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Genetic Association of Waist-to-Hip Ratio With Cardiometabolic Traits, Type 2 Diabetes, and Coronary Heart Disease

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IMPORTANCE In observational studies, abdominal adiposity has been associated with type 2 diabetes and coronary heart disease (CHD). Whether these associations represent causal relationships remains uncertain.

OBJECTIVE To test the association of a polygenic risk score for waist-to-hip ratio (WHR) adjusted for body mass index (BMI), a measure of abdominal adiposity, with type 2 diabetes and CHD through the potential intermediates of blood lipids, blood pressure, and glycemic phenotypes.

DESIGN, SETTING, AND PARTICIPANTS A polygenic risk score for WHR adjusted for BMI, a measure of genetic predisposition to abdominal adiposity, was constructed with 48 single-nucleotide polymorphisms. The association of this score with cardiometabolic traits, type 2 diabetes, and CHD was tested in a mendelian randomization analysis that combined case-control and cross-sectional data sets. Estimates for cardiometabolic traits were based on a combined data set consisting of summary results from 4 genome-wide association studies conducted from 2007 to 2015, including up to 322 154 participants, as well as individual-level, cross-sectional data from the UK Biobank collected from 2007-2011, including 111 986 individuals. Estimates for type 2 diabetes and CHD were derived from summary statistics of 2 separate genome-wide association studies conducted from 2007 to 2015 and including 149 821 individuals and 184 305 individuals, respectively, combined with individual-level data from the UK Biobank.

EXPOSURES Genetic predisposition to increased WHR adjusted for BMI.

MAIN OUTCOMES AND MEASURES Type 2 diabetes and CHD.

RESULTS Among 111 986 individuals in the UK Biobank, the mean age was 57 (SD, 8) years, 58 845 participants (52.5%) were women, and mean WHR was 0.875. Analysis of summary-level genome-wide association study results and individual-level UK Biobank data demonstrated that a 1-SD increase in WHR adjusted for BMI mediated by the polygenic risk score was associated with 27-mg/dL higher triglyceride levels, 4.1-mg/dL higher 2-hour glucose levels, and 2.1-mm Hg higher systolic blood pressure (each $P < .001$). A 1-SD genetic increase in WHR adjusted for BMI was also associated with a higher risk of type 2 diabetes (odds ratio, 1.77 [95% CI, 1.57-2.00]; absolute risk increase per 1000 participant-years, 6.0 [95% CI, CI, 4.4-7.8]; number of participants with type 2 diabetes outcome, 40 530) and CHD (odds ratio, 1.46 [95% CI, 1.32-1.62]; absolute risk increase per 1000 participant-years, 1.8 [95% CI, 1.3-2.4]; number of participants with CHD outcome, 66 440).

CONCLUSIONS AND RELEVANCE A genetic predisposition to higher waist-to-hip ratio adjusted for body mass index was associated with increased risk of type 2 diabetes and coronary heart disease. These results provide evidence supportive of a causal association between abdominal adiposity and these outcomes.

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Supplemental content

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Obesity, typically defined on the basis of body mass index (BMI), is a leading cause of type 2 diabetes and coronary heart disease (CHD) in the population.[1,2] However, for any given BMI, body fat distribution can vary substantially; some individuals store proportionally more fat around their visceral organs (abdominal adiposity) than on their thighs and hip.[3] Waist-to-hip ratio (WHR) adjusted for BMI is a surrogate measure of abdominal adiposity and has been correlated with direct imaging assessments of abdominal fat.[4,5]

In observational studies, abdominal adiposity has been associated with cardiometabolic disease[6,7]; however, whether this association is causal remains unclear. For example, unmeasured lifestyle factors[8] might confound observational studies that link WHR adjusted for BMI with type 2 diabetes and CHD. Furthermore, reverse causality could similarly lead to a statistically robust but noncausal relationship. For example, individuals with subclinical CHD might develop abdominal adiposity because of an inability to exercise.

Mendelian randomization is a human genetics tool that leverages the random assortment of genetic variants at time of conception to facilitate causal inference.[9] Because genetic predisposition to abdominal adiposity is determined by DNA sequence variants, it is less likely to be affected by confounding or reverse causality. In this study, a mendelian randomization approach was used to determine whether a genetic predisposition to increased WHR adjusted for BMI is associated with cardiometabolic quantitative traits, type 2 diabetes, and CHD.

Key Points

Question Is genetic evidence consistent with a causal relationship among waist-to-hip ratio adjusted for body mass index (a measure of abdominal adiposity), type 2 diabetes, and coronary heart disease?

Findings In this mendelian randomization study, a polygenic risk score for increased waist-to-hip ratio adjusted for body mass index was significantly associated with adverse cardiometabolic traits and higher risks for both type 2 diabetes and coronary heart disease.

Meaning These results provide evidence supportive of a causal association between abdominal adiposity and the development of type 2 diabetes and coronary heart disease.

Methods

Study Design and Instruments

Observational epidemiology studies test association of an exposure (eg, WHR adjusted for BMI) with an outcome (eg, CHD). However, unobserved confounders may affect both exposure and outcome, thus biasing the observed association (**Figure 1**; eMethods A in the Supplement). Because genetic variants are both randomly assorted in a population and assigned at conception, they are largely unassociated with confounders and can be used as instrumental variables to estimate the causal association of an exposure (WHR adjusted for BMI) with an outcome.[9]

This mendelian randomization approach has 3 assumptions.[10] First, genetic variants used as an instrument must be associated with the exposure of interest (eg, WHR adjusted for BMI) (assumption 1 in Figure 1). Second, genetic variants must not be associated with confounders (assumption 2 in Figure 1). Third, genetic variants must not be associated with outcome independently of the exposure (assumption 3 in Figure 1). The second and third assumptions are collectively known as independence from pleiotropy. Mendelian randomization can be extended to conduct a mediation analysis, estimating the proportion of an observed association of an exposure (WHR adjusted for BMI) with an outcome (CHD) that occurs through a given mediator (Figure 1).

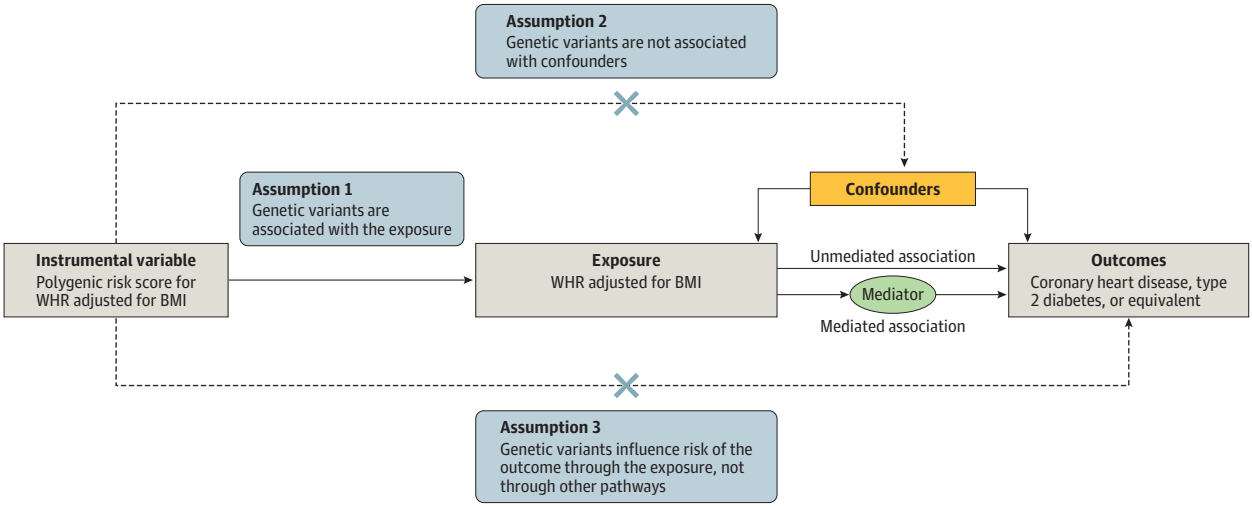
A mendelian randomization study using publicly available, summary-level data from large-scale genome-wide association studies (GWASs) (both cross-sectional and case-control data sets) as well as individual-level data from the UK Biobank (a cross-sectional data set) was conducted (**Figure 2**).[12-18] The primary instrument was a polygenic risk score for WHR adjusted for BMI. A recent large-scale GWAS from the Genome-Wide Investigation of Anthropometric Traits (GIANT) Consortium identified 48 single-nucleotide polymorphisms (SNPs), or genetic variants, associated with WHR adjusted for BMI (eTable 1 in the Supplement).[14] Combining these 48 SNPs into a weighted polygenic risk score enabled quantification of the genetic predisposition to increased WHR adjusted for BMI for each individual.

Data Sources and Study Participants

Summary-level data from 6 GWAS consortia were used (GWASs conducted from 2007 to 2015) (eTable 3; eMethods B in the Supplement).[12-18] For WHR, BMI, waist circumference, hip circumference, and WHR adjusted for BMI, data from the GIANT Consortium was used (GWASs conducted from 2007 to 2013)[14,15]; this study included 322 154 individuals of European descent for BMI and 210 088 individuals of European descent for waist circumference, hip circumference, WHR, and WHR adjusted for BMI. The results from 5 additional GWAS (conducted from 2007 to 2015) examining blood lipids, glycemic traits, renal function, type 2 diabetes, and CHD, and predominantly including individuals of European descent, were also assessed.[11,13,16,17,19,20] Summary results for type 2 diabetes and CHD were derived from studies of 149 821 individuals (Diabetes Genetics Replication and Meta-analysis [DIAGRAM][13]) and 184 305 individuals (Coronary Artery Disease Genome-Wide Replication and Meta-analysis plus the Coronary Artery Disease Genetics Consortium [CARDIOGRAMplusC4D][11]), respectively. Informed consent was obtained from all participants of contributing studies. Contributing studies received ethical approval from their respective institutional review boards.

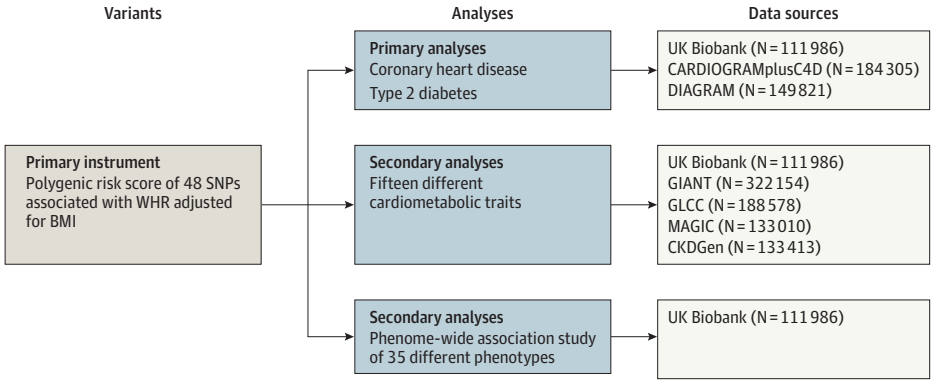
Individual-level data from 111 986 individuals of European ancestry from the UK Biobank, collected from 2007 to 2011, were also used (**Table**; eMethods C in the Supplement). The UK Biobank received ethical approval from the research ethics committee (reference number 11/NW/0382). Analysis of the UK Biobank data was approved by the Partners Health Care institutional review board (protocol 2013P001840). Informed consent was obtained from all participants by the UK Biobank.

Figure 1. Assumptions of a Mendelian Randomization Analysis



Genetic variants, which are assigned at birth and largely randomly assorted in a population, can be used as instrumental variables to estimate the causal association of an exposure (eg, waist-to-hip ratio [WHR] adjusted for body mass index [BMI]) with an outcome of interest (eg, coronary heart disease). This approach rests on 3 assumptions. First, the genetic variants must be associated with the exposure (assumption 1). Second, the genetic variants must not be associated with confounders (assumption 2). Third, the genetic variants must influence risk of the outcome through the exposure and not through other pathways (assumption 3). Mendelian randomization can be extended to estimate the association of exposure with outcome that is mediated by a given a mediator (eg, triglycerides).

Figure 2. Study Design



A polygenic score of 48 single-nucleotide polymorphisms was used as an instrument to estimate the causal association of waist-to-hip ratio (WHR) adjusted for body mass index (BMI) with cardiometabolic quantitative traits, type 2 diabetes, and coronary heart disease; sources of data for analysis included the UK Biobank and publicly available genome-wide association studies. CARDIOGRAMplusC4D indicates Coronary Artery DIsease Genome-wide Replication and Meta-analysis plus the Coronary Artery Disease Genetics Consortium[11]; CKDGen, Chronic Kidney Disease Genetics Consortium[12]; DIAGRAM, Diabetes Genetics Replication and Meta-analysis[13]; GIANT, Genetic Investigation of Anthropometric Traits[14,15]; GLGC, Global Lipids Genetics Consortium[16]; MAGIC, Meta-analyses of Glucose and Insulin-Related Traits Consortium[17]; SNP, single-nucleotide polymorphism.

WHR adjusted for BMI was derived in the UK Biobank through inverse normal transformation of WHR after adjustment for age, sex, and BMI (as in the GIANT Consortium[14]). Type 2 diabetes and CHD were both ascertained at baseline by self-report, followed by a verbal interview with a trained nurse to confirm the diagnosis (eTable 4 in the Supplement). Type 2 diabetes was defined as report of type 2 diabetes, report of type 2 diabetes unspecified, or current use of insulin medication. CHD was defined as report of previous myocardial infarction or diagnosis of angina or hospitalization for myocardial infarction (*International Statistical Classification of Diseases and Related Health Problems, Tenth Revision* codes I21-I23).

In addition to the primary outcomes of type 2 diabetes and CHD, a phenome-wide association study (an analysis of the association of a genetic variant or polygenic risk score with a broad range of diseases, outcomes, or both) for 35 additional diseases, including endocrine, renal, urologic, gastrointestinal, neurologic, musculoskeletal, respiratory, and cancer disorders, was conducted in the UK Biobank to attempt to iden-

tify whether the polygenic risk score for WHR adjusted for BMI is associated with any additional disorders (eTable 4 in the Supplement).

Statistical Analysis

For analyses of both summary-level data and UK Biobank data, a weighted polygenic risk score was derived based on the magnitude of association of each SNP with WHR adjusted for BMI in the previously published GIANT analysis.[19] The association of polygenic risk score with each continuous trait and dichotomous outcome was then calculated after standardization to a 1-SD predicted change in WHR adjusted for BMI.

For the summary-level data, this approach is equivalent to an inverse-variance-weighted fixed-effects meta-analysis of the association of each SNP with the trait or outcome of interest (eg, CHD), divided by the association of each SNP with WHR adjusted for BMI.[21] Explicitly, if x is the association of each SNP with the outcome of interest, and w the association of each SNP with WHR adjusted for BMI, then the estimated genetic association of WHR adjusted for BMI with the outcome was calculated as a fixed-effects meta-analysis of x/w for all SNPs.

To validate that the polygenic risk score for WHR adjusted for BMI was a strong instrument for WHR adjusted for BMI (assumption 1 in Figure 1), an F statistic for the instrument was calculated in the UK Biobank. An F statistic is a measure of the significance of an instrument (the polygenic risk score) for prediction of the exposure (WHR adjusted for BMI), controlling for additional covariates (age, sex, 10 principal components of ancestry, and a dummy variable for the array type used in genotyping). An F statistic greater than 10 is evidence of a strong instrument.[22]

For individual-level data from the UK Biobank, logistic regression was used to determine association of a polygenic risk score for WHR adjusted for BMI and dichotomous outcomes (type 2 diabetes, CHD, and 35 additional diseases) (eMethods C in the Supplement).[23] Linear regression was used for continuous traits (anthropometric traits and blood pressure) in the UK Biobank. All UK Biobank analyses included adjustment for age, sex, 10 principal components of ancestry, and a dummy variable for the array type used in genotyping. The inclusion of principal components of ancestry as covariates is commonly implemented to correct for population stratification according to ancestral background.[24]

To test assumption 2 (independence of polygenic risk score for WHR adjusted for BMI from potential confounders) (Figure 1), the relationship of the polygenic risk score to smoking, alcohol use, physical activity, vegetable consumption, red meat consumption, and breastfeeding status as a child was determined among individuals in the UK Biobank. Test for trend was performed across quartiles of the polygenic risk score for WHR adjusted for BMI using logistic regression, with each potential confounder as the outcome. For comparison, individuals in the UK Biobank were stratified into quartiles by observational WHR adjusted for BMI and test for trend performed using logistic regression.

Five additional sensitivity analyses were conducted to test the robustness of the results (eMethods D in the Supplement).

Table. Characteristics of UK Biobank Participants

Characteristic	No. (%) or Mean (SD)
No. Individuals	111 986
Age, mean (SD), y	56.9 (7.9)
Men, No. (%)	53 141 (47.5)
UK BiLEVE array, No. (%)[a]	38 505 (34.4)
Blood pressure, mean (SD), mm Hg[b]	
Systolic	143.6 (21.8)
Diastolic	84.5 (11.8)
Body mass index, mean (SD)[c]	27.5 (4.8)
Waist-to-hip ratio, mean (SD)	0.875 (0.09)
Diabetes mellitus, No. (%)	5690 (5.1)
Coronary heart disease, No. (%)	5639 (5.0)

[a] Participants genotyped using the UK BiLEVE array rather than the UK Biobank Axiom array.

[b] Baseline blood pressure was missing for 7681 individuals. Reported measurements are after adjustment for treatment (addition of 15 mm Hg to systolic blood pressure and 10 mm Hg to diastolic blood pressure).

[c] Calculated as weight in kilograms divided by height in meters squared.

Three additional polygenic risk scores were used, including one that included variants not significantly associated with BMI, a second that included variants significantly associated with gene expression in adipose tissue, and a third that included variants significantly associated with increased WHR adjusted for BMI in women but not in men. The association of genetic variants with BMI was adjusted for, and median regression was used (eMethods D in the Supplement).[10] The rationale for these sensitivity analyses is provided in eMethods D.

Absolute increases associated with WHR adjusted for BMI for type 2 diabetes and CHD were calculated using the United States population incidence of type 2 diabetes and CHD (eMethods E in the Supplement). Tests for nonlinear associations of a genetic predisposition to increased WHR adjusted for BMI with type 2 diabetes and CHD were performed using nonlinear instrumental variable estimation (eMethods F in the Supplement).[25]

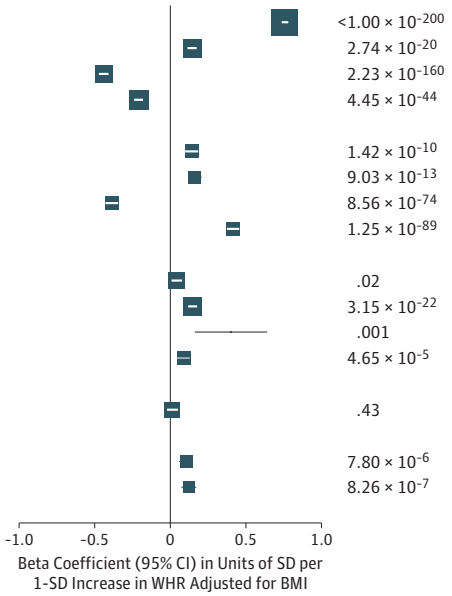
The threshold of statistical significance for type 2 diabetes and CHD (main outcome measures) was $P < .025$ (.05/2 = .025). The threshold of significance for the analysis of 15 traits was $P < .0033$ (.05/15 = .0033). The threshold of significance in the phenome-wide association analysis was $P < .0014$ (.05/35 = .0014).

Mediation Analysis

Among continuous traits, the polygenic risk score for WHR adjusted for BMI was most strongly associated with plasma triglyceride levels. The extent to which the polygenic risk score association with CHD was mediated by plasma triglycerides was tested using mediation analysis, conducted post hoc after triglyceride level was identified as the cardiometabolic trait most strongly associated with WHR adjusted for BMI. An estimate of the genetic association of triglyceride level on CHD risk, previously derived by Do et al[26] (odds ratio [OR], 1.52 per 1-SD increase in triglyceride level),[26] was used to calculate the predicted magnitude of increased CHD risk based on the observed association of the WHR adjusted for

Figure 3. Association of 48-SNP Polygenic Risk Score for WHR Adjusted for BMI With Cardiometabolic Quantitative Traits

Trait	Association in Clinical Units (95% CI)[a]	Association in Units of SD (95% CI)	P Value
Anthropometric			
WHR	0.068 (0.066 to 0.07)	0.76 (0.74 to 0.78)	$<1.00 \times 10^{-200}$
Waist circumference, cm	2 (1.5 to 2.4)	0.14 (0.11 to 0.17)	2.74×10^{-20}
Hip circumference, cm	-4.1 (-4.4 to -3.8)	-0.44 (-0.47 to -0.41)	2.23×10^{-160}
BMI[b]	-1.0 (-1.1 to -0.9)	-0.21 (-0.24 to -0.18)	4.45×10^{-44}
Lipids			
Total cholesterol, mg/dL	5.6 (3.9 to 7.3)	0.14 (0.10 to 0.18)	1.42×10^{-10}
LDL-C, mg/dL	5.7 (4.1 to 7.2)	0.16 (0.12 to 0.21)	9.03×10^{-13}
HDL-C, mg/dL	-6.0 (-6.6 to -5.3)	-0.39 (-0.43 to -0.35)	8.56×10^{-74}
Triglycerides, mg/dL	27 (25 to 30)	0.42 (0.37 to 0.46)	1.25×10^{-89}
Glycemic			
Fasting glucose, mg/dL	0.56 (0.11 to 1.0)	0.04 (0.01 to 0.08)	.02
Fasting insulin, log (pmol/L)	0.07 (0.05 to 0.08)	0.15 (0.12 to 0.18)	3.15×10^{-22}
Two-hour glucose, mg/dL	4.1 (1.6 to 6.5)	0.40 (0.16 to 0.64)	.001
HbA_{1c}, %	0.05 (0.02 to 0.07)	0.09 (0.05 to 0.13)	4.65×10^{-5}
Renal function			
eGFR, mL/min/1.73 m^2	0.70 (−1.1 to 2.5)	0.01 (-0.02 to 0.05)	.43
Blood pressure			
Systolic, mm Hg	2.1 (1.2 to 3.0)	0.10 (0.06 to 0.15)	7.80×10^{-6}
Diastolic, mm Hg	1.3 (0.8 to 1.8)	0.12 (0.07 to 0.17)	8.26×10^{-7}



Results are standardized to a 1-SD increase in waist-to-hip ratio (WHR) adjusted for body mass index (BMI) due to polygenic risk score. For systolic blood pressure, a 1-SD genetic increase in WHR adjusted for BMI is associated with a 2.1-mm Hg higher systolic blood pressure (95% CI, 1.2-3.0) or a 0.1-SD increase in systolic blood pressure (95% CI, 0.059-0.15). For anthropometric traits, estimates from Genetic Investigation of Anthropometric Traits (GIANT) derived using inverse variance–weighted fixed-effects meta-analysis[14,15]) were pooled with data from the UK Biobank (derived instrumental variables regression adjusting for age, sex, 10 principal components of ancestry, and array type) using inverse variance–weighted fixed-effects meta-analysis. For lipids, glycemic, and renal function traits, estimates were derived from genome-wide association studies (Global Lipids Genetics,[16] Meta-analyses of Glucose and Insulin-Related Traits,[17] and Chronic Kidney Genetics Consortia,[12] respectively). For blood pressure, estimates were derived from UK Biobank. Two-hour glucose refers to measured blood glucose levels 2 hours after consumption of dissolved glucose. The threshold of significance was $P < .0033$ (.05/15 = .0033). Size of data markers is inversely proportional to variance of estimate. To convert total cholesterol, LDL-C, and HDL-C values to mmol/L, multiply by 0.0259; triglyceride values to mmol, multiply by 0.0113; and glucose values to mmol/L, multiply by 0.0555. eGFR indicates estimated glomerular filtration rate; HbA_{1c}, hemoglobin A_{1c}; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; OR, odds ratio; WHR, waist-to-hip ratio.

[a] Units reported in column 1.

[b] Calculated as weight in kilograms divided by height in meters squared.

BMI polygenic risk score with triglyceride level (estimated using linear regression). To derive the remaining proportion of CHD risk unaccounted for by an increase in triglyceride levels, the magnitude of association of the change in triglyceride level with CHD was subtracted from the estimate of the genetic association of WHR adjusted for BMI with CHD (estimated using logistic regression).

Analyses were performed using R version 3.2.3 (R Project for Statistical Computing) and Stata version 12 (StataCorp).

Results

The characteristics of UK Biobank participants are reported in the Table. The mean age was 56.9 (SD, 7.9) years, mean systolic blood pressure was 143.6 mm Hg (SD, 21.8), and mean diastolic blood pressure was 84.5 mm Hg (SD, 11.8); 5639 participants (5.0%) had CHD, and 5690 (5.1%) had type 2 diabetes.

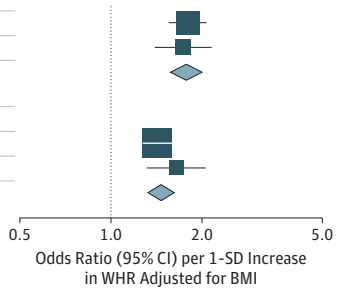
A 48-SNP polygenic risk score for WHR adjusted for BMI was a strong instrumental variable (F = 1713), statistically accounting for 1.5% of variance in WHR adjusted for BMI in the UK Biobank, thus validating assumption 1 in Figure 1.

To test assumption 2 (independence of polygenic risk score for WHR adjusted for BMI from potential confounders, Figure 1), the relationship of the polygenic risk score to smoking, alcohol use, physical activity, vegetable consumption, red meat consumption, and breastfeeding status as a child was determined among individuals in the UK Biobank. In each case, no significant relationship was noted (eTable 5 in the Supplement). For comparison, a similar analysis that categorized individuals according to observed WHR adjusted for BMI (instead of genetic predisposition to WHR adjusted for BMI) was conducted (eTable 6 in the Supplement). In this observational epidemiology analysis, WHR adjusted for BMI was associated with each potential confounder.

A 1-SD increase in WHR adjusted for BMI due to the polygenic risk score was associated with a 1-point decrease in BMI (95% CI, 0.87-1.1), a 2-cm increase in waist circumference (95% CI, 1.5-2.4), a 4.1-cm decrease in hip circumference (95% CI, 3.8-4.4), and an increase of 0.068 in WHR (95% CI, 0.066-0.070)(**Figure 3**). A 1-SD increase in WHR adjusted for BMI due to the polygenic risk score was associated with higher total cholesterol level (5.6 [95% CI, 3.9-7.3] mg/dL [0.15 {95% CI, 0.10-0.19} mmol/L]), higher low-density

Figure 4. Association of 48-SNP Polygenic Risk Score for WHR Adjusted for BMI With Type 2 Diabetes and Coronary Heart Disease

Instrument	Cases, No.	Controls, No.	Odds Ratio (95% CI) per 1-SD Increase in WHR Adjusted for BMI	P Value
Type 2 diabetes				
DIAGRAM	34 840	114 981	1.79 (1.55-2.07)	1.88×10^{-15}
UK Biobank	5690	106 296	1.73 (1.40-2.15)	6.80×10^{-7}
Fixed-effects model P = .80 for interaction			1.77 (1.57-2.00)	7.30×10^{-21}
Coronary heart disease				
CARDIOGRAMplusC4D	60 801	123 504	1.42 (1.27-1.59)	7.58×10^{-10}
UK Biobank	5639	106 347	1.64 (1.31-2.06)	1.46×10^{-5}
Fixed-effects model P = .26 for interaction			1.46 (1.32-1.62)	9.90×10^{-14}



Results are standardized to a 1-SD increase in waist-to-hip ratio adjusted for body mass index due to polygenic risk score. Estimates were independently derived in genome-wide association studies (CARDIOGRAMplusC4D for coronary heart disease and DIAGRAM for type 2 diabetes) and the UK Biobank. The threshold of significance was $P < .025$ (0.05/2 = 0.025). Size of data markers is inversely proportional to variance of estimate. CARDIOGRAMplusC4D indicates Coronary Artery DIsease Genome-Wide Replication and Meta-analysis plus the Coronary Artery Disease Genetics Consortium; DIAGRAM, Diabetes Genetics Replication and Meta-analysis.

lipoprotein cholesterol level (5.7 [95% CI, 4.1-7.2] mg/dL [0.15 {95% CI, 0.11-0.19} mmol/L]), higher triglyceride level (27 [95% CI, CI, 25-30] mg/dL [0.31 {95% CI, 0.28-0.34} mmol/L]), and lower high-density lipoprotein cholesterol level (6.0 [95% CI, 5.3-6.6] mg/dL [0.16 {0.14-0.17} mmol/L]). A 1-SD increase in WHR adjusted for BMI due to the polygenic risk score was associated with higher log-transformed fasting insulin levels (0.07 [95% CI, 0.05-0.08] log[pmol/L]), higher 2-hour glucose levels (4.1 [95% CI, 1.6-6.5] mg/dL [0.23 {95% CI, 0.09-0.36} mmol/L), and higher systolic blood pressure (2.1 [95% CI, 1.2-3.0] mm Hg).

A 1-SD increase in WHR adjusted for BMI due to the polygenic risk score was associated with a higher risk of type 2 diabetes (OR, 1.77 [95% CI, 1.57-2.00]; absolute risk increase per 1000 participant-years, 6.0 [95% CI, 4.4-7.8]; $P = 7.30 \times 10^{-21}$; number of participants with type 2 diabetes outcome, 40 530) (**Figure 4**). A 1-SD increase in WHR adjusted for BMI due to the polygenic risk score was also associated with higher risk of CHD (OR, 1.46 [95% CI, 1.32-1.62]; absolute risk increase per 1000 participant-years, 1.8 [95% CI, 1.3-2.4]; $P = 9.90 \times 10^{-14}$; number of participants with CHD outcome, 66 440) (Figure 4).

Five sensitivity analyses (eMethods D, eFigures 1-9 in the Supplement) of the genetic association of WHR adjusted for BMI with cardiometabolic traits, type 2 diabetes, and CHD were conducted to examine if results were influenced by pleiotropy (ie, a violation of assumptions 2 or 3 in Figure 1). Four of the 5 sensitivity analyses were consistent with the results not being influenced by pleiotropy (eFigures 1-7 in the Supplement). In the fifth sensitivity analysis, 8 SNPs associated with increased WHR adjusted for BMI in women but not men were combined in an additive risk score. If increased WHR adjusted for BMI causes CHD (rather than results being due to pleiotropy), then a risk score that increases WHR adjusted for BMI in women but not in men should increase risk of CHD in women but not in men. Although a numerically greater magnitude of association with type 2 diabetes and CHD was noted in women as compared with men, no significant difference was observed ($P = 0.10$ and $P = 0.11$, respectively, for interaction) (eFigures 8 and 9, eMethods D in the Supplement).

Using the polygenic risk score of 48 SNPs associated with WHR adjusted for BMI, a phenome-wide association study of 35 additional diseases in the UK Biobank was conducted (**Figure 5**). There was no significant association of WHR adjusted for BMI with any of these diseases at the Bonferroni-adjusted level of significance ($P < .0014$).

In mediation analysis, the association of polygenic risk score for WHR adjusted for BMI with CHD was attenuated from an OR of 1.46 (95% CI, 1.32-1.62) to an OR of 1.23 (95% CI, 1.11-1.36), after accounting for the association of the polygenic risk score with triglyceride level (eFigure 10 in the Supplement).

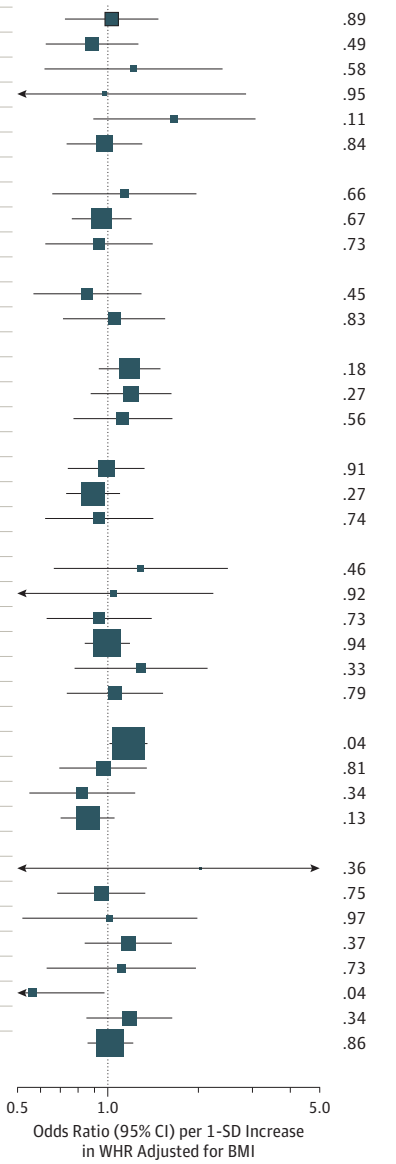
Discussion

Mendelian randomization analyses tested if human genetic evidence supported a causal relationship of WHR adjusted for BMI (a measure of abdominal adiposity) with type 2 diabetes and CHD. Genetic predisposition to higher WHR adjusted for BMI was associated with increased levels of quantitative risk factors (lipids, insulin, glucose, and systolic blood pressure) as well as a higher risk for type 2 diabetes (OR, 1.77 [95% CI, 1.57-2.00] per 1-SD higher WHR adjusted for BMI) and CHD (OR, 1.46 [95% CI, 1.32-1.62] per 1-SD higher WHR adjusted for BMI).

These results permit several conclusions. First, these findings lend human genetic support to previous observations associating abdominal adiposity with cardiometabolic disease.[6,7] In the INTERHEART acute myocardial infarction case-control study, a 1-SD higher WHR was associated with increased odds of myocardial infarction (OR, 1.37 [95% CI, 1.33-1.40]) after adjustment for BMI and other covariates.[6] However, residual confounding or reverse causality may have contributed to these associations. Indeed, in this study, observational WHR adjusted for BMI was strongly associated with potential confounders, illustrating a limitation of observational

Figure 5. Phenome-Wide Association Study Testing if 48-SNP Polygenic Risk Score for WHR Adjusted for BMI Is Associated With a Range of Disease Phenotypes

Outcome	Cases, No.	Controls, No.	Odds Ratio (95% CI) per 1-SD Increase in WHR Adjusted for BMI	*P* Value
Cardiovascular				
Stroke	2035	109 951	1.03 (0.72-1.46)	.89
Atrial fibrillation or flutter	2194	109 792	0.88 (0.62-1.26)	.49
Heart failure	586	111 400	1.21 (0.62-2.39)	.58
Aortic stenosis	190	111 796	0.97 (0.33-2.85)	.95
Peripheral vascular disease	682	111 304	1.65 (0.89-3.07)	.11
Venous thromboembolism	3271	108 715	0.97 (0.73-1.30)	.84
Endocrine				
Hyperthyroidism	866	111 120	1.13 (0.65-1.96)	.66
Hypothyroidism	5415	106 571	0.95 (0.76-1.19)	.67
Gout	1605	110 381	0.93 (0.62-1.40)	.73
Renal or urologic				
Enlarged prostate	1567	110 419	0.85 (0.57-1.29)	.45
Uterine fibroids	1632	110 354	1.04 (0.71-1.54)	.83
Gastrointestinal				
Gastric reflux	4864	107 122	1.18 (0.93-1.49)	.18
Irritable bowel syndrome	2672	109 314	1.19 (0.87-1.62)	.27
Gallstones	1825	110 161	1.12 (0.77-1.63)	.56
Neurologic or psychiatric				
Migraine	3155	108 831	0.98 (0.73-1.32)	.91
Depression	6636	105 350	0.89 (0.73-1.09)	.27
Anxiety	1539	110 447	0.93 (0.62-1.41)	.74
Musculoskeletal				
Back pain	581	111 405	1.28 (0.66-2.49)	.46
Joint pain	377	111 609	1.04 (0.49-2.22)	.92
Osteoporosis	1730	110 256	0.93 (0.63-1.39)	.73
Osteoarthritis	9655	102 331	0.99 (0.84-1.18)	.94
Sciatica	1030	110 956	1.28 (0.77-2.13)	.33
Prolapsed disk	1849	110 137	1.05 (0.73-1.52)	.79
Respiratory				
Asthma	13 896	98 090	1.17 (1.01-1.35)	.04
COPD	2350	109 636	0.96 (0.69-1.34)	.81
Pneumonia	1576	110 410	0.82 (0.55-1.23)	.34
Hay fever	6251	105 735	0.85 (0.70-1.05)	.13
Cancer				
Lung	113	111 873	2.02 (0.46-8.90)	.36
Breast	2378	109 608	0.95 (0.68-1.33)	.75
Colorectal	610	111 376	1.01 (0.52-1.97)	.97
Skin	2475	109 511	1.16 (0.84-1.62)	.37
Prostate	835	111 151	1.10 (0.63-1.95)	.73
Cervical	870	111 116	0.56 (0.32-0.97)	.04
Other	2398	109 588	1.17 (0.85-1.63)	.34
Any	9494	102 492	1.02 (0.85-1.21)	.86



Results are standardized to a 1-SD increase in waist-to-hip ratio adjusted for body mass index due to polygenic risk score. All estimates were derived in UK Biobank using instrumental variables regression (adjusting for age, sex, and 10 principal components of ancestry). The threshold for significance was $P < .0014$ (0.05/35 = 0.0014). Size of data markers is inversely proportional to variance of estimate. COPD indicates chronic obstructive pulmonary disease; OR, odds ratio; SNP, single-nucleotide polymorphism.

epidemiology. Here, these prior findings were extended by testing a polygenic risk score that appeared independent of measured confounders (eTable 5 in the Supplement). Elevated levels of triglyceride-rich lipoproteins, a risk factor for CHD with genetic and experimental evidence for causality,[26,27] appeared to mediate a substantial proportion of the increased risk for CHD.

Second, these results suggest that body fat distribution, beyond simple measurement of BMI, could explain part of the variation in risk of type 2 diabetes and CHD noted across individuals and subpopulations. For example, increased abdominal adiposity at a given BMI has been proposed as an explanation for the excess risk of CHD observed in South Asians.[28] Similarly, greater abdominal adipose tissue at a given BMI has been proposed to underlie the excess risk of CHD at a given BMI among men compared with women.[29] In the INTERHEART study, which observed a similar strength of association of WHR adjusted for BMI with myocardial infarc-

tion as the genetic estimate reported here, 33.7% of myocardial infarctions were attributed to increased WHR compared with 10.8% of infarctions attributed to overweight and obesity (BMI >25).[6] When combined with the evidence supportive of causality reported here, these results raise the potential that abdominal adiposity, independent of elevated BMI, is a major driver of global CHD burden.

Third, WHR adjusted for BMI might prove useful as a biomarker for the development of therapies to prevent type 2 diabetes and CHD. Although a substantial focus of drug development has been toward therapeutics to reduce overall adiposity,[30] there has been little effort toward the development of therapies that modify body fat distribution to reduce abdominal adiposity. Ongoing research to understand the mechanistic links between the numerous genetic loci that influence WHR adjusted for BMI may lead to novel therapeutic strategies to reduce abdominal adiposity and reduce the risk of type 2 diabetes and CHD.

The mendelian randomization approach used in this study rests on 2 major principles (Figure 1). First, it requires a strong link between the genetic variants used as an instrument and the exposure (WHR adjusted for BMI, assumption 1 in Figure 1). The 48-SNP polygenic risk score explained 1.5% of variance in WHR adjusted for BMI and had an F statistic of 1713 in the UK Biobank, classifying it as a strong instrument with negligible weak instrument bias.[31] Second, mendelian randomization assumes the absence of pleiotropy, that is, it assumes that the genetic variants used as an instrument affect the outcome (CHD) through the exposure (WHR adjusted for BMI) and not through any other pathway or confounding factors (assumptions 2 and 3 in Figure 1). Although it is not possible to directly test whether pleiotropy is present in any mendelian randomization study,[32] a number of steps were taken in this study to reduce the risk of pleiotropy, including use of 3 different genetic instruments, use of weighted median regression, and use of an instrument associated with higher WHR adjusted for BMI in women but not men. Results from 4 of 5 of these sensitivity analyses were consistent with the primary results. Tests for interaction using sex-specific instruments for CHD and diabetes were directionally consistent with expectation but did not demonstrate significant heterogeneity of effect by sex. This analysis required individual-level data available only in UK Biobank participants and may have been underpowered to detect a difference. Future research that explores such sex-specific instruments in larger data sets may prove more conclusive.

This study has several limitations. First, although a number of approaches were used in an attempt to rule out pleiotropy, it is possible that these results represent a shared genetic basis between WHR adjusted for BMI and CHD rather than a causal relationship. Second, prevalent events largely derived from a verbal interview with a nurse were used for the phenome-wide association study of 35 different disorders. Although these events are likely to be of greater specificity and sensitivity than coded mortality data, they have not been independently validated. Third, the phenome-wide association study may have been underpowered to detect an association of genetic WHR adjusted for BMI with outcomes other than type 2 diabetes and CHD. Fourth, this analysis was restricted to individuals of European ancestry; the association of genetic WHR adjusted for BMI with type 2 diabetes and CHD may differ by ethnicity or genetic ancestry.

Conclusions

A genetic predisposition to higher WHR adjusted for BMI was associated with increased risk of type 2 diabetes and CHD. These results provide evidence supportive of a causal association between abdominal adiposity and these outcomes.

ARTICLE INFORMATION

Author Contributions: Dr Emdin had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Drs Emdin and Khera contributed equally.
Concept and design: Emdin, Khera, Kathiresan.
Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: Emdin, Khera, Natarajan, Kathiresan.
Critical revision of the manuscript for important intellectual content: Emdin, Khera, Klarin, Zekavat, Hsiao, Kathiresan.
Statistical analysis: Emdin, Khera, Natarajan, Hsiao, Kathiresan.
Administrative, technical, or material support: Klarin, Kathiresan.

Conflict of Interest Disclosures: All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Dr Khera reported receiving personal fees from Merck and Amarin Pharmaceuticals. Dr Kathiresan reported receiving grants from Bayer Healthcare, Amarin, and Regeneron; serving on scientific advisory boards for Catabasis, Regeneron Genetics Center, Merck, Celera, and Genomics PLC; receiving personal fees from Novartis, Sanofi, AstraZeneca, Alnylam, Eli Lilly, Lerink Partners, Noble Insights, Bayer, and Ionis; receiving consulting fees from Regeneron, Merck, Quest Diagnostics, Novartis, Amgen, Genentech, Corvidia, Genomics PLC, Ionis Pharmaceuticals, and Eli Lilly; and holding equity in Catabasis and San Therapeutics. No other authors reported disclosures.

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