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

Rønn, Pernille Falberg; Andersen, Gregers Stig; Lauritzen, Torsten; Christensen, Dirk Lund; Aadahl, Mette; Carstensen, Bendix; Grarup, Niels; Jørgensen, Marit Eika

Published in:
BMJ Open

DOI:
10.1136/bmjopen-2020-038071

Publication date:
2020

Document version
Publisher's PDF, also known as Version of record

Document license:
CC BY

Citation for published version (APA):
Abdominal visceral and subcutaneous adipose tissue and associations with cardiometabolic risk in Inuit, Africans and Europeans: a cross-sectional study

Pernille Falberg Rønn,1,2 Gregers Stig Andersen,1 Torsten Lauritzen,3 Dirk Lund Christensen,4 Mette Aadahl,5,6 Bendix Carstensen,1 Niels Grarup,7 Marit Eika Jørgensen1,8,9

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.

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 Europeans8 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 Aborigians and African ancestry populations, \textsuperscript{3} \textsuperscript{4} \textsuperscript{7} \textsuperscript{9} \textsuperscript{11} \textsuperscript{12} with some studies showing ethnic differences in the trend of the associations, \textsuperscript{8} \textsuperscript{11} \textsuperscript{12} and others showing similar trends across ethnic groups. \textsuperscript{3} \textsuperscript{4} \textsuperscript{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.\textsuperscript{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.\textsuperscript{15} 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.\textsuperscript{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.\textsuperscript{16} 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.\textsuperscript{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.\textsuperscript{15} \textsuperscript{17} \textsuperscript{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 homeostasis 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.\textsuperscript{14} \textsuperscript{16} In Kenya Diabetes Study whole blood glucose was analysed by the glucose dehydrogenase method on a HemoCue B-Glucose 201+ device.\textsuperscript{20} The measures were converted to fasting plasma glucose ($\times1.12$) to be comparable with the other studies. Serum insulin was measured by an AutoDELFI A 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) $\times$ fasting plasma insulin (pmol)/6.945)/22.5.\textsuperscript{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.\textsuperscript{14} Two readings were done in Health2008 and if systolic BP $\geq$140 mm Hg or diastolic BP $\geq$90 mm Hg, the measurements were repeated twice at the same visit. The two lowest values were used and averaged.\textsuperscript{15} 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.\textsuperscript{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.\textsuperscript{14} \textsuperscript{16} \textsuperscript{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”. Physical activity was measured objectively using a combined accelerometer and heart rate monitor (Actiheart, CamNTech, Cambridge, UK) following the same protocol as previously described. 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. 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. Data were imputed from as many variables as possible to increase the probability that missing values depend on observed data only. 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. A mean estimate of the relevant parameters was averaged across the 50 copies, and SEs and p values were computed after Rubin’s rules.

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 percentile change. All models were adjusted for age, age2, smoking, PAEE and BMI. SAT was included in the models with VAT and vice versa. Age2 was included to improve model fit because changes in body fat increase rapidly with age. Models with glucose homeostasis outcomes were additionally adjusted for 

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 homeostasis 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) |
|-----------------|-----------------|-----------------|-----------------|-----------------|
|                 | Men             | Inuit           | African         | European        |
|                 | N               | Inuit           | African         | European        |
| n               | 5113            | 1272            | 579             | 340             |
| 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 |
| 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 |
| 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 |
| BMI (kg/m²)     | 5079            | 25.1 (22.3 to 28.7) | 20.3 (18.8 to 22.4) | 26.0 (23.9 to 28.9) | <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 |
| 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 |
| 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 |
| Fasting glucose (mmol/L) | 5015 | 3.7 (2.6 to 4.7) | 1.5 (0.9 to 2.5) | 3.3 (2.4 to 4.2) | <0.001 |
| 2-hour glucose (mmol/L) | 4964 | 5.4 (4.4 to 6.4) | 5.2 (4.4 to 6.3) | 5.9 (5.0 to 6.9) | <0.001 |
| Fasting insulin (pmol/L) | 5049 | 19.0 (13.0 to 30.8) | 29.5 (21.0 to 46.0) | 25.0 (17.0 to 38.0) | <0.001 |
| 2-hour insulin (pmol/L) | 5073 | 64.0 (31.0 to 142.0) | 125.0 (66.0 to 225.0) | 148.0 (81.0 to 251.0) | <0.001 |
| 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 |
| Diastolic blood pressure (mm Hg) | 5083 | 74.0 (68.0 to 80.0) | 80.0 (74.0 to 86.0) | 76.5 (69.0 to 84.0) | <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 |
| Total cholesterol (mmol/L) | 5057 | 3.9 (3.2 to 4.5) | 5.4 (4.7 to 6.1) | 5.8 (5.0 to 6.6) | <0.001 |
| HDL-cholesterol (mmol/L) | 5035 | 1.1 (0.9 to 1.3) | 1.3 (1.0 to 1.5) | 1.7 (1.4 to 2.0) | <0.001 |
| LDL-cholesterol (mmol/L) | 4997 | 2.3 (1.8 to 2.8) | 3.4 (2.8 to 4.1) | 3.5 (2.8 to 4.2) | <0.001 |
| Triglycerides (mmol/L) | 5057 | 0.9 (0.7 to 1.2) | 1.4 (1.0 to 1.9) | 1.0 (0.8 to 1.4) | <0.001 |
| Glucose-lowering drugs, n (%) | 5113 | 0.0 (0.0) | 2.0 (0.2) | 31.1 | <0.001 |
| Blood pressure-lowering drugs, n (%) | 5113 | 3.0 (0.5) | 26.7 (7.6) | 258.15 (15.5) | <0.001 |

Continued
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>
<thead>
<tr>
<th>Lipid-lowering drugs, n (%)</th>
<th>5113</th>
<th>60 (4.7)</th>
<th>0 (0.0)</th>
<th>&lt;0.001</th>
<th>19 (0.9)</th>
<th>0 (0.0)</th>
<th>&lt;0.001</th>
</tr>
</thead>
<tbody>
<tr>
<td>TBC1D4 variant, n (%)</td>
<td>4795</td>
<td>801 (17.0)</td>
<td>579 (10.0)</td>
<td>0 (0.0)</td>
<td>340 (10.0)</td>
<td>0 (0.0)</td>
<td>403 (27.3)</td>
</tr>
</tbody>
</table>

**Table 1 Continued**
| Men | Inuit | African | European | P_{interaction} | Women | Inuit | African | European | P_{interaction} |
|-----|-------|---------|----------|---------------|-------|-------|---------|----------|---------------|---------------|
|    |       |         |          |               |       |       |         |          |               |               |
| Fastiging 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) | 0.06 (−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) | 0.36 (1.13 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) | 1.61 (−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 (1.1 to 1.17) | 1.09 (1.04 to 1.14) | 1.08 (1.01 to 1.15) | 0.076 |
| SAT | 1.04 (1.1 to 1.09) | 1.15 (1.06 to 1.25) | 1.05 (0.96 to 1.15) | 0.048 | 1.07 (1.03 to 1.11) | 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.
Bibliotek. Protected by copyright.
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. For instance, deep SAT has been found to be equally correlated to the metabolic syndrome as VAT. 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 and it has been suggested that the amount of VAT accelerates after menopause in women independently of age. 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. 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 gener-
ally 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 circumfer-
ence is highly correlated with VAT and SAT such adjust-
ment yielded multicollinearity in the models. Other
studies have either adjusted for BMI,11 12 waist circum-
ference69 or both.7 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 anticapate
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 combi-
nation of a low HDL-C and normal triglycerides has
been reported in African populations with insulin resis-
tance,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. More-
over, no one in the African population were treated for
dyslipidaemia and very few for hypertension, which is
often seen in sub-Saharan African populations43 indi-
cating that either these conditions are undiagnosed,
untreated or occur less frequently in this African popu-
lation 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 inter-
play 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 pres-
sure 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 asso-
ciations with cardiometabolic risk factors in Inuit as in
Europeans even after adjustment for BMI. The differ-
ences 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 back-
ground 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 objec-
tively 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 iden-
tify 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 biased
estimates.29

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

References

1. Deurenberg Y, M夏ller I, van der Hout AA, et al. Body mass index, waist-
hip ratio, and the prediction of cardiovascular disease in middle-aged


risk in postmenopausal women: the Women’s Health Initiative Randomized

2002;360(9334):1638-1641.

5. Javed S, Kandir D, Zaman A. Metabolic syndrome and cardiovascular

6. Knowler WC, Bennett PH, Fowler SE, et al. The pathophysiology of

7. Knowler WC, Bennett PH, Fowler SE, et al. The pathophysiology of

8. Knowler WC, Bennett PH, Fowler SE, et al. The pathophysiology of
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. 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, and may also vary according to ethnicity.

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. 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.

**Author affiliations**

1Clinical Epidemiology, Steno Diabetes Center Copenhagen, Gentofte, Denmark
2Department of Public Health, Centre for Arctic Health, Aarhus University, Aarhus, Denmark
3Department of Public Health, General Practice, Aarhus University, Aarhus, Denmark
4Department of Public Health, Global Health Section, University of Copenhagen, Copenhagen, Denmark
5Center for Clinical Research and Prevention, Frederiksberg and Bispebjerg Hospital, Frederiksberg, Denmark
6Department of Public Health, Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark
7Novo Nordisk Foundation, Center for Basic Metabolic Research, Faculty of Health and Medical Sciences, University of Copenhagen, Kobenhavn, Denmark
8National Institute of Public Health, University of Southern Denmark, Copenhagen, Denmark
9Greenland University, Nuuk, Greenland

**Acknowledgements** The authors thank the participants in all three studies, and Dr Soren Brage and Kate Westgate, MRC Cambridge University, for their work with the physical activity data. The authors also appreciate the support from Professor Eva Cecilia Bonefeld-Jørgensen and Centre for Arctic Health, Aarhus University.

**Contributors** MJ, DLC and MA designed the studies and collected data; NG was responsible for analysing the genetic data; PR analysed data and wrote the paper; GSA, MA, TL, MJ, DLC, NG and BC contributed to interpretation of results and edited the paper. All authors read and approved the final manuscript.

**Funding** The Inuit Health in Transition Study was supported by Karen Elise Jensen’s Foundation, NunaFonden, Medical Research Council of Denmark, Medical Research Council of Greenland and the Commission for Scientific Research in Greenland. Health2008 was supported by the Timber Merchant Vilhelm Bang’s Foundation, the Danish Heart Foundation and the Health Insurance Foundation. The Kenya Diabetes Study was supported by DANIDA, Cluster of International Health (University of Copenhagen), Steno Diabetes Center A/S, Beckett Foundation, Dagmar Marshall Foundation, Dr Thorvald Madsen’s Grant, Kong Christian den Tiende’s Foundation and Brdr. Hartmann Foundation. The Novo Nordisk Foundation Center for Basic Metabolic Research is an independent Research Center at the University of Copenhagen partially funded by an unrestricted donation from the Novo Nordisk Foundation (www.metabol.ku.dk). The present study was financed by Centre for Arctic Health (Aarhus University).

**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, 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).

**Provenance and peer review** Not commissioned; externally peer reviewed.

**Data availability statement** Data are available in 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 request. Data from the Inuit Health in Transition study are made freely available in the Danish public repository, on September 20, 2020 at Kobenhavns Universitetsbibliotek. Protected by copyright.

**Bibliotek. Protected by copyright.**
REFERENCES


