Association of genetic variants related to gluteofemoral versus abdominal fat distribution with type 2 diabetes, coronary disease, and cardiovascular risk factors

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Abstract

Importance: Body fat distribution, usually measured using waist-to-hip ratio (WHR), is an important contributor to cardio-metabolic disease independent of body mass index (BMI). Whether mechanisms that increase WHR via lower gluteofemoral (hip) or via higher abdominal (waist) fat distribution affect cardio-metabolic risk is unknown.

Objective: To identify genetic variants associated with higher WHR specifically via lower gluteofemoral or higher abdominal fat distribution and estimate their association with cardio-metabolic risk.

Design, Setting, and Participants: Genome-wide association studies (GWAS) for WHR combined data from the UK Biobank cohort and summary statistics from previous GWAS (data collection: 2006-2018). Specific polygenic scores for higher WHR via lower gluteofemoral or via higher abdominal fat distribution were derived using WHR-associated genetic variants showing specific association with hip or waist circumference. Associations of polygenic scores with outcomes were estimated in three population-based cohorts, a case-cohort study and summary statistics from 6 GWAS (data collection: 1991-2018).

Exposures: Over 2.4 million common genetic variants (GWAS); polygenic scores for higher WHR (follow-up analyses).

Main outcomes and measures: BMI-adjusted WHR and unadjusted WHR (GWAS); compartmental fat mass measured by dual-energy X-ray absorptiometry (DEXA), systolic, diastolic blood pressure, low-density lipoprotein cholesterol, triglycerides, fasting glucose, fasting insulin, type 2 diabetes and coronary disease risk (follow-up analyses).

Results: Among 452,302 European-ancestry UK Biobank participants, mean age was 57 (SD=8) years and mean WHR was 0.87 (SD=0.09). In genome-wide analyses, 202 independent genetic variants were associated with higher BMI-adjusted WHR (N=660,648) and unadjusted WHR (N=663,598). In DEXA analyses (N=18,330), the hip- and waist-specific polygenic scores for higher WHR were specifically associated with lower gluteofemoral and higher abdominal fat, respectively. In follow-up analyses (N=636,607), both polygenic scores were associated with higher blood pressure, triglycerides and higher risk of diabetes (waist-specific score: odds ratio [OR], 1.57 [95% CI, 1.34-1.83], absolute risk increase per 1000 participant-years [ARI], 4.4 [95% CI, 2.7-6.5], P<.001; hip-specific score: OR, 2.54 [95% CI, 2.17-2.96], ARI, 12.0 [95% CI, 9.1-15.3], P<.001) and coronary disease (waist-specific score: OR, 1.60 [95% CI, 1.39-1.84], ARI, 2.3 [95% CI, 1.5-3.3], P<.001; hip-specific score: OR, 1.76 [95% CI, 1.53-2.02], ARI, 3.0 [95% CI, 2.1-4.0], P<.001), per 1 SD increase in BMI-adjusted WHR.

Conclusions and Relevance: Distinct genetic mechanisms may be linked to gluteofemoral and abdominal fat distribution that are the basis for the calculation of the waist-to-hip ratio. If replicated in additional diverse populations, these findings may have implications for risk assessment and treatment of diabetes and coronary disease.

Key points

Question: Do genetic variants that are related to body fat distribution via lower levels of gluteofemoral (hip) fat or via higher levels of abdominal (waist) fat show associations with diabetes or coronary disease risk?

Findings: In genetic studies including up to 636,607 people, distinct polygenic risk scores for increased waist-to-hip ratio via lower gluteofemoral or via higher abdominal fat distribution were significantly associated with higher levels of cardio-metabolic risk factors and higher risk for type 2 diabetes and coronary disease.

Meaning: Genetic mechanisms specifically linked to lower gluteofemoral or higher abdominal fat distribution may independently contribute to the relationship between body shape and cardio-metabolic risk.

Introduction

The distribution of body fat is associated with the propensity of overweight individuals to manifest insulin resistance and its associated metabolic and cardiovascular complications.[1-5] The waist-to-hip ratio (WHR) is a widely-used, convenient and robustly validated indicator of fat distribution and is linked to the risk of type 2 diabetes and coronary disease independently of body mass index (BMI).[1-5] This observation has been used to infer that accumulation of fat in the abdominal cavity is an independent causal contributor to cardio-metabolic disease. Whilst many studies support this assertion and plausible mechanisms have been proposed, the waist-to-hip ratio can also be increased by a reduction in its denominator, the hip circumference. Evidence from several different forms of partial lipodystrophy[6,7] and functional studies of peripheral adipose storage compartments[8-10] suggests that a primary inability to expand gluteofemoral or hip fat can also underpin subsequent cardio-metabolic disease risk. Emerging evidence from the analysis of common genetic variants associated with greater insulin resistance but lower levels of hip fat suggests that similar mechanisms may also be relevant to the general population.[11-14]

In this study, large-scale human genetic data were used to investigate whether genetic variants related to body fat distribution via lower levels of gluteofemoral (hip) fat or via higher levels of abdominal (waist) fat are associated with type 2 diabetes or coronary disease risk.

Methods

Study design

A multi-stage approach was adopted (**Table 1**). In Stage 1, genome-wide association studies (GWAS) of waist-to-hip ratio with ($WHR_{BMI\text{-}adjusted}$) and without ($WHR_{unadjusted}$) adjustment for BMI were performed to identify genetic variants associated with fat distribution. Stage 1 included data from European ancestry participants of the UK Biobank study and summary statistics from previously-published GWAS of the Genetic Investigation of Anthropometric Traits (GIANT) consortium.[15] In Stage 2, general, hip- and waist-specific polygenic scores for higher WHR were derived using 202 genetic variants independently associated with WHR in Stage 1. Stage 2 included data from European ancestry participants of UK Biobank and summary statistics from GIANT.[15] In Stage 3, associations of polygenic scores with compartmental fat mass measured by dual-energy X-ray absorptiometry (DEXA) were estimated in European ancestry participants from the UK Biobank, Fenland and EPIC-Norfolk studies. In Stage 4, associations of polygenic scores with six cardio-metabolic risk factors and with risk of type 2 diabetes and coronary artery disease were estimated using data from European ancestry participants of UK Biobank, the EPIC-InterAct case-cohort study and summary statistics from 6 previously-published GWAS. All studies were approved by local institutional review boards and ethics committees and participants gave written informed consent.

Studies and participants

UK Biobank (data collection: 2006-2018) is a prospective population-based cohort study of people aged 40-69 years who were recruited in 2006-2010 from 22 centers located in urban and rural areas across the United Kingdom.[16]

Fenland (data collection: 2005-2018) is a prospective population-based cohort study of

people born in 1950-1975 and recruited in 2005-2015 from outpatient primary care clinics in Cambridge, Ely and Wisbech (United Kingdom).[11]

EPIC-Norfolk (data collection: 1993-2018) is a prospective population-based cohort study of individuals aged 40-79 and living in the Norfolk county (rural areas, market towns and the city of Norwich) in the United Kingdom at recruitment from outpatient primary care clinics in 1993-1997.[17]

EPIC-InterAct (data collection: 1991-2018) is a case-cohort study nested within the European Prospective Investigation into Cancer and Nutrition (EPIC) study, a prospective cohort study.[18] EPIC study participants who developed type 2 diabetes after study baseline constituted the incident case group of EPIC-InterAct and a randomly-selected group of individuals free of diabetes at baseline constituted the subcohort.

Summary statistics from 11 GWAS published by research consortia between 2012 and 2015 were used in the different stages of the study (**eMethods 1 and eTable 1**). These included genetic variant associations with BMI, $WHR_{BMI\text{-}adjusted}$, $WHR_{unadjusted}$, waist- and hip-circumference from the GIANT consortium,[15,19] associations with fasting glucose and fasting insulin from the Meta-analyses of Glucose and Insulin-related Traits consortium (MAGIC),[20,21] associations with triglycerides and low-density lipoprotein cholesterol (LDL-C) from the Global Lipid Genetic consortium (GLGC),[22] associations with type 2 diabetes from the Diabetes Genetics Replication and Meta-analysis (DIAGRAM) consortium[23] and with coronary artery disease from the Coronary Artery Disease Genome-wide Replication and Meta-analysis plus the Coronary Artery Disease Genetics consortium (CARDIOGRAMplusC4D).[24] Data collection took place in 2012-2016.

Detailed descriptions of study design, sources of data, and participants in each stage are in **Tables 1-2, eMethods 1 and eTables 1-3**.

Outcomes

Outcomes of the study were WHR (Stage 1 and 2b), hip and waist circumference (Stage 2a), compartmental body fat masses (Stage 3), six cardio-metabolic risk factors (systolic and diastolic blood pressure, fasting glucose, fasting insulin, triglycerides and LDL-C; Stage 4) and two disease outcomes (type 2 diabetes and coronary disease; Stage 4).

Stage 1 and 2: WHR was defined as the ratio of the circumference of the waist to that of the hip, both of which were estimated in cm using a Seca 200-cm tape measure. BMI-adjusted WHR was obtained by calculating the residuals for a linear regression model of WHR on age, sex and BMI.

Stage 3: compartmental fat masses were measured in grams by DEXA, a whole-body, low-intensity X-ray scan that precisely quantifies fat mass in different body regions. In UK Biobank, DEXA measures were obtained using a GE-Lunar iDXA instrument. In Fenland and EPIC-Norfolk, DEXA scans were performed using a Lunar Prodigy advanced fan beam scanner (GE Healthcare, Bedford, UK). Participants were scanned by trained operators using standard imaging and positioning protocols. All the images were manually processed by one trained researcher, who corrected DEXA demarcations according to a standardized procedure as illustrated in **eFigure 1** and described in **eMethods 1**. In brief, the arm region included the arm and shoulder area, the trunk region included the neck, chest, abdominal and pelvic areas. The abdominal region was defined as the area between the ribs and the pelvis, and was enclosed by the trunk region. The leg region included all of the area below the lines that form the lower borders of the trunk. The gluteofemoral region included the hips and upper thighs, and overlapped both leg and trunk regions. The upper demarcation of this region was below the top of the iliac crest at a distance of 1.5 times the abdominal height. The DEXA CoreScan® software (GE Healthcare, Bedford UK) was used to determine visceral abdominal fat mass within the abdominal region.

Stage 4, risk factors: systolic and diastolic blood pressures were defined as the values of arterial blood pressure in mmHg measured using an Omron monitor during the systolic and diastolic phases of the heart cycle. Fasting insulin and fasting glucose were defined as the values of insulin (log-transformed and expressed in log-pmol/L) in serum and glucose (mmol/L) in whole blood measured in fasting state in non-diabetic individuals as previously described.[20,21] Triglycerides (log-transformed and expressed in log-mmol/L) and LDL-C (mmol/L) levels in the circulation were measured using biochemical assays (triglycerides and 24% of LDL-C values in the GLGC study[22]) or derived with the Friedewald formula (76% of LDL-C values in the GLGC study[22]) as previously described.[22]

Stage 4, disease outcomes: for disease outcomes analyses in UK Biobank, binary definitions of prevalent disease status and a case-control analytical design were used in line with previous work.[11,25,26] Definition of prevalent diabetes was consistent with validated algorithms.[25] Participants were classified as cases of prevalent type 2 diabetes if they met the following two criteria: (1) self-reported type 2 diabetes diagnosis or self-reported diabetes medication at nurse interview or at digital questionnaire, or electronic health record consistent with type 2 diabetes (International Statistical Classification of Diseases and Related Health Problems version 10 [ICD-10] code E11); and (2) age at diagnosis >36 years or use of oral anti-diabetic medications (to remove likely type 1 diabetes cases). Controls were participants who (1) did not self-report a diagnosis of diabetes of any type, and (2) did not take any diabetes medications, and (3) did not have an electronic health record of diabetes of any type. In EPIC-InterAct, the outcome was incident type 2 diabetes. Incident type 2 diabetes case status was defined on the basis of evidence of type 2 diabetes from self-report, primary care registers, drug registers (medication use), hospital record or mortality data.[18] Incident type 2 diabetes cases were considered to be verified if evidence from a minimum of two of these independent sources was present.[18] Participants free from type 2 diabetes at

baseline were randomly selected from participating EPIC-study cohorts and constituted the subcohort group of EPIC-InterAct. Participants with prevalent diabetes at study baseline were excluded from EPIC-InterAct. In UK Biobank, prevalent coronary artery disease was defined as either (1) myocardial infarction or coronary disease documented in the participant's medical history at the time of enrolment by a trained nurse or (2) an electronic health record of acute myocardial infarction or its complications (ICD-10 codes I21-I23). Controls were participants who did not meet any of these criteria.

Statistical analysis

Stage 1: in UK Biobank, GWAS analyses were performed using BOLT-LMM,[27] which fits linear mixed-models accounting for relatedness between individuals using a genomic kinship matrix.[27,28] An inverse-variance weighted, fixed-effect meta-analysis of results from UK Biobank and GIANT was performed using METAL.[29] This study focused on 2,446,094 common genetic variants in autosomal chromosomes (i.e. not X or Y chromosome) with minor allele frequency ≥0.5% captured in both UK Biobank and GIANT. Restriction to European ancestry individuals, use of linear mixed-models (UK Biobank) and adjustment for genetic principal components and genomic inflation factor (GIANT) were used to minimize type I error. Quality measures of genuine genetic association signal versus possible confounding by population stratification or relatedness included the mean χ^2 statistic, the linkage-disequilibrium score (LSDC) regression intercept and its attenuation ratio (**eMethods 2**), as recommended for genetic studies of this size using linear mixed model estimates.[28] Values of LDSC-regression intercept below 1.5 and an attenuation ratio statistic (a measure of proportionality between LDSC-regression intercept and χ^2 statistic calculated as: [LDSC intercept – 1] / [mean χ^2 statistic – 1]) equal to or below 0.08 are consistent with optimal control of genetic confounding.[28] Genetic variants were taken forward to Stage 2 if they were

associated with both $WHR_{BMI\text{-}adjusted}$ and $WHR_{unadjusted}$ at the conventional genome-wide level of statistical significance[30] ($P<5\times10^{-08}$ in each analysis). The use of both BMI-adjusted and unadjusted results prevented the inclusion of variants associated with higher WHR via collider bias[31] or via a primary association with higher BMI. A forward-selection process was used to select independent genetic variants for Stage 2. At each iteration, the genetic variant with the lowest P-value for $WHR_{BMI\text{-}adjusted}$ was selected, while genetic variants within 1,000,000 base pairs either side of that genetic variant were discarded from further iterations. The resulting list of genetic variants was further filtered on the basis of pairwise linkage disequilibrium such that the final list of independent genetic variants had no or negligible correlation (pairwise $R^2<.05$). Full details about genetic analyses are in **eMethods 2**.

Stage 2: polygenic scores capturing genetic predisposition to higher WHR were derived by combining the 202 independent genetic variants from Stage 1 (or subsets of the 202 variants as described below), weighted by their association with $WHR_{BMI\text{-}adjusted}$ in Stage 1. A general polygenic score for higher WHR was derived by combining all 202 genetic variants. A waist-specific polygenic score capturing genetic predisposition to higher WHR via higher abdominal fat was derived by combining 36 variants specifically associated with waist (P<.00025, a Bonferroni correction for 202 genetic variants) but not with hip circumference (P>.20, an arbitrary threshold). A hip-specific polygenic score capturing genetic predisposition to higher WHR via lower gluteofemoral fat was derived by combining 22 variants specifically associated with hip (P<.00025) but not with waist circumference (P>.50, a stricter arbitrary threshold which was necessary because of residual associations with waist circumference of a polygenic score initially derived using P>.20, **eMethods 3**). A fourth polygenic score was derived by combining 144 genetic variants not included in the waist- or hip-specific polygenic scores.

The statistical performance of these polygenic scores was assessed by estimating the

proportion of the variance in $WHR_{BMI\text{-}adjusted}$ accounted for by the score (variance explained) and by the F-statistic (**eMethods 4**). The F-statistic is a measure of the ability of the polygenic score to predict the independent variable ($WHR_{BMI\text{-}adjusted}$). Values of F-statistic above 10 have been considered to provide evidence of a statistically-robust polygenic score.[26,32] Statistical power calculations for the association with disease outcomes were also performed (**eMethods 4 and eFigure 2**).

Stage 3 and 4: associations of polygenic scores with DEXA phenotypes, cardio-metabolic risk factors and outcomes were estimated in each study separately and results were combined using fixed-effect inverse-variance weighted meta-analysis. In individual-level data analyses, polygenic scores were calculated for each study participant by adding the number of copies of each contributing genetic variant weighted by its association estimate in SD units of $WHR_{BMI\text{-}adjusted}$ per allele from Stage 1. Association of polygenic scores with outcomes were estimated using linear, logistic or Cox regression models as appropriate for outcome type and study design. Regression models were adjusted for age, sex and genetic principal components or a genomic kinship matrix to minimize genetic confounding. In UK Biobank disease outcomes analyses, prevalent disease status was defined as a binary variable and logistic regression was used to estimate the odds ratio of disease per 1 SD increase in $WHR_{BMI\text{-}adjusted}$ due to a given polygenic score. In EPIC-InterAct, Cox regression weighted for case-cohort design was used to estimate the hazard ratio of incident type 2 diabetes per 1 SD increase in $WHR_{BMI\text{-}adjusted}$ due to a given polygenic score. In summary statistics analyses, estimates equivalent to those of individual-level analyses were obtained using inverse-variance weighted meta-analysis of the association of each genetic variant in the polygenic score with the outcome, divided by the association of that genetic variant with $WHR_{BMI\text{-}adjusted}$.[33] These analytical approaches assume normal distributions for polygenic scores and continuous outcomes. They also assume a linear relationship of the polygenic score with

continuous outcomes (linear regression), or with the log-odds of binary outcomes (logistic regression), or with the log-hazard of incident disease (Cox regression). All of these assumptions were largely met in this study (**eMethods 5, eTable 4 and eFigures 3-6**). Meta-analyses of log-odds ratios and log-hazard ratios of disease assumed that these estimates are similar, an assumption which was shown to be reasonable in a sensitivity analysis conducted in EPIC-InterAct (**eMethods 5 and eFigure 7**).

In Stage 3 and 4, associations with continuous outcomes were expressed in standardized or clinical units of outcome per 1 SD increase in $WHR_{BMI\text{-}adjusted}$ (corresponding to 0.056 ratio units of age-, sex- and BMI-residualized WHR in UK Biobank) due to a given polygenic score (**eMethods 5 and eTable 5**). Associations with disease outcomes were expressed as odds ratios (OR) for outcome per 1 SD increase in $WHR_{BMI\text{-}adjusted}$ due to a given polygenic score. Absolute risk increases (ARI) for disease outcomes were estimated using the estimated ORs and the incidence of type 2 diabetes or coronary disease in the United States (**eMethods 5**). The threshold of statistical significance for association with DEXA phenotypes was P<.0016 (0.05/32=0.0016, Bonferroni correction for 8 outcomes and 4 polygenic scores), that for association with cardio-metabolic risk factors was P<.0021 (0.05/24=0.0021, Bonferroni correction for 6 outcomes and 4 polygenic scores), and that for association with type 2 diabetes and coronary disease was P<.0063 (0.05/8=0.0063, Bonferroni correction for 2 outcomes and 4 polygenic scores). All reported P-values were from 2-tailed statistical tests.

In addition to deriving specific polygenic scores, the independent association of gluteofemoral or abdominal fat distribution with outcomes was studied using multivariable genetic association analyses adjusting for either of these two components of body fat distribution (**eMethods 6 and eFigure 8**). Adjusting for abdominal fat distribution measures was used as a way of estimating the residual association of the polygenic score with outcomes via gluteofemoral fat distribution, while adjusting for gluteofemoral fat distribution

measures as a way of estimating the residual association via abdominal fat distribution (**eFigure 8**). To obtain adjusted association estimates, multivariable weighted regression models were fitted in which the association of the 202-variant general polygenic score (exposure) with cardio-metabolic risk factors or diseases (outcomes) was estimated while adjusting for a polygenic score comprising the same 202 genetic variants but weighted for measures of abdominal fat distribution or measures of gluteofemoral fat distribution (covariates).[34] A detailed description of these analysis methods and their assumptions is in **eMethods 6 and eFigures 8-9**. This method was also used to conduct a post hoc exploratory analysis of the association of the hip-specific polygenic score with cardio-metabolic disease outcomes after adjusting for visceral abdominal fat mass estimates.

Six different secondary or sensitivity analyses were conducted to estimate the association of polygenic scores with other phenotypes including high-density lipoprotein cholesterol (HDL-C), triglyceride/HDL-C ratio, height, and non-diabetic hyperglycemia, and to assess the robustness of the main analysis to associations with height, sex-specific associations, or the possibility of false positive associations in Stage 1 or Stage 2 (**eMethods 7**).

Statistical analyses were performed using STATA v14.2 (StataCorp, College Station, Texas 77845 USA), R v3.2.2 (The R Foundation for Statistical Computing), BOLT-LMM v2.3.2[27,28] and METAL v2011-03-25.[29]

Results

Genetic predisposition to higher WHR via lower gluteofemoral or via higher abdominal fat

Among 452,302 European ancestry participants of UK Biobank, mean age was 57 (SD=8) years, women were 245,351 (54%) and mean WHR was 0.87 (SD=0.09; **Table 2**). In genome-wide association analyses of $WHR_{BMI\text{-}adjusted}$ (N=660,648, mean χ^2=2.50, LDSC-regression intercept, 1.098 [95% CI, 1.063, 1.134], attenuation ratio, 0.07 [95% CI, 0.04, 0.09]) and $WHR_{unadjusted}$ (N=663,598, mean χ^2=2.68, LDSC-regression intercept, 1.096 [95% CI, 1.064, 1.129], attenuation ratio, 0.06 [95% CI, 0.04, 0.08]) there was evidence of optimal control for genetic confounding (**eMethods 2, eFigures 10-11**). A total of 202 independent genetic variants were associated with both $WHR_{BMI\text{-}adjusted}$ and $WHR_{unadjusted}$ ($P<5\times10^{-08}$ in each analysis; **eTable 6, eFigures 12-13**). These 202 genetic variants were used to derive polygenic scores for higher WHR (**Table 1**). The 202-variant general score (variance in $WHR_{BMI\text{-}adjusted}$ explained by score in UK Biobank=3.4%, F-statistic=12,231), 22-variant hip-specific score (variance explained=0.4%, F-statistic=1,550), 36-variant waist-specific score (variance explained=0.4%, F-statistic=1,444), and 144-variant general score (variance explained=2.6%, F-statistic=9,177) were statistically robust polygenic scores for $WHR_{BMI\text{-}adjusted}$ (**eMethods 4 and eFigure 2**).

In 18,330 people with DEXA compartmental fat measures, all polygenic scores for higher WHR were associated with a higher abdominal-to-gluteofemoral fat mass ratio, a refined measure of body fat distribution, but were associated with different patterns of compartmental fat mass distribution (**Figure 1, eFigures 14-15**). The general 202-variant and 144-variant polygenic scores were associated with higher visceral abdominal and lower gluteofemoral fat mass (**Figure 1A, eFigure 15**). The waist-specific polygenic score for higher WHR was associated with higher abdominal fat mass, but not with gluteofemoral or leg fat mass (**Figure 1B**). The hip-specific polygenic score for higher WHR was associated

with lower gluteofemoral and leg fat mass, but did not show statistically-significant associations with abdominal fat mass (**Figure 1B**). Participants with higher values of the hip-specific polygenic score had numerically higher visceral abdominal fat mass, but the difference was not statistically significant when accounting for multiple tests (**Figure 1B**).

Associations with cardio-metabolic risk factors and disease outcomes

In 636,607 people, the 202-variant polygenic score for higher WHR was associated with higher odds of type 2 diabetes and coronary artery disease and an unfavorable cardio-metabolic risk profile (**eFigure 16**), consistent with previous studies of ~50 genetic variants.[15,26,35] In secondary analyses, there were associations with lower HDL-C, higher triglyceride/HDL-C ratio and higher odds of non-diabetic hyperglycemia (**eMethods 7 and eTables 7-8**). Associations with cardio-metabolic disease outcomes were similar in men and women with no evidence of sex-interaction ($P_{interaction}$ for type 2 diabetes=0.19; $P_{interaction}$ for coronary artery disease=0.80; **eTable 9**).

Both hip-specific and waist-specific polygenic scores for higher WHR were associated with higher systolic, diastolic blood pressure and triglycerides (**Figure 2A**), with similar association estimates for a 1 SD increase in $WHR_{BMI\text{-}adjusted}$. While the hip-specific polygenic score was associated with higher fasting insulin and higher LDL-C, the waist-specific polygenic score did not have statistically-significant associations with these traits (**Figure 2A**). Both the hip-specific and the waist-specific polygenic scores were associated with higher odds of type 2 diabetes and coronary disease (**Figure 2B**), similarly in men and women (**eTable 9**). The hip-specific polygenic score had a statistically larger association estimate for diabetes than the waist-specific polygenic score per 1 SD increase in $WHR_{BMI\text{-}adjusted}$ (OR, 2.54 [95% CI, 2.17-2.96] vs 1.57 [1.34-1.83]; ARI, 12.0 [95% CI, 9.1-15.3] vs 4.4 [95% CI, 2.7-6.5] cases per 1000 participant-years; $P_{heterogeneity}<.001$; **Figure 2B**). In a

post-hoc multivariable analysis adjusting for visceral abdominal fat mass estimates, the hip-specific polygenic score showed a statistically-significant association with higher odds of type 2 diabetes and coronary disease (OR for diabetes per 1 SD increase in $WHR_{BMI\text{-}adjusted}$ due to the hip-specific polygenic score, 2.84 [95% CI, 1.98-4.08], ARI, 14.4 [95% CI, 7.6-24] cases per 1000 participant-years, P<.001; OR for coronary disease, 1.74 [95% CI, 1.35-2.25], ARI, 2.9 [95% CI, 1.4-4.9] cases per 1000 participant-years, P<.001). The 144-variant polygenic score showed associations with risk factors and disease outcomes similar to those observed for the 202-variant general polygenic score (**eFigure 15**). Sensitivity analyses supported the robustness of the main analysis to sex-specific associations, associations with height, or the possibility of false positive associations in Stage 1 or Stage 2 (**eMethods 7, eTables 9-11**).

In multivariable analyses adjusting for hip circumference estimates, the 202-variant polygenic score had a pattern of association with compartmental fat mass, cardio-metabolic risk factors and disease outcomes which was similar to that of the waist-specific polygenic score (**eFigure 8D and eFigure 17**). The 202-variant polygenic score remained associated with higher risk of type 2 diabetes and coronary disease even when adjusting for hip circumference and leg fat mass in the same model (**eTable 12**).

In multivariable analyses adjusting for waist circumference estimates, the 202-variant polygenic score had a pattern of association with compartmental fat mass, cardio-metabolic risk factors and disease outcomes which was similar to that of the hip-specific polygenic score (**eFigure 8C and eFigure 17**). The 202-variant polygenic score remained associated with higher risk of type 2 diabetes and coronary disease even when adjusting for waist circumference and visceral abdominal fat mass in the same model (**eTable 12**).

In multivariable analyses adjusting for both waist and hip circumference estimates, the 202-variant polygenic score was not associated with risk of type 2 diabetes or coronary

disease (**eFigure 8B and eTable 12**).

Discussion

This large study identified distinct genetic variants associated with a higher WHR via specific associations with lower gluteofemoral or higher abdominal fat distribution. Both these distinct sets of genetic variants were associated with higher levels of cardio-metabolic risk factors and a higher risk of type 2 diabetes and coronary disease. While this study supports the theory that an enhanced accumulation of fat in the abdominal cavity may be a cause of cardiovascular and metabolic disease, it also provides novel evidence of a possible independent role of the relative inability to expand the gluteofemoral fat compartment.

Previous studies of ~50 genomic regions associated with BMI-adjusted WHR[15] have shown an association between genetic predisposition to higher WHR and higher risk of cardio-metabolic disease,[26,35] mirroring the well-established BMI-independent association of a higher WHR with incident cardiovascular and metabolic disease in large-scale observational studies.[2,3] While these results have been widely interpreted as supportive of the role of abdominal fat deposition in cardio-metabolic risk independent of overall adiposity, the etiologic contribution of lower levels of gluteofemoral and peripheral fat to these associations has not been considered.

The results of this study support the hypothesis that an impaired ability to preferentially deposit excess calories in the gluteofemoral fat compartment leads to higher cardio-metabolic risk in the general population. This is consistent with observations in severe forms of partial lipodystrophy[6,7] and with the emerging evidence of a shared genetic background between extreme lipodystrophies and fat distribution in the general population.[11] This large human genetic study adds to a growing body of evidence linking gluteofemoral and subcutaneous adipose tissue biology with a favorable metabolic profile.[8-10] The hip-specific polygenic score for higher WHR was not significantly associated with measures of central fat in DEXA analyses and, in a post hoc analysis, its association with cardio-metabolic disease outcomes

was independent of visceral abdominal fat mass. These associations may perhaps reflect the secondary deposition within ectopic fat depots, such as liver, cardiac and skeletal muscle and pancreas, of excess calories that cannot be accommodated in gluteofemoral fat.[36,37]

It has been hypothesized that the association between fat distribution and cardio-metabolic risk is due to an enhanced deposition of intra-abdominal fat generating a molecular milieu that fosters abdominal organ insulin resistance.[38] The results of this study support a role of abdominal fat distribution, but they also suggest that impaired gluteofemoral fat distribution may contribute to the relationship between body shape and cardio-metabolic health outcomes.

Limitations

This study has several limitations. First, as this is an observational study, it cannot establish causality. Second, the discovery and characterization of genetic variants was conducted in a large dataset but was limited to individuals of European ancestry. While the genetic determinants of anthropometric phenotypes may be partly shared across different ethnicities,[15,39,40] further investigations in other populations and ethnicities will be required for a complete understanding of the genetic relationships between body shape and cardio-metabolic risk. Third, this study was largely based on population-based cohorts, the participants of which are usually healthier than the general population, and used analytical approaches that deliberately minimize the influence of outliers, in this case people with extreme fat distribution. Genetic studies in people with extreme fat distribution may help broaden understanding of the genetic basis of this risk factor. Fourth, while disease case definitions were based on widely-adopted criteria, misclassification of cases/controls cannot be excluded, which would bias association estimates towards the null. Fifth, absolute risk increase estimates are based on incidence rates and odds ratios calculated in different

populations and therefore assume that these populations are similar. Sixth, P-value thresholds used to exclude associations with the other component of fat distribution for genetic variants included in waist- or hip-specific polygenic scores were arbitrarily chosen, but are more stringent than traditionally used cutoffs (e.g. P>.05) and polygenic score results were confirmed by multivariable genetic analyses which were independent of such thresholds. Seventh, this analysis focused on common genetic variants captured in both UK Biobank and GIANT and, by design, did not investigate the role of rare genetic variation or of other variants captured by dense imputation in UK Biobank. Eighth, there was a statistically-significant difference in the association of hip- versus waist-specific polygenic scores with diabetes risk, with greater estimated magnitude of association for the hip-specific polygenic score. However, given that the difference in absolute risk was small, this observation does not necessarily represent a strong signal of mechanistic difference or differential clinical importance in the relationship between the gluteofemoral versus abdominal components of fat distribution and diabetes risk.

Conclusions

Distinct genetic mechanisms may be linked to gluteofemoral and abdominal fat distribution that are the basis for the calculation of the waist-to-hip ratio. If replicated in additional diverse populations, these findings may have implications for risk assessment and treatment of diabetes and coronary disease.

Acknowledgement

Data access: L.A.L had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Conflict of Interest Disclosures: R. A. S. is an employee and shareholder of GlaxoSmithKline Plc. (GSK). S.O'R. reports personal fees from CVMED TASAP Pfizer Advisory Board, personal fees from AstraZeneca CVMD iMed External Scientific Panel, personal fees from MedImmune Cardiovascular & Metabolic Disease (CVMD) iMed Advisory Board, personal fees from ERX Pharmaceuticals Scientific Advisory Board, outside the submitted work. The other authors report no conflict of interest relative to this study.

Tables

Table 1. Summary of the study design.

Stage and aim	Independent variables	Outcome variables	Outcome data sources	Statistical significance
Stage 1: Genetic discovery Identify genetic variants associated with fat distribution	~2.4 million common genetic variants genome-wide	BMI-adjusted WHR (N=660,648) and unadjusted WHR (N=663,598)	UK Biobank; GIANT (summary statistics)	$P<5 \times 10^{-08}$ in each analysis
Stage 2a: Derivation of polygenic scores for higher WHR[a] Select genetic variants into polygenic scores for higher WHR capturing different components of fat distribution	202 independent genetic variants from Stage 1	Hip (N=664,446) and waist (N=683,549) circumference	UK Biobank; GIANT (summary statistics)	Hip- or waist specific WHR-associated genetic variant: P<.00025 for association with either hip or waist and at least P>0.2 for association with the other
Stage 2b: Polygenic score performance Assess polygenic scores performance using variance explained and F-statistic	Four polygenic scores for higher WHR[a]	BMI-adjusted WHR (N=350,721)[b]	UK Biobank	F-statistic >10
Stage 3: Polygenic score validation Association of polygenic scores for higher WHR with detailed compartmental fat distribution measures	Polygenic scores for higher WHR from Stage 2b	Arm, trunk, abdominal, abdominal visceral, abdominal subcutaneous, gluteofemoral, leg fat mass and abdominal/gluteofemoral fat mass ratio measured by DEXA (N=18,330)	Fenland; EPIC-Norfolk; UK Biobank	P<.0016
Stage 4: Cardio-metabolic risk association Association of polygenic scores for higher WHR with cardiovascular risk factors and disease outcomes	Polygenic scores for higher WHR from Stage 2b	Risk factors: systolic (N=451,402), diastolic (N=451,415) blood pressure; fasting insulin (N=108,557), fasting glucose (N=133,010); triglycerides (N=188,577), LDL-C (N=188,577) Outcomes: type 2 diabetes (69,677 cases, 551,081 controls), coronary disease (85,358 cases, 551,249 controls)	Risk factors: UK Biobank; MAGIC (summary statistics); GLGC (summary statistics) Disease outcomes: UK Biobank; EPIC-InterAct; DIAGRAM (summary statistics); CARDIoGRAMplusC4D (summary statistics)	P<.0021 for risk factors P<.0063 for disease outcomes

Abbreviations: WHR, waist-to-hip ratio; BMI, body mass index; DEXA, dual-energy X-ray absorptiometry; LDL-C, low-density lipoprotein cholesterol. Studies participating in each stage are described in details in the Methods section, Table 2, eMethods 1 and eTables 1-3.

513 a The four polygenic scores included: (1) general polygenic score for higher WHR including all 202 independent genetic variants from Stage 1; (2) waist-specific
514 polygenic score for higher WHR including 36 genetic variants associated with waist but not hip in Stage 2a; (3) hip-specific polygenic score for higher WHR
515 including 22 genetic variants associated with hip but not waist in Stage 2a; (4) general polygenic score for higher WHR including 144 genetic variants not
516 included in the waist-specific or hip-specific polygenic scores.
517 b Variance explained was estimated using linear regression models in unrelated European ancestry participants of UK Biobank.[16]

Table 2. Participants of UK Biobank included in this study.

Study	UK Biobank
Country	United Kingdom
Genotyping chip	Affymetrix UK BILEVE and UK Biobank Axiom arrays
Imputation panel	Haplotype Reference Consortium r1.1
Participants, N	452,302
Female sex, N (%)	245,351 (54)
Male sex, N (%)	206,951 (46)
Age at baseline, mean years (SD)	57 (8)
Age at baseline in women, mean years (SD)	57 (8)
Age at baseline in men, mean years (SD)	57 (8)
Currently smoking, N (%)	47,036 (10)
Currently smoking in women, N (%)	21,867 (9)
Currently smoking in men, N (%)	25,165 (12)
BMI, mean kg/m^2 (SD)[a]	27.4 (4.8)
BMI in women, mean kg/m^2 (SD)	27.0 (5.1)
BMI in men, mean kg/m^2 (SD)	27.9 (4.2)
Waist-to-hip ratio, mean (SD) [b]	0.87 (0.09)
Waist-to-hip ratio in women, mean (SD)	0.82 (0.07)
Waist-to-hip ratio in men, mean (SD)	0.94 (0.07)
Waist circumference, mean cm (SD) [c]	90 (13.5)
Waist circumference in women, mean cm (SD)	85 (12.5)
Waist circumference in men, mean cm (SD)	97 (11.4)
Hip circumference, mean cm (SD) [d]	103 (9.2)
Hip circumference in women, mean cm (SD)	103 (10.3)
Hip circumference in men, mean cm (SD)	104 (7.6)
Systolic blood pressure, mean mmHg (SD)[e]	138 (19)
Systolic blood pressure in women, mean mmHg (SD)[e]	135 (19)
Systolic blood pressure in men, mean mmHg (SD)[e]	141 (17)
Diastolic blood pressure, mean mmHg (SD)[f]	82 (10)
Diastolic blood pressure in women, mean mmHg (SD)[f]	81 (10)
Diastolic blood pressure in men, mean mmHg (SD)[f]	84 (10)

a Missing in 1,594 participants (0.4%).
b Missing in 883 participants (0.2%).
c Missing in 790 participants (0.2%).
d Missing in 838 participants (0.2%).
e Missing in 863 participants (0.2%).
f Missing in 850 participants (0.2%).
Exact numbers of participants included in each genetic analysis are in eTable 1.
Abbreviations: N, number of participants; BMI, body mass index; SD, standard deviation.

Figure legends

Figure 1. Associations with compartmental fat mass of polygenic scores for higher WHR. ***Panel A*** shows associations with compartmental fat mass for the 202-variant general polygenic score for higher WHR. Associations are reported in clinical or standardized units of continuous outcome per 1 SD increase in $WHR_{BMI\text{-}adjusted}$ (corresponding to 0.056 ratio units of age-, sex- and BMI-residualized WHR in UK Biobank) due to the polygenic score. The statistical significance threshold for analyses reported in this panel was P<.0016. ***Panel B*** shows associations with compartmental fat mass for the waist- (orange) or hip- (dark blue) specific polygenic scores for higher WHR. Associations were estimated in up to 18,330 European ancestry individuals from the UK Biobank,[16] Fenland[11] and EPIC-Norfolk[17] studies. Associations are reported in clinical or standardized units of continuous outcome per 1 SD increase in $WHR_{BMI\text{-}adjusted}$ (corresponding to 0.056 ratio units of age-, sex- and BMI-residualized WHR in UK Biobank) due to the polygenic score used in a given analysis. The statistical significance threshold for analyses reported in this panel was P<.0016. Abbreviations: N, number of participants; SD, standard deviation; CI, confidence interval; WHR, waist-to-hip ratio; BMI, body mass index.

Figure 2. Associations with cardio-metabolic risk factors and disease outcomes of waist- or hip-specific polygenic scores for higher WHR. ***Panel A*** shows associations with cardio-metabolic risk factors for the waist- (orange) or hip- (dark blue) specific polygenic scores for higher WHR. Associations are reported in clinical or standardized units of continuous outcome per 1 SD increase in $WHR_{BMI\text{-}adjusted}$ (corresponding to 0.056 ratio units of age-, sex- and BMI-residualized WHR in UK Biobank) due to the polygenic score used in a given analysis. Data on blood pressure were from UK Biobank[16]; data on LDL-C and triglycerides were from Global Lipids Genetics consortium[22]; data on fasting insulin and fasting glucose were from the Meta-analyses of Glucose and Insulin-related traits consortium[20,21]. The statistical significance threshold for analyses reported in this panel was P<.0021. ***Panel B*** shows associations with type 2 diabetes and coronary artery disease risk for the waist- (orange) or hip- (dark blue) specific polygenic scores for higher WHR. Associations are reported in odds ratio or absolute risk increase per 1 SD increase in $WHR_{BMI\text{-}adjusted}$ (corresponding to 0.056 ratio units of age-, sex- and BMI-residualized WHR in UK Biobank) due to the polygenic score used in a given analysis. Associations with type 2 diabetes were estimated in 69,677 cases and 551,081 controls from the DIAGRAM consortium[23], EPIC-InterAct[18] and UK Biobank[16]. Associations with coronary artery disease were estimated in 85,358 cases and 551,249 controls from UK Biobank[16] and the CARDIoGRAMplusC4D consortium[24]. The statistical significance threshold for analyses reported in this panel was P<.0063. Abbreviations: N, number of participants; SD, standard deviation; CI, confidence interval; LDL-C, low-density lipoprotein cholesterol; WHR, waist-to-hip ratio; BMI, body mass index; OR, odds ratio; ARI, absolute risk increase; py, participant-years of follow-up.

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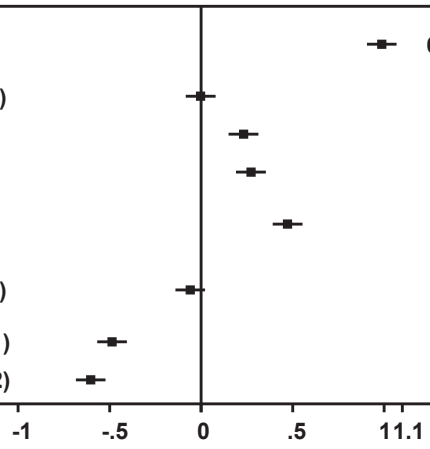
Figure 1

A

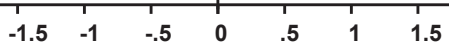
Outcome	N	Beta (95% CI) in clinical units	Beta (95% CI) in SD units	P
Abdominal/gluteofemoral Fat mass ratio	18,325	0.21 (0.19, 0.22)	0.99 (0.91, 1.07)	6.7×10^{-126}
Arms fat mass, grams	18,330	0 (-69, 69)	-0.00 (-0.08, 0.08)	0.95
Trunk fat mass, grams	18,330	1330 (867, 1792)	0.23 (0.15, 0.31)	2.2×10^{-08}
Abdominal fat mass, grams	18,325	318 (224, 412)	0.27 (0.19, 0.35)	4.9×10^{-11}
Visceral Abdominal fat mass, log (grams)	18,267	0.8 (0.6, 0.9)	0.47 (0.39, 0.55)	4.4×10^{-30}
Subcutaneous Abdominal fat mass, grams	18,278	-40 (-93, 13)	-0.06 (-0.14, 0.02)	0.15
Gluteofemoral fat mass, grams	18,325	-755 (-878, -632)	-0.49 (-0.57, -0.41)	6.3×10^{-32}
Leg fat mass, grams	18,329	-1920 (-2175, -1664)	-0.60 (-0.68, -0.52)	3.2×10^{-48}



Beta (95% CI) in SD units
per 1 SD increase in $WHR_{BMI\text{-}adjusted}$

B

Outcome	N	Beta (95% CI) in clinical units	Beta (95% CI) in SD units	P
Abdominal/gluteofemoral Fat mass ratio	18,325	0.24 (0.20, 0.29)	1.17 (0.94, 1.41)	3.4×10^{-22}
		0.17 (0.13, 0.22)	0.83 (0.60, 1.05)	1.1×10^{-12}
Arms fat, grams	18,330	365 (156, 573)	0.42 (0.18, 0.66)	0.00051
Trunk fat, grams	18,330	3931 (2544, 5261)	0.68 (0.44, 0.91)	2.4×10^{-08}
Abdominal fat, grams	18,325	849 (566, 1131)	0.72 (0.48, 0.96)	2.5×10^{-09}
Visceral abdominal fat, log (grams)	18,267	1.1 (0.7, 1.5)	0.68 (0.45, 0.92)	1.8×10^{-08}
Subcutaneous abdominal fat, grams	18,278	379 (226, 538)	0.57 (0.34, 0.81)	2.3×10^{-06}
Gluteofemoral fat, grams	18,325	46 (-308, 416)	0.03 (-0.20, 0.27)	0.79
Leg fat, grams	18,329	-384 (-1152, 352)	-0.12 (-0.36, 0.11)	0.31
Arms fat, grams	18,330	-217 (-408, -17)	-0.25 (-0.47, -0.02)	0.033
Trunk fat, grams	18,330	-520 (-1850, 809)	-0.09 (-0.32, 0.14)	0.44
Abdominal fat, grams	18,325	-35 (-306, 236)	-0.03 (-0.26, 0.20)	0.80
Visceral abdominal fat, log (grams)	18,267	0.5 (0.1, 0.8)	0.29 (0.06, 0.52)	0.013
Subcutaneous abdominal fat, grams	18,278	-279 (-432, -126)	-0.42 (-0.65, -0.19)	0.00033
Gluteofemoral fat, grams	18,325	-1248 (-1603, -909)	-0.81 (-1.04, -0.59)	2.5×10^{-12}
Leg fat, grams	18,329	-2815 (-3551, -2111)	-0.88 (-1.11, -0.66)	2.6×10^{-14}



Waist-specific polygenic score for higher WHR

Hip-specific polygenic score for higher WHR

Beta (95% CI) in SD units
per 1 SD increase in $WHR_{BMI\text{-}adjusted}$

Figure 2

A

Outcome	N	Beta (95% CI) In clinical units	Beta (95% CI) In SD units	P	$P_{heterogeneity}$ in association estimates, waist- vs hip-specific polygenic score
Systolic blood pressure, mmHg	451,402	3 (2, 4)	0.15 (0.11, 0.20)	2.4×10^{-11}	0.68
		3 (2, 4)	0.14 (0.10, 0.19)	2.1×10^{-10}	
Diastolic blood Pressure, mmHg	451,415	2 (1, 2)	0.16 (0.11, 0.20)	1.3×10^{-11}	0.085
		1 (1, 2)	0.10 (0.06, 0.15)	5.5×10^{-06}	
LDL-C, mmol/L	188,577	0.0 (-0.1, 0.1)	-0.03 (-0.13, 0.07)	0.52	1.9×10^{-06}
		0.3 (0.2, 0.4)	0.30 (0.21, 0.40)	9.3×10^{-10}	
Triglycerides, log (mmol/L)	188,577	0.21 (0.16, 0.26)	0.37 (0.28, 0.46)	8.9×10^{-16}	0.14
		0.26 (0.21, 0.31)	0.46 (0.37, 0.55)	7.0×10^{-25}	
Fasting glucose, mmol/L	133,010	0.05 (-0.01, 0.11)	0.07 (-0.01, 0.16)	0.085	0.97
		0.05 (-0.01, 0.11)	0.08 (-0.01, 0.16)	0.068	
Fasting insulin, log (pmol/L)	108,557	0.10 (0.03, 0.15)	0.16 (0.05, 0.26)	0.0035	0.054
		0.18 (0.12, 0.24)	0.30 (0.20, 0.40)	6.5×10^{-09}	

B

Outcome	Cases	Controls	ARI (95% CI), cases/1000 py	OR (95% CI)	P	$P_{heterogeneity}$ in association estimates, waist- vs hip-specific polygenic score
Type 2 diabetes	69,677	551,081	4.4 (2.7, 6.5)	1.57 (1.34, 1.83)	1.3×10^{-08}	1.7×10^{-05}
			12.0 (9.1, 15.3)	2.54 (2.17, 2.96)	1.7×10^{-32}	
Coronary artery disease	85,358	551,249	2.3 (1.5, 3.3)	1.60 (1.39, 1.84)	1.1×10^{-10}	0.36
			3.0 (2.1, 4.0)	1.76 (1.53, 2.02)	1.3×10^{-15}