy, and this would not comply with Danish legislation. Requests for data should be addressed to Professor Allan Linneberg (allan. linneberg@regionh.dk) who will provide the data access in accordance with the Danish Data Protection Agency. Data from the Kenya Diabetes Study can for ethical or legal reasons not be made publicly available due to participant privacy and a formal request would have to be handed in to the Kenya Medical Research Institute Ethical Committee (seru@kemri.org) to comply with limitations in the ethical approval given in 2005.

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