**Distinct opposing associations of upper and lower body fat depots with metabolic and cardiovascular disease risk markers**

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**Abstract**

**Background**

To examine the associations of total and regional adiposity with metabolic and cardiovascular disease (CVD) risk markers.

**Methods**

This cross-sectional study included 1,080 (53.8% men, aged 39-44 years) individuals from South India. Anthropometry (height, weight, waist and hip circumference), body composition assessment using dual energy X-ray absorptiometry (DXA), blood pressure (BP), and plasma glucose, insulin and lipids were measured.  Regression analysis was used to examine associations of standardized fat measurements with type 2 diabetes (T2D), insulin resistance (IR), hypertension and hypertriglyceridemia and continuous measurements of BP, glucose, insulin, HOMA-IR and lipids. Contour plots were constructed to visualize the differential effect of upper and lower fat depots.

**Results**

DXA-measured fat depots were positively associated with metabolic and CVD risk markers. After adjusting for fat mass index, upper body fat remained positively, while lower body fat was negatively associated with risk markers. A one standard deviation (SD) increase in android fat showed higher odds ratios (ORs) for T2D (6.59; 95%CI 3.17, 13.70), IR (4.68; 95%CI 2.31, 9.50), hypertension (2.57; 95%CI 1.56, 4.25) and hypertriglyceridemia (6.39; 95%CI 3.46, 11.90) in men. A 1SD increase in leg fat showed a protective effect with ORs for T2D (0.42; 95%CI 0.24, 0.74), IR (0.31; 95%CI 0.17, 0.57) and hypertriglyceridemia (0.61; 95%CI 0.38, 0.98). The magnitude of effect was greater with DXA-measured fat compared with anthropometry.

**Conclusion**

At any level of total body fat, upper and lower body fat depots demonstrate opposite risk associations with metabolic and CVD risk markers in Asian Indians.

**Keywords**: Android, gynoid, visceral fat, leg fat, cardiovascular, metabolic, Asian Indians

**Introduction**

Ethnic-specific differences in body composition (fat and skeletal mass) may contribute to ethnic-specific relationships between obesity and related metabolic and cardiovascular disease (CVD) [1-3].The prevalence of these obesity-related outcomes vary considerably among individuals with similar body mass index (BMI) and not all obese individuals develop metabolic complications, suggesting that these effects cannot be exclusively attributable to overall fatness. Individual variation in regional body fat distribution could explain the metabolic and CVD risk heterogeneity associated with excess adiposity [4, 5].

The metabolically unhealthy phenotype characterised by greater abdominal fat accumulation is often linked to visceral adipose tissue (VAT) [6]. The relative increase in lower body adiposity, which is largely subcutaneous fat in the gluteal, femoral and thigh region is shown to be independently associated with a healthier metabolic and CVD profile [7]. Detailed investigations of specific upper and lower fat depots have also shown that these two fat depots are not entirely similar, and differ by their developmental, morphological and functional characteristics [8, 9].

Evidence of dichotomy between upper and lower fat depots in relation to disease risk is based on studies among individuals of European descent [10-12]. Whilst significant relationships between central adiposity and various health outcomes have been consistently reported across various ethnic groups, including Asian Indians, evidence of the protective effect of lower adiposity depots in this population is lacking. This is important in the Indian context as Indians possess an inherent body phenotype characterised by higher overall fat mass, central adiposity and lower lean mass at any given BMI (thin-fat phenotype) compared with Europeans [13-15], and the role of lower body fat depots remains less recognized.

The current study therefore aimed to examine the associations of metabolic and CVD risk factors with anthropometry and DXA-quantified total and regional fat in a cohort of middle-aged men and women from South India and compare the magnitude of effect of DXA-measured fat with anthropometry on cardiometabolic outcomes.

**Methods**

**Participants**

We included cross-sectional data on 1,080 adults (aged 39-44 years) from the Phase-6 adult follow-up (2013-14) of the Vellore birth cohort (VBC) recruited from urban and adjoining rural areas in Vellore, Tamil Nadu, India. The cohort is described in detail elsewhere [16]. Briefly, it includes men and women born during 1969-73 and followed through infancy, childhood, adolescence and adulthood.

**Demographic and clinical measurements**

Sociodemographic information was collected using standardized questionnaires and included information on educational status, smoking and alcohol consumption, physical activity (PA) and socio-economic status (SES). PA was calculated based on time spent in different types of work, domestic tasks, leisure activities and in walking and cycling with or without a load. Time periods for each activity were multiplied by metabolic constants derived from published tables of the relative energy expenditure of each task and summed to create a final PA score [17].

Anthropometry [height, weight, waist circumference (WC) and hip circumference (HC)] was measured using standardised protocols. Height was measured using a stadiometer and weight on an electronic weighing scale. WC was measured using a non-stretchable tape applied mid-way between the lower costal margin and the iliac crest in the mid-axillary line. HC was measured over light clothing at the widestpart, usually between the greater trochanter and the lower buttock level. All anthropometric measurements were recorded to the nearest 0.1 unit. BMI was calculated as the ratio of weight (kg) to height2 (m2). Blood pressure (BP) was recorded using a digital sphygmomanometer (Omron M3 Corporation, Tokyo, Japan) in the sitting position after five minutes at rest. Three consecutive anthropometry and BP measurements were taken and the average of these was used for the analysis.

Blood samples were collected for fasting plasma glucose, fasting plasma insulin and lipids (total cholesterol, triglycerides, HDL- and LDL-cholesterol) concentrations. Following a 75g oral glucose load, 120-minute glucose was measured in all participants, except for individuals with known type 2 diabetes (T2D), in whom 120-minute glucose was measured after a regular meal. Glucose and lipids were measured by enzymatic methods and serum insulin by a chemiluminescence immunoassay. The HOMA-IR was calculated using the online HOMA-IR calculator (http://www.dtu.ox.ac.uk/homa).

**DXA measurements**

Whole-body composition was measured on a Hologic DXA machine in the fan beam mode (QDR-4500A; Hologic, Waltham, MA, USA) using the software provided by the manufacturer (QDR for Windows Version 11.1.2). The regions of interest were automatically defined and included (i) Android – the area overlying the abdomen and lying between a superior line drawn at 20% of the distance between the iliac crest and inferior margin of the skull base and an inferior line drawn at the upper margin of the iliac crest; (ii) Gynoid – the portion of the legs from the greater femoral trochanter, extending caudally to the mid-thigh; (iii) Leg – the area of the entire leg (partially overlapping with gynoid fat); (iv) visceral adipose tissue (VAT) mass, calculated using an inbuilt algorithm; (v) total fat mass and (vi) total lean mass. Abdominal subcutaneous adipose tissue (aSAT) was manually calculated as the difference between android fat and VAT. Fat mass index (FMI) was calculated as the ratio of total fat (kg) to height2 (m2).

**Outcome definitions**

International Diabetes Federation criteria were used to define T2D (fasting glucose ≥7.0 mmol/l and 2h-glucose ≥11.1 mmol/l) [18]. Insulin resistance (IR) was defined as HOMA-IR >2.45 and >1.93 for males and females respectively, which corresponds to the 75th percentile within-cohort values after exclusion of individuals with obesity and T2D. Hypertension was defined as stage 1 when systolic blood pressure (SBP) was between 130-139 mmHg or diastolic blood pressure (DBP) between 80-89 mmHg and stage 2 if SBP ≥140 mmHg or DBP ≥90 mmHg and/or on medication for hypertension [19]. Hypertriglyceridemia was defined based on National Cholesterol Education Programme guidelines as serum triglycerides ≥1.5 mmol/l [20].

**Statistical** a**nalysis**

Descriptive characteristics of the study participants are presented as mean and standard deviation (SD) for symmetrical data and median and inter-quartile range (IQR) for skewed data. Categorical variables are presented as frequency and percentage. To enable comparison of effects of anthropometry and DXA-fat measurements, standardized scores were created for exposure variables using the Fisher-Yates transformation. Correlations between anthropometry and DXA-measured adiposity depots are presented unadjusted, as well as adjusted for BMI (for WC and HC) or FMI (for DXA-fat) and age. Linear regression was performed for the continuous outcome variables and estimates presented as unstandardized regression coefficient (β) and 95% confidence intervals (95%CI) for the normally distributed variables and the eβ (95% CI) for log transformed variables (fasting glucose, 120-min glucose, fasting insulin, HOMA-IR and triglycerides). Logistic regression was performed for the binary outcomes (ordinal logistic regression for hypertension) and the effect size presented as the odds ratio (OR) and 95% CI. Individuals with T2D, hypertension, IR and hypertriglyceridemia were not excluded from the analysis, but were adjusted for as confounders in analyses of the continuous risk markers. All regression analyses were performed separately for men and women and shown as (i) Model 1:  adjusted for age, place of residence (rural or urban), alcohol and tobacco use and PA score (ii) Model 2: additionally adjusted for FMI (for DXA-fat and lean mass) or BMI (for the anthropometric measures). Linear regression models were additionally adjusted for medication use (glucose, insulin, HOMA-IR for anti-diabetic medication and SBP, DBP for anti-hypertensive medication). The results are presented stratified by sex as significant interaction effects were observed between the sexes. Multicollinearity was tested with the variance inflation factor. To compare the magnitude of effect of DXA with anthropometric measurements, we used the Akaike Information Criterion (AIC) and adjusted R2 values. When two models were compared for the same outcome, the smaller the AIC values the stronger the effect, while similar AIC values or values ≤ 2 apart indicate no difference in the strength of association, and values 10 or more apart indicate a definitive difference.  All analyses were performed using STATA IC/16.0 (StataCorp LLC, College Station, Texas, USA).

Using R version 3.1, contour plots were produced to show the opposing associations of three pairs of upper and lower body adiposity measures: (i) android and gynoid; (ii) visceral and leg fat; (iii) waist and hip circumference with continuous metabolic traits (fasting glucose, HOMA-IR, triglycerides and SBP). The plots show a three-dimensional surface on a two-dimensional plane, with the upper and lower body adiposity measures on the x- and y-axes respectively, and the risk factor displayed as contour lines.  The Mahalanobis distance was calculated to find an ellipse containing 95% of the observations [21]. Contour lines were drawn within this ellipse and were obtained from a fully quadratic function of the x- and y-variables. The plots are presented unadjusted and adjusted for FMI or BMI.

**Results**

Summary statistics of the study participants, stratified by sex, are presented in **Table 1**. The mean age of the participants was 41.4 years (SD ±1.0). Women had greater BMI and HC, and higher total fat mass, total fat percentage, fat mass index, gynoid and leg fat, than men. Men were more centrally obese, evidenced by higher WC and VAT, and also had higher total lean mass. The mean (± SD) BMI of men and women was 24.5 (4.2) and 26.4 (6.2) kg/m2 respectively. The proportions of women who were overweight (BMI ≥25 kg/m2, 37.5%) and obese (BMI ≥30 kg/m2, 24.1%) were almost double those in men (overweight: 18.4%; obesity: 9.3%). Despite lower BMI and total fat mass, metabolic parameters (mean glucose, insulin and lipids) were higher in men. All the categorical metabolic outcomes were higher in men except for insulin resistance. Notable sex differences were found for hypertriglyceridemia (men: 41.9%; women: 16.4%) and hypertension (men: 26.9%; women: 11.5%). Alcohol and tobacco use were more prevalent in men (50.4% and 36.5% respectively) than women (0% and 5.2%) and men had lower PA scores.

**Correlations between DXA-measured fat depots and anthropometry**

All DXA measures of total and regional fat depots showed strong positive correlations with WC, HC and BMI (**Table 2**). When adjusted for either BMI or FMI, all estimates were attenuated, but remained significant. Android fat and aSAT showed similar correlations with anthropometric measures, while the correlations of VAT with anthropometry were lower, in both sexes. Android fat was more strongly correlated with WC in both men (r=0.92) and women (r=0.86), than observed for VAT (men: r=0.82; women: r=0.69). Among lower body adiposity measures, gynoid and leg fat mass showed strong correlations with HC respectively in both men (r=0.89 and 0.88) and women (r=0.85 and 0.86) respectively.

**Associations of body fat depots with CVD and metabolic risk**

Total and regional fat masses, total lean mass, FMI, WC, HC and BMI were positively associated with CVD risk factors, indicating that an increase in both fat and lean mass are associated with increased risk of T2D, IR, hypertension and hypertriglyceridemia **(Table 3).** In the FMI unadjusted estimates, all central abdominal fat components (android/aSAT/VAT) showed highest risk estimates for CVD risk factor outcomes compared with total fat mass, while in women the risk estimates were nearly comparable to total fat mass. Overall, the risk estimates were comparable between DXA-fat depots and anthropometry. WC and HC showed positive associations with all the outcomes, with higher estimates for WC compared to HC. The findings were similar for the continuous risk factors; VAT showed strongest associations with fasting glucose, SBP, DBP, cholesterol and triglyceride levels, and android fat with fasting insulin and HOMA-IR (**Supplementary table 1**).  The estimates for lower adiposity depots were directionally similar but were lower.

**Effect of FMI or BMI adjusted fat depots with metabolic and CVD risk**

When regional fat associations were adjusted for either FMI for DXA measures or BMI for anthropometry, the risk estimates were attenuated, and became directionally opposite for the upper and lower body fat depots. Upper body fat depots had positive associations with risk markers, while lower body fat depots had negative associations (**Tables 3 & Supplementary table 1**). Among upper body fat depots, android fat tended to be associated with the most adverse risk profile, while among lower body fat depots, leg fat tended to have the most ‘protective’ estimates. A one standard deviation (SD) increase in android fat showed higher odds ratios (ORs) for T2D (6.59; 95%CI 3.17, 13.70), IR (4.68; 95%CI 2.31, 9.50), hypertension (2.57; 95%CI 1.56, 4.25) and hypertriglyceridemia (6.39; 95%CI 3.46, 11.90) in men. A 1SD increase in leg fat showed a protective effect with ORs for T2D (0.42; 95%CI 0.24, 0.74), IR (0.31; 95%CI 0.17, 0.57) and hypertriglyceridemia (0.61; 95%CI 0.38, 0.98). Similar opposite associations were observed in women. WC showed directionally similar association to upper body DXA fat measures, while HC showed directionally similar associations to lower body DXA fat measures, though their associations with risk markers were weaker.

**Anthropometry vs DXA-measured fat depots**

In non-nested logistic regression models, the AICs’ for the models were compared to determine the predictive strength of anthropometric vs DXA fat depots (**Table 4**). For all outcome variables, android fat had a lower AIC compared with WC, while gynoid fat had the lowest AIC among the lower body adiposity measures, confirming that the magnitude of effect on metabolic and CVD risk is greater with absolute measurements of fat using DXA compared with anthropometry.

**Combined effect of upper and lower fat adiposity on CVD risk**

**Figures 1** (unadjusted model) **and 2** (adjusted for FMI) show the combined associations of lower and upper fat depots with CVD risk factors. Overall, the elliptical shape showed that upper body fat and lower body fat tend to increase together and risk factors increase with increments in both upper and lower body fat. However, at any level of lower body fat, greater upper body fat is consistently associated with higher risk factors, while an increase in lower body fat is associated with little change in risk factors. When adjusted for total body fat, there are clear opposing associations, with upper body fat being positively associated, and lower body fat negatively associated, with the risk factors and this is more evident at higher levels of total adiposity (**Figure 2**). These findings were further confirmed in an analysis of the association of the average of upper and lower fat depots (their combined effect) and the difference between them (upper body fat minus lower body fat) to CVD risk factors (**Supplementary tables 2 & 3).**

The relationship of potential confounding variables used as adjustors (age, place of residence (rural or urban), alcohol and tobacco use, physical activity score) with adiposity measurements and CVD risk factors are presented in **Supplementary tables 4, 5 and 6**.

**Discussion**

Our systematic evaluation of the relationship between anthropometric and DXA-measured total and regional fat depots with metabolic and CVD risk traits in 1,080 Asian Indians confirms that greater body fat at any location is associated with higher cardiometabolic risk. However, at any level of total body fat, upper and lower adiposity depots demonstrate opposite associations with CVD and metabolic traits with upper body fat being detrimental, while lower body fat is ‘protective’. Our results further confirm that DXA measures of fat are better indicators of CVD risk compared with anthropometry.

Our results align with our own previous work among UK men and women, and other published literature [9-12, 22-24]. The strong correlations observed between DXA-measured total and regional fat with anthropometry is not surprising as they correlate strongly with one another and reflect overall adiposity, and WC and HC are surrogate markers of regional adiposity. The inability of anthropometric measurements to differentiate between fat, skeletal and bone mass could lead to erroneous estimation of body fat and particularly in Asian Indians, who tend to have disproportionately higher fat mass at any given BMI than white Caucasians [25].

Our results are consistent with published literature linking central adiposity to increased metabolic and CVD risk [13, 14, 26].Mechanisms by which the metabolically unhealthy central fat contribute to greater cardiometabolic risk, is shown to be mediated through dysregulated adipokine production, subclinical inflammation, high lipid turnover and increased fatty acid release directly into the circulation [27].Beyond VAT, studies have also shown clustering of cardiometabolic risk with abdominal subcutaneous fat (aSAT) in Asian Indians, and our results support these observations [28], but contrast with findings from other populations that show protective associations with CVD risk [11,29,30]. A possible explanation is that aSAT in our study was not an actual DXA-measurement, but a derived variable (the difference between android fat and VAT) and may not accurately reflect aSAT when directly measured. It is also possible that Asian Indians have increased amounts of deeper aSAT than superficial aSAT, which is morphologically and functionally similar to VAT [31] and this warrants further investigation.

Our results confirm the independent protective effect of lower adiposity depots on metabolic and CVD risk similar in Asian Indians similar to other ethnic groups [10, 11, 23, 24, 32]. The largest epidemiological investigation (INTERHEART study) showed an independent association between larger HC and lower risk of myocardial infarction [33] and prospective studies have also shown that larger hips associate with lower risk for T2D and coronary heart disease, and less aortic calcification and arterial stiffness [34-36]. These observations are further supported by Okura et al, who showed improved CVD risk profile with increased leg fat following a 14-week diet and exercise intervention [37]. Physiological studies have shown that lower body fat, which is largely subcutaneous, has increased capacity to accommodate fat undergoing redistribution, and has a reduced lipid turnover rate and thus acts as a ‘metabolic sink’, protecting other tissues from lipid overflow and lipotoxicity [38, 39]. Thus, high capacity for adipose tissue expandability in the subcutaneous compartments, particularly in lower body is an important determinant of the metabolically healthy phenotype.

 Previous evidence on the relationship between lean mass and cardiometabolic risk has been variable [40-43]. In this population, it is more likely that the paradoxical relationship between DXA lean mass and cardiometabolic parameters is intrinsic to the population (or Indian body phenotype, with intrinsic low muscle mass).

We acknowledge some of the strengths and limitations of our study. This is the first study to examine comprehensively the relationship between CVD risk factors and body fat distribution in Asian Indians, and the first to demonstrate the protective effect of lower fat depots in this ethnic group. Robust measurements of body fat using DXA, actual biochemical measurements, a large sample size and adjustments for a wide range of cofounders are major strengths. Quantification of fat using DXA overcomes the misclassification with anthropometry. This is a population-based cohort recruited from both rural and urban settings and therefore representative of the population studied. Our study is population-based and therefore the findings are likely to be generalisable to the wider Indian population. However, the narrow age range (39-44 years) limits generalisability to other age groups. The cross-sectional nature of the study limits establishing temporal relationship and causality, and therefore cause-effect inferences cannot be made. Nevertheless, the results are important in the context of a disproportionately high fat percentage observed in the Indian population. Another limitation is that estimated VAT was based on the manufacturers’ automated algorithm, and not from a population-specific predictive equation.   The regression models did not take into account other confounders which could potentially influence both the exposures and outcomes, such as dietary habits, menopausal status or objectively measured PA, due to non-availability of data.

**Conclusion**

Our results confirm that more fat in the gynoid and leg region relative to central and total fat is protective against CVD and metabolic risk in Asian Indians, similar to other ethnic groups. The model comparison of DXA Vs anthropometric measures indicate that circumference measurements are less specific than DXA-measured fat depots. Our findings highlight the importance of precise estimation of fat using DXA in future epidemiological and genetic investigations particularly in Asian Indians.

**Data availability statement:** The data underlying this article will be shared on reasonable request to the corresponding author.

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**Ethics approval:** This study was approved by the institutional review board of the Christian Medical College and Hospital, Vellore and all participants provided informed consent.

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**Conflict of Interest**: None declared

**Author contributing statement:** MSG, BA, FK, CHDF, CO and SKV provided substantial contribution to conception and design, acquisition of data, or analysis and interpretation of data. FSG, NT, FJ and TVP were involved in acquisition of data. MGS and SKV drafted the first version of the manuscript. All authors were involved in revision of the manuscript and approved the final version to be published. MSG and SKV are accountable for all aspects of the work and the accuracy and integrity of the data.

**References**

1. Haldar S, Chia SC, Henry CJ. Body composition in Asians and Caucasians: comparative analyses and influences on cardiometabolic outcomes. Adv Food Nutr Res. 2015 Jan 1;75:97-154.
2. Norgan NG. Population differences in body composition in relation to the body mass index. Eur J Clin Nutr. 1994 Nov 1;48:S10-25.
3. Lear SA, Kohli S, Bondy GP, Tchernof A, Sniderman AD. Ethnic variation in fat and lean body mass and the association with insulin resistance. J Clin Endocrinol Metab. 2009 Dec 1;94(12):4696-702.
4. Deurenberg-Yap M, Schmidt G, van Staveren WA, Deurenberg P. The paradox of low body mass index and high body fat percentage among Chinese, Malays and Indians in Singapore. Int J Obes. 2000 Aug;24(8):1011-7.
5. Zong G, Zhang Z, Yang Q, Wu H, Hu FB, Sun Q. Total and regional adiposity measured by dual‐energy X‐ray absorptiometry and mortality in NHANES 1999‐2006. Obesity. 2016 Nov;24(11):2414-21.
6. Després JP, Lemieux I. Abdominal obesity and metabolic syndrome. Nature. 2006 Dec;444(7121):881-7.
7. Manolopoulos KN, Karpe F, Frayn KN. Gluteofemoral body fat as a determinant of metabolic health. International journal of obesity. 2010 Jun;34(6):949-59.
8. Karpe F, Pinnick KE. Biology of upper-body and lower-body adipose tissue—link to whole-body phenotypes. Nat Rev Endocrinol. 2015 Feb;11(2):90.
9. Jensen MD. Role of body fat distribution and the metabolic complications of obesity. The J Clin Endocrinol Metab. 2008 Nov 1;93(11\_supplement\_1):s57-63.
10. Wiklund P, Toss F, Weinehall L, Hallmans G, Franks PW, Nordstrom A, et al. Abdominal and gynoid fat mass are associated with cardiovascular risk factors in men and women. J Clin Endocrinol Metab. 2008 Nov 1;93(11):4360-6.
11. Vasan SK, Osmond C, Canoy D, Christodoulides C, Neville MJ, Di Gravio C, et al. Comparison of regional fat measurements by dual-energy X-ray absorptiometry and conventional anthropometry and their association with markers of diabetes and cardiovascular disease risk. Int J Obes. 2018 Apr;42(4):850-7.
12. Van Pelt RE, Evans EM, Schechtman KB, Ehsani AA, Kohrt WM. Contributions of total and regional fat mass to risk for cardiovascular disease in older women. Am J Physiol Endocrinol Metab. 2002 May; 282(5):E1023-8.
13. Banerji MA, Faridi N, Atluri R, Chaiken RL, Lebovitz HE. Body composition, visceral fat, leptin, and insulin resistance in Asian Indian men. J Clin Endocrinol Metab. 1999 Jan 1;84(1):137-44.
14. Raji A, Seely EW, Arky RA, Simonson DC. Body fat distribution and insulin resistance in healthy Asian Indians and Caucasians. J Clin Endocrinol Metab. 2001 Nov 1;86(11):5366-71.
15. Lear SA, Kohli S, Bondy GP, Tchernof A, Sniderman AD. Ethnic Variation in Fat and Lean Body Mass and the Association with Insulin Resistance, The Journal of Clinical Endocrinology & Metabolism, 2009 Dec 1;94 (12): 4696–4702.
16. Antonisamy B, Raghupathy P, Christopher S, Richard J, Rao PS, Barker DJ, et al. Cohort profile: the 1969–73 Vellore birth cohort study in South India. Int J Epidemiol. 2009 Jun 1;38(3):663-9.
17. Raghupathy P, Antonisamy B, Geethanjali FS, Saperia J, Leary SD, Priya G, et al. Glucose tolerance, insulin resistance and insulin secretion in young south Indian adults: Relationships to parental size, neonatal size and childhood body mass index. Diabetes Res Clin Pract. 2010 Feb 1;87(2):283-92.
18. Alberti KG, Zimmet PZ. Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1: diagnosis and classification of diabetes mellitus. Provisional report of a WHO consultation. Diabet Med. 1998 Jul;15(7):539-53.
19. Whelton PK, Carey RM, Aronow WS, Casey DE Jr, Collins KJ, Dennison Himmelfarb C, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. J Am Coll Cardiol 2018;71:e127–248.
20. Expert Panel on Detection E. Executive summary of the third report of the National Cholesterol Education Program (NCEP) expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (Adult Treatment Panel III). JAMA. 2001; 285(19):2486-97.
21. Riani M, Zani S. Generalized distance measures for asymmetric multivariate distributions. Advances in Data Science and Classification. Studies in Classification, Data Analysis, and Knowledge Organization. 1998, Heidelberg: Springer-Berlin.
22. Aasen G, Fagertun H, Halse J. Regional fat mass by DXA: high leg fat mass attenuates the relative risk of insulin resistance and dyslipidaemia in obese but not in overweight postmenopausal women. Scand J Clin Lab Invest. 2008 Jan 1;68(3):204-11.
23. Fu X, Song A, Zhou Y, Ma X, Jiao J, Yang M, et al. Association of regional body fat with metabolic risks in Chinese women. Public Health Nutr. 2014 Oct;17(10):2316-24.
24. Snijder MB, Zimmet PZ, Visser M, Dekker JM, Seidell JC, Shaw JE. Independent and opposite associations of waist and hip circumferences with diabetes, hypertension and dyslipidemia: the AusDiab Study. Int J Obes. 2004 Mar;28(3):402-9.
25. Lear SA, Humphries KH, Kohli S, Birmingham CL. The use of BMI and waist circumference as surrogates of body fat differs by ethnicity. Obesity. 2007 Nov;15(11):2817-24.
26. Ramachandran A, Snehalatha C, Dharmaraj D, Viswanathan M. Prevalence of glucose intolerance in Asian Indians: urban-rural difference and significance of upper body adiposity. Diabetes care. 1992 Oct 1;15(10):1348-55.
27. Nielsen S, Guo Z, Johnson CM, Hensrud DD, Jensen MD. Splanchnic lipolysis in human obesity. J Clin Invest. 2004 Jun 1;113(11):1582-8.
28. Goel K, Misra A, Vikram NK, Poddar P, Gupta N. Subcutaneous abdominal adipose tissue is associated with the metabolic syndrome in Asian Indians independent of intra-abdominal and total body fat. Heart. 2010 Apr 1;96(8):579-83.
29. Porter SA, Massaro JM, Hoffmann U, Vasan RS, O'Donnel CJ, Fox CS. Abdominal subcutaneous adipose tissue: a protective fat depot? Diabetes care. 2009 Jun 1;32(6):1068-75.
30. McLaughlin T, Lamendola C, Liu A, Abbasi F. Preferential fat deposition in subcutaneous versus visceral depots is associated with insulin sensitivity. J Clin Endocrinol Metab. 2011 Nov 1;96(11):E1756-60.
31. Marinou K, Hodson L, Vasan SK, Fielding BA, Banerjee R, Brismar K, et al. Structural and functional properties of deep abdominal subcutaneous adipose tissue explain its association with insulin resistance and cardiovascular risk in men. Diabetes care. 2014 Mar 1;37(3):821-9.
32. Snijder MB, Visser M, Dekker JM, Goodpaster BH, Harris TB, Kritchevsky SB, et al. Low subcutaneous thigh fat is a risk factor for unfavourable glucose and lipid levels, independently of high abdominal fat. The Health ABC Study. Diabetologia. 2005 Feb;48(2):301-8.
33. Yusuf S, Hawken S, Ounpuu S, Bautista L, Franzosi MG, Commerford P, et al. Obesity and the risk of myocardial infarction in 27 000 participants from 52 countries: a case-control study. The Lancet. 2005 Nov 5;366(9497):1640-9.
34. Choi SI, Chung D, Lim JS, Lee MY, Shin JY, Chung CH, et al. Relationship between regional body fat distribution and diabetes mellitus: 2008 to 2010 Korean National Health and Nutrition Examination Surveys. Diabetes Metab J. 2017 Feb;41(1):51
35. Wiklund P, Toss F, Jansson JH, Eliasson M, Hallmans G, Nordström A, et al. Abdominal and gynoid adipose distribution and incident myocardial infarction in women and men. Int. J. Obes. 2010 Dec;34(12):1752-8.
36. Tankó LB, Bagger YZ, Alexandersen P, Larsen PJ, Christiansen C. Central and peripheral fat mass have contrasting effect on the progression of aortic calcification in postmenopausal women. Eur. Heart J. 2003 Aug 1;24(16):1531-7.
37. Okura T, Nakata Y, Yamabuki K, Tanaka K. Regional body composition changes exhibit opposing effects on coronary heart disease risk factors. Arterioscler Thromb Vasc Biol. 2004 May 1;24(5):923-9.
38. Lemieux I. Energy partitioning in gluteal-femoral fat: does the metabolic fate of triglycerides affect coronary heart disease risk? Arterioscler Thromb Vasc Biol. 2004; 24(5):795-7.
39. Frayn K. Adipose tissue as a buffer for daily lipid flux. Diabetologia. 2002 Sep;45(9):1201-10.
40. Neeland IJ, Turer AT, Ayers CR, Berry JD, Rohatgi A, Das SR, et al. Body fat distribution and incident cardiovascular disease in obese adults. J Am Coll Cardiol. 2015 May 19;65(19):2150-1.
41. Knowles R, Carter J, Jebb SA, Bennett D, Lewington S, Piernas C. Associations of Skeletal Muscle Mass and Fat Mass With Incident Cardiovascular Disease and All-Cause Mortality: A Prospective Cohort Study of UK Biobank Participants. J Am Heart Assoc. 2021 May 4;10(9):e019337.
42. Shishikura K, Tanimoto K, Sakai S, et al. Association between skeletal muscle mass and insulin secretion in patients with type 2 diabetes mellitus. *Endocr J* 2014;61:281–7.
43. Lee DH, Keum N, Hu FB, Orav EJ, Rimm EB, Willett WC, et al. Predicted lean body mass, fat mass, and all cause and cause specific mortality in men: prospective US cohort study. BMJ. 2018 Jul 3;362:k2575.

**Figure legends**

**Figure 1:** Contour plots demonstrating the combined effect of upper and lower adiposities unadjusted for total fat represented by Fat mass index/ Body mass index.

**Figure 2:** Contour plots demonstrating the combined effect of upper and lower adiposities adjusted for total fat represented by Fat mass index/ Body mass index.

**Table legends**

**Table 1:**

**a**Mean (SD); bn (%); cmedian (inter-quartile range); dThe DEXA measures are available for 1044 participants (men=558, women=486). The p value indicates the significance of the difference between sexes.

**Table 2:**

aCorrelations were not significant at 5% level. All measures were standardized using z-scores prior to correlation calculation; WC- waist circumference; HC- hip circumference; BMI-body mass index; FMI-Fat mass index. Age-adjusted correlations are similar to unadjusted correlations and data not shown**.**

**Table 3:**

All body fat depots are converted into SD scores. Each cell represents a single regression equation.

a p<0.001; bp<0.01; cp<0.05

Model 1: adjusted for age, place of residence, physical activity, tobacco use and alcohol use

Model 2: dModel 1 additionally adjusted for fat mass index; eModel 1 additionally adjusted for Body mass index

f Ordinal logistic regression

**Table 4:**

All body fat depots are converted into SD scores. Each cell represents a single regression equation.

aOutcome = Anthropometry fat depot + adjusted for age + place of residence + physical activity + tobacco use + alcohol use + BMI

 bOutcome = DEXA derived fat depot + adjusted for age + place of residence + physical activity + tobacco use + alcohol use + FM